Roux-en-Y Gastric Bypass for obesity and type 2 diabetes:
Clinical outcomes and mechanistic investigations

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Acknowledgments

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<td>Angiotensin converting enzyme</td>
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<td>ACTH</td>
<td>Adrenocorticotphin</td>
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<td>ADA</td>
<td>American Diabetes Association</td>
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<tr>
<td>AG</td>
<td>Acylated ghrelin</td>
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<td>AGB</td>
<td>Adjustable gastric banding</td>
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<td>AgRP</td>
<td>Agouti related peptide</td>
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<td>ARB</td>
<td>Angiotension receptor blocker</td>
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<tr>
<td>BAT</td>
<td>Brown adipose tissue</td>
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<tr>
<td>BD</td>
<td>Twice daily</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BPD</td>
<td>Biliopancreatic diversion</td>
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<tr>
<td>CART</td>
<td>Cocaine and amphetamine regulated transcript</td>
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<td>CCK</td>
<td>Cholecystokinin</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
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<td>dAG</td>
<td>Des-acylated ghrelin</td>
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<tr>
<td>DAG</td>
<td>Diacylglycerol</td>
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<td>DBP</td>
<td>Diastolic blood pressure</td>
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<td>Diabetes prevention program</td>
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<td>DPP4-I</td>
<td>Dipeptidyl peptidase 4 inhibitor</td>
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<td>DPS</td>
<td>Finish diabetes prevention study</td>
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<td>DSE</td>
<td>Diabetes support and education</td>
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<td>EE</td>
<td>Energy expenditure</td>
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<td>EWBL</td>
<td>Excess body weight loss</td>
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<td>FDA</td>
<td>Food and drug administration</td>
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<td>FFA</td>
<td>Free fatty acids</td>
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<tr>
<td>FGF</td>
<td>Fibroblast growth factor</td>
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<td>FPG</td>
<td>Fasting plasma glucose</td>
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<tr>
<td>GB</td>
<td>Gastric bypass</td>
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<tr>
<td>GIP</td>
<td>Glucose dependent insulinoetric peptide</td>
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<td>GLP-1</td>
<td>Glucagon like peptide-1</td>
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<td>GOAT</td>
<td>Ghrelin O-Acyltransferase</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Glycated haemoglobin</td>
</tr>
<tr>
<td>HDEC</td>
<td>Health and Disability Ethics Committee</td>
</tr>
<tr>
<td>HDL</td>
<td>High density lipoprotein</td>
</tr>
<tr>
<td>HEC</td>
<td>Hyperinsulinaemic euglycaemic clamp</td>
</tr>
<tr>
<td>HOMA</td>
<td>Homeostatic model assessment</td>
</tr>
<tr>
<td>IACV</td>
<td>Inter-assay coefficient of variation</td>
</tr>
<tr>
<td>IDF</td>
<td>International diabetes federation</td>
</tr>
<tr>
<td>IGF</td>
<td>Insulin-like growth factor</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>IR</td>
<td>Insulin receptor</td>
</tr>
<tr>
<td>IWQOL</td>
<td>Impact of weight on quality of life</td>
</tr>
<tr>
<td>JIB</td>
<td>Jejunoileal bypass</td>
</tr>
<tr>
<td>Kcal</td>
<td>Kilocalories</td>
</tr>
<tr>
<td>Kg</td>
<td>Kilogram</td>
</tr>
<tr>
<td>Kj</td>
<td>Kilojoules</td>
</tr>
<tr>
<td>LAGB</td>
<td>Laparoscopic adjustable gastric banding</td>
</tr>
<tr>
<td>LDL</td>
<td>Low density lipoprotein</td>
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<tr>
<td>LEP-R</td>
<td>Leptin receptor</td>
</tr>
<tr>
<td>LPL</td>
<td>Lipoprotein lipase</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean arterial pressure</td>
</tr>
<tr>
<td>MCR</td>
<td>Melanocortin receptor</td>
</tr>
<tr>
<td>ml</td>
<td>Millilitre</td>
</tr>
<tr>
<td>mmHg</td>
<td>Millimetres of Mercury</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NEFA</td>
<td>Non-esterified fatty acids</td>
</tr>
<tr>
<td>Nmol</td>
<td>Nanomoles</td>
</tr>
<tr>
<td>NW</td>
<td>Normal weight</td>
</tr>
<tr>
<td>NZ</td>
<td>New Zealand</td>
</tr>
<tr>
<td>NZSSD</td>
<td>New Zealand Society for the Study of Diabetes</td>
</tr>
<tr>
<td>OD</td>
<td>Once daily</td>
</tr>
<tr>
<td>OGTT</td>
<td>Oral glucose tolerance test</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>OW</td>
<td>Overweight</td>
</tr>
<tr>
<td>OXM</td>
<td>Oxyntomodulin</td>
</tr>
<tr>
<td>PA</td>
<td>Physical activity</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
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</tr>
<tr>
<td>POMC</td>
<td>Proopiomelanocortin</td>
</tr>
<tr>
<td>PSWL</td>
<td>Placebo subtracted weight loss</td>
</tr>
<tr>
<td>PYY</td>
<td>Polypeptide YY</td>
</tr>
<tr>
<td>QDS</td>
<td>Four times daily</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>REE</td>
<td>Resting energy expenditure</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver operated curve</td>
</tr>
<tr>
<td>RPG</td>
<td>Random plasma glucose</td>
</tr>
<tr>
<td>RYGB</td>
<td>Roux-en-Y gastric bypass</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SE</td>
<td>Standard error</td>
</tr>
<tr>
<td>SG</td>
<td>Sleeve Gastrectomy</td>
</tr>
<tr>
<td>SGLT2</td>
<td>Sodium glucose cotransporter 2</td>
</tr>
<tr>
<td>SNP</td>
<td>Single nucleotide polymorphism</td>
</tr>
<tr>
<td>SOS</td>
<td>Swedish Obesity study</td>
</tr>
<tr>
<td>TEF</td>
<td>Thermic effect of food</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>UTN</td>
<td>Universal trial number</td>
</tr>
<tr>
<td>VLCD</td>
<td>Very low calorie diet</td>
</tr>
<tr>
<td>VSG</td>
<td>Vertical sleeve gastrectomy</td>
</tr>
<tr>
<td>WAT</td>
<td>White adipose tissue</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>WOC</td>
<td>Wakefield Obesity Clinic</td>
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ABSTRACT

The prevalence of obesity is increasing at a rapid rate internationally, paralleled with an increase in the number of people with type 2 diabetes. Whilst the cornerstone of management of both conditions is lifestyle change, dietary interventions tend to result in only minimal weight loss which is frequently regained over the subsequent years. Medical therapies for weight loss are only moderately more effective, whilst those used in the management of diabetes control hyperglycaemia rather than addressing the underlying pathophysiology. Bariatric surgery has therefore emerged as an apparently effective technique for both conditions, particular when occurring in association. Whilst high quality short term follow up studies now support bariatric surgery as the most effective treatment option available, there is a lack of longer term outcome studies to support its durability and safety. In chapter 1 of this thesis, I provide a summary of the current view of the pathophysiology of both obesity and type 2 diabetes, along with a review of non-surgical and surgical interventions. Lastly, I provide an overview of the research exploring the mechanisms by which bariatric surgery may induce these effects.

In this thesis I report findings from a long term follow up study involving 118 participants following Roux-en-Y Gastric bypass surgery. The mean duration of follow up was 10.2 years, with the mean body weight loss 29.6% (38.5kg) at last follow up. 28% of participants with type 2 diabetes prior to surgery remained with type 2 diabetes at follow up, whilst 72% had improved glucose tolerance. Significant reductions in blood pressure and lipid markers were observed, as well as a reduced likelihood of depression, gout, and sleep apnoea after surgery. Quality of life was better when compared against non-surgical BMI matched controls. Furthermore, I report that the variable definitions of both diabetes at baseline and glycaemic outcomes used in the bariatric literature, results in significantly different published outcomes, and is an impediment to comparative analysis.

In addition, I report the findings of two studies exploring further the mechanisms underlying the effects of bariatric surgery on durable weight loss and glucose homeostasis. In the first study, I demonstrate that whilst the acute hormonal stress response to RYGB surgery is short lived, an ongoing inflammatory response, still evident six days after surgery, should be considered when assessing changes in glucose homeostasis within this period. In the second study, I begin a line of research exploring the association between altered gut peptide physiology after bariatric surgery and longer term weight outcomes. These mechanistic studies are performed to both optimise outcomes following RYGB surgery, and to better understand the pathophysiology of obesity and type 2 diabetes.
1 CHAPTER ONE: LITERATURE REVIEW

1.1 Overview of obesity and type 2 diabetes

1.2 Non-surgical management of obesity and type 2 diabetes

1.3 Bariatric surgery for the management of obesity and type 2 diabetes

1.4 Mechanisms underlying the effects of bariatric surgery on type 2 diabetes and obesity
1.1 Overview of obesity and type 2 diabetes

1.1.1 Rising prevalence and cost of obesity and type 2 diabetes

The prevalence of both type 2 diabetes and obesity has risen significantly over the past five decades, and is projected to rise further in the coming years. Obesity is a strong risk factor for the development of type 2 diabetes, and therefore the prevalence of type 2 diabetes is closely related to that population’s obesity prevalence.¹

A recent population study revealed that approximately 35% of the adult population of the United States are obese (BMI ≥ 30 kg/m²), and, perhaps more surprisingly, that the average weight of the same population now lies someway above the “healthy” range BMI (Average BMI = 28 kg/m², NR = 19-25 kg/m²).² The picture in New Zealand is no less concerning; the “Health of New Zealand adults” survey of 2012 demonstrated that 28.4% of New Zealand adults are obese, whilst 63.8% are overweight or obese (BMI >25 kg/m²).³ Of particular concern is the marked disparity in prevalence rates between ethnic groups within New Zealand. The rates in Caucasians approximate to the national averages; however, the rates of obesity and overweight in Maori (44.4 and 75.3% respectively) and Polynesians (62.1 and 84.8% respectively) are extreme. Furthermore, the issue is evident in childhood where 27% of Maori and 19% of Pacific Islander children in New Zealand are obese. The likelihood of obesity in New Zealand is positively associated with neighbourhood deprivation, and varies significantly across the nation (Figure 1-1).

The International Diabetes Federation (IDF) has published regular reports on the prevalence of diabetes since 2000. The latest publication from 2011 drew upon 133 studies assessing prevalence in 91 countries.⁴ Prevalence rates for the remaining 125 countries were estimated by extrapolating the prevalence in a country considered comparable with respect to ethnic, geographical, and socio-economic similarities. 8.3% of the world population had type 2 diabetes in 2011, although there are significant regional differences. (Figure 1-2) Prevalence rates in excess of 20% were reported in
Figure 1-1  Estimated prevalence of a) obesity and b) type 2 diabetes by New Zealand district health board (reproduced from “Obesity and diabetes in New Zealand: Parliamentary library research paper, October 2014)
4 countries (Nauru, Kiribati, Marshall Islands, and Kuwait), whilst 3 regions (Middle East and North Africa, Western Pacific, and Central and South America) had prevalence rates in excess of 10%. Recent research suggests that the prevalence of type 2 diabetes in the United states has increased by 75% over the 20 year period from 1988–1994 to 2005–2010, and that an increased prevalence was evident in each age group.\textsuperscript{5} Other countries have seen a similar steep rise in the prevalence of diabetes perhaps illustrated most dramatically by studies conducted in China over the past 30 years. The prevalence of type 2 diabetes was calculated at just 1% in 1980, but had increased to 5.5% in 2001, and 11.6% in 2013.\textsuperscript{6,7,8}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{prevalence-diabetes-by-region.png}
\caption{Prevalence of type 2 diabetes by region, expressed as millions of cases with percentage change from 2000 to 2030.\textsuperscript{9}}
\end{figure}

The 2013/2014 New Zealand health survey showed that 198,000 adults (5.5%) in New Zealand had diabetes, with men more likely to have diabetes than women (6.3% in males, 4.8% in females). Pacific (9%), Maori (7%), and Asian (6%) adults were all more likely to have diabetes than the national average. Furthermore, the prevalence of diabetes increased with age in each ethnic group, such that the prevalence of diabetes in New Zealand adults over the age of 75 years exceeded 15%. As with obesity, the prevalence varies widely throughout the nation. It should be noted that adults with type 2 diabetes are frequently unaware of their diagnosis, or chose not to accept it. Illustrating this, the New Zealand Ministry of Health virtual diabetes
registry reported a 21% higher prevalence of type 2 diabetes; 241,381 New Zealand Adults were recorded as having type 2 diabetes in 2013 on the basis of laboratory testing. Given the asymptomatic nature of early dysglycaemia, it is likely the true prevalence is higher still.

Based on trajectories calculated by comparing prevalence data across the previous 10 years, the IDF predicts significant increases in diabetes prevalence in all world regions over the next 30-40 years (Figure 1-2). The world prevalence is predicted to increase from 8.3% to 9.9%, although given the significant increases in population forecast in each region, this amounts to an absolute additional 181 million people with type 2 diabetes worldwide (187% increase from 366 million cases in 2011). An American study projected a US prevalence of 33% by 2050 if prevalence rates continue to increase at the current rate, but suggested true prevalence rates may be closer to 20% given improvements in pre-diabetes management. Whilst diabetes control appears to have improved during the same time period, only 1 in 5 patients with diabetes achieves target concentrations of HbA1c, blood pressure, and lipid concentrations.

The financial burden placed on New Zealand’s health resulting from obesity and type 2 diabetes is significant. A 2006 study estimated that the annual health care cost attributable to increased BMI (overweight or obesity) alone was NZ$686 million, representing 4.5% of the health budget. The cost is greater still once lost productivity as a direct consequence of increased BMI is factored in, and may be as high as NZ$849 million. Although there is considerable overlap, type 2 diabetes also presents significant health care costs. A PricewaterhouseCoopers study to calculate current and projected health care costs attributable to type 2 diabetes reported an annual cost of NZ$600 million in 2008, and a projected increase to NZ$1.8 billion by 2022.

It is clear therefore that strategies to reduce the prevalence of type 2 diabetes and obesity are of paramount importance. Whilst the greatest gains may be made by preventing the development of these conditions, effective interventions to treat existing disease are needed. The following chapters present the pathophysiology of obesity and type 2 diabetes, and non-surgical interventions for both conditions. Finally, bariatric surgery as an intervention for each condition is discussed, along with notes on the mechanism of action.
1.1.2 Pathophysiology of obesity

Obesity is the consequence of a net positive energy imbalance, where intake (ingested calories) exceeds expenditure (basal metabolic rate, thermic effect of food, physical activity) over a prolonged period of time. Body weight is maintained within surprisingly narrow thresholds throughout life in healthy individuals, with changes in adiposity the predominant contributor to changes in body weight. The average adult male will gain 0.25 to 0.5kg of body weight per year, equating to a difference as little as 10 kilocalories per day of energy intake versus expenditure.\(^1\) This precise balance is maintained over long periods of time despite significant fluctuations in daily intake and expenditure, and has been calculated to equate to an imbalance in cumulative intake and expenditure of 0.17% over 10 years.\(^2\) In this section I will discuss the current model of human energy homeostasis and factors that are believed to underlie the increasing prevalence of obesity.

1.1.2.1 Human adipose tissue

Fundamental to any effective physiological system regulating energy homeostasis are mechanisms by which body habitus can be communicated to cerebral centres, so that adaptive responses to weight loss or gain can be enacted. As adiposity is the predominant determinant of obesity, it stood to reason that cerebral “awareness” of fat is required for this physiological model to be plausible. This concept was first proposed by Kennedy over 60 years ago, who suggested a ‘lipostatic model’ whereby metabolites would circulate in proportion to adiposity.\(^3,4\) In this section, I will discuss adipose tissue as a functional endocrine unit, and the role of the major adipose hormones Leptin and adiponectin.

Adipose tissue constitutes approximately 28% and 40% of total body weight in adult males and females respectively in a population characterised by a high proportion of obesity and overweight.\(^5\) Adipose tissue is composed of two forms; white and brown adipose tissue (WAT/BAT), although recent evidence suggests a third form known as beige adipose tissue.\(^6\) The predominant role of BAT is to generate heat via thermogenesis. BAT contains abundant mitochondria which uniquely express uncoupling protein (UCP-1). Numerous factors have been shown to regulate BAT activity including thyroid hormones, FGF21, cardiac derived
natriuretic peptides, and insulin, although neuronal mediators are predominant.\textsuperscript{21,22,23,24,25} Sympathetic activation, via adrenergic receptor subtype ADRB3, is the primary neuronal regulator of BAT, and allows thermogenesis to associate with ambient external temperature. Brain derived natriuretic factor (BDNF) and bone morphogenetic proteins (BMP7/8b) both increase BAT activity, either through activation of existing tissue or through ‘browning’ white adipose tissue.\textsuperscript{26,27} Whilst the role of BAT thermogenesis appears primarily to relate to body temperature maintenance, it is clear that this system can be utilised to expend surplus energy under some circumstances.\textsuperscript{25}

Mature adipocytes constitute 30-70\% of WAT, with the remainder being progenitor cells.\textsuperscript{28} A single cytoplasmic lipid droplet constitutes over 90\% of the white adipocyte volume. The major role of WAT is to store triglyceride for release (lipolysis) and utilisation as energy, particularly during periods of reduced dietary energy intake. Whilst the exact mechanisms remain to be elucidated, it is apparent that the sympathetic nervous system is the major stimulator of WAT lipolysis.\textsuperscript{29} Along with provision of thermal insulation, WAT has a number of other endocrine and secretory roles.\textsuperscript{30} WAT is a primary site for fat soluble vitamin storage, and also expresses 1α-hydroxylase which converts 25-hydroxycholecalciferol to 1,25-hydroxycholecalciferol.\textsuperscript{31} The presence of 11β-hydroxysteroid allows the conversion of cortisone to cortisol.\textsuperscript{32} A large number of proteins, often referred to as adipokines, are secreted by WAT including Adipsin, tumour-necrosis factors, interleukin-6, plasminogen activating factors, lipoprotein lipase, resistin, leptin, and adiponectin; the last of these hormones is discussed below.

1.1.2.1.1 Leptin

Arguably the most important WAT secreted hormone is leptin, identified over twenty years ago through study of the hyper obese \textit{ob}/\textit{ob} mouse.\textsuperscript{33,34} Leptin consists of 166 amino acids and is encoded by the \textit{OB} gene located on chromosome 7.\textsuperscript{35,36} Whilst WAT is the major site of leptin production, synthesis also occurs in BAT, heart, placenta, stomach, and ovaries.\textsuperscript{37} The leptin receptor (LEP-R or OB-R), encoded by the OBR gene on chromosome 1, is expressed predominantly in the hypothalamus and cerebellum, but also within the vasculature and stomach.\textsuperscript{37,38} Serum leptin concentrations are proportionate to adipose tissue volume, and therefore concentrations correlate positively with body fat content in humans.\textsuperscript{40} Leptin freely crosses the blood-brain barrier and cerebral spinal leptin concentrations also correlate with
Leptin acts centrally via the hypothalamic LEP-R, which in turn stimulates the release of numerous anorexigenic peptides that reduce adiposity by decreasing appetite and increasing thermogenesis (see below).

Whilst low leptin concentrations are observed in a small subgroup of obese individuals, human OB mutations are rare. However, individuals who harbour heterozygous frame shift mutations in the OB gene have lower leptin concentrations and an increased prevalence of obesity than controls. Furthermore, leptin treatment in these individuals results in reduced appetite and consequent weight loss. Thus, it may be hypothesized that leptin treatment in obese individuals may also support weight loss. Contrary to this assumption however, is the finding that leptin concentrations generally remain elevated in obese individuals. Furthermore, recombinant leptin therapy does not promote weight loss in obese individuals despite clear increases in serum leptin concentrations.

The concept of leptin resistance was therefore postulated as an explanation for these apparent contradictory findings, and supported by documentation of the development of resistance in rat models exposed to long term leptin infusion. Over eating leads to rapid rises in leptin concentrations, and early research focused on the possible effect this may have on hypothalamic leptin receptor expression. Although leptin deficiency appears to increase hypothalamic leptin receptor expression in ob/ob mice, it is not clear that a similar decrease in expression occurs in states of elevated leptin concentrations. Whilst the same group showed decreases in leptin receptor mRNA concentrations in the hypothalamic areas of obese mice treated with leptin, other groups have found no differences in leptin receptor expression between healthy and obese humans.

Obesity related leptin resistance may better be explained by alterations in movement across the blood brain barrier with differing body weight. The peripheral administration of leptin to diet induced obese mice leads to longer term leptin resistance. This is rapidly overcome once leptin is centrally infused, as evident by weight loss. Furthermore, the ratio of cerebrospinal and plasma leptin concentrations in humans is lower in obese subjects when compared to normal weight individuals. Both of these findings support a defect in central transfer of leptin underlying the apparent leptin resistance seen in obesity, as opposed to ‘true’ resistance at the target cellular level. In addition, blood brain barrier leptin transport defects appear to be acquired consistent with the notion of leptin resistance relating to obesity rather than being
causal; the study of rat models has documented the onset of apparent leptin transport dysfunction only after significant weight gain.\textsuperscript{56}

### 1.1.2.1.2 Adiponectin

Adiponectin production is specific to WAT, and accounts for 0.01 to 0.05\% of the total plasma protein content.\textsuperscript{57} However, and in direct contrast to leptin, the serum level of adiponectin paradoxically decreases with increasing body fat.\textsuperscript{58} Furthermore, adiponectin concentrations increase during caloric restriction, possibly as a result of increased bone marrow adipose tissue secretion.\textsuperscript{59} The mechanism underlying this phenomenon remains to be elucidated, and a recent meta-analysis did not support an association between adiponectin concentrations and body mass index.\textsuperscript{60} However, it is possible that visceral fat mass may be associated with adiponectin concentrations.\textsuperscript{61} It is interesting to note however that women have significantly higher circulating adiponectin concentrations than men, suggesting a modulating role of sex hormones.\textsuperscript{62} To support this, concentrations of adiponectin vary with differing body fat distributions, such that higher adiponectin concentrations are seen with increased lower extremity and truncal obesity.\textsuperscript{63} Adiponectin concentrations rise following weight loss as a consequence of any intervention.\textsuperscript{64,65}

Adiponectin acts via adiponectin receptors 1 and 2 (ADIPOR/2) and T-cadherin.\textsuperscript{57} The functions of adiponectin demonstrated thus far include promotion of beta cell function and survival, and thereafter, the enhancement of peripheral insulin sensitivity, and anti-inflammatory effects.\textsuperscript{66,67,68} Higher adiponectin concentrations appear to protect against the development of diabetes, and conversely, hypoadiponectinaemia is independently associated with the risk of diabetes and the metabolic syndrome.\textsuperscript{69,70,71} Adiponectin predominantly enhances insulin sensitivity by decreasing hepatic glucose output via AMP-activated protein kinase pathways, although an additional effect on peripheral skeletal muscle can not be discounted.\textsuperscript{72}

### 1.1.2.2 The hypothalamus in human energy homeostasis

Experiments in rodents established conclusively that the hypothalamus was fundamentally involved in energy homeostasis. Drawing on previous observations, Hetherington and Ranson observed a significant increase in adiposity following electrolytic hypothalamic ablation in rats in their seminal work published 75 years ago.\textsuperscript{73} The identification of leptin as a messenger that
could convey information about adiposity to the hypothalamus, lead to the rapid characterisation of the neural circuits that modulate energy homeostasis. Further evidence for the critical role of each of these neurotransmitters has been obtained through the study of human monogenic syndromes that result in obesity.\textsuperscript{74} Leptin acts by activating arcuate nucleus proopiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART) neurons, whilst anabolic neuropeptide Y (NPY) and Agouti-related peptide (AgRP) neurons are suppressed by leptin.\textsuperscript{75} POMC/CART neurons project to the lateral hypothalamic area, where they inhibit the release of melanocortin-stimulating hormone (MSH) and orexins A and B, and the paraventricular nucleus, where they stimulate the release of thyrotroph releasing hormone (TRH), corticotroph releasing hormone (CRH) and oxytocin.\textsuperscript{75} NPY/ArGP neurons also project to the lateral hypothalamic area and paraventricular nucleus, but have opposing effects on post neuron peptide release. MSH and orexin A and B are orexigenic (increase appetite) peptides, whilst TSH and CRH have predominantly anorexigenic effects.

The melanocortin system, now known to be critical to functional energy homeostasis, is defined as neurons expressing either POMC or AgRP, or melanocortin receptors with affinity for neuropeptides released by these neurons.\textsuperscript{76} POMC is a polypeptide precursor with eight potential cleavage sites that are targets for cleavage enzymes.\textsuperscript{77} The presence or absence of these enzymes in each tissue expressing POMC dictates local concentrations of post cleavage peptides. In the hypothalamus POMC is predominantly cleaved to αMSH and βMSH which interact with melanocortin receptor 3 and 4 (MC3-R/MC4-R).\textsuperscript{78} Humans with loss of function mutations in the MC4-R receptor present in childhood with severe obesity, and this monogenic disorder has been shown to be present in up to 6% of severely obese children.\textsuperscript{79} Whilst homozygotes are more severely affected than heterozygotes, penetrance also varies, and mutations resulting in a degree of retained post receptor signal capacity are less severely affected.\textsuperscript{80}

It is likely that multiple other peptides are involved in the hypothalamic regulation of energy homeostasis. Insulin receptor dysfunction mice develop diet sensitive obesity associated with increases in adiposity, leptin, and insulin concentrations.\textsuperscript{81} Insulin receptors are present within the arcuate nucleus POMC neurons in separate populations from those that express the leptin receptor.\textsuperscript{82} It therefore appears that both leptin and insulin function as lipostatic hormones, indicating energy repletion to the hypothalamus.\textsuperscript{83} Endocannabinoids appear to play a role in regulating feeding behaviour through interactions in the paraventricular nucleus, possibly by
increasing the release of TRH and CRH, and augmenting the effect of ghrelin. Endocannabinoid receptor agonists have been shown to increase food intake, whilst antagonists result in weight loss in overweight adults as demonstrated in recent randomised controlled trials. The peroxisome proliferator activated receptor γ (PPARγ) is a nuclear receptor for which a high affinity ligand has not yet been identified; it has been suggested that the receptor may instead act as sensor of ambient fatty acid concentration. The receptor is expressed in WAT and also within the hypothalamus, and central antagonism of this receptor results in negative energy balance in high-fat diet rodents. This in keeping with clinical experience of using PPARγ agonists (thiazolidinediones, see 1.2.2) for the management of type 2 diabetes where weight gain is an undesired side effect of therapy. Further research is required to define the role of the central PPARγ receptor in human energy homeostasis. Other potential peptide regulators of hypothalamic energy homeostasis are the subject of current research as possible therapeutic targets.

1.1.2.3 Gut peptide physiology and role in energy homeostasis

Along with the adipocyte derived hormones leptin and adiponectin described above, a large number of additional hormones produced in the gastrointestinal tract have a role in energy homeostasis and are discussed below. Whilst leptin is predominantly involved in conveying information related to the longer term regulation of energy balance, gastrointestinal peptides, frequently released in direct response and proportion to ingested food, play key roles in the short term regulation of food intake.

1.1.2.3.1 Ghrelin

Ghrelin, a 28 amino acid protein manufactured and secreted from mucosal oxyntic glands located in the gastric fundus, and to a lesser extent the proximal intestine and pancreatic islets, is the only known endogenous stimulant of appetite in humans. Two major isoforms can be identified in the circulation; acylated ghrelin (AG) and des-acylated ghrelin (dAG). Acylation occurs during post translational modification, and involves the covalent linkage of medium-chain fatty acid groups. Ghrelin O-Acyltransferase (GOAT) has recently been identified as the enzyme required for acylation to occur, and may have other physiological effects independent
of this role. \textsuperscript{92} dAG results either from lack of acylation at this post translational stage, or later enzymatic removal of the acyl group. dAG is the major circulatory isoform, present at greater than 4 times the concentration of AG. \textsuperscript{93} Acylation is required for ghrelin to bind to the growth hormone secretagogue receptor (GHSR) expressed in the hypothalamus and brainstem, through which most of its biological effects are mediated.

AG is likely to act as a meal initiator by modulating feelings of hunger. \textsuperscript{91} In healthy individuals, ghrelin concentrations are highest in the fasting state, before falling to nadir concentrations at one to two hours after commencement of the meal. \textsuperscript{94} Thus, suppression of AG after meals in healthy individuals is likely to be important in indirectly promoting appropriate satiety. Fasting concentrations are often two fold higher than minimal daily concentrations, although a single measurement of AG during the post-breakfast trough (90 minutes following commencement of the meal) correlates well with the total 24 hour mean AG level. \textsuperscript{94} Administration of intravenous AG to achieve circulatory concentrations equivalent the fasting state increase food intake by up to 30% in both healthy and obese individuals. \textsuperscript{95,96}

Circulating total ghrelin concentrations are decreased in simple obesity, but the normal suppressive effect of food consumption on ghrelin concentrations is attenuated in obese persons suggesting a blunting of the normal flux of ghrelin with food intake and starvation. \textsuperscript{97,98} This finding along with the previously confirmed orexigenic effects of AG, has led to a number of attempts to favourably modulate the weight associated effects of ghrelin through pharmaceutical means. Antagonists against the GHSR receptor have been developed by a number of pharmaceutical companies but, with the exception of some but not all early phase rodent studies, have not yet demonstrated a favourable weight effect in humans. \textsuperscript{99,100} Therapies which neutralize circulating AG are also under active investigation but, again, have encountered difficulties. A vaccine involving antibodies directed against circulating AG has been developed, and early rodent studies demonstrated weight loss in recipient animals associated with increasing antibody titres. \textsuperscript{101} However, similar work in humans has not replicated these findings, and concerns about the permanency of antibodies against AG, and consequent long term adverse metabolic effects, may limit further work in this area. \textsuperscript{99} Finally, inhibition of GOAT, and thus reduced acylation of ghrelin, is an attractive method by which to selectively modify the physiological effects of circulating ghrelin. Recent work has demonstrated that the administration of synthetic peptide coenzyme A conjugate (GO-CoA-
Tat) to rodents reduces feed seeking behaviour even in the fasted state. Human studies are required to further investigate the potential of this therapeutic strategy.

Recently, the physiological effects of dAG have been clarified in more detail, with many authors now stating that dAG should be considered a separate hormone rather than a simple metabolic by-product of AG. This is on the basis of numerous recent studies supporting a GHSR independent role of ghrelin, along with its ability to either antagonise or agonise the effects of AG. dAG appears to induce insulin secretion in rodent cell lines, and its continued ability to do this despite the co-administration of a GHSR antagonist, suggests that it does so via a separate receptor. Additionally, dAG appears to improve pancreatic beta cell survival and protect against chemically induced (Streptozotocin) beta cell damage in rodent pancreases. Furthermore, obesity associated with insulin resistance has been shown in some studies to be associated with a higher AG/dAG ratio than seen in obesity associated with insulin resistance and in healthy individuals. Using modern assays that better discriminate the relative contribution of AG and dAG to total ghrelin concentrations, some studies suggest that the lower total fasting ghrelin concentrations seen in simple obesity are a consequence of decreased dAG, and that AG remains similar to concentrations in healthy individuals. This interpretation is however contradictory to other studies in the field and requires clarification. Nonetheless, dAG analogs have been developed and are currently under investigation in the management of diabetes.

1.1.2.3.2 Polypeptide YY

Polypeptide YY (PYY) is a 36 amino acid peptide, closely related to pancreatic peptide, and secreted by endocrine L cells in the ileum, colon, and rectum, which co-secrete glicentin, GLP-1, and GLP-1. Its major role appears to be as an anorexigenic hormone, although it likely to play a role in glucose homeostasis. PYY is secreted in response to the presence of nutrients in the intestinal lumen, and is elevated 30-60 minutes after eating. The release of PYY is proportional to the caloric content of the ingested meal, and concentrations remain elevated for up to six hours. Higher concentrations of PYY are released in response to a fat rich meal, when compared with carbohydrate or protein. It is a substrate for dipeptidyl peptidase 4 inhibitor which cleaves PYY to PYY3-36. Thus PYY1-36 is the major form in the fasting state, whilst PYY3-36 is the major form in the post prandial state. PYY3-36 crosses the blood brain
Chapter 1: Literature review

barrier and binds to receptors in the arcuate nucleus, which results in a reduction in neuropeptide Y expression.\textsuperscript{114,115}

PYYs role as a satiety signal is evident by the finding that peripheral administration of PYY to healthy normal weight humans results in a 30% reduction in food intake, as a consequence of a reduction in hunger.\textsuperscript{115} A similar effect is seen following the infusion of PYY in obese individuals.\textsuperscript{116} Furthermore, concentrations of PYY are lower in fasting state in obese individuals, and a blunted PYY response to meals is seen.\textsuperscript{116} In addition to reducing food intake, PYY administration delays gastric emptying, reduces intestinal motility, and decreases pancreatic secretions. It is thus an attractive target for pharmacological obesity treatments, although research in this area is ongoing.

1.1.2.3.3 Amylin

Amylin, or Islet Amyloid Polypeptide (AIP), is produced by the beta cells of the endocrine pancreas and complements the action of insulin by regulating gastric motility and acid secretion, satiety, and glucagon homeostasis.\textsuperscript{117,118} Amylin is secreted in response to a carbohydrate load within the same granules that contain insulin and c-peptide, at a molar ratio of approximately 1:100 with respect to insulin.\textsuperscript{119} Fasting amylin concentrations are increased in obesity associated with normal insulin sensitivity, whilst insulin resistance is associated with a reduced fasting amylin level. The amylin response to a glucose load is increased in obesity and insulin resistance, but is significantly reduced or absent in type 1 diabetes or late type 2 diabetes in parallel with insulin deficiency.\textsuperscript{120} Amylin binds to the amylin receptor complex (ACR) composed of a G protein-coupled receptor and a receptor modifying protein, which is expressed in the brain, liver, muscle and throughout the gastrointestinal tract.\textsuperscript{121}

Exogenous supraphysiological amylin reduces rat food intake rapidly, whilst a reduction in meal size is evident in humans.\textsuperscript{122,123} Administration of an injectable amylin analog (Pramlintide) at supraphysiological doses to obese human participants with type 2 diabetes resulted in modest weight loss of 0.5–1.5kg over a 12 month period of study.\textsuperscript{124} Activation of the area postrema by amylin appears to be fundamental for this effect.\textsuperscript{117} Additionally, there is evidence for a minor role of amylin on weight maintenance in rodents at physiological concentrations, as amylin gene knockout mice are up to 29% heavier than controls.\textsuperscript{125} Administration of amylin antagonists to rodents stimulates increased meals sizes, whilst a similar effect is achieved by selective ablation of the rodent area postrema.\textsuperscript{126,117} Future research into the therapeutic use
of amylin as an anti-obesity agent will need to consider that obesity may reflect a state of relative amylin resistance. Hyperinsulinaemia, and thus hyperamylinaemia, commonly seen in association with obesity has been reported to result in down regulation of amylin receptors.\textsuperscript{119}

Amylin decreases gastric motility through activation of receptors located in the gastric fundus and the higher centres.\textsuperscript{119} Whilst the mechanism is unclear, this effect appears to be appropriately blocked during hypoglycaemia.\textsuperscript{127} The major nuclei regulating gastric motility are located within the brainstem, and amylin receptors are readily identifiable within these tissues. Gastric-brainstem nervous connections are mediated via the vagus nerve. The selective ablation of these brainstem nuclei in rodents, or vagotomy, results in a loss of the amylin induced reduction of gastric motility.\textsuperscript{128,129} Injection of an amylin analogue in rodents reduced gastric emptying, whilst administration of an amylin analogue (Pramlintide) to humans with type 1 or type 2 diabetes had a similar effect.\textsuperscript{130,131}

Amylin inhibits glucagon secretion, although likely plays a lesser role in the regulation of glucagon than insulin. The physiological effects of glucagon are discussed in detail below, and primarily involve effects on the liver (increased glycogenolysis and gluconeogenesis) and increased lipolysis.\textsuperscript{132} Thus, the amylin response to ingestion of a meal is important in reducing unnecessary endogenous glucose production otherwise mediated by glucagon. The literature around the use of amylin to modulate glucagon physiology is discussed below.

\subsection*{1.1.2.3.4 Cholecystokinin (CKK)}

CKK is released from duodenal mucosal cells in response to ingested fat and protein, and is involved in exocrine pancreas and gallbladder function.\textsuperscripts{133} Two distinct receptors have been identified (CCKA and CCKB) and CCK appears to mediate its cerebral affects via CCKA which is expressed within the hypothalamus.\textsuperscript{134} Infusion of CCK in humans reduces caloric intake by reducing portion size and duration of eating.\textsuperscript{135} Consequently, CCKA receptor antagonists increase caloric intake and reduce satiety.\textsuperscript{136} CCK concentrations rise rapidly during a meal suggesting its primary role may be as an indicator of satiety. However, CCK has not been shown to be a useful therapeutic target as reduced food intake appears to be compensated by increased meal frequency.\textsuperscript{137}
1.1.2.3.5 Glucagon like peptide 1 (GLP-1), glucose dependent insulinotropic peptide (GIP), and oxyntomodulin (OXM)

GLP-1, GLP, and OXM are products of post-translational processing of the preproglucagon gene, which is expressed in the brain, pancreas, and intestine. Bayliss and Starling first proposed the existence of intestinal hormones influencing glucose homeostasis in 1902, and subsequent experiments demonstrated that the administration of duodenal extracts to patients with diabetes occasionally ameliorated glycosuria. The term “incretin” was coined in the early 1930s for a proposed hormone produced by the upper gastrointestinal tract in response to ingested food that induced hypoglycaemia, whilst the phrase “incretin effect” came to be applied to observation that ingested glucose provoked a more rapid release of insulin than intravenous administration. However, a series of negative experiments to further test this hypothesis in 1940 resulted in an absence of research in this area over the next few decades, until the identification of confirmed gastrointestinal hormones in the 1970s.

GLP predominantly affects glucose homeostasis, whilst GLP-1 and OXM have additional roles in appetite regulation. GLP-1 is produced in two forms by intestinal L cells, GLP-1(7-37) and GLP-1(7-36) amide, both of which are rapidly degraded in the circulation by dipeptidyl peptidase 4 (DPP4) to GLP-1(9-37) and GLP-1(9-36)amide respectively. These two metabolites account for 80% of plasma immunoreactive GLP-1 but are physiologically inactive with respect to insulin secretion. OXM is released in tandem to GLP-1 from intestinal L cells. GIP, secreted by intestinal K cells, is also degraded by DPP4 to GIP(3-42) which accounts for 60% of plasma GIP. The GIP receptor (GIPR) and GLP-1 receptor (GLP-1R) are G protein receptor complexes expressed widely in humans. GLP-1 and OXM both exert their physiological effects via the GLP-1R although there remains some debate as to whether a second, as yet unidentified, receptor mediating some of GLP-1’s effects exists. Additionally, it remains possible that OXM has a unique receptor, with studies showing similar physiological effects of GLP-1 and OXM at equal concentrations, despite the GLP-1R having a clearly greater affinity for GLP-1.

GLP-1 and OXM concentrations are low in the fasting state, and rapidly increase after a meal. The rise in GLP-1 is detectable at approximately 10 minutes after ingestion, and there is a wide body of evidence to suggest that the presence of nutrients in the intestinal lumen rather than a neuronal signal is the stimulus for GLP-1 and GIP release. The mechanisms underlying how L cells “sense” nutrients are not established, although the increase in GLP-1 associates
with the size and calorie content of the ingested meal.\textsuperscript{149,150} The peripheral administration of GLP-1 results in anorexigenic effects through a number of pathways. Hypothalamic GLP1-R receptors convey satiety and reduce food intake via the arcuate and paraventricular nuclei.\textsuperscript{151} Delayed gastric emptying and a reduction in gastric acid secretion is also evident. Obesity appears to be associated with a blunted GLP-1 response to a meal, such that circulating AUC GLP-1 concentrations are lower after a meal in obese compared to lean humans, and this is corrected somewhat by weight loss.\textsuperscript{152} However, unlike leptin, sensitivity to GLP-1 appears to be conserved in obesity, with peripheral administration exerting anorexigenic effects.\textsuperscript{153} OXM also reduces food intake in rodents and humans following peripheral and central (rodents) administration, although the role of OXM in energy regulation remains to be fully investigated. The peripheral administration of OXM to normal weight humans resulted in an immediate reduction in calorie intake of approximately 20%, possibly in part by reducing ghrelin secretion.\textsuperscript{134} The therapeutic use of GLP-1 mimetics as weight loss agents is now widespread following the publication of a large number of randomised trials illustrating efficacy.\textsuperscript{154} Long acting OXM analogs are currently under development and are an attractive target for weight loss therapy.\textsuperscript{155}

With respect to glucose homeostasis, the important roles of GLP-1 and GIP both in health and in the pathophysiology of type 2 diabetes, are well established.\textsuperscript{143} Both hormones stimulate glucose dependent insulin release, and both increase beta cell insulin synthesis.\textsuperscript{156} The demonstration that in patients with type 2 diabetes, post prandial hyperglucagonaemia is suppressed by intravenous but not oral glucose raised the possibility that glucagonotropic peptides released from the gastrointestinal tract were at play.\textsuperscript{157} Indeed, the administration of GIP appears to increase glucagon concentrations during an intravenous glucose infusion to those seen during oral glucose administration, and increases glucagon release in the fasting state.\textsuperscript{158,159}

\section*{1.1.2.4 An integrated model of energy homeostasis}

Thus, current knowledge on mechanisms underlying human energy homeostasis allow for the construction of a model whereby short and long term determinants of energy status can be differentiated. Lipostatic hormones including leptin and insulin convey information on whole body adiposity to the hypothalamus allowing awareness of long term energy stores and
requirements. The hypothalamus regulates both energy intake and energy expenditure, drawing upon additional indicators regarding health, etc. Short term regulators of energy intake derive predominantly from the gastrointestinal tract and regulate appetite, satiety, glucose homeostasis, and digestion. This group includes ghrelin, PYY, Amylin, GLP-1, GIP, and CCK with effects mediated via interactions with the hypothalamus or gastrointestinal/pancreatic structures.

1.1.2.5 The aetiology of obesity

The current model explaining the recent dramatic rise in the prevalence of obesity considers that genetic, environmental, and lifestyle factors all contribute, in the context of a permissive physiological state that evolved primarily to counteract energy insufficiency. In simplified terms, obesity results from the persistent consumption of a higher number of calories in comparison to those that are expended.

Dietary intake has increased significantly over the past few decades, and particularly the proportion of calories obtained from fat. Fat provided 15% of total daily calories in the average British diet in 1890, but had increased to 42% one hundred years later. Fat contains nine calories per gram intake, whilst protein and carbohydrate provide only 4 calories per gram. Food portions have increased in size, especially when food consumed out of the home is considered. A significant number of studies in adults and children have demonstrated an association between dietary fat and adiposity. However, recent studies have suggested that apportioning all the blame on dietary fat may be unjustified. Two studies from Finland and American in the early 1990s failed to show clear associations between body weight and dietary fat intake, despite evident relationships between energy intake and body weight. Consideration of dietary fat added very little beyond energy intake as a predictor of body weight in the Nurses’ Health Study. Multiple studies in American children have not only suggested that dietary fat intake is falling (from approximately 37% to 33% between 1973 and 1993), but that caloric intake did not increase enough over this period despite to account for the accelerating prevalence of childhood obesity. It is worth noting, however, that dietary recording via diet diaries has limitations and may particularly under report fat intake. Attention has therefore turned to the role of increasing carbohydrate intake as an alternative dietary explanation for the rise in obesity. Australian data suggests that energy intake in adults
increased by 4% (350 Kj/day) between 1983 and 1995 and that this increase could be attributed to an increase in carbohydrate.\textsuperscript{172} This finding was supported by studies in American (NHANES data) and European populations, and that carbohydrate intake was a useful additional predictor of body weight in association with overall energy intake.\textsuperscript{173,174} An increase in energy intake of this degree would equate to weight gain of approximately 1kg per year if energy expenditure was not increased.

An increase in the prevalence of urban as opposed to rural living has likely reduced energy expenditure in many individuals; whilst urban work is frequently rather sedentary, those living in rural areas are more likely to expend calories through manual labour.\textsuperscript{175,176} American data in 2000 suggested that less than 30% of the population were achieving the recommended weekly concentrations of physical activity, whilst 40% had sedentary lifestyle.\textsuperscript{177} Canadian children have a significantly lower risk of obesity through participation in organised and unorganised sport, whilst increasing television and computer use are positively associated with obesity.\textsuperscript{178} Over 60% of American children watch more than two hours of television daily, whilst 25% watch a staggering four hours or more.\textsuperscript{179} Resting energy expenditure, as the major contributor to total energy expenditure, is definitively measured only through the use of laborious double label water techniques, suitable only for research settings. Population resting energy expenditure is instead calculated using models that make a large number of assumptions and frequently extrapolate from other ethnic populations.\textsuperscript{180} Further research is required to better approximate resting energy expenditure so that the contribution of this to whole body energy balance can be accounted for in studies.

1.1.2.6 Summary

Human energy homeostasis is tightly regulated and involves input from adipose tissue and the gut to hypothalamic centres mediating food intake. The recent significant increase in obesity in most populations places a huge cost burden on medical services, and is explained by multiple drivers, which includes both decreases in physical activity and changes in energy intake, of which an increase in carbohydrate predominant caloric intake may prove to be the most important.
1.1.3 Pathophysiology of type 2 diabetes

Diabetes mellitus is defined as occasional or persistent plasma glucose concentrations above accepted normal range thresholds. These thresholds are established on the basis of clear causal relationships with end organ microvascular complications, although do differ internationally (Table 1-1). Diabetes may be the result of an autoimmune beta cell ileitis (type 1), may occur in the presence of monogenic disorders disrupting normal glucose homeostasis, may develop during and remain isolated to pregnancy, or may occur as an effect of secondary medical disorders. Type 2 diabetes mellitus describes a process where dysglycaemia has developed as a consequence of an inadequate beta cell response to insulin resistance, which is itself generally the result of excess weight adiposity. Type 2 diabetes is the focus of the discussion below.

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1.1.3.1 Identification of insulin as the major regulator of glucose homeostasis

Total pancreatectomy was shown to result in the rapid fatal development of severe diabetes (characterised at that time by glycosuria) in dogs over 120 years ago. Investigators therefore reasonably assumed that a product of the pancreas was integral in preventing glycosuria; this concept was further developed to isolate the source of this product to the endocrine Islets of Langerhans. In 1900, Opie described hyaline degeneration within the islets of Langerhans during autopsy studies of patients with diabetes. The following year, Ssobolew demonstrated the importance of these islets in glucose homeostasis though experimental ligation of the pancreatic ducts in a number of mammalian species. This resulted in destruction of the exocrine enzyme secreting components of the pancreas, leaving the endocrine tissue intact; these animals would remain without glycosuria for some weeks after the procedure. However, none of these investigators or others were able to successfully extract the product responsible for correcting glycosuria prior to the animal’s death.

Frederick Banting (1891 to 1941), based at the University of Toronto, is credited as the primary driver behind the discovery of insulin. His introduction to the field was somewhat fortuitous and occurred following his review of a case report published in the November 1920 edition of Surgery, Gynaecology, and Obstetrics. This report described the post mortem finding of a pancreatic stone completely obstructing the pancreatic duct as the cause of fatal pancreatitis. The author was surprised to note that the majority of the endocrine cells had survived intact, and drew comparisons with the earlier work of Ssobolew. Banting was clearly fascinated by this finding, and designed his now famous study: “Ligate pancreatic ducts of dogs. Wait six to eight weeks for degeneration. Remove the residue and extract”.

Banting convinced colleagues to support the experiment and, with the assistance of Charles Best initiated proceedings in 1921. Professor John MacLeod advised on experimental design to ensure the studies could produce a scientifically sound conclusion. The technique was successful and administration of the resultant extract did reduce glycosuria in pancreatectomized dogs. The name Insulin (Insula, Latin for Island), which was first suggested by De Meyer, was subsequently universally accepted. Additional purification was followed by the first use of this extract diabetic humans, with rapid improvements in glycosuria and ketosis. For their work, Banting and MacLeod received the Noble prize in 1923.
1.1.3.2 Insulin

Insulin is the primary hormonal regulator of carbohydrate metabolism and plays a predominant role in glucose homeostasis. Insulin secretion is biphasic comprised of a first phase characterised by rapid glucose dependent release of preformed mature insulin, and a second phase characterised by the predominantly non-glucose dependent synthesis and release of additional insulin. The first phase is initiated within 1 minute of a glucose bolus, peaks at between 3 and 5 minutes, and lasts approximately 10 minutes. The second phase of insulin secretion is also initiated rapidly after a glucose bolus or non-nutrient stimuli, but is not measurable until approximately 10 minutes. Unlike first phase secretion, second phase secretion persists for the duration of hyperglycaemia. An increase in ambient glucose concentrations is the stimuli for “first phase” insulin release. Glucose enters the beta cell via the GLUT 2 transporter and is phosphorylated to glucose-6-phosphate (G6P) by glucokinase, a process which generates ATP. Glucokinase therefore acts as a “sensor” of plasma glucose concentrations, and provides a mechanism by which insulin secretion can be appropriately matched to glucose requirements. The consequent increase in intracellular ATP concentrations drives the closure of transmembrane K+-ATP-dependent channels resulting in membrane depolarization, which results in activation of transmembrane voltage dependent calcium channels. Thus, an increase in beta cell glucose concentrations, results in increased beta cell calcium concentrations which promotes the movement of insulin containing secretory granules to the membrane for exocytosis.

“Second phase” insulin release is stimulated by both nutrient (glucose, fructose, mammose, galactose) and non-nutrient (neural, hormonal, amino acids) triggers. An awareness of, or consumption of food triggers second phase insulin secretion via cholinergic vagal nerve stimulation, through the activation of beta cell phospholipase C and protein kinase C. This so called “cephalic insulin response” will not occur under normal circumstances in the fasting state or in the context of hypoglycaemia, and is critical in post-prandial glucose homeostasis. In contrast adrenergic stimuli generally inhibit insulin secretion. Catecholamine release during exercise or stress, prompts a reduction in basal insulin output, mediated via alpha 2 adrenoreceptors. Multiple gastrointestinal hormones including GLP1 (discussed in chapter 1-x) and cholecystokinin enhance insulin secretion, and are themselves released at least in part by nutrient dependent mechanisms. Somatostatin inhibits insulin release, although can provoke hypoglycaemia in therapeutic circumstances through inhibition of additional
hormones that favour an increase in plasma glucose.\textsuperscript{198} Leptin also inhibits the release of insulin by provoking activation of the K+\textsuperscript{+}-ATP-dependent channel, thereby preventing membrane depolarisation, via a leptin receptor expressed on the beta cell membrane.\textsuperscript{199} Arginine increases the intracellular movement of potassium and thereby enhances membrane depolarization and insulin release; like the cephalic insulin response, arginine mediated insulin release only occurs at normal or elevated concentrations of plasma glucose.\textsuperscript{200}

The insulin receptor (IR) is encoded by the INSR gene on chromosome 11, and is activated by insulin, and the insulin like growth factor proteins (IGF1 and IGF2). IR is a dimeric protein complex comprised of two extracellular alpha subunits and two beta subunits that span the cell membrane. The subunits are linked by disulphide bonds. Activation of the receptor through insulin binding to the extracellular alpha subunits, results in a conformational alteration in the intracellular beta subunits. ATP binding may then occur, facilitating phosphorylation of the beta unit conferring tyrosine kinase activity, which mediates the intracellular actions of insulin via phosphorylation of insulin responsive substrates (IRS). IRS phosphorylation enhances the affinity of IRS to bind other signalling molecules, and allows activation of intracellular molecular cascades.\textsuperscript{201} 4 IRS are known to exist along with a related protein (Gab1, Grb2-associated binder-1) differing with respect to target hormones and tissue distribution.\textsuperscript{201,202} IRS1 and IRS2 share wide tissue distribution although it has been suggested that IRS1 is the predominant mediator of insulin action in skeletal muscle, whilst IRS2 is predominantly active at the liver.\textsuperscript{201}

Insulin acts widely throughout human tissues, but predominantly acts at the skeletal muscle and adipose tissue to promote glucose uptake and at the liver to facilitate a number of physiological processes. Glucose uptake into skeletal muscle and adipose tissue, via GLUT4, is insulin dependent. Under experimental conditions of intravenously infused glucose and induced hyperinsulinaemia, this uptake accounts for up to 80\% of whole body insulin dependent glucose uptake.\textsuperscript{203} In the post prandial phase, insulin promoted the synthesis of glycogen in skeletal muscle and lipogenesis in adipose tissue.\textsuperscript{188} Skeletal muscle glycolysis during rigorous physical activity provides anaerobic energy, whilst free fatty acids (and consequently ketone) bodies can be released from adipose tissue to provide energy to other non-glucose dependent organs. The effect of insulin on skeletal muscle protein metabolism varies depending on the dose of provided insulin; insulin deficiency promoted protein catabolism and the release of amino acids, whilst the presence of insulin suppresses this process. At higher doses however, insulin has an anabolic effect on muscle.\textsuperscript{204} Insulin’s
primary role in regulating hepatic aspects of glucose homeostasis is to directly and indirectly inhibit hepatic glucose production. Indeed, hepatic glucose production may account for up to 80% of endogenous glucose production in the fasted state.\textsuperscript{205} Insulin acts directly to inhibit both hepatic gluconeogenesis and glycogenolysis (whilst promoting glycogen synthesis), and indirectly by reducing the production of gluconeogenic precursors (circulating lipids, glycerol, and protein) by other tissues, and also by inhibiting pancreatic glucagon secretion.\textsuperscript{206} Studies in dogs suggest that the direct hepatic action of insulin may predominate, but it remains unclear whether this is true in humans.\textsuperscript{207} Insulin enhances the production of nitric oxide, which is the predominant factor regulating vascular endothelial relaxation in large arteries.\textsuperscript{208} Glucose uptake in the brain is independent of insulin; nonetheless, insulin plays a major role in regulating a number of cerebral functions.\textsuperscript{209} Insulin has been shown to mediate some aspects of both cognition and feeding behaviour, in that increasing cerebral insulin concentrations reduce food intake.\textsuperscript{210} Furthermore, insulin plays an integral role in maintenance and function of the brain endothelial cells that form the blood brain barrier; altered transport across the blood brain barrier in states of hyperglycaemia has been attributed to alterations in insulin’s ability to perform these functions.\textsuperscript{209} Insulin has documented effects in a number of other tissues including the pancreas, pituitary, kidneys, and bones.

\subsection*{1.1.3.3 The role of insulin resistance in type 2 diabetes}

The development of the insulin radioimmunoassay by Yalow in 1960 allowed insulin concentrations in patients presenting with maturity onset diabetes to be assessed accurately for the first time.\textsuperscript{211} Unlike those with type 1 diabetes, these patients were found to have normal or elevated concentrations of insulin, and secreted insulin in response to food intake. However, insulin therapy did not correct the hyperglycaemia suggesting the concept of insulin resistance, although early investigators considered the possibility of this phenomenon being the result of an absence of insulin sensitiser.\textsuperscript{212} Insulin resistance has since been defined by many authors as a reduction in the ability of insulin to induce both glucose disposal and reduce endogenous glucose production in target tissues.\textsuperscript{213} The theory that insulin resistance was significantly increased in patients with type 2 diabetes was further supported by work in the 1960s and 1970s in a number of pioneering experiments in humans\textsuperscript{214,215} As skeletal muscle is the major site of glucose disposal in healthy individuals, development of tools to assess insulin
physiology in these tissues have been of prime importance. De Fronzo and colleagues developed the euglycaemic hyperinsulinaemic clamp over 30 years ago and subsequently confirmed reduced glucose disposal in people with type 2 diabetes.\textsuperscript{216,217} The euglycaemic hyperinsulinaemic clamp remains the gold standard assessment of insulin resistance.

The mechanisms underlying insulin resistance remain poorly understood however but include inflammation, mitochondrial dysfunction, hyperinsulinaemia, hepatic fat content, lipotoxicity, and endoplasmic reticulum stress, many of which are associated with obesity.\textsuperscript{218,219} Additional factors such as aging, genetic predisposition, and pregnancy play a role, whilst insulin resistance is a feature of many medical disorders, mediated by one or more of the above mechanisms. However, an association between lipids and insulin resistance is clear, and predominantly relates to the intracellular accumulation of lipid in tissues whose function is modified by the action of insulin. Hepatocyte ectopic lipid accumulation is the result of either increased hepatic uptake of lipids, or decreased export. Lipoprotein lipase (LPL) has been shown to be a key regulator of hepatic lipid import, through the study of LPL over expression or knockout rodent models.\textsuperscript{220,221} In healthy adult humans, muscle insulin resistance is predicted by intramyocellular diacylglycerol content rather than ambient plasma fatty acid concentrations.\textsuperscript{222,223} It appears that diacylglycerol (DAG) accumulation is the key lipid driving insulin resistance at both the liver and muscle. DAG promotes insulin resistance through activation of members of the protein kinase C family, which in turn alter post receptor signalling.\textsuperscript{218} The primary role that DAG plays in lipid accumulation mediated insulin resistance is evidenced by the observation that mice that overexpress diacylglycerol acyltransferase (DGAT, converting DAG to triglycerides) have marked intramyocellular triglyceride accumulation, but do not exhibit increased muscle insulin resistance.\textsuperscript{224}

Insulin resistance appears to be an early feature of type 2 diabetes and is evident almost universally in patients with earlier forms of dysglycaemia (impaired glucose tolerance/impaired fasting glucose/prediabetes).\textsuperscript{225} Indeed, glucose disposal during a clamp study, as a surrogate of insulin resistance may be reduced by 50% or more in those with type 2 diabetes when compared with control.\textsuperscript{226,227} However, insulin stimulated glucose uptake is reduced in patients with impaired glucose tolerance and type 2 diabetes to a similar degree.\textsuperscript{227} Furthermore, there is little if any relationship between fasting glucose and insulin resistance in patients with impaired glucose tolerance or type 2 diabetes.\textsuperscript{227} It is therefore apparent that insulin resistance
alone cannot explain the development of hyperglycaemia, and that this must be accompanied by inappropriate insulin production.

1.1.3.4 Increasing importance of beta cell dysfunction in the pathogenesis of type 2 diabetes

Confirmation that insulin secretion is under the control of a feedback loop allowing a connection with ambient plasma glucose concentrations, was provided in seminal studies by Kahn and colleagues. Using a minimal model approach, they described a hyperbolic relationship between insulin sensitivity and beta cell function in healthy young humans with normal glucose tolerance, such that for any reduction in insulin sensitivity, a proportionate increase in beta cell insulin secretion would occur. The exact mechanisms by which target tissue indicates insulin requirements however remains to be elucidated. Hyperglycaemia, in the context of type 2 diabetes, therefore implies the presence of beta cell dysfunction. Further studies have confirmed this dysfunction by demonstrating a reduced insulin response to intravenous glucose, and changes in the pulsatile and oscillatory nature of insulin secretion. Furthermore, the insulin response to non-glucose dependent stimuli (arginine, gastrointestinal hormones, sulphonylurea therapy) is diminished in patients with established type 2 diabetes. It is therefore clear that both insulin resistance and beta cell dysfunction are the hallmarks of type 2 diabetes.

However, beta cell dysfunction is apparent long before the onset of type 2 diabetes in patients at risk of dysglycaemia, even when glucose tolerance remains normal. First degree relatives of persons with type 2 diabetes, who are themselves obese and have evidence of insulin resistance, have a poorer beta cell response than would be predicted by concurrent measurements of insulin sensitivity, even when glucose tolerance appears normal. An impaired beta cell response is also evident in obese individuals with impaired glucose tolerance. Furthermore, individuals known to be at higher risk of future development of type 2 diabetes (women with polycystic ovary syndrome or previous gestational diabetes) also have poorer beta cell responses than would be predicted based on the hyperbolic relationship to insulin sensitivity. Insulin resistance is present under certain conditions, but a continuum of deteriorating beta cell function from adequate to insufficient, characterises the progress from normal glucose tolerance to prediabetes to type 2 diabetes.
1.1.3.5 Genetic and environmental factors underlying insulin resistance and beta cell dysfunction

The first gene to be clearly associated with the development of type 2 diabetes was PPARγ (peroxisome proliferator-activated receptor-γ), with a specific substitution (Pro12Ala) conferring a 4.35 fold increased likelihood for the presence of type 2 diabetes in Japanese Americans.\textsuperscript{236} Subsequent research has identified over 50 single nucleotide polymorphisms (SNP) that associate with the development of type 2 diabetes.\textsuperscript{237, 238} Whilst the exact mechanism associating each SNP with type 2 diabetes has not been defined, the majority appear to impact on beta cell function.\textsuperscript{238}

However, the presence of susceptible single nuclear polymorphisms explains less than 10% of type 2 diabetes heritability, although polygenic factors likely explain a significant proportion of the remainder.\textsuperscript{237} Indeed, genetic risk scores, aimed at predicting the presence of type 2 diabetes on the basis of present SNPs, do not perform any better than calculations based on traditional metabolic risk factors.\textsuperscript{239} Furthermore, the rapidly increasing prevalence of type 2 diabetes in most societies indicates factors beyond genetics are likely to be important predictors of the development of type 2 diabetes. Environmental factors are therefore clearly of high importance in the pathophysiology of this condition, and the interaction between genes and the environment may assume even greater importance.

Ageing alone reduces glucose tolerance; both increasing insulin resistance and decreasing beta cell function contribute.\textsuperscript{240} Physical activity and exercise share complex roles in the pathogenesis of type 2 diabetes. Long term aerobic exercise improves insulin sensitivity such that reduced insulin release is required to maintain normal glucose tolerance.\textsuperscript{241, 242, 243} However, high intensity exercise for 10 to 15 minutes results in a rise in glucose concentrations (albeit in persons with type 1 diabetes).\textsuperscript{244} Furthermore, numerous studies have recently identified the benefits of short duration (10 seconds) high intensity exercise in reducing post exercise hypoglycaemia which may be mediated by increased catecholamine concentrations.\textsuperscript{245} Multiple studies have now shown that physical exercise is an important and effective intervention in patients with type 2 diabetes and results in improved glucose control.\textsuperscript{246, 247} An imbalance between energy intake and expenditure is clearly associated with glucose intolerance, but it is apparent that specific dietary constituents also play a role.\textsuperscript{248} A reduction
in the insulin response to carbohydrate ingestion with increasing age is an important factor underlying age related changes in glucose tolerance. Dietary fat has been shown to directly impact upon insulin resistance and beta cell dysfunction, as well as being a primary modulator in the development of obesity. However, multiple randomised controlled trials of specific macronutrient diets in the management of established type 2 diabetes have failed to clearly show superiority over other macronutrient diets. Medical conditions or treatments such as disorders of cortisol excess can impact glucose tolerance. Finally, it is likely that exposure to a number of naturally occurring and synthetic environmental chemicals impact both on glucose tolerance and increase the risk of obesity. However, after accounting for each of the above mentioned genetic and environmental risk factors, it is clear that a considerable amount of the risk underlying the development of glucose intolerance remains; it is likely that the majority of this residual can be attributed to obesity and body fat distribution (see 1.1.4).

1.1.3.6 The gastrointestinal tract in the pathogenesis of type 2 diabetes

Numerous gastrointestinal processes that either facilitate nutrient digestion or convey information regarding food intake to the brain are evident in healthy humans, and dysfunction of these processes is apparent once glucose intolerance has developed. Hormones that also regulate weight are reviewed in section 1.1.2.3

1.1.3.6.1 Glucagon

Pancreatic glucagon, secreted by islet alpha cells, has perhaps received less attention than other pathophysiological factors, but clearly has a role in type 2 diabetes. Glucagon, a polypeptide containing 29 amino acids, is produced by the cleavage of proglucagon by proprotein convertase 2, a process which produces similar hormones elsewhere in the gastrointestinal tract (see GLP-1, 1.1.2.3.5). Alpha cells appear to be scattered throughout the islets and junctional cell communication is required to regulate the secretion of glucagon, such that glucagon secretion is many fold higher in isolated alpha cells than those within intact islets.
Glucagon secretion is stimulated by hypoglycaemia, cholecystokinin, amino acids, and activation of the autonomic nervous system, along with glucose-dependent insulino tropic peptide (GIP). Insulin, somatostatin, leptin, amylin, GLP-1, and increased zinc secretion from beta cells all have inhibitory effects on glucagon secretion. Of these regulatory factors it has been argued that an absence of insulin and zinc are of most importance; hypoglycaemia directly is likely to be of minor physiological relevance. Whilst insulin induces glucagon suppression through hyperpolarisation of the alpha cell membrane, the mechanism via which GLP-1 induces a similar response remains unclear. GLP-1 receptor expression on the alpha cell is variably reported in the literature but is likely to be low; it is possible that GLP-1 may instead mediate its effect on glucagon via somatostatin, receptors for which are widely expressed on alpha cells. The major target for glucagon is the liver where it binds to the glucagon receptor expressed in high numbers on hepatocytes. Glucagon increases hepatic glucose output both through increasing glycogenolysis and gluconeogenesis, whilst also inhibiting glycogenesis and glycolysis.

Hyperglucagonaemia as an early feature of type 2 diabetes was recognised over forty years ago, although the exact role of this pathophysiological feature remains to be fully elucidated. The alpha cell does not respond normally to physiological stimuli in the context of type 2 diabetes. There is a blunted alpha cell response to hyperglycaemia when a reduction in glucagon secretion is required. Furthermore, the ingestion of a protein rich meal invokes an exaggerated glucagon response. The alpha cell to beta cell ratio appears to be increased in type 2 diabetes as a result of beta cell apoptosis, but the total alpha cell mass appears unchanged. It is possible that alpha cell resistance to insulin, in parallel with insulin resistance in other tissues, is a significant contributor to these changes in alpha cell function. Obese individuals with either prediabetes or type 2 diabetes have impaired alpha cell responses to oral glucose ingestion, even when hyperinsulinaemia is present. In addition, insulin receptor knockout mice have significantly higher glucagon concentrations than normal controls.

Furthermore, it is clear that glucagon plays a significant role in glycaemic dysfunction under these circumstances. The clear association between insulin action at the alpha cell and glucagon release is evident in patients with uncontrolled type 1 diabetes. Near total insulin deficiency is associated with very high glucagon concentrations, whilst inhibition of glucagon secretion in this context significantly reduced the hyperglycaemia and ketogenesis that would
otherwise be expected.\textsuperscript{265,266} Further studies using somatostatin to either inhibit glucagon release or inhibit insulin release, with physiological replacement of glucagon, indicate that glucagon action may account for up to 50\% of total hepatic glucose production in the fasting state.\textsuperscript{267,268} Recent work using glucagon receptor knockout mice showed that fasting hyperglycaemia does not develop even after streptozotocin induced complete insulin deficiency, illustrative of the fundamental role glucagon plays in fasting hyperglycaemia.\textsuperscript{269,270} As noted previously, in type 2 diabetes glucagon suppression in response to ingestion of a meal is blunted, and therefore, in the context of inappropriate hyperglucagonaemia, hepatic glucose production continues in the post prandial state. It is therefore apparent that hyperglucagonaemia, most likely directly the result of impaired alpha cell sensitivity to insulin, is a significant factor underlying both fasting and post prandial hyperglycaemia in type 2 diabetes.

Thus, reduction of glucagon action would appear to be an attractive strategy for the development of pharmaceutical agents for glucose control in diabetes.\textsuperscript{132} Concerns regarding hepatic accumulation of lipids and glycogen as an adverse consequence of glucagon regulating therapy have been alleviated to some extent by studies in glucagon receptor knock out mouse models where these concerns did not materialise.\textsuperscript{271} Three classes of pharmaceutical agents that effect glucagon action are currently in use; GLP-1 mimetics and dipeptidyl peptidase 4 inhibitors, and the amylin mimetic Pramlintide and are discussed later (see chapter 1.2.2).

### 1.1.3.7 Inflammation in diabetes

Both type 2 diabetes and obesity are closely associated with systemic inflammation, and markers including c-reactive protein (CRP) and interleukin-6 are related to insulin sensitivity and beta cell function (see chapter 1.1.4). However, inflammation at the level of the beta cell is likely to be a significant contributor to beta cell dysfunction.\textsuperscript{272} Whilst glucose is the primary beta cell stimulus regulating insulin secretion, persistently elevated glucose concentrations prompts beta cell apoptosis in humans (glucotoxicity). High concentrations of free fatty acids (lipotoxicity) have more recently been shown to have similar deleterious effect.\textsuperscript{273,274} Apoptosis is mediated by the actions of interleukin-1\beta (IL-1\beta), a cytokine produced by the beta cell itself which induces apoptosis by activating the transcription factor nuclear factor-\kappaB (NF-\kappaB).\textsuperscript{275} The specific role of this cytokine was confirmed by the finding that the addition of a naturally
occurring IL-1 receptor antagonist to cultured human islets exposed to hyperglycaemia reduced beta cell apoptosis. A randomised trial of recombinant IL-1 receptor antagonist (Anakinra) has shown early and durable benefits with respect to overall glucose control and beta cell function in a cohort of overweight recruits with sub-optimally controlled type 2 diabetes. It is therefore likely that inflammation at the beta cell, and mediated in part by nutrient exposure is a primary driver behind the reduced beta cell mass evident in type 2 diabetes. This illustrates an interesting overlap between the accepted aetiological models of type 1 and type 2 diabetes.

1.1.3.8 Summary

Type 2 diabetes is a heterogeneous disorder characterised by the presence of insulin resistance and beta cell dysfunction. Environmental factors are the predominant drivers of both pathophysiological hallmarks, although genetic susceptibility (particularly with respect to beta cell function) plays a role. Research into the gastrointestinal and inflammatory factors involved in the pathophysiology of type 2 diabetes is in its infancy but is likely to lead to novel therapeutic strategies.
1.1.4 Linking obesity and type 2 diabetes

As noted above, obesity is the predominant modifiable risk factor for the development of type 2 diabetes, and the prevalence of type 2 diabetes has increased in proportion to the population increase in the prevalence of obesity. Interactions between the increased adipocyte tissue mass, and the secretion and action of insulin provide a mechanism to link these disorders.\textsuperscript{278}

1.1.4.1 Obesity and Insulin resistance

Adipocytes produce a wide range of hormones and peptides, many of which have the potential to affect systemic insulin sensitivity. Retinol-binding protein-4 (RBH4) enhances hepatic glucose production by increasing the expression of gluconeogenic enzymes within hepatocytes, but also increases muscle insulin resistance.\textsuperscript{279} A number of cytokines have been implicated in the link between obesity and insulin resistance; tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)) and interleukin-6 (IL-6) both circulate at higher concentrations in obesity, and up regulate intracellular pathways in target tissues that promotes insulin resistance.\textsuperscript{280}

The release of non-esterified fatty acids (NEFA) from adipocytes through lipolysis is likely to be a significant contributor to the development of insulin resistance.\textsuperscript{281} In humans, insulin resistance and improved glucose tolerance are seen rapidly after a rise or fall respectively in NEFA concentrations.\textsuperscript{282,283} Whilst it appears that post receptor insulin signalling is negatively affected by NEFA, the exact mechanisms underlying this association remain to be clarified.

In contrast to the above deleterious effects, adipose tissue also produces adiponectin (see 1.1.2.1.2) which acts as an insulin sensitiser and reduces hepatic glucose output. Thus adiposity, has both positive and negative effects on glucose homeostasis and this appears to be dependent on the site and volume of adipose accumulation. It has long been known that central adiposity, both in overweight and lean individuals, tends to result in more marked insulin resistance than weight matched individuals with a more peripheral distribution of adiposity.\textsuperscript{284} Intra-abdominal adipose tissue is less sensitive to the suppressive effects of insulin than peripheral subcutaneous adipose tissue, resulting in greater lipolysis and consequently a higher output of NEFA.\textsuperscript{285} Because the output of the intra-abdominal adipose tissue drains into the portal circulation, this results in an increased likelihood of hepatic insulin resistance.
Furthermore, whilst central adipocytes secrete a greater concentration of adiponectin per unit than peripheral adipocytes, the peripheral total adipocyte mass is significantly greater than the central unit.\textsuperscript{285,286} Therefore, the insulin sensitising effect of adiponectin may be greater in those with peripheral adiposity.

\section*{1.1.4.2 Obesity and the beta cell}

As discussed above (see 1.1.3.4) beta cell dysfunction is by definition present once glucose intolerance is evident, long before the onset of type 2 diabetes. Whilst a reduction in total beta cell mass is evident, it has also been suggested that each beta cell is on average functioning at approximately 25% of its capacity once type 2 diabetes is present. This is evident both with respect to an impaired insulin release in response to a glucose stimulus, and to other secretagogues such as GLP-1. The exact mechanisms underlying this impairment remain unclear but it is likely that individuals are genetically predisposed to beta cell maladaptation. Thus, beta cell dysfunction may be indirectly related to obesity in the sense that beta cells cannot overcome obesity driven insulin resistance.

However, as with insulin resistance, an increase in circulating NEFA, proportional to total body adipocyte mass, may also adversely and directly affect beta cell function. Whilst the infusion of fatty acids enhances rodent insulin secretion in the acute phase, impairment of both insulin synthesis and secretion is seen with chronic exposure.\textsuperscript{287,288} Similar effects are seen in humans.\textsuperscript{289} Thus, the increased concentrations of NEFA observed in obesity may provide a mechanism to link this state to both insulin resistance directly and beta cell dysfunction directly and indirectly.\textsuperscript{290}
1.2 Non-surgical management of obesity and type 2 diabetes

1.2.1 Obesity

The management of obesity is approached in the same manner as any other chronic medical condition that predominantly presents an increased risk for secondary medical disorders. The benefits of any intervention must be balanced against the risks, with interventions that carry the greatest risk primarily reserved for those who stand to receive the greatest benefit. However, as in the management of diabetes (see below) it is tempting to view the treatment of obesity in a stepwise fashion starting with lifestyle changes, through to pharmaceutical therapy, through to bariatric surgery. In practice, however, management strategies should be personalised, and more aggressive interventions should be considered early if clearly required.

The cornerstone of any approach to obesity is appropriate lifestyle modification alongside other selected interventions. Simplified, any person wishing to lose weight needs to reduce caloric intake and increase physical activity to induce a negative energy balance. The optimal diet for weight loss has been the subject of a significant volume of research in recent times. Both the diabetes prevention program (DPP) and Look-AHEAD studies (see 1.2.2) prescribed a low fat, caloric restricted diet and demonstrated weight loss of 5.5kg and 7.9kg placebo extracted weight loss respectively at an average of 2.8 and 1.0 years. Multiple randomised controlled trials of diets composed of varying proportions of macronutrients (protein, carbohydrate, fat) have shown similar outcomes with a recent review showing a mean weight loss of -4.4% in fifteen highly cited selected randomised controlled trials. Thus, the primary factor underlying successful weight loss is caloric restriction, with macronutrient content related perhaps more to diet tolerability and adherence. This concept was supported by a study performed by Sacks et al, where 811 obese adults (mean BMI 33.0 kg/m²) were randomised to one of four diets containing varying percentages of protein, carbohydrate, and fat, but all resulting in a caloric deficit of approximately 750 kcal/day. Dietary plans were provided each fortnight, and group education sessions were held either weekly or fortnightly. The mean weight loss at 12 months for all participants was 6kg (-7% body weight change), although weight regain was seen in the second 12 months of the study. The net weight change
at 24 months was similar irrespective of the dietary intervention at 4kg. Disappointingly, only 15% of participants had a body weight reduction of greater than 10% at study end.

The tolerability of a diet is clearly an important factor in weight loss durability. A study by Dansinger et al demonstrated weight loss through the use of a number of varying prescribed diets in all participants who were able to adhere to their diet. Furthermore, this study and others have suggested that adherence is often reasonable for three to six months, after which a return to less healthy eating habits heralds weight regain. Therefore, future dietary strategies will need to aim to match each individual seeking weight loss with a particular diet most likely to be tolerable to that individual. However, patient choice in dietary pattern may not be a predictive factor for successful weight loss.296

An increase in physical activity, whilst less helpful for inducing weight loss, has been shown to be important in maintaining weight loss in a large number of studies.297,298 Moderate intensity physical activity of between 150 and 250 minutes per week is required to prevent weight regain, but will only induce weight loss if concurrent moderate caloric restriction is undertaken.299 More frequent physical activity (>250 minutes per week) is required before weight loss without dietary restriction is seen. Behavioural therapy, incorporating goal setting, self-monitoring, and stimulus control, is also an important aspect of successful weight loss and maintenance.300

Medical options for the management of obesity are currently limited, following the withdrawal of a number of previously used drugs as a result of significant side effects.301 The development of new agents has been protracted and is not without difficulty, in part because regulators are rightly wary of the likely very high population exposure to licensed anti-obesity agents. Previous management strategies have suggested that there may be an indication for pharmaceutical agents to support weight loss, alongside dietary and physical activity interventions, in those with a BMI >30 kg/m² or >27 kg/m² if obesity related comorbidities are present.302 These criteria apply to an increasingly large proportion of the New Zealand population, and thus any unforeseen complications resulting from these medications would likely have a hugely significant adverse population health effect. Furthermore, whilst an attractive model for weight loss might involve early pharmaceutical therapy to induce early weight loss followed by maintenance lifestyle changes, it is clear that weight regain would be likely under these circumstances. Thus pharmaceutical therapy, once commenced, would need
to be continued in the long-term and the individual exposure to these agents would be significant.\textsuperscript{303} Criteria for obesity drug licensing have tended to favour, but not enforce, placebo subtracted weight loss of >10\%, on the basis that this degree of weight loss is required to gain health benefits.\textsuperscript{304} Historically, single agent treatment achieves less significant effects than this; thus this well-intended criteria may have the unfortunate effect of restricting future market development, especially as the therapeutic strategies towards weight loss move more towards a multifaceted approach.

Whilst pharmaceutical agents could potentially target either energy intake or expenditure, no agent has yet been produced which can successfully increase energy expenditure without unacceptable side effects. Agents acting on energy intake can be divided between those resulting in reduced digestion or absorption of foods, or those acting on appetite or satiety. Currently only 2 anti-obesity agents (orlistat and phentermine) are available in New Zealand, and three new anti-obesity agents are either in use or are close to market internationally (Table 1-2). Additionally, existing medications such as the incretin mimetics have shown great promise as anti-obesity agents.

1.2.1.1 Medications that effect fat absorption or metabolism

Orlistat, a gastric and pancreatic lipase inhibitor, is the solitary anti-obesity drug currently available to New Zealand clinicians. Digestive inhibition leads to a 30\% decrease in absorbed fat, which is excreted along with the drug in the faeces. Weight loss is modest, with most randomised studies showing placebo subtracted weight loss (PSWL) of -2.9kg (equating to approximately 2-5\% of total body weight) alongside dietary and physical activity interventions.\textsuperscript{304, 305, 306} Additional beneficial cardiovascular effects (reduction in total cholesterol and LDL cholesterol) have been reported in large randomised intervention studies, as well as a modest but statistically significant reduction in progression to type 2 diabetes in those patients who already had evidence of glycaemic dysfunction.\textsuperscript{307} Gastrointestinal side effects occur as a consequence of increased stool fat content; increased flatulence, oily stool, faecal urgency are seen in up to 40\% of patients, although it should be noted that dropout rates, at least in the context of a clinical trial, do not exceed placebo.\textsuperscript{305,306,307} The frequency of gastrointestinal side effects reduces with time, although patients should be prescribed fat soluble vitamins (A, D, E, and K) alongside Orlistat therapy to prevent deficiencies.\textsuperscript{307} A novel
lipase inhibitor Cetilistat, may have an improved tolerability profile to Orlistat and is the subject of current phase 3 studies.\textsuperscript{308}

1.2.1.2 Medications that reduce food intake

The majority of anti-obesity drugs that affect food intake do so primarily by affecting central neurotransmitter physiology. The sympathomimetic Phentermine was the first medication approved by the FDA specifically for the treatment of obesity in 1959; numerous others have come to market since but have been withdrawn following the documentation of severe side effects (Fenfluramine and dexfenfluramine (valvulopathy), Aminorex (pulmonary hypertension), Phenylpropanolamine (stroke), Rimonabant (suicidal ideation) and Sibutramine (Myocardial infarction and stroke)) and will not be considered in this chapter.\textsuperscript{309} Other drugs (e.g. Topiramate), despite showing promise as weight loss agents, have been limited by poor tolerability at the required doses. Nonetheless, weight loss outcomes with these medications are often more significant than with other current pharmaceutical strategies; thus, recent approaches to obesity drug development have focused on either combined therapy (enabling exposure to lower doses of constitutive agents) or modifications of existing therapies (e.g. Lorcaserin, see below) so that negative effects are avoided.

Phentermine suppresses appetite primarily by increasing the hypothalamic release of noradrenaline. A meta-analysis of 6 randomised studies showed PSWL of -3.6kg (95% CI, -0.6 to -6.0) when phentermine was administered to obese persons for a mean of 13 weeks alongside lifestyle and dietary changes.\textsuperscript{310} Diethylproprion, which has a similar mechanism of action to Phentermine, is occasionally used, although the few published head to head studies suggest a similar weight loss effect as to that seen with Phentermine.\textsuperscript{310} Few studies exist exploring the longer term use of either drug as a single agent and none longer than 12 months. However, a small study of 108 obese women followed for 36 weeks on Phentermine therapy showed PSWL of >-7.8kg.\textsuperscript{311} Thus, both drugs are approved only for up to 12 weeks treatment as an adjunct to other measures. Despite concerns about the potential for addiction seen with other amphetamines, neither drug appears to cause psychological dependence or drug craving when used at the doses suggested for weight loss therapy.\textsuperscript{312}
Topiramate, an anticonvulsant approved for the treatment of epilepsy and migraine, has long been known to be associated with weight loss in some recipients. The mechanism remains incompletely understood, but PSWL of -5.6kg was noted in a meta-analysis of 11 studies. However, a high frequency of side effects including paraesthesia, psychomotor disturbance, and abnormal taste lead to a high dropout rate in interventional studies. A combination of Phentermine and Topiramate (Qsymia), at a dose often 10-50 times lower than required when Topiramate has been studied as a single agent, has recently been approved by the FDA as an anti-obesity agent. This approval was on the basis of a phase 3 randomised 56 week trial of 2 dose regimens versus placebo. Phentermine/Topiramate 92/15mg daily was associated with PSWL of -8.8kg; however, depression and/or anxiety related adverse occurred at almost double the frequency seen with the lower dose (Phentermine/Topiramate 46/7.4mg daily, PSWL -6.7kg) where the frequency was similar to placebo. Thus, the FDA have approved Phentermine/Topiramate 46/7.5mg daily for chronic weight management in obese patients (BMI>30mg/kg² or 27mg/kg² if obesity related co-morbidities are present) and suggest a review after 12 weeks of therapy. If weight loss at that point is < 3%, patients may either stop the medication or increase to the higher dose, with regular observation for adverse effects.

Lorcaserin, a serotonin 2C (5-HT₂C) agonist, was also approved by the FDA in 2012 as an anti-obesity agent on the basis of a 12 month randomised trial of 2 dose regimens versus placebo, in conjunction with a nutritional and physical activity program. Hypothalamic serotonin receptor agonism results in appetite suppression, whilst the specificity of Lorcaserin for the 2C receptor subtype, as opposed to the 2B receptor located on cardiac valvular tissue, reduces the risk of valvulopathy, seen with the now withdrawn non-specific 5-HT agonists Fenfluramine and Dexfenfluramine. Subjects randomised to Lorcaserin 10mg BD achieved a modest mean PSWL of -2.9kg, whilst Lorcaserin 10mg OD resulted in PSWL of -1.8kg. Additionally, whilst a number of cardiovascular or lipid parameters were beneficially effected to a statistically significant degree in those on Lorcaserin, the clinical significance of these relatively small effects is debatable. Furthermore, the concern regarding valvular disease has not definitively been dismissed, and further study will be required to provide reassurance that the long term use of Lorcaserin is safe, especially in patients with pre-existing valvular dysfunction.

Numerous other agents are at various stages of development. A combination of Naltrexone, an opiate receptor antagonist used primarily for the treatment of opioid addiction and alcoholism, and Bupropion, a dopamine and noradrenaline reuptake inhibitor used...
Chapter 1: Literature review

individually for the treatment of depression and smoking cessation respectively, has shown promise as an anti-obesity agent. A phase 3 randomised study of Naltrexone/Buproprion slow release 32/360mg versus placebo, in conjunction with lifestyle changes, demonstrated a PSWL of -2.9% in an intention to treat analysis. The FDA declined an application to approve this preparation in 2011 due to concerns about the longer-term cardiovascular safety profile of Naltrexone in particular.

Developed primarily as anti-diabetic agents, the GLP-1 receptor agonists have shown promise as weight loss agents. GLP-1 acts centrally to increase satiety, and also delays gastric emptying further reducing appetite. A meta-analysis of nearly 3400 subjects enrolled in 21 studies, demonstrated a PSWL of -2.9kg (CI -3.6 to -2.2), although the majority of these studies focused on obese patients with type 2 diabetes. When placebo controlled trials alone were considered (10 trials), the PSWL was a more modest -1.9kg (-2.9 to -0.9). However, lingering concerns as to an association between pharmaceutical GLP-1 exposure and pancreatitis, pancreatic tumour development, and medullary thyroid cancer means that further long term studies are required before these drugs can be recommended as anti-obesity agents. Rimonabant, an endocannabinoid receptor antagonist, resulted in a mean of 4.7 kg PSWL in four randomised controlled trials, but significant concerns as to the psychiatric side effects have resulted in the withdrawal of this drug.\textsuperscript{86,319}
Table 1-2  Overview of drug options in the management of obesity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual dose</th>
<th>Mechanism</th>
<th>PSWL (kg) $^{1}$</th>
<th>Side effects</th>
<th>Available in New Zealand?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>120mg up to TDS</td>
<td>Lipase inhibitor</td>
<td>2.8</td>
<td>Oily stool, flatulence, change in bowel habit</td>
<td>Yes (NS) $^{2}$</td>
</tr>
<tr>
<td>Phentermine</td>
<td>37.5mg OD</td>
<td>Increased central noradrenaline activity</td>
<td>3.6</td>
<td>Tachycardia, palpitation, Hypertension, GI upset</td>
<td>Yes (NS) $^{3}$</td>
</tr>
<tr>
<td>Phentermine/Topiramate</td>
<td>46/7.5mg OD</td>
<td>Increased central noradrenaline activity/</td>
<td>6.7</td>
<td>Dry mouth, paraesthesia, constipation, respiratory infections</td>
<td>No</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>10mg OD/BD</td>
<td>Hypothalamic Serotonin receptor agonism</td>
<td>2.9</td>
<td>Neuropsychiatric, cognitive related adverse events</td>
<td>No</td>
</tr>
<tr>
<td>Naltrexone/Bupropion</td>
<td>32/360mg OD</td>
<td>Opioid receptor antagonist/dopamine-noradrenaline reuptake inhibitor</td>
<td>2.9% (change in kg not reported)</td>
<td>Nausea, constipation, headache</td>
<td>No</td>
</tr>
<tr>
<td>GLP-1 receptor agonist</td>
<td>Exenatide 10mg BD/</td>
<td>Increased central satiety/ Delayed gastric emptying</td>
<td>1.9</td>
<td>Nausea, vomiting</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Liraglutide up to 1.8mg OD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PSWL = Placebo subtracted weight loss; TDS = Thrice daily; OD = Once daily; BD = Twice daily; S = Subsidised; NS = Not subsidised; 1= Expected weight loss expressed as placebo subtracted weight loss; 2 = Weight control in adults with initial BMI≥30kg/m$^{2}$, in conjunction with low fat, calorie controlled diet; 3 = Available as a sustained release capsule (15-30mg daily) Short term adjunct to medical monitored comprehensive weight reduction regimen in obese patient (BMI≥30kg/m$^{2}$); 4 = It should be noted that the duration of study for each of the listed medications differs significantly (see text and referenced studies for details.)
1.2.2 Type 2 diabetes

Effective management of type 2 diabetes requires control of hyperglycaemia, as well as attention to microvascular and macrovascular risk factors through the management of blood pressure, dyslipidaemia, cardiovascular risk, and treatment of neuropathy. In this section, only control of glycaemia is reviewed, but a more comprehensive review can be found elsewhere.\textsuperscript{320}

Lifestyle modification programs are effective in the prevention and management of type 2 diabetes and appear to have durable results.\textsuperscript{321} The Finnish Diabetes Prevention Study (DPS) randomised 522 overweight participants with impaired glucose tolerance to either individualised, supported intensive diet-exercise counselling (weight reduction goal of 5\% of more, moderate physical activity for 30 minutes daily) or a control group provided with verbal and written advice only.\textsuperscript{322} A 43\% reduction in the relative risk of progression to type 2 diabetes was evident at a mean follow up of 7 years in the intensive therapy group.\textsuperscript{323} The US diabetes prevention study (DPS) randomised 3234 obese (mean BMI 34.0 kg/m\textsuperscript{2}) individuals with impaired fasting and post-prandial glucose tolerance to standard lifestyle recommendations plus Metformin 850mg twice daily, standard lifestyle recommendations plus placebo, or intensive lifestyle modifications.\textsuperscript{324} The intensive therapy targeted weight loss of 7\% or more of baseline weight and 150 minutes or more of moderate intensity physical activity; individuals were supported by an individualised taught curriculum provided over 24 weeks, and subsequently attended consolidative group sessions. At 2.8 years of follow up, the intensive treatment reduced the relative risk of type diabetes by 58\% when compared to the standard/placebo group, whilst Metformin reduced the risk by 31\%. At a mean of 10 years of follow up the relative risks were 34\% and 18\% reduced respectively when compared to placebo, whilst additional work has confirmed the cost effectiveness of this approach.\textsuperscript{325,326}

Once type 2 diabetes is established, the goal of management is to encourage “healthful eating patterns, emphasizing a variety of nutrient-dense foods in appropriate portion sizes...”.\textsuperscript{320} A number of large randomised controlled studies have explored the effectiveness of weight loss as treatment in type 2 diabetes. Perhaps the most widely cited, the Look-AHEAD study recruited 5145 overweight individuals with type 2 diabetes and assigned participants to either an intensive lifestyle intervention (ILI, caloric restriction to achieve a minimum 7\% reduction in body weight, portion controlled nutrition, and 175 minutes weekly of moderate physical activity) or diabetes support and education (DSE).\textsuperscript{327} ILI was supported through individual and group sessions at least every fortnight, whilst DSE participants attended 3 group sessions over the 12 month study period. Participants in the ILI group
lost a mean of 8.6% of their baseline weight over 12 months, whilst mean HbA1c dropped by 10 mmol/mol (56 to 46 mmol/mol), in comparison with weight loss of 0.7% and an HbA1c reduction of 0.1 mmol/mol in the DSE group. Additional studies have supported these findings, although it must be noted that an improvement in glycaemic control has not been reported in all weight loss studies in participants with type 2 diabetes, despite clear weight loss.\textsuperscript{328,329,330,331,332} Whilst caloric restriction is clearly required for weight loss, studies exploring the effect of varying macronutrient nutrition on type 2 diabetes control have been inconclusive.\textsuperscript{250} However, the benefits of adjusting insulin therapy to ingested carbohydrate in type 1 diabetes are clearly documented, and the principles can be applied to those with type 2 diabetes using insulin.\textsuperscript{333,334}

Metformin reduces hepatic glucose production and to a lesser extent enhances peripheral glucose dispersal.\textsuperscript{335} It is recommended as first line pharmacological therapy in combination with lifestyle modification for the treatment of type 2 diabetes by most guidelines (Figure 1-3). Sulphonylurea medications increase glucose independent insulin secretion, by activating voltage dependent potassium channels on the beta cell membrane, thereby promoting depolarisation and insulin release.\textsuperscript{336} These two agents have been the cornerstone of the pharmacological management of type 2 diabetes for over sixty years. Metformin and sulphonylureas reduce HbA1c values by approximately 10 to 20 mmol/mol in treatment naive individuals when compared with placebo, and are generally equivalent in head to head trials.\textsuperscript{337} However, sulphonylurea therapy is associated with weight gain and an increased risk of hypoglycaemia, whilst Metformin is weight neutral and does not independently promote hypoglycaemia.\textsuperscript{338,339} Metformin is however associated with frequent gastrointestinal side effects and should be titrated from a low starting dose to reduce the risk of these limiting effects.\textsuperscript{340} Additionally, metformin promotes the accumulation of lactate through its hepatic actions, and can promote clinically significant lactic acidosis when lactate accumulation is favoured by other co-existent medical disorders (cardiac/renal failure).\textsuperscript{341,342}

The Thiazolidinediones (TZD) were the first class of medications developed specifically for the treatment of type 2 diabetes, but have fallen out of favour in recent years.\textsuperscript{343} They improve insulin sensitivity, thereby reducing hepatic glucose output and increasing peripheral glucose dispersal, by activating the peroxisome proliferator-activated receptor $\gamma$.\textsuperscript{344} Troglitazone (idiosyncratic hepatic injury) and Rosiglitazone (cardiac events) have since been withdrawn from the market because of associated severe side effects, although the FDA have recently reapproved the use of Rosiglitazone. Pioglitazone remains licensed in most countries.\textsuperscript{341} The effect on HbA1c reductions is generally equivalent to Metformin and sulphonylureas in placebo controlled and head to head studies.\textsuperscript{337} Like
Metformin, Pioglitazone does not increase the risk of hypoglycaemia, but may promote weight gain and fluid retention, which appears to increase the risk of heart failure in those with co-existent conditions promoting cardiac dysfunction. Pioglitazone use is also associated with a reduction in bone mineral density and an increase in bone turnover markers, and an increase in the relative risk of hip and other fractures.\textsuperscript{345-347} There is conflicting evidence as to whether pioglitazone use is associated with an increased risk of bladder cancer, although recent studies are reassuring.\textsuperscript{348, 349, 350} Three additional agents that are not currently in widespread use are

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**Figure 1-3** The current approach to the pharmacological management of hyperglycaemia in type 2 diabetes (reproduced from ADA/EASD position statement)\textsuperscript{351}.

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DPP-4-i, DPP-4 inhibitor; fx, fractures; GI, gastrointestinal; GLP-1-RA, GLP-1 receptor agonist; GU, genitourinary; HF, heart failure; Hypo, hypoglycaemia; SGLT2-i, SGLT2 inhibitor; SU, sulfonylurea. \textsuperscript{†}Consider initial therapy at this stage when HbA1C is ≥9% (≥75 mmol/mol). \textsuperscript{‡}Consider initial therapy at this stage when blood glucose is ≥300–350 mg/dL (≥16.7–19.4 mmol/L) and/or HbA1c ≥10–12% (≥86–108 mmol/mol), especially if patient is symptomatic or if catabolic features (weight loss, ketosis) are present, in which case basal insulin 1 mealtime insulin is the preferred initial regimen. \textsuperscript{§}Usually a basal insulin (e.g., NPH, glargine, detemir, degludec).
Acarbose, colesevelam, and pramlintide. Acarbose is a competitive inhibitor of alpha glucosidase, and enzyme present in the brush border of the small intestine that breaks down carbohydrates prior to absorption. Acarbose therefore reduces post prandial hyperglycaemia although the optimal effect is generally mild; most studies show an HbA1c reduction of 5 to 10 mmol/mol when compared against placebo. Furthermore, gastrointestinal side effects are common and include flatulence, abdominal discomfort, and altered bowel habit. Colesevelam is a bile acid sequestrant and is a well established therapy for hyperlipidaemia. The observation that treatment was associated with mild improvements in glycaemia lead to interest in its potential in type 2 diabetes. Most studies suggest a reduction of approximately 5-10 mmol/mol following treatment, although gastrointestinal side effects are again limiting. The mechanism of action remains unclear but a recent study suggested a more pronounced increase in circulating incretins and improved glucose disposal. Pramlintide is a synthetic amylin analogue that represents an attractive method for treating hyperglycaemia but decreasing glucagon release (and therefore reducing hepatic glucose production), slowing gastric emptying, and decreasing food intake. However, the reduction in HbA1c and weight has been modest in randomised controlled trials (approximately 5 mmol/mol) in participants with type 2 diabetes, and currently pramlintide is more frequently used in the management of type 1 diabetes.

Sodium glucose cotransporter 2 inhibitors (SGLT2) are the most recent addition to the options for managing hyperglycaemia in type 2 diabetes. These agents increase urinary glucose excretion by inhibiting the SGLT2 in the proximal nephron; a reduction in HbA1c of approximately 5-10 mmol/mol has been reported in most studies, and appears similar to other standard available oral agents. In addition, use of these agents is associated with small reductions in both weight (approximately 2kg) and systolic/diastolic blood pressure, and have a similarly low incidence of hypoglycaemia to metformin monotherapy. Volume depletion predictably may occur and can be clinically relevant in those patients using anti-hypertensive diuretic therapy. An increase in urinary tract infections, including thrush, is apparent but not limiting in most studies. Whilst diabetes ketoacidosis has been reported as a possible complication in patients with type 2 diabetes treated with SGLT2 therapy, the incidence is not clearly different from that observed in observational studies involving patients with type 2 diabetes from the general population, and it is unclear whether these patients were insulin deficient. Conflicting data on the effect of SGLT2 therapy on bone turnover has been published, although most studies have shown no changes. Whilst short term studies have not shown a difference in fracture risk, longer term observation is required to allay this concern.
Pharmaceutical manipulation of the incretin endocrine system has proved to be a highly valuable addition to the treatment armoury for the type 2 diabetes. Two broad classes of agents exist; dipeptidyl peptidase 4 inhibitors (DPP4-I) and injectable GLP-1 receptor agonists. DPP4 cleaves GLP-1 to functionally inactive peptides, and therefore inhibition of this enzyme increases the duration of action of endogenous GLP-1. A number of oral DPP4-I are now available and in widespread use. The effect on HbA1c is modest with most studies demonstrating a reduction of approximately 5 mmol/mol when used as monotherapy, and results in less of an additional reduction in HbA1c when used as a second line treatment. However, as the glucose lowering effect is glucose dependent, DPP4-I have an incidence of hypoglycaemia similar to placebo, and are generally weight neutral. DPP4-I appear not to impact on cardiovascular outcomes directly, with neither favourable or harmful effects evident in large randomised trials.

GLP-1 receptor agonists are administered subcutaneously and exert their favourable glycaemic effects by increasing insulin secretion in a glucose dependent manner, reducing glucagon secretion (thereby reducing hepatic glucose production), slowing gastric emptying, and increasing satiety. A reduction in HbA1c of 5-20 mmol/mol has been demonstrated in most randomised studies, as well as modest weight loss of 2-4 kg. Like DPP4-I, GLP-1 receptor agonists are not associated with a significantly increased risk of hypoglycaemia but can cause nausea and vomiting. Concern that GLP-1 receptor agonists may increase the risk of pancreatitis is not supported by recent meta-analyses, although longer observation is required.

Whilst progressive beta cell dysfunction is characteristic of type 2 diabetes, most patients retain some endogenous insulin production even many years after diagnosis. Therefore, insulin therapy in type 2 diabetes is predominantly aimed at controlling hyperglycaemia rather than the more complex treatment regimens required in type 1 diabetes where additional consequences of insulinopenia need consideration. The majority of patients with type 2 diabetes requiring insulin therapy are commenced initially on basal treatment with either an intermediate or long acting insulin at a dose of 0.1 to 0.2 units per kilogram of body weight per day. Basal insulin as the initial regimen has merit as it provides less complexity than prandial insulin, and predominantly effects fasting hyperglycaemia which is a frequent feature at this stage of diabetes management. Prandial insulin can be added if significant post meal glucose excursions are evident despite optimal basal dosing. Recent studies however have suggested that the addition of a GLP-1 receptor agonist as opposed to prandial insulin, in those with suboptimal glycaemia control on basal insulin, may be preferable, and is associated with improved glycaemic control, weight loss, and less frequent hypoglycaemia. Whilst a basal-bolus approach (basal insulin plus separate injections of rapid acting insulin with each meal) best mimics endogenous
physiology, mixed insulin preparations are available for situations where basal-bolus treatment is less ideal.\textsuperscript{375}

1.2.3 Summary

Obesity and type 2 diabetes are increasingly prevalent conditions that frequently co-exist in individuals. It is clear that the impact of each condition on health resources internationally and in New Zealand is significant, and will remain so unless effective strategies to both prevent the development and manage the consequences of obesity and type 2 diabetes are developed.

Current therapeutic options for both conditions are limited, and generally control rather than cure. Studies exploring the role of lifestyle and pharmacological interventions for obesity and type 2 diabetes illustrate this, with only very infrequent participants with established disease attaining a normal BMI or glycaemic status following the intervention.

There is therefore a clear need to explore other therapeutic options that ideally address the unifying pathophysiological factors underlying the development of obesity and type 2 diabetes, likely in combination with current approaches. Furthermore, interventional strategies would need to be durable and cost effective to justify intervention in large numbers of a population. In the next section, I will explore the role of bariatric surgery under these circumstances.
1.3 Bariatric surgery for the management of obesity and type 2 diabetes

1.3.1 Evolution of bariatric surgery

Population obesity, to the extent that medical interventions are a necessity, is very much a recent phenomenon, and the history of surgery intended to induce weight loss extends back only over the past one hundred years. At the turn of the 20th century, jaw wiring was occasionally performed with this intent, but was frequently unsuccessful not least because recipients could still consume calorie rich liquid meals if they wished. Consequently poor dental hygiene, emesis with an increased frequency of aspiration, and the clearly undesirable cosmetic effects rendered this procedure obsolete by 1950.

The concept of gastric/intestinal surgery to induce weight loss was first proposed by Kremen in the early 1950’s, following the observation that resection of a measured segment of the dog intestine resulted in weight loss and fat malabsorption despite maintenance of caloric intake. The first such procedures in humans were performed in 1953 by Victor Henricksson (Sweden) and Richard Varco (USA), and further refined by Payne (USA) in 1963. Paynes' initial procedure (jejunocolic bypass) involved transecting the jejunum and anastomosing the proximal segment directly to the transverse colon. Thus, ingested food was diverted from the majority of the small intestine and the proximal segment of the colon. The jejeunuleal bypass (JIB) was developed as an alternative by the other proponents and subsequently adopted by Paynes. Unsurprisingly the procedure resulted in significant complications as a result of fat malabsorption, malnutrition, electrolyte disturbances, and hepatic dysfunction and the procedure was abandoned. However, the majority of recipients lost significant amounts of weight within the first few months after surgery, and the principle of a surgical treatment to correct obesity was born.

Around this time, other surgeons noted that patients undergoing gastrectomy for indications other than obesity (ulceration, etc.) lost weight and maintained this weight loss. In 1967, Mason described the earliest gastric bypass procedure whereby the stomach was divided into two segments using a staple line, and attaching the proximal gastric segment to the jejunum. Early weight loss was again
evident but was associated with severe dumping syndrome, marginal ulcers, malabsorption, and anatomical defects including staple failure. The procedure underwent a number of modifications until a variation of a Roux-en-Y bypass was generally preferred (Figure 1-4). This procedure involves the formation of a small pouch (<30cc in volume) from the proximal gastric segment, and transection of the jejunum approximately 70cm from the pyloric sphincter. The distal jejunum (Roux limb) is then anastomosed to the gastric pouch, whilst an entero-entero anastomosis is fashioned between the blind proximal loop and the distal small intestine. A number of bariatric surgeons including Torres,
Linner, and Alden have had significant input into the development of gastric bypass, but Mathias Fobi from California is perhaps the procedures most widely recognised proponent. Indeed, he described the Fobi pouch whereby a silastic ring or band is placed slightly proximal to the gastrojejunal anastomosis and prevents stoma dilatation which had limited earlier surgical techniques. Fobi further described transection of the stomach so that the blind loop is entirely isolated from the fashioned pouch. This procedure, performed either in an open or laparoscopic manner, is now the most widely performed variation of the gastric bypass.

The biliopancreatic diversion (BPD) procedure (Figure 1-4) developed as a modification of the JIB and was first performed by Scopinaro (Italy) in 1979. The procedure results in the fashioning of a small horizontal gastric pouch with removal of the remaining gastric tissue, and the formation of a gastroenterotomy. The blind duodenal stump is closed, and the remaining proximal intestine is connected back to the distal ileum. Whilst weight loss is often greater following this procedure than others, it is performed only in a small number of centres due to significant side effects, particularly frequent and voluminous stools.

The two remaining widely performed bariatric procedures were developed purely to induce restriction. Gastric banding (GB), developed in the early 1980s, involves the placement of tight plastic band around the upper stomach, so that a pouch is fashioned. An adjustable band is inserted laparoscopically with modern surgery, and whilst band failure and weight regain were legitimate concerns early on, proponents point to the lower operative risks and hospital stays. Furthermore, the lack of a malabsorptive component and the easy reversibility are favourable. Sleeve gastrectomy (SG) is the modern variation of the now seldom performed vertical banded gastroplasty (VBG). Whilst initially considered a restrictive procedure, there is considerable evidence to suggest that the mechanism of action extends beyond this. Indeed, in terms of induced physiological changes, SG shares more in common with RYGB than LAGB (see 1.4). The procedure involves significantly reducing the volume of the stomach by resecting the outer curvature leaving a tube like remnant from the gastroesophageal sphincter to the pyloric sphincter. Whilst developed as a restrictive procedure, many studies have since demonstrated therapeutic effects unexplained simply by restriction.
1.3.2 Impact of bariatric surgery on weight outcomes

Hundreds of studies of varying quality have reported on weight outcomes following bariatric surgery. In this section I will present only outcomes from randomised controlled trials including more than 20 participants where a bariatric procedure was compared against a non-surgical obesity therapy, and reported weight changes as a primary or secondary outcome. In addition, studies are separated by BMI inclusion thresholds at baseline. Firstly, I have presented only the studies that recruited participants with a body mass index of greater than or equal to 35 kg/m$^2$, consistent with the majority of society statements recommending the indications for bariatric surgery in patients with type 2 diabetes.$^{392}$ Studies that included participants with a BMI of greater than or equal to 27 kg/m$^2$ are reported separately. It should be noted that weight outcomes are reported diversely within the bariatric literature. Whilst many studies report weight loss as total body weight loss % (BWL%, see 2.2.1), others instead report excess weight loss percentage (EWBL%). Excess weight is calculated as the total body weight minus the ideal body weight, estimated from data compiled originally for medical insurance assessments. The use of EWBL% almost always results in a greater value than BWL%, whilst use of differing ideal body weight estimates, medium frame versus maximum frame etc., results in significant variation in the use of EWBL%.$^{393}$ Whilst EWBL% is considered by many to be more meaningful in a clinical sense, I have used BWL% where possible throughout this thesis to enable better comparison with the published literature.

1.3.2.1 Studies reporting weight outcomes in those with a pre-surgery BMI of $\geq 35$ kg/m$^2$

Only 4 randomised controlled trials reporting weight outcomes after bariatric surgery in those with a preoperative body mass index of greater than or equal to 35 kg/m$^2$ were identified (Table 1-3).$^{394,395,396,397}$ Each had a duration of follow up of 12 to 24 months and showed a body weight loss of 27.8 to 33.6%. In 2002 Mingrone et al reported weight outcomes in 79 participants randomised to BPD surgery or a lifestyle intervention, primarily consisting of a prescribed diet.$^{394}$ BMI in those randomised to the surgical arm was 48.2 and 32.8 kg/m$^2$ at baseline and 12 months respectively, equating to a body weight loss of 29.4%. O’Brien and colleagues performed a randomised controlled trial of LAGB versus a lifestyle intervention in 50 adolescents (14 to 18 years of age); participants randomised to the surgical arm were also asked to maintain regular physical activity with 30 minutes moderate exercise daily.$^{395}$ Mean BMI at baseline in the surgical group was 42.3 kg/m$^2$ which had
fallen to $29.6 \text{ kg/m}^2$ (28.3\% body weight loss) after 24 months of follow up. Interim weight outcomes were not reported. Mingrone performed a second randomised controlled trial in 2012, recruiting 60 participants between the ages of 30 and 60 with a history of type 2 diabetes of at least five years duration.\textsuperscript{396} Participants were randomised to either an intensive lifestyle/medical therapy, RYGB, or BPD. The combined mean baseline BMI in the two surgical arms was $46.0 \text{ kg/m}^2$ and $29.3 \text{ kg/m}^2$ after two years of follow up, equating to a total body weight loss of 33.6\%. Again interim weight changes were not reported. Finally, Dixon and colleagues reported weight loss of 27.8\% at 24 months following AGB in 60 patients with recently diagnosed obstructive sleep apnoea.\textsuperscript{397}

### 1.3.2.2 Studies reporting weight outcomes in those with a pre-surgery BMI of ≥27 kg/m\textsuperscript{2}

A further six randomised controlled trials were identified when studies allowing recruitment of patients with a BMI of greater than or equal to 27 kg/m\textsuperscript{2} were included (Table 1-4).\textsuperscript{397,398,399,400,401,402} With the exception of the study by Schauer and colleagues, all studies defined a BMI of 30 kg/m\textsuperscript{2} as the lower threshold for inclusion. As with the above studies, each reported significant weight loss, although the final BMI and total body weight loss was lower in all studies than that seen in studies recruiting more obese patients (with the exception of the study by Mingrone et al\textsuperscript{395}). Two studies from the Melbourne obesity group both reported outcomes at 24 months in participants randomised to either LAGB or a lifestyle/medication program.\textsuperscript{397,398} Participants in the 2008 study all had established type 2 diabetes, although this was not a requirement for participation in the earlier 2006 study. Participants in both studies had lost a little over 20\% of their body weight at final follow up. Ikramuddin and Liang both performed studies of RYGB in participants with established type 2 diabetes.\textsuperscript{399,400} Follow up was conducted over a 12 month period, and whilst each study controlled against a lifestyle intervention, an additional arm in the Liang study employed the lifestyle intervention with the addition of the GLP-1 mimetic Exenatide. Liang also recruited only those with established hypertension. Participants in both surgical groups lost significantly greater body weight than any control group, with 21.8\% body weight loss in the Ikramuddin study, and 24.5\% body weight loss in the Liang study. Schauer and Courcoulas both compared RYGB against SG (Schauer) or LAGB (Courcoulas) against a lifestyle intervention and both reported outcomes at 36 months.\textsuperscript{402,403}
Table 1-3  Summary of studies reporting weight outcomes following bariatric surgery in those with a BMI of ≥35 kg/m² at baseline

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention 1</th>
<th>Intervention 2</th>
<th>Duration of follow up (months)</th>
<th>Baseline BMI (kg/m²)</th>
<th>Baseline Weight (kg)</th>
<th>Follow up BMI (kg/m²)</th>
<th>Follow up Weight (kg)</th>
<th>Body weight loss (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mingrone394</td>
<td>BPD</td>
<td>Lifestyle</td>
<td>12</td>
<td>48.2</td>
<td>133.9</td>
<td>32.8</td>
<td>94.5</td>
<td>29.4</td>
</tr>
<tr>
<td>O'Brien395</td>
<td>LAGB</td>
<td>Lifestyle</td>
<td>24</td>
<td>42.3</td>
<td>120.7</td>
<td>29.6</td>
<td>86.1</td>
<td>28.3</td>
</tr>
<tr>
<td>Mingrone396</td>
<td>BPD/RYGB</td>
<td>Lifestyle</td>
<td>24</td>
<td>46.0</td>
<td>133.9</td>
<td>29.3</td>
<td>86.9</td>
<td>33.6</td>
</tr>
<tr>
<td>Dixon397</td>
<td>LAGB</td>
<td>Lifestyle</td>
<td>24</td>
<td>46.3</td>
<td>134.9</td>
<td>36.6</td>
<td>107.0</td>
<td>27.8</td>
</tr>
</tbody>
</table>

Table 1-4  Summary of additional studies reporting weight outcomes following bariatric surgery in those with a BMI of ≥27 kg/m² at baseline

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention 1</th>
<th>Intervention 2</th>
<th>Duration of follow up (months)</th>
<th>Baseline BMI (kg/m²)</th>
<th>Baseline Weight (kg)</th>
<th>Follow up BMI (kg/m²)</th>
<th>Follow up Weight (kg)</th>
<th>Body weight loss (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O'Brien398</td>
<td>LAGB</td>
<td>Lifestyle</td>
<td>24</td>
<td>33.7</td>
<td>96.1</td>
<td>26.4</td>
<td>74.5</td>
<td>21.6</td>
</tr>
<tr>
<td>Dixon399</td>
<td>LAGB</td>
<td>Lifestyle</td>
<td>24</td>
<td>36.9</td>
<td>105.6</td>
<td>29.5</td>
<td>84.6</td>
<td>21.1</td>
</tr>
<tr>
<td>Ikramuddin400</td>
<td>RYGB</td>
<td>Lifestyle</td>
<td>12</td>
<td>34.9</td>
<td>98.8</td>
<td>25.8</td>
<td>73.0</td>
<td>21.8</td>
</tr>
<tr>
<td>Liang401</td>
<td>RYGB</td>
<td>Lifestyle</td>
<td>12</td>
<td>30.5</td>
<td>82.0</td>
<td>24.5</td>
<td>70.0</td>
<td>24.5</td>
</tr>
<tr>
<td>Schauer402</td>
<td>RYGB/SG</td>
<td>Lifestyle</td>
<td>36</td>
<td>36.6</td>
<td>103.8</td>
<td>28.9</td>
<td>80.0</td>
<td>22.8</td>
</tr>
<tr>
<td>Courcoulas403</td>
<td>RYGB/LAGB</td>
<td>Lifestyle</td>
<td>36</td>
<td>35.6</td>
<td>100.0</td>
<td>28.7</td>
<td>80.0</td>
<td>20.0</td>
</tr>
</tbody>
</table>
All participants in each study had type 2 diabetes and were a similar mean BMI and age at baseline. All participants in surgical arms in both studies lost significantly more weight than those in the lifestyle arms. It is interesting to note however, that those who underwent RYGB lost significantly more weight than those who had undergone SG or LAGB. Body weight loss after RYGB in the Schauer study was 26.2% and 21.3% after SG (p=0.02), whilst body weight loss after RYGB and LAGB in the Courcoulas study was 25% and 15% respectively. Furthermore, interim weight analysis in the Schauer study suggested gradual weight regain after initial weight loss in those who had undergone SG, which was not observed in the RYGB arm.

1.3.2.3 Summary

There is therefore good evidence from randomised controlled trials to support the efficacy of bariatric surgery as a short to medium term weight loss intervention when compared against optimal lifestyle modifications. Longer follow up studies are required to confirm durability, with no high quality study yet published reporting outcomes beyond 36 months.
1.3.3 Impact of bariatric surgery on type 2 diabetes related glycaemia

1.3.3.1 Glycaemic outcomes following bariatric surgery

Whilst primarily developed as an intervention for weight loss, early pioneers of bariatric surgery recognised the early and sustained glycaemic benefits that those with pre-operative type 2 diabetes appeared to gain from surgery. The publication of an increasing number of studies reporting superior outcomes in those undergoing surgery in comparison to those optimising lifestyle and medical strategies only has confirmed the value of bariatric surgery in the treatment armoury for type 2 diabetes. Thus, in 2011, the International Diabetes Federation published a position statement on the position of bariatric surgery in the treatment armoury for type 2 diabetes, and concluded by acknowledging that bariatric surgery should be considered earlier in the management of obese persons with type 2 diabetes. In this chapter, a number of recent studies that have contributed to this opinion are presented.

The published literature on diabetes outcomes following bariatric surgery is extensive, and the quality of study methodology is variable. For the purposes of this chapter, a literature search was performed to capture all studies published up to 2015. Studies of bariatric surgery versus a non-surgical group or alternative bariatric procedures, and reported glycaemic outcomes at least 12 months following surgery were selected for inclusion. The design of each of these studies varies, and the list includes prospective randomised controlled studies, and prospective and retrospective case controlled studies. Additionally, a number of meta-analyses including data from smaller, uncontrolled studies are discussed. A summary of the included studies is presented below (Table 1-5).

1.3.3.2 Definition of diabetes outcome

A number of terms intended to represent varying degrees of diabetes improvement are utilised within the bariatric surgery literature. The conflict that may arise through the use of significantly different biochemical thresholds for diabetes remission or control, is illustrated using our research population later in this thesis (see 3.2).
However, use of terms such as ‘cure’, ‘resolved’ or ‘remission’ in this context is controversial for a number of reasons. Firstly, the diagnosis of diabetes itself is not dichotomous; rather thresholds of glycaemia have been defined on the basis of the associated risk of micro and macro vascular complications. It is not yet known whether these thresholds remain true in a post-bariatric surgery population, and consequently diagnostic criteria validated for a non-surgical population may be misleading when applied to those who have undergone bariatric surgery. Secondly, the concept of “glycaemic memory” is well established, and relates to the latent effect that glycaemic control may have on improved outcomes later life, irrespective of changes in glycaemic control in the intervening period. The UKPDS trial illustrated this concept most vividly; participants randomised to the intensive treatment arm of the study predictably had significantly improved glycaemic control during the study period in comparison to those receiving standard treatment. Glycaemic control (as measured using HbA1c) deteriorated in the intensive arm following study completion, such that HbA1c concentrations became comparable between the two groups within 12 months. At study end, and for the first years thereafter, cardiovascular mortality rates were not different between the two groups. However, those who had been randomised to the intensive therapy arm had significantly lower cardiovascular mortality rates when reassessed 10 years later, suggesting that the period of improved glycaemic control during the study period had reduced the risk (albeit latently) of cardiovascular disease. While improvements in cardiovascular disease after bariatric surgery has also been reported, it is not known what proportion of this improvement may be attributed to glycaemic improvement versus the combination with improvements in other cardiovascular risk factors such as hypertension and dyslipidemia. Conversely, whether the risk of microvascular and macro vascular disease among those who have achieved sustained normoglycaemia after bariatric surgery ever returns to the level seen among those without previous diabetes remains to be seen. Furthermore, progressive decline (albeit potentially reversible) in pancreatic beta cell function over time is characteristic of type 2 diabetes and it is unknown whether bariatric surgery alters this process. Hence some of the heterogeneity in diabetes outcomes reported between studies may be due to the age and ethnicity of participants, the degree of obesity associated with diabetes, duration of diabetes, duration and extent of insulin therapy; each as potential markers of residual beta cell function. Thirdly, use of the term “cure” for a chronic disease mediated predominantly by lifestyle may not be helpful in encouraging longer term compliance to favourable dietary and exercise strategies. Regardless of these caveats, a better understanding of glycaemic outcomes following bariatric surgery is important for pre-operative patient counselling as to the likely glycaemic benefits from the procedure.
In the absence of definitive evidence addressing each of the issues above, the literature reporting diabetes outcomes following bariatric surgery is notable for the degree of variability with which diabetes remission is defined. This is often confusing, and has possibly contributed to the delays seen for bariatric surgery to be accepted as an appropriate therapeutic option in the management of obese persons with type 2 diabetes. An agreed set of definitions of diabetes outcomes would ideally be used when reporting on bariatric surgery outcomes, and thus the American Diabetes Association (ADA) released a consensus statement in 2009 providing recommendations on the definition of glycaemic outcomes post bariatric surgery. This suggested the use of the terms “partial remission” (HbA1C<6.5% (47 mmol/L), fasting glucose 100-125 mg/dl (5.6 – 6.9 mmol/L)), and “complete remission” (HbA1c “in the normal range”, fasting glucose <100mg/dl (5.6 mmol/L)) provided that each of these assessments were persistent for at least 1 year duration, and in the absence of active pharmacologic therapy or ongoing procedures. Additionally, the ADA defined prolonged remission as the thresholds required for satisfaction of complete remission, maintained for at least 5 years. Furthermore, comparison of bariatric surgery with non-surgical intensive medical management can only rely on achievement of similar glycaemic targets rather than diabetes remission as defined by achieving such glycaemic targets in the absence of glucose lowering therapy. Indeed, the concept of a population glycaemic target is likely outdated. The ACCORD study demonstrated an increased risk of mortality with intensive therapy compared against control, whilst other studies have demonstrated a U shaped curve when plotting HbA1c against mortality risk. This appears to be particularly relevant in those with established heart disease. Thus, achieving an HbA1c specified by the above criteria may not be the target for an individual patient.

1.3.3.3 Review of diabetes outcomes following bariatric procedures

The literature reporting on diabetes outcomes following bariatric surgery is extensive and ranges from small case series through to high quality randomised controlled studies. A number of meta-analyses have attempted to address this diversity of study quality, and some of these publications are discussed later in this chapter. For the purposes of this chapter, only those studies that included a comparison or control group (either an alternative bariatric procedure or lifestyle/medical therapies) and reported on outcomes at 12 months or beyond are included. A summary of the included studies is presented in Table 1-5 (page 73).
1.3.3.3.1 Studies reporting diabetes outcomes at 12 months

Gastric bypass versus lifestyle/medical therapy

3 studies were identified reporting diabetes outcomes at 12 months following gastric bypass. “Diabetes control” was achieved by 41-75% of those in the gastric bypass arm in these studies with the variability likely due to differences in the definitions utilised to define diabetes control and in the baseline characteristics of the participants in each study.411,412, 413

Hofso and colleagues performed a comparison study of gastric bypass versus a lifestyle based intervention in 146 morbidly obese adults (mean BMI 45.6 kg/m$^2$) and reported outcomes at 12 months.411 Ikramuddin and colleagues performed a 12 month randomised study of intensive medical management versus intensive medical management plus Roux-en-Y gastric bypass.412 120 obese participants (BMI 30-39 kg/m$^2$) with type 2 diabetes were recruited, and a primary composite outcome incorporating achievement of diabetes, blood pressure and lipid control targets was reported. Serrot and colleagues performed a retrospective case control study of obese (BMI 30-35 kg/m$^2$) participants with type 2 diabetes who had undergone gastric bypass in their institution versus a control group (BMI matched persons with type 2 diabetes from a primary care database).413

Considerable variability in study methodology and the tested intervention was evident. The study by Ikramuddin and colleagues defined only diabetes control and accepted a higher HbA1c threshold (<7.0% (53 mmol/mol)) than the other two studies; thus, this study reported the highest rates of diabetes control. The studies by Hofso and Serrot both reported diabetes remission, requiring absence of glucose lowering medications) and control defined by a lower HbA1c threshold, but were confounded by a higher mean age of participant in the surgical arm (56 vs. 42 years), and a higher HbA1c at baseline (8.2 vs. 7.1% (66 vs. 54 mmol/mol).

The control intervention employed in each study also differed considerably. Hofso and colleagues offered an intensive lifestyle intervention; each participant in this arm was referred to a specialist inpatient weight loss centre and had four stays within the centre during the 12 month study period. Each admission was for between 1 and 4 weeks. Participants received numerous interventions during each stay including input from a medical doctor, a nurse, a physiotherapist, and a specialist trained nurse. Physical activity was increased, and all participants were provided with education on a healthy diet, which they were encouraged to
follow. Group sessions focused on the psychosocial and emotional aspects of obesity and weight loss. Weight loss drugs were not used. Phone contact was maintained fortnightly while participants were away from the weight loss centre. The lifestyle intervention offered by Ikramuddin and colleagues was less intensive and consisted of a reduced energy diet for all participants with the aim of weight loss in the order of 0.5 to 1 kilogram per week. Increased physical activity was encouraged, and each participant had regular face to face contact with a study interventionist to discuss behavioural and social issues around weight loss. Orlistat (and Sibutramine prior to withdrawal from the US market) were available for use by those in the lifestyle arm if agreed weight loss targets were not met. The contemporary American Diabetes Association guidelines for the management of type 2 diabetes were followed for the medical management of each participant in the study.

26% and 29% of participants in the Hofso study in the gastric bypass and lifestyle intervention arms respectively had type 2 diabetes at baseline. Diabetes remission was defined as a fasting glucose <5.6 mmol/L, and a 2 hour glucose of <7.8 mmol/L post 75g oral glucose tolerance test, and an HbA1c of < 6.2% (44 mmol/mol) in the absence of glucose lowering therapy. In addition, the study authors defined partial diabetes remission as glucose concentrations below the diagnostic thresholds at baseline (<7.0 and 11.1 mmol/L for fasting and 2 hour glucose respectively) and an HbA1c < 6.5% (47 mmol/mol) without the use of glucose lowering therapy. The overall diabetes remission rate by this criteria was significantly greater in the gastric bypass arm versus those in the lifestyle intervention arm (70 vs. 33%, OR 4.7 (1.2–18.4). However, none of the participants in the lifestyle intervention arm achieved complete diabetes remission, whilst 11 out of the 14 participants (55% of those with type 2 diabetes at baseline) achieved complete diabetes remission at 12 months follow up. 75% of those randomised to gastric bypass in the Ikramuddin study achieved diabetes control (defined solely as an HbA1c of <7% (53 mmol/L)) at 12 months versus 32% of those randomised to intensive medical management only (OR, 6.0; 95% CI, 2.6-13.9). Whilst the primary composite outcome was achieved in 49% (versus 19%) of those undergoing gastric bypass, there was no difference between the two arms when blood pressure and lipid outcomes were assessed as independent outcomes. In the study by Serrot and colleagues, diabetes remission was defined as an HbA1c <5.7% (39 mmol/mol) in the absence of glucose lowering medications, whilst diabetes control was defined as an HbA1c <6.5% (47 mmol/mol) in the absence of glucose lowering medications. At the 12 month follow up assessment 4/17 (24%) of surgical participants had achieved diabetes remission and a further 7 (41%) of participants had achieved diabetes control. Classification outcomes in the
control group were not reported. The mean HbA1c in those who had undergone surgery fell from a baseline level of 8.2% ([66 mmol/mol] ± 2.0%) to 6.1% ([43 mmol/mol] ± 2.7%), but did not change significantly in the control group ([7.0 (53 mmol/mol) ± 0.7% to 7.1 (54 mmol/mol) ± 1.8%]).

**Gastric bypass versus Sleeve gastrectomy**

Two randomised controlled studies and one prospective non-randomised study reported outcomes at 12 months following either gastric bypass or sleeve gastrectomy, with two of these studies including a lifestyle/medical arm. In addition, a further randomised controlled study primarily reporting on 24 month outcomes, presented 12 month outcomes. Lee and colleagues reported 12 month diabetes outcomes following randomisation to gastric bypass or sleeve gastrectomy in 60 overweight (BMI 25-35 kg/m²) Taiwanese participants with sub-optimally controlled type 2 diabetes. Schauer and colleagues reported on diabetes outcomes of overweight and obese American participants (BMI 27-43 kg/m²) and type 2 diabetes at 12 months of follow up. 150 participants were recruited and randomised in equal numbers to one of three interventional arms (intensive medical therapy, gastric bypass plus intensive medical management, and sleeve gastrectomy plus intensive medical management). Vidal and colleagues performed a non-randomised prospective study comparing outcomes of severely obese (BMI >35kg/m²) participants with type 2 diabetes (n=91) who underwent either gastric bypass (n=52) or laparoscopic sleeve gastrectomy (n=39). The groups were matched at baseline for duration, control, and treatment of diabetes.

Again, the studies were significantly different from one another. Lee defined diabetes remission as a fasting glucose of <126 mg/dl (7.0 mmol/L) and HbA1c of <6.5% (47 mmol/mol) and the absence of diabetes medications. Participants were assessed by an extensive multidisciplinary team prior to surgery but the study does not report on medical interventions used in the post-operative period. 93% of those randomised to gastric bypass achieved diabetes remission at 12 months versus 47% of those who had undergone sleeve gastrectomy. Schauer defined diabetes control/remission as an HbA1c <42 mmol/mol with or without the use of diabetes medications, which was achieved by 12% of those randomised to medical therapy only, 42% of those randomised to the gastric bypass arm, and 37% of those randomised to the sleeve gastrectomy arm. The definition of diabetes remission utilised for this study was...
clearly limited by the acceptance of an HbA1c < 42 mmol/mol as evidence for remission even in the context of ongoing diabetes medication use. It could be argued that those who required ongoing glucose lowering therapy should be defined as being, at best, partial responders. However, all of those in the gastric bypass arm who achieved diabetes remission did so without the ongoing use of diabetes medications, whilst 28% of those in the sleeve gastrectomy arm who were reported as achieving diabetes remission continued to require glucose lowering therapy; all of those in the medical management alone arm who achieved the primary endpoint remained on glucose lowering therapy. Lee defined diabetes remission as a fasting glucose <126 mg/dl (7.0 mmol/L) and an HbA1c within the normal range (3.4-5.5% (14-37 mmol/mol)) in the absence of glucose lowering medications. At 12 months following surgery diabetes remission had been achieved by 84.6% of those who had undergone gastric bypass and 84.6% of those who had undergone laparoscopic sleeve gastrectomy. Interestingly, the study authors found no relationship between weight loss and diabetes remission, but did note a significant association between duration and severity, as defined by treatments required and HbA1c at baseline, of diabetes and diabetes remission.

Whilst each study used stringent criteria for diabetes remission/control, it should be noted that participants in the study by Lee and colleagues demonstrating superior efficacy of GBP compared to SG, had a significantly lower BMI at baseline versus those in the studies by Schauer and Vidal which both showed similar efficacy of GBP compared to SG. The apparent marked increase in surgical participants achieving diabetes remission in the study by Vidal (approximately 85%) when compared to those in the study by Schauer (approximately 40%) is of interest as, despite a similar age at surgery (mean approximately 48 years), participants in the Schauer study were not as super-obese, had a longer pre-operative duration of diabetes (approximately 8 years versus approximately 4 years) and a 4 fold higher pre-operative use of insulin (approximately 44% versus 10%), which may indicate less beta cell reserve.

Biliopancreatic diversion versus lifestyle/medical therapy

Scopinaro and colleagues performed a prospective, historical case controlled study of biliopancreatic diversion surgery versus medical management in overweight or obese persons (BMI 25-34.9 kg/m²) with type 2 diabetes. Participants who underwent biliopancreatic diversion surgery had a mean age of 56 years and established diabetes, with a mean duration
of diabetes of 11 years, mean HbA1c at baseline of 78 mmol/mol, and 12/30 participants requiring insulin therapy at baseline). The study authors defined three categories of diabetes outcomes; Diabetes remission was defined as a fasting glucose <126 mg/dl (7.0 mmol/L), and an HbA1c ≤6.0% (42 mmol/mol) without the use of glucose lowering medications; controlled diabetes was defined as an HbA1c ≤7.0% (53 mmol/mol) in the absence of glucose lowering medication; improved diabetes was defined as a >1% (10-11 mmol/mol) reduction in Hba1c concentrations when compared to baseline. No participants in the historical control group achieved diabetes remission or diabetes control during one year of treatment (mean HbA1c at baseline = 8.8% (73 mmol/mol)). Whilst two thirds of participants required an increase in their medication doses during this 12 month period, no participant was able to reduce medication doses. In contrast, diabetes remission was achieved by 30% of those who had undergone biliopancreatic diversion, and diabetes control by a further 53% (83% total). However, five participants (out of 12) who required insulin therapy at baseline remained on insulin therapy at 12 months following biliopancreatic surgery.

The relative low rate of diabetes remission following biliopancreatic diversion in this study, in contrast to very high rates more commonly reported following this procedure, may be explained by the baseline characteristics of the study cohort. Specifically, this was an older cohort than other studies discussed above (mean age = 56.4 years), and participants had both a longer duration of diabetes (mean = 11.2 years) and a higher Hba1c (mean = 9.6% (81 mmol/mol)) at baseline.

1.3.3.3.2 Studies reporting on outcomes from 12 to 24 months

Gastric bypass versus lifestyle/medical therapy

Two studies of gastric bypass versus lifestyle medical therapy were identified that reported on outcomes at 24 months.\(^{418,422}\) A study by Adams and colleagues continued to follow up their cohort for a total of 72 months and is therefore discussed in the following section. Leslie and colleagues performed a retrospective case control study of outcomes following gastric bypass versus medical managements for obese persons with type 2 diabetes.\(^{418}\) Rather than define diabetes outcomes using simply glycaemic markers, the study authors elected to use a composite end point of treatment goals as recommended by the American Diabetes Association
for the management of type 2 diabetes (HbA1c <7.0% (53 mmol/mol), low-density lipoprotein <100mg/dl, systolic blood pressure <130mmHg). 152 and 115 participants who had undergone gastric bypass or medical therapy alone respectively were included in the analysis. The percentage of participants satisfying the ADA treatment goals who had undergone gastric bypass was 10.5% at baseline, increasing to 38.2% at 24 months follow up. A smaller, non-significant increase was noted in the medical therapy group from 13.9% at baseline versus 17.4% at 24 months.

Laparoscopic adjustable gastric band versus lifestyle/medical therapy

One study was identified that reported on diabetes outcomes 24 months following laparoscopic adjustable gastric banding. Dixon and colleagues reported diabetes outcomes at 24 months on 60 obese participants (BMI 30-40 kg/m², age range 20-60 years) with type 2 diabetes randomised to either laparoscopic adjustable gastric banding or an intensive lifestyle program without the use of bariatric surgery. The lifestyle program was comprehensive and administered via a multidisciplinary team consisting of a physician, dietitian, and diabetes nurse via face to face meetings at 6 week intervals. A low energy diet with reduced saturated fats was prescribed along with increased exercise activity; very low calorie diets and/or weight loss pharmaceutical agents were also available for use. Diabetes remission was defined as a fasting glucose level of <126 mg/dl (7.0 mmol/L) and an Hba1c <6.2% (44 mmol/mol) in the absence of glucose lowering therapy. This was achieved by 73% of those who in the laparoscopic adjustable gastric band arm versus 11-23% in the control arm. This is based on the assumption that diabetes remission was (23%) or was not (11%) achieved by 4 participants randomised to the lifestyle arm who did not complete the study. Furthermore, improvement in diabetes control was evident in those who underwent gastric banding with 26/30 participants not requiring glucose lowering therapy at study end versus 2 at baseline.

The percentage of participants who achieved diabetes remission in the surgical arm of this study was high, and particularly notable given that the mean age at which participants underwent surgery (46.6 years), the mean HbA1c at baseline (7.8% (62 mmol/mol)), and a mean BMI at surgery (37.0 kg/m²) was comparable to baseline characteristics of cohorts in other studies discussed in this chapter following gastric bypass or biliopancreatic diversion surgery. However, only one participant in the surgical group used insulin therapy at baseline, and although
duration of diabetes at surgery was not reported, the exclusion of participants with evidence of microvascular complications (retinopathy, nephropathy) is likely to result in the selection of those with a more recent diagnosis of diabetes, and therefore an increased likelihood of residual preserved beta cell function.

**Bariatric surgery versus lifestyle/medical therapy**

Three studies were identified that reported on outcomes in studies incorporating two or more bariatric surgery modalities.\(^{420,421,428}\) The Swedish Obesity Study (SOS) reported on outcomes at 24 months in addition to those at 120 months and is thus discussed in the section below. The studies by Kashyap and Mingrone both included a gastric bypass arm but reported markedly different diabetes outcomes at 24 months (33 versus 75% respectively). Kashyap and colleagues undertook a prospective randomised study of optimal medical therapy versus either gastric bypass or sleeve gastrectomy in 60 moderately obese (mean BMI =36.1 kg/m\(^2\)) participants with type 2 diabetes at baseline.\(^{420}\) Mingrone and colleagues performed a single centre randomised controlled study of gastric bypass versus biliopancreatic diversion versus medical/lifestyle therapy only.\(^{421}\)

All patients in the study by Kashyap et al received intensive medical therapy as recommended by the American Diabetes Association, including dietary modifications, increased frequency of capillary glucose measurements, and the use of all available glucose lowering agents. In addition, each participant received nutritional counselling by a study dietitian and underwent a psychological assessment, in part to assess suitability for bariatric surgeon. Participants were then randomly allocated to either ongoing medical therapy alone, gastric bypass surgery, or sleeve gastrectomy. In the Mingrone study, 60 participants (age 30-60, BMI >35 kg/m\(^2\)) were recruited, each of whom had had type 2 diabetes for at least 5 years and had a current HbA1c of >7.0% (53 mmol/mol). Each participant had visits with a multidisciplinary team (including a diabetologist, dietitian, and study nurse) at baseline and then 1, 3, 6, 9, 12 and 24 months following commencement of the intervention. Dietary and physical activity advice was provided to those in the medical arm. The dietary prescription comprised <30% total fat, <10% saturated fat, and high fibre content, with ≥30 minutes of brisk walking every day. Diabetes medications were adjusted based on regular HbA1c measurements.
The authors used significantly different definitions of diabetes outcomes that could potentially result in discordant outcomes. Diabetes remission was defined by Kashyap as an HbA1c of less than 42 mmol/mol (6.0%). 44% and 26% of those who had undergone gastric bypass and sleeve gastrectomy respectively had an HbA1c of <6.0% (42 mmol/mol) at 12 months follow up, compared with 6% of those who had received medical therapy alone. However, a reduction in the number of participants satisfying criteria for diabetes control at 24 months was evident (33, 11, and 6% for gastric bypass, sleeve gastrectomy, and medical therapy respectively). In keeping with the definition suggested by the American Diabetes Association, Mingrone defined diabetes remission as a fasting plasma glucose level < 100 mg/dl (5.6 mmol/L) and an HbA1c level < 6.5% (48 mmol/mol) for at least 1 year without active pharmacologic therapy. Diabetes remission was achieved by 95% of those in the biliopancreatic diversion arm, 75% of those in the gastric bypass arm, and none of those in the medical arm. Biliopancreatic diversion and gastric bypass were associated with a likelihood of diabetes remission of at least 9.5 (95% CI, 2.54 to 35.51; P<0.001) and 7.5 (95% CI 1.97 to 28.61; P<0.001) respectively when compared with medical therapy alone. Two participants randomised to the medical therapy arm of the study did not complete the 24 months of follow up, and for the purposes of calculating remission odds ratios the authors chose to conservatively assume that both of these participants had achieved diabetes remission.

Thus, whilst Mingrone utilised seemingly more stringent criteria for resolution including a fasting glucose and HbA1c threshold, and the absence of glucose lowering medication, it should be noted though that this study accepted an HbA1c of <6.5% (48 mmol/mol) as evidence of diabetes remission. However, allowing for this difference does not explain the discordancy between these studies which is also not easily explained by differing baseline characteristics; whilst the two cohorts undergoing gastric bypass were of similar ages at operation (mean = 47.9 years and 43.9 years for the Kashyap and Mingrone studies respectively), and had a similar duration and control of diabetes at baseline (7.4/6.0 years, 9.0%(75 mmol/mol)/8.5%(69 mmol/mol) respectively), participants in the Mingrone study had a significantly higher BMI (44.6 versus 36.1 kg/m²). Additionally, differences in the medical/lifestyle program utilised in each study (prescribed for those in the surgical arms alongside surgery) do not appear likely to be a factor in this anomaly, as none of the medical/lifestyle arm of the Mingrone study achieved diabetes remission, in comparison to 6% of participants in the equivalent arm of the Kashyap study.
As noted earlier, the 95% diabetes remission rate in the biliopancreatic diversion arm of the above study by Mingrone and colleagues is significantly higher than the 30% at 12 months seen in the study by Scopinaro discussed in the section above. Again, this is likely to be explained by the older age at surgery, and longer duration of diabetes of participants in the Scopinaro study.

1.3.3.3 Studies reporting on outcomes beyond 2 years

Bariatric surgery versus lifestyle/medical therapy

Two studies reporting on outcomes beyond two years, comparing bariatric surgery against non-surgical interventions were identified.\(^{422,423}\) Adams and colleagues performed a prospective study recruiting obese adults (BMI>35kg/m\(^2\)) who underwent gastric bypass surgery over a 10 year period (n=418).\(^{422}\) Two control groups were included, the first of which included participants who had sought but not undergone gastric bypass surgery (n=417), and a second group comprised of obese adults selected from a regional registry (n=321). An explanation as to why each of the participants in the first control group had not undergone gastric bypass was not provided in the manuscript, which is an important omission as this likely adds significant selection bias. Pontiroli and colleagues performed a prospective case controlled study of outcomes following laparoscopic adjustable gastric banding versus optimisation of lifestyle and medical therapies.\(^{423}\) The study investigators recruited 122 sequential patients (age range 18-66) referred for the management of obesity, who met contemporary criteria for bariatric surgery (BMI > 40 kg/m\(^2\), or BMI > 35 kg/m\(^2\) in the presence of obesity related co-morbidities).

The prevalence of diabetes within each group in the Adams study at baseline was not presented, although the mean HbA1c was 42 mmol/mol or less in each group. Diabetes at baseline was defined as a fasting glucose of >126mg/dl (7.0 mmol/l), and/or an HbA1c of >6.5% (47 mmol/mol), and/or the use of glucose lowering medications, whilst remission of diabetes was defined as an Hba1c and fasting glucose within the normal reference range (absolute figures not provided) in the absence of ongoing glucose lowering therapy. Using these definitions, diabetes remission was achieved by 75% (95% CI, 63%-87%) and 62% (95% CI, 49%-75%) at 2 and 6 years post-surgery respectively in the gastric bypass group. Diabetes remission rates at 6 years were significantly lower in those who had either sought gastric bypass but not undergone surgery (8%; 95%CI,0%-16%, OR, 16.5 versus gastric bypass) and population controls
(6%; 95% CI, 0%-13%, OR, 21.5). The study authors also noted a significantly lower incidence of new diagnoses of diabetes during 6 year follow up in the gastric bypass group (2%; 95% CI, 0%-4%) in comparison to those in the first control group (17%; 95% CI 10%-24%, OR 0.11 favouring gastric bypass; 95% CI 0.04-0.34) and those in the population control group (15%; 95% CI 9%-21%, OR 0.21 favouring gastric bypass; 95% CI, 0.06-0.67).

The absence or presence of type 2 diabetes was clarified in the Pontiroli study through an oral glucose tolerance test based on standard diagnostic criteria. The participants were then followed within two intervention studies; the primary intervention study assessed the effect of laparoscopic adjustable gastric banding on the preventing progression from normal glucose tolerance or prediabetes to overt type 2 diabetes, whilst the secondary intervention study assessed the effect on only those with established type 2 diabetes. Thus, 37 participants with established type 2 diabetes were enrolled in the secondary intervention section of the study. Each of these participants was offered laparoscopic adjustable gastric banding; 17 consented to surgery with the remainder wishing to utilise lifestyle/medical options. The applied definition of diabetes remission was not specifically provided in the published manuscript, although it is implied that contemporary diagnostic criteria for the diagnosis of thresholds of dysglycaemia were utilised. Thus, diabetes remission would be diagnosed on the basis of a fasting glucose level <6.1 mmol/L, and a 2 hour post glucose level of <7.8 mmol/L, presumably also in the absence of glucose lowering medications. HbA1c measurements were recorded but are not specifically reported in the context of diabetes remission. Using this definition, diabetes remission was achieved by 45% at four years by those who had undergone laparoscopic adjustable gastric banding, and 4% of those who had declined surgery. Of note, none of those who had undergone laparoscopic adjustable gastric banding as a part of the primary prevention component of the study developed diabetes during the four years of follow up, whilst 17% of those who declined surgery did so.

**Studies comparing different forms of bariatric surgery**

Five studies meeting criteria have been published reporting outcomes of differing bariatric procedures beyond two years, some of which are extensions of previously reported cohorts. Iaconelli and colleagues performed a prospective case controlled study...
of conventional lifestyle and medical therapy versus biliopancreatic diversion in obese participants with type 2 diabetes. The study team enrolled 110 obese participants with type 2 diabetes and initiated a three month run-in intervention comprising dietary optimisation. At the end of the run-in period, participants who met the inclusion criteria for the study (age 25-60 years, BMI >35 kg/m², and a residual diagnosis of type 2 diabetes on the basis of standard criteria, n=50) were offered either conventional lifestyle and medical therapy alone, or conventional therapy plus biliopancreatic diversion surgery (n=28 and 22 respectively). The institutional ethics board declined an initial application to allow randomisation to each group, due to the long duration of planned follow up. Conventional therapy included dietary, exercise and medication optimisation as per current American Diabetes Association guidelines. The authors did not specify the definition used for diabetes remission in the study, although it is implied that diagnostic thresholds commonly used at the initiation of the study (fasting glucose >7.0 mmol/L (on 2 occasions) and/or a 2 hour glucose > 11.1 mmol/L following a 75g oral glucose tolerance test) were utilised to assess diabetes outcome. Allowing for these limitations, diabetes remission was achieved by 100% of participants at 12 months by those who had undergone biliopancreatic diversion surgery; the authors noted that none of these participants redeveloped diabetes during the remainder of follow up to 10 years. The mean HbA1c at 10 years in the conventional treatment and biliopancreatic diversion surgery arms was 7.8% (62 mmol/mol) and 4.9% (30 mmol/mol) respectively.

Pinheiro and colleagues performed a randomised study of two variations of Roux-en-Y gastric bypass in 105 participants with type 2 diabetes and severe obesity (BMI >50kg/m²). The diagnosis of diabetes and diabetes outcomes was defined on the basis of diagnostic thresholds. The primary intent of the study was to assess the varying effect of the resulting length of both the biliary and Roux limb of the gastric bypass. In group 1, the biliary and Roux limbs were 50 and 150 cm respectively, whilst in group 2 the biliary and Roux limbs were 100 and 250cm respectively, the so called long-long limb Roux-en-Y gastric bypass. At 48 months follow up, diabetes control (glycaemic markers below diabetes diagnostic thresholds in the absence of glucose lowering medication) was achieved in 58% of those in group 1 and 93% of those in group 2. A statistically higher proportion of participants in group 2 had improvement of dyslipidaemia, whilst there was no difference in the improvement in hypertension.
Pournaras et al performed a prospective comparison study of gastric bypass (n=22) versus gastric banding (n=12) in severely obese participants with type 2 diabetes. The study design allowed for an assessment of diabetes outcomes, along with exploration of the mechanism underlying the expected improvements in diabetes control. The study investigators defined diabetes remission based on contemporary diagnostic thresholds; a fasting plasma glucose <7 mmol/L in the absence of medical treatment for at least 3 days, and a 2-hour plasma glucose <11.1 mmol/L following an oral glucose tolerance test (OGTT). In addition, an HbA1c <6.0% (42 mmol/mol) after 3 months without the use of glucose lowering medication was required. Participants had established diabetes at baseline with a mean duration of diabetes of >5 years; 55% of those who underwent gastric bypass and 30% of those who underwent gastric banding required insulin therapy prior to surgery. 68% of those in the gastric bypass arm had achieved diabetes remission at 12 months of follow up versus none in the gastric banding arm despite similar weight loss (20-25% body weight) at that assessment. At 36 months follow up, the percentage of those in diabetes remission had increased to 72% and 17% for gastric bypass and gastric banding respectively.

Following publication of diabetes outcome results after bariatric surgery at 12 months, Schauer and colleagues performed a further analysis of follow up outcomes at 36 months. Of the original 150 randomised participants who had been randomised in equal numbers to intensive medical therapy, gastric bypass plus intensive medical therapy, and sleeve gastrectomy plus intensive medical therapy, were evaluated. As in the original study, diabetes remission was defined as an HbA1c of <42 mmol/mol with or without the use of diabetes medications, and was achieved by 38% and 24% of those who had undergone gastric bypass and sleeve gastrectomy respectively, versus 5% of those randomised to intensive medical therapy alone. Glycaemic relapse, defined as satisfying criteria for diabetes remission at 12 months but not at 36 months, was seen in 80% of participants in the medical therapy group, 24% of those who had undergone gastric bypass group, and 50% of those who had undergone sleeve gastrectomy. Decrease in BMI following surgery (odds ratio, 1.33 for every 1 unit (mg/m2); 95% CI, 1.15 to 1.56; P<0.001) and the pre-surgical duration of type 2 diabetes (duration <8 versus >8 years; odds ratio, 3.3; 95% CI, 1.2 to 9.1; P = 0.02) were the only two predictors of diabetes outcome following either form of bariatric surgery.

The Swedish Obese Subjects Study (SOS study) was a very large prospective non-randomised study performed in Sweden between 1987 and 2000. Following a large scale national
recruitment drive, 4047 participants who met the study criteria (BMI >34 kg/m² for men, BMI >38 kg/m² for women, age 37-60 years) were recruited and offered either non-surgical or, if appropriate, surgical interventions. Surgery was performed at 25 national centres and included gastric banding, sleeve gastrectomy, and gastric bypass. Each participant who had chosen bariatric surgery was matched at the time of surgery to a participant who had elected medical therapy only, based on 18 variables including demographic, metabolic, psychosocial, and personality parameters. Medical and lifestyle therapies were not standardised for this trial. The intervention for both the surgically treated participant, and their matched medical therapy only control, was considered to have commenced on the day of surgery.

Outcomes following 10 years of follow up were reported in 2004 and included data on all 4047 participants enrolled in the SOS study with at least 2 years of follow up data available, and 1703 participants who had 10 years of follow up data available. The study authors reported both diabetes incidence since baseline and diabetes outcomes. The majority of enrolled participants did not have type 2 diabetes at baseline, although the study authors were still able to report on approximately 200 participants who did and had follow up data extending to 10 years. The criteria used to define both disease and disease outcome were the same, and were reflective of contemporary diabetes diagnostic thresholds. Thus, diabetes remission was defined as a fasting glucose of <7.0 mmol/L (126 mg/dl) in the absence of glucose lowering medications.

590/4047 and 202/4047 participants had type 2 diabetes at baseline and 2 or 10 years of follow up data available respectively. Of those with 2 years of follow up data, 246/342 (72%) of surgical participants and 52/248 (21%) of control participants had achieved diabetes remission (Odds ratio 8.42 95%CI 5.68-12.5). Over the same period, 8% of control participants who did not have diabetes at baseline (n=1402) developed type 2 diabetes, compared to 1% of those who had undergone bariatric surgery (n=1489). Of those with 10 years of follow up data, 42/118 (36%) of surgical participants and 11/84 (13%) of control subjects had achieved diabetes remission (Odds ratio 3.45 95%CI 1.64-7.28). As expected the incidence of new diabetes in those who did not have type 2 diabetes at baseline, had increased further at 10 years such that 24% and 7% of control and surgical participants respectively had developed diabetes.
1.3.3.4 Meta-analyses of studies reporting on diabetes outcomes following bariatric surgery

A large number of meta-analyses using a diverse range of selection criteria have been published. The majority report on weight or short term outcomes only and are therefore beyond the scope of this chapter. The reader is directed towards meta-analyses performed by Lai, Maggard-Gibbons, and Gloy and colleagues which all included either studies discussed in the paragraphs above, or studies reporting on diabetes outcomes <12 months following surgery.\textsuperscript{429,430,431} In addition, Parikh and colleagues have recently published a meta-analysis of 39 studies reporting on diabetes outcomes in subjects with a BMI <35kg/m\textsuperscript{2}.\textsuperscript{432}

The largest meta-analysis thus far published reporting outcomes of bariatric surgery (gastric banding, gastroplasty, RYGB and biliopancreatic diversion/duodenal switch (BD/DS)) included all studies published between 1990 and 2006, and updated a previous meta-analysis by the same group.\textsuperscript{433,434} The meta-analysis included 621 studies, within which 103 arms specifically reported on diabetes outcomes (3188 subjects). All study designs were included, with each study was assigned a level of evidence. 22.3\% of the cohort (30,160/135,246 subjects) had pre-operative diabetes. Weight loss across the whole cohort, expressed as excess body weight lost (EBWL\%), was 48.98\% for gastric banding, 56.48\% for gastroplasty, 63.25\% for RYGB, and 73.72\% for BD/DS at ≥ 2 year follow up, although the majority of subjects remained obese (Mean pre-operative BMI 47.86, mean post-operative BMI 33.89kg/m\textsuperscript{2}). Weight loss assessed at ≥ 2 years exceeded that reported at shorter post-operative intervals for each modality. Weight loss in patients with pre-operative diabetes was similar with 67.1 and 58.01\% EBWL at <2 or ≥ 2 year follow up respectively when all surgical modalities were included (67.10 and 64.7\% for RYGB specifically). Sub group analysis of the subjects with diabetes included in the meta-analysis revealed that resolution of diabetes, defined as cessation of diabetes medications and either normal fasting glucose (<100 mg/dl (5.5 mmol/L)) or an HbA1c < 6\% (42 mmol/mol) across the whole cohort was 78.1\% (80.27 and 74.59\% at <2 and ≥ 2 year follow up respectively. Resolution or improvement, defined as a reduction in number or dose of diabetes medications, or an improvement in fasting glucose to between 100-125 mg/dl (5.5 - 6.9 mmol/L), was seen in 86.61\% (86.0 and 87.24\% respectively). Further assessment based on surgical procedure revealed that resolution of diabetes was seen in 56.73\% (54.99 and 58.29\% at <2 and ≥ 2 year follow up respectively) following gastric banding, 79.74\% (81.44 and 77.46\%) following gastroplasty, 80.28\% (81.60 and 70.90\%) following RYGB, and 95.05\% (94.0 and 95.85\%) following BD/DS.
In addition the authors performed a sub-analysis on 12 studies that included only subjects with diabetes (n=963) and reported overall resolution of diabetes in 79.29% (81.81 and 62.08%), and resolution or improvement in 98.91% (98.56 and 100%). It should be noted however that data for ≥ 2 year follow up in studies that recruited only those with diabetes included only 48 subjects (31 who underwent RYGB and 17 who underwent gastric banding). Of those who underwent RYGB, 80.65% remained in remission from diabetes at ≥2 years whilst all patients had experienced at least improvement in glycaemic control. Less impressively, only 41% (7/17 subjects) who had undergone gastric banding remained in remission from diabetes at 2 years. Additionally, the definition of resolution or improvement of diabetes, or even the diagnosis of diabetes itself, varied significantly across the included studies. Overt diabetes was generally defined as an HbA1c of > 53 mmol/mol (7%) whilst most international organisations that accept HbA1c as a diagnostic tool currently suggest cut off values of between 45 and 50 mmol/mol, with a lower range reflective of less severe abnormalities in glucose homeostasis. Secondly, resolution of diabetes was confirmed in some studies on the basis of a measured fasting glucose without the requirement of either further testing or perhaps more robust HbA1c assessments. Improvements in diabetes control was also defined biochemically as a reduction of fasting glucose to between 5.5 -6.9 mmol/L irrespective of HbA1c. As the rationale behind glucose lowering in patients with diabetes is to prevent longer term micro and macro vascular complications, and HbA1c correlates best with the risk of these complications irrespective of day to day fluctuations in plasma glucose measurements, this approach may incorrectly attribute improvement to an otherwise unaltered state. The authors acknowledge that only 4.7% of the contributing studies were randomised controlled trials, and the level of evidence was generally poor. Only 1.6% (10/621) studies were assessed as contributing class 1 evidence (systematic reviews) as per the Oxford Centre for evidence based medicine criteria.

Yip and colleagues performed a large meta-analysis including all studies that reported on diabetes outcomes following either gastric bypass or sleeve gastrectomy. Inclusion criteria used to identify suitable studies were the recruitment of patients aged 18 years or over, the presence of type 2 diabetes prior to bariatric surgery, participants undergoing either gastric bypass or sleeve gastrectomy, and the reporting of glycaemic outcomes with specified criteria. On this basis, 2655 studies were assessed, of which 33 were considered appropriate for inclusion. The majority of these (30, 18 prospective and 12 retrospective) were not randomised, and 31/33 studies compared either gastric bypass or sleeve gastrectomy against a lifestyle/medical therapy “control” group. Two of the randomised controlled studies compared gastric bypass against sleeve gastrectomy. Reflective of the available literature reporting on diabetes outcomes following bariatric surgery, only 8/35 studies of
outcomes following gastric bypass and 1/16 studies of outcomes following sleeve gastrectomy had a duration of follow up of >12 months. Reported definitions of glycaemic outcome required an HbA1c level below a specified threshold in the absence of glucose lowering therapy.

Using this definition, diabetes remission was achieved by 67% and 56% in those who had undergone gastric bypass and sleeve gastrectomy respectively at 3 months, 76% and 68% at 12 months, and 81% and 80% at 36 months. The authors noted that the differing definition of diabetes remission used had a significant effect on reported outcomes; in those participants who had undergone sleeve gastrectomy, collective studies that defined diabetes remission as an HbA1c <6.0% (42 mmol/mol), <6.5% (47 mmol/mol) or <7.0% (53 mmol/mol) reported diabetes remission in 44.0%, 67.8% and 75.8% of participants respectively.
### Table 1-5  Summary of studies reporting long term glycaemic outcomes following bariatric surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention 1</th>
<th>Intervention 2</th>
<th>Duration of follow up</th>
<th>Study design</th>
<th>Definition of diabetes outcome</th>
<th>Diabetes at baseline (%)</th>
<th>Diabetes outcome at study end (%) based on study specific definition *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hofso et al</td>
<td>Gastric bypass</td>
<td>Lifestyle</td>
<td>12 months</td>
<td>Prospective case control</td>
<td>Complete = FG &lt;5.6 mmol/L, and 2HrG of &lt;7.8 mmol/L, and HbA1c of &lt;6.2% (44 mmol/mol) in the absence of glucose lowering therapy. Partial = FG &lt;7.0 mmol/L, and 2HrG&lt;11.1 mmol/L, and HbA1c &lt; 6.5% (47 mmol/mol).</td>
<td>26</td>
<td>29</td>
</tr>
<tr>
<td>Ikramuddin et al</td>
<td>Gastric bypass</td>
<td>Lifestyle</td>
<td>12 months</td>
<td>Randomised</td>
<td>HbA1c &lt;7% (53 mmol/L)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Kashyap et al</td>
<td>Gastric bypass/Sleeve gastrectomy</td>
<td>Medical therapy</td>
<td>12 months</td>
<td>Randomised</td>
<td>HbA1c &lt;6.0% (42 mmol/mol)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Lee et al</td>
<td>Gastric bypass</td>
<td>Sleeve gastrectomy</td>
<td>12 months</td>
<td>Randomised</td>
<td>FG &lt;126 mg/dl (7.0 mmol/L) and HbA1c of &lt;6.5% (47 mmol/mol) in the absence of glucose lowering medications</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Schauer et al</td>
<td>Gastric bypass/Sleeve gastrectomy</td>
<td>Lifestyle</td>
<td>12 months</td>
<td>Randomised</td>
<td>HbA1c &lt;42 mmol/mol with or without the use of diabetes medications</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention 1</td>
<td>Intervention 2</td>
<td>Duration of follow up</td>
<td>Study design</td>
<td>Definition of diabetes outcome</td>
<td>Diabetes at baseline (%)</td>
<td>Diabetes outcome at study end (%) based on study specific definition</td>
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<tr>
<td>Scopinaro et al</td>
<td>Biliopancreatic diversion</td>
<td>Medical therapy</td>
<td>12 months</td>
<td>Prospective historical case control</td>
<td>FG &lt;126 mg/dl (7.0 mmol/L) and HbA1c &lt;6.0% (42 mmol/mol) in the absence of glucose lowering medications</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Serrot et al</td>
<td>Gastric bypass</td>
<td>Medical therapy</td>
<td>12 months</td>
<td>Retrospective case control</td>
<td>HbA1c &lt;5.7% (39 mmol/mol) in the absence of glucose lowering medications for remission, HbA1c &lt;6.5% (47 mmol/mol) in the absence of glucose lowering medications for control</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Vidal et al</td>
<td>Gastric bypass / Sleeve gastrectomy</td>
<td>Medical therapy</td>
<td>12 months</td>
<td>Prospective comparison</td>
<td>FG &lt;126 mg/dl (7.0 mmol/L), and HbA1c 3.4-5.5% (14-36 mmol/mol) in the absence of glucose lowering medications</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Adams et al</td>
<td>Gastric bypass</td>
<td>Referred for but did not undergo surgery/ Population control</td>
<td>24 months</td>
<td>Prospective comparison</td>
<td>HbA1c and fasting glucose within the normal reference range</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kashyap et al</td>
<td>Gastric bypass / Sleeve gastrectomy</td>
<td>Medical therapy</td>
<td>24 months</td>
<td>Randomised</td>
<td>HbA1c &lt;6.0% (42 mmol/mol)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention 1</td>
<td>Intervention 2</td>
<td>Duration of follow up</td>
<td>Study design</td>
<td>Definition of diabetes outcome</td>
<td>Diabetes at baseline (%)</td>
<td>Diabetes outcome at study end (%) based on study specific definition *</td>
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<tr>
<td>Leslie et al</td>
<td>Gastric bypass</td>
<td>Medical therapy</td>
<td>24 months</td>
<td>Retrospective case control</td>
<td>Composite end point of ADA defined treatment goals (HbA1c&lt;7.0% (53 mmol/mol), LDL&lt;100mg/dl, SBP&lt;130mmHg)</td>
<td>100</td>
<td>100 38 17</td>
</tr>
<tr>
<td>Mingrone et al</td>
<td>Gastric bypass/biliopancreatic diversion</td>
<td>Medical/Lifestyle</td>
<td>24 months</td>
<td>Randomised</td>
<td>FG &lt; 100 mg/dl (5.6 mmol/L) and HbA1c level &lt; 6.5% (45 mmol/mol) for at least 1 year without active pharmacologic therapy</td>
<td>100</td>
<td>100 75 / 95 0</td>
</tr>
<tr>
<td>Sjostrom et al</td>
<td>Bariatric surgery</td>
<td>Medical/Lifestyle</td>
<td>24 months</td>
<td>Prospective case control</td>
<td>FG &lt; 7.0 mmol/L or the use of glucose lowering medication</td>
<td>100</td>
<td>100 72 21</td>
</tr>
<tr>
<td>Pournaras et al</td>
<td>Gastric bypass</td>
<td>Gastric band</td>
<td>36 months</td>
<td>Prospective comparison</td>
<td>FG &lt;7.0 mmol/L and 2hrG &lt;11.1 mmol/L and HbA1c &lt;42 mmol/mol in the absence of glucose lowering medication for &gt; 3 months</td>
<td>100</td>
<td>100 72 17</td>
</tr>
<tr>
<td>Schauer et al</td>
<td>Gastric bypass/sleeve gastrectomy</td>
<td>Lifestyle</td>
<td>36 months</td>
<td>Randomised</td>
<td>HbA1c &lt;42 mmol/mol with or without the use of diabetes medications</td>
<td>100</td>
<td>100 38 / 24 5</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention 1</td>
<td>Intervention 2</td>
<td>Duration of follow up</td>
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<tr>
<td>Pinheiro et al</td>
<td>Gastric bypass&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Gastric bypass&lt;sup&gt;b&lt;/sup&gt;</td>
<td>48 months</td>
<td>Randomised</td>
<td>Normal range glucose concentrations in the absence of glucose lowering medication</td>
<td>100</td>
<td>100 93 58</td>
</tr>
<tr>
<td>Pontiroli et al</td>
<td>Laparoscopic adjustable gastric band</td>
<td>Offered but declined laparoscopic adjustable gastric band</td>
<td>48 months</td>
<td>Prospective case control</td>
<td>FG &lt; 6.1 mmol/L, and 2hrG &lt; 7.8 mmol/L in the absence of glucose lowering medications</td>
<td>100</td>
<td>100 45 4</td>
</tr>
<tr>
<td>Adams et al</td>
<td>Gastric bypass</td>
<td>Referred for, but did not undergo surgery/ Population control</td>
<td>72 months</td>
<td>Prospective case control</td>
<td>Hba1c and fasting glucose within the normal reference range</td>
<td>NR</td>
<td>NR 62 8 / 6</td>
</tr>
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<td>Iaconelli et al</td>
<td>Biliopancreatic diversion</td>
<td>Medical therapy</td>
<td>120 months</td>
<td>Prospective case control</td>
<td>Not specified – implied that contemporary criteria for the diagnosis of diabetes used</td>
<td>100</td>
<td>100 100 45&lt;sup&gt;i&lt;/sup&gt;</td>
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<tr>
<td>Sjostrom et al</td>
<td>Bariatric surgery&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Medical/Lifestyle&lt;sup&gt;e&lt;/sup&gt;</td>
<td>120 months</td>
<td>Prospective case control</td>
<td>FG &lt; 7.0 mmol/L or the use of glucose lowering medication</td>
<td>100</td>
<td>100 36 13</td>
</tr>
</tbody>
</table>

<sup>a</sup> = Figures in parentheses represent number achieving partial/incomplete control as per study specific definitions, unless otherwise indicated, <sup>b</sup> = Diabetes outcome inclusive of participants who achieved either complete or partial remission, <sup>c</sup> = Inclusive of participants who were deemed to have achieved diabetes control defined as an HbA1c < 7.0% (53 mmol/mol) in the absence of glucose lowering medication, <sup>d</sup> = Inclusive of gastric banding, sleeve gastrectomy, and gastric bypass, <sup>e</sup> = Medical/lifestyle arm was not standardised, <sup>f</sup> = Further follow up of participants reported earlier by Schauer et al. 91% of participants available for this further analysis, <sup>g</sup> = Biliary limb of 50cm, Roux limb of 150cm, <sup>h</sup> = Biliary limb of 100cm, Roux limb of 250cm, <sup>i</sup> = Remission rate at 12 months – 120 month figure not provided, although mean HbA1c at that stage was 62 mmol/mol
1.3.3.5 Summary of glycaemic outcomes

Early improvements in glucose homeostasis were noted soon after the first bariatric procedures were performed, and a huge volume of evidence validating this phenomenon has since been published. Whilst the study quality and design has varied considerably, the overall assessment of this literature strongly supports bariatric surgery as valid treatment option, at least for glycaemic control, for obese persons with type 2 diabetes. Indeed, in well designed randomised controlled trials, bariatric surgery is far superior to conventional lifestyle and medical therapy in terms of achieving improvements in glycaemic status alone. Studies presented in this chapter that included a lifestyle/medical arm illustrate the difficulty in achieving improvements in diabetes control that could constitute remission even in a research setting; when stringent criteria for diabetes remission were applied, on average 10% or less of participants in these arms achieved diabetes remission. These findings are clearly of high importance when considering the relative benefit of bariatric surgery in comparison to other treatment options for the management of type 2 diabetes in obese persons.

The marked study heterogeneity with respect to criteria and severity of type 2 diabetes at recruitment, BMI at baseline, specific bariatric procedure performed even amongst studies purportedly studying the same bariatric modality, definitions of glycaemic outcomes utilised, and concurrent use of medical/lifestyle therapies, means that an absolute stratification of each bariatric procedure to the relative impact on glycaemic control is not possible. Nonetheless, the suggestion of a trend of increasing benefit on glycaemic control with gastric banding (diabetes remission/control at greater than 12 months follow up, seen in 17-73% of included studies), sleeve gastrectomy (11-85%), gastric bypass (24-93%), and biliopancreatic diversion (30-100%) is in keeping with the increasing weight loss seen respectively with each of these procedures in the published literature. In many respects, the interest lies in the analysis of studies reporting on sleeve gastrectomy and gastric bypass as these two procedures are perhaps more comparable than other bariatric procedures. With one exception where 85% diabetes remission rates were seen in both arms, all other studies that included both gastric bypass and sleeve gastrectomy, showed improved rates of diabetes remission in those who had undergone gastric bypass. Indeed, this relationship was preserved when one considers outcomes at each follow up interval with improved diabetes remission rates following gastric bypass at 12 months (42-93% versus 23-85% in those undergoing gastric bypass and sleeve gastrectomy respectively), 24 months (33 versus 11%, one study reported), and greater than 24 months (38 versus 24%, one study reported). Whether this apparent benefit on glycaemic outcome of gastric bypass against sleeve gastrectomy translates into clinically meaningful improvements, or is associated with favourable
diabetes related outcomes, such as improvements in micro and macro vascular complications (see section below), remains to be fully clarified, as significant reductions in body weight alone are seen following either procedure.

Understandably, many physicians treating patients with type 2 diabetes have historically been reluctant to refer these patients for bariatric surgery, given a paucity of published data on longer term outcomes, and higher long term complication rates with earlier forms of bariatric surgery. This is especially true of younger patients, where the expected long lifespan following surgery clearly increases the risk that any longer term consequences of surgery may negatively affect outcomes. The studies presented above go some way to providing reassurance in this respect, and whilst well designed studies assessing the longer term effect of bariatric surgery on glycaemic complications are needed, longer term effects on glycaemic status alone are clearly impressive when compared with other currently available therapies. At present there is no randomised data comparing outcomes beyond 36 months for bariatric surgery against lifestyle/dietary interventions or alternative bariatric procedures. Many authors feel that the more pertinent contemporary question is not if bariatric surgery should at the forefront of therapeutic strategies for obese persons with type 2 diabetes, but more “how early” it is performed. Inclusion criteria for many publically funded bariatric surgery programmes internationally select on the presence of more rather than fewer obesity or diabetes related complications; increasing evidence as to the long term efficacy and safety of bariatric procedures would surely therefore require that this approach is reassessed.

In summary, whilst the degree of improvement varies across the published literature, the evidence thus far supports a significant and clinically important durable effect of bariatric surgery on glycaemic status. Control groups included in these studies highlight the difficulty in achieving these results without bariatric surgery, even in the context of intensive research based lifestyle and medical interventions. Further research is required to assess other diabetes related outcomes, but, as per recent statements from the International diabetes federation (IDF), bariatric surgery should now be considered early in the management of obese persons with type 2 diabetes.
1.3.4 Factors predicting glycaemic outcome following bariatric surgery

A number of diabetes and non-diabetes factors have been associated with glycaemic outcome following bariatric surgery.\textsuperscript{436} Weight loss appears to be an important predictor of remission, with higher remission rates amongst those who lose more weight, and conversely, higher rates of persistent diabetes with inadequate weight loss.\textsuperscript{437,438,439,440,441} Whilst some studies have shown an association between pre-operative BMI and likelihood of remission, others have suggested that outcomes are similar in those with mild or severe obesity.\textsuperscript{440,442,443,444} Young patients appear to have higher rates of diabetes remission after bariatric surgery than older patients.\textsuperscript{442,443,445,446} Diabetes parameters at baseline are also of clear importance in predicting glycaemic outcomes after bariatric surgery. A short duration of diabetes prior to surgery has been shown in many studies to predict diabetes remission,\textsuperscript{440,443,445,447,448,449} whilst the use of insulin or sulphonylurea therapy at baseline appears to reduce the likelihood of remission.\textsuperscript{438,443,450,451} Improved glycaemic control at baseline is favourable,\textsuperscript{443,446,448} as is a higher fasting c-peptide level.\textsuperscript{440,443,446,449,452} Considering each of these variables and others, a model has been created that appears to be of use in predicting glycaemic outcomes in participants with type 2 diabetes prior to RYGB (Figure 1-5). The DiaRem model incorporates age, HbA1c at surgery, use of insulin, and type of oral antidiabetic medication used to calculate a likelihood of remission.\textsuperscript{436}

**Figure 1-5** A pre-operative diabetes remission (DiaRem) score predicting the probability of diabetes remission after RYGB surgery (reprinted from\textsuperscript{436}):

<table>
<thead>
<tr>
<th>Prediction factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
</tr>
<tr>
<td>If age &lt; 40, enter 0 →</td>
<td></td>
</tr>
<tr>
<td>If age 40–49, enter 1 →</td>
<td></td>
</tr>
<tr>
<td>If age 50–59, enter 2 →</td>
<td></td>
</tr>
<tr>
<td>If age 60+, enter 3 →</td>
<td></td>
</tr>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td></td>
</tr>
<tr>
<td>If HbA1c &lt; 6.5, enter 0 →</td>
<td></td>
</tr>
<tr>
<td>If HbA1c 6.5–6.9, enter 2 →</td>
<td></td>
</tr>
<tr>
<td>If HbA1c 7.0–8.9, enter 4 →</td>
<td></td>
</tr>
<tr>
<td>If HbA1c 9.0+, enter 6 →</td>
<td></td>
</tr>
<tr>
<td><strong>Other diabetes medications</strong></td>
<td></td>
</tr>
<tr>
<td>If not using sulfonylureas or not using ISA, enter 0 →</td>
<td></td>
</tr>
<tr>
<td>If on sulfonylureas and ISA, enter 2 →</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment with Insulin</strong></td>
<td></td>
</tr>
<tr>
<td>If not using insulin, enter 0 →</td>
<td></td>
</tr>
<tr>
<td>If using insulin, enter 10 →</td>
<td></td>
</tr>
</tbody>
</table>

DiaRem Score (sum of individual components) →

Likelihood of diabetes remission after RYGB can be calculated by totalling score:

0–2 (88–99%), 3–7 (64–88%), 8–12 (23–49%), 13–17 (11–33%), 18–22 (2–16%)
1.3.5 Impact of bariatric surgery on microvascular complications of type 2 diabetes

The effect of bariatric surgery on microvascular outcomes is important to understand so as to allow the recommendation of appropriate post-surgery surveillance. Unfortunately, the direct impact of bariatric surgery on diabetes microvascular complications is relatively under reported. Even large randomised trials conducted in this field have usually failed to report microvascular outcomes, instead focusing on glycaemic effects, mortality, and surgery related morbidity. Whilst prospective data reporting retinal outcomes exists, there is little published data thus far to address whether bariatric surgery has an impact on neuropathy and nephropathy.

1.3.5.1 Retinopathy

A rapid improvement in glucose concentrations in those with diabetic retinopathy has long been suggested to increase the risk of retinopathy deterioration. Indeed, analysis of early outcomes in the diabetes control and complications trial (DCCT) where participants with type 1 diabetes were randomised to intensive or conventional glucose control, demonstrated a two fold greater risk of retinopathy progression (13.1 versus 7.6%) in the interventional group within the first 12 months. However, this study and subsequently many others have confirmed the favourable longer term effects of intensive glucose control on retinopathy outcomes, and that these benefits outweigh shorter term risks. It is therefore reasonable to question whether the dramatic improvements in glucose concentrations commonly seen following bariatric surgery may be harmful. Indeed, occasional case reports have been published of adverse early retinal effects following surgery.

Bariatric surgery was associated with a reduction in the cumulative incidence of microvascular complications in the Swedish Obese Study at a median follow up of 10 years. Retinopathy was not worsened or improved at two years follow up in the STAMPEDE study. A study of 28 patients undergoing various bariatric procedures with established diabetic retinopathy showed improvements in retinal disease on assessment 12 to 18 months after surgery. Bariatric surgery was associated with a lower risk of progressive retinopathy compared to routine non-surgical care in a retrospective cohort study using retinal photographs, although the study did not report how long after surgery subsequent retinal assessments were performed. A recent meta-analysis including studies reporting retinopathy
changes as a primary outcome after bariatric surgery (four studies, 148 patients) suggested that patients with pre surgery diabetic retinopathy (n=68) generally had no change or an improvement in retinal features (76.5%), whilst only 8% of those with no evidence of retinopathy prior to surgery progressed after surgery.\textsuperscript{463} Nonetheless, 25% of those with pre surgery diabetic retinopathy experienced worsening of their retinal disease following surgery.

Thus, the data so far is not conclusive but outcomes from larger studies have generally supported a beneficial effect of improved glycaemic control via bariatric surgery on retinal outcomes. Ongoing retinal surveillance is likely to be required given the reasonable prevalence of persistent or progressive disease.

1.3.5.2 Nephropathy

The Swedish obese study showed an adjusted hazard ratio of 0.37 for the development of albuminuria in participants with pre-operative type 2 diabetes and normal urinary albumin concentrations undergoing bariatric surgery versus non-surgical controls. Furthermore, as noted above, a cumulative reduction in microvascular complications was evident at 10 years of follow up.\textsuperscript{459} However, participants undergoing surgery had lost a considerable greater amount of weight than those in the control groups, and weight loss has been shown to be an independent predictor of urinary albumin normalisation following bariatric surgery.\textsuperscript{464} Diabetic nephropathy resolved in 58% of participants with pre-operative microalbuminuria at 6.5 years of follow up in a study by Schauer’s group, although microalbuminuria developed in 25% of those with normal albumin excretion at baseline.\textsuperscript{465} Few other studies of bariatric surgery have reported renal outcomes; two recent reviews note that no randomised studies specifically reporting on diabetic nephropathy outcomes have been published.\textsuperscript{466,467} Presently, it is therefore prudent to continue surveillance for the development of progression of diabetic nephropathy after bariatric surgery has been performed.

1.3.5.3 Neuropathy

Fewer studies still have reported specifically on the effect of bariatric surgery on diabetic neuropathy. A pilot study reporting outcomes in twelve patients with type 2 diabetes and diabetic neuropathy undergoing RYGB showed resolution of neuropathy in 67% at 6 months.\textsuperscript{468} However, a second recent
study showed significant change in nerve conduction in patients with preoperative type 2 diabetes was noticed following RYGB.\textsuperscript{469} With the exception of the Swedish Obese Study reported above, there is little or no other published high quality data on neuropathy outcomes following bariatric surgery.

1.3.6 Impact of bariatric surgery on macrovascular complications of type 2 diabetes and obesity

Bariatric surgery is associated with a reduction in all-cause mortality, predominantly because of an apparent reduction in cardiovascular outcomes. A meta-analysis by Pontiroli et al including nearly 200,000 participants from fourteen controlled trials specifically reporting cardiovascular outcomes demonstrated a reduced risk of global mortality (odds ratio 0.48, 95% confidence interval 0.34 to 0.64) and cardiovascular events (OR 0.54, CI 0.41 to 0.70), in agreement with a previous meta-analysis on this subject.\textsuperscript{470,471} In addition, the relative risk of myocardial infarction (OR 0.46, CI 0.30 to 0.69) and stroke (OR 0.49, CI 0.32 to 0.75) were reduced following bariatric surgery.

The three major contributors to this meta-analysis were the Swedish Obese Study (SOS) and two American studies.\textsuperscript{472,473,474} Twenty eight cardiovascular deaths occurred during a median follow up of 14.7 years out of the 2010 participants who had undergone bariatric surgery in the SOS (see 1.3.3.3.3), in comparison with 49/2037 participants in the non-surgical control group (adjusted hazard ratio 0.47, CI 0.29 to 0.76).\textsuperscript{472} Furthermore, a reduction in cardiovascular events in general was observed. Adams et al reported long term cardiovascular outcomes in 7925 participants who had undergone bariatric surgery (mean follow up 7.1 years) against 7925 severely obese individuals matched for age, sex, and BMI.\textsuperscript{473} They reported a 40% relative mortality risk reduction in the surgical group, and a 56% relative risk reduction in cardiovascular outcomes (2.6 versus 5.9 per 10,000 years). Miranda and colleagues reported a death adjusted hazard ratio of 0.76 (0.60 to 0.96) at follow up of between 5.9 and 8.5 years following bariatric surgery (most of which had undergone RYGB) when compared against non-surgical controls.\textsuperscript{474}

Therefore, in contrast to the paucity of data for microvascular outcomes after bariatric surgery, it appears clear that bariatric surgery reduces mortality, with a predominant reduction in all cause cardiovascular outcomes and mortality.
1.3.7 Effect of bariatric surgery on lipids

Obesity and type 2 diabetes are strongly associated with dyslipidaemia, which contributes significantly to the increased cardiovascular risk associated with these conditions. The dyslipidaemia of obesity and type 2 diabetes is characterised predominantly by fasting and postprandial hypertriglyceridaemia, which further promotes reduced high density lipoprotein (HDL) and increased low density lipoprotein (LDL) concentrations. In obesity, increased adiposity leads to impaired lipoprotein lipase expression and reduced activity, resulting in the accumulation of free fatty acids (FFA). These FFA in turn promote hepatic triglyceride production, which consequently increases very low density lipoprotein formation. In health, insulin impairs the release of FFA from adipocytes; thus, hypertriglyceridaemia is further favoured by the insulin resistance characteristic of type 2 diabetes.

Bariatric surgery results in favourable improvements to the dyslipidaemia of obesity and type 2 diabetes. However, current evidence would suggest that a) outcomes may be different depending on the bariatric procedure, and b) the effect may be to some extent independent of weight loss. Gastric bypass has been shown to have favourable effects on triglyceride and HDL concentrations in a number of studies, although the effect is variable and may be weight dependent. Similar outcomes have been observed following SG, although LDL concentrations have not been shown to fall following either GB or SG. Schauer and colleagues reported a 28% increase in HDL concentrations and a 40% reduction in triglyceride concentrations at 12 months following SG when compared to baseline values.

In contrast, RYGB appears to be associated with favourable changes in HDL, LDL, and triglyceride concentrations. Mingrone and colleagues reported a 30% increase in HDL concentrations, a 17% reduction in LDL concentrations, and a 21% reduction in triglyceride concentrations at 24 months following RGYB. Benaiges and colleagues performed a non-randomised prospective study of 51 patients undergoing SG and 51 patients undergoing RYGB. As noted above, improvements were seen in HDL and triglyceride concentrations following procedures, although an additional significant 20% reduction in LDL concentrations was seen following RYGB. This effect was not seen in those who had undergone GB despite a similar degree of excess body weight loss during the study period. Consistent findings have been reported by Nguyen and colleagues and Woodard and colleagues, although the reduction in LDL following surgery was substantially greater in the former (74%). There is insufficient literature at the present time to adequately compare bariatric procedures with respect to effect on HDL and triglycerides. Remarkably similar improvements in both HDL and triglyceride concentrations were demonstrated at 1 year following SG or RYGB as discussed above, although the
increase in HDL concentrations was significantly greater at 1 year following SG when compared to RYGB in the study by Benaiges and colleagues. The mechanism underlying the apparently unique ability of RYGB to induce reductions in LDL is unclear, but LDL reductions have also been reported following BPD. This raises the possibility that intestinal bypass or malabsorption is beneficial with respect to LDL specific dyslipidaemia. It is interesting to note that weight outcomes have been similar in comparative studies that have demonstrated an LDL lowering effect of RYGB, suggesting that this aspect may be weight independent. Further research is required to clarify these questions.

Thus in summary, all bariatric procedures appear to have a beneficial effect on HDL and triglyceride concentrations. In addition, RYGB and BPD appear to lower LDL concentrations, whilst the effect of bariatric procedures, particularly those that are not purely restrictive, on dyslipidaemia may be independent to some extent on weight outcomes. It should be noted however, that the use of lipid lowering medication is high in populations considered for bariatric surgery. Thus, lipid lowering agent use at baseline may confound analysis of the size effect of bariatric surgery, after which these agents may be withdrawn.

1.3.8 Summary

Bariatric surgery results in significant weight loss irrespective of the chosen procedure, although weight regain may occur in some patients. Furthermore, bariatric surgery results in improvement in glycaemic control in the majority of those with pre-operative type 2 diabetes, with this effect appearing durable over many years of follow up. Longer term follow up of randomised participants is required though to alleviate concerns as to weight regain and diabetes relapse following surgery.

Bariatric surgery reduces all-cause mortality in patients with and without type 2 diabetes, and particularly reduces the likelihood of cardiovascular morbidity and mortality. One factor possibly underlying this effect is a generally favourable effect on lipid profiles. Further study is required to clarify the effects on diabetes related microvascular outcomes, although a favourable effect on retinal disease appears likely. Both weight and glycaemic outcomes after bariatric surgery far exceed those achieved by lifestyle and/or pharmaceutical therapies. There has therefore been considerable interest in improving understanding of the mechanisms underlying these improvements to both better understand the pathophysiology of each related disorder, and to explore whether these improvements can be induced in a non-surgical manner.
1.4 Mechanisms underlying the effects of bariatric surgery

In this chapter I will discuss the mechanisms underlying the effect of bariatric surgery both on weight loss and improvements in glucose homeostasis. Whilst the principles through which surgery induces weight loss have become significantly clearer over recent years, the relative importance of each of these factors requires clarification.\textsuperscript{491,492} In contrast, there remains considerable debate as to the role of various postulated mechanisms in the improvements in glucose homeostasis frequently seen following surgery.

1.4.1 Factors that reduce net caloric availability

As discussed above (chapter 1.2.1), weight loss will occur when energy expenditure exceeds energy intake. Whilst contributory, changes in energy expenditure induced through increased physical activity are proportionally small in comparison to the reduction in energy intake that can be induced through modified dietary behaviour. Thus, the fundamental aspect underlying successful weight loss is caloric restriction, and a reduction in caloric intake after bariatric surgery is a consistent finding.\textsuperscript{493,494,495} In this section I will discuss the current literature exploring the mechanism by which bariatric surgery may decrease caloric intake.

1.4.1.1 Reduced food intake

Bariatric surgery was developed with the intent of causing malabsorption, as it was assumed that a reduction in net caloric intake would be an effective method of inducing weight loss. Indeed, the earliest bariatric procedure, jejeno-ileal bypass (JIB), focused almost entirely upon this surgical goal. More recent ‘malabsorptive’ procedures such as Roux-en-Y gastric bypass additionally fashioned a reduced gastric volume, but retain the principle of gastrointestinal diversion with the intent of inducing malabsorption.

Recent research in animal models however suggest that a reduction in food intake rather than malabsorption may be the primary driver of reduced caloric availability. One study assessed weight loss in rats after RYGB, VSG, paired feeding (food intake matched to surgical groups) without surgery,
and ad lib fed rats undergoing sham bariatric surgery.\textsuperscript{496} A significantly lower body weight loss was observed at day 28 and 105 in the surgical and paired fed rats in comparison to ad lib fed rats. There was no difference in the degree of weight change across the study period between rats in the RYGB, VSG, or paired feeding groups, although the mean weight in each group from day 60-80 on was comparable to baseline. The same group have demonstrated a similar phenomenon in other studies.\textsuperscript{497,498}

Contradictory to these findings, a second group demonstrated 47% greater weight loss at 12 weeks in rats whose food intake was matched to that of rats who had undergone RYGB.\textsuperscript{499} As with the above study, rats in the paired feeding arm lost only 11% of their body weight by four weeks and had returned to baseline body weight at 3 months. Additionally, rats in the RYGB arm lost only a relatively modest 14% of their body weight. Cumulative caloric intake was reported in the surgical group in comparison to an ad lib fed sham surgery group, and whilst the net caloric intake over 20 weeks was 16.8% lower in the RYGB rodents, the cumulative intake of calories across this period was similar to that in the above study (approximately 8500 calories). A second group studied rats undergoing either JIB or a sham surgical procedure.\textsuperscript{500} The animals fed \textit{ad libitum}, but a small group of 10 rats in the sham surgery arm were instead pair fed to match food intake in the JIB group. The mechanism by which paired feeding was achieved was not reported. Whilst the paired fed rats initially displayed weight loss comparable to that seen in the JIB arm, weight regain was seen by 8-12 weeks in the paired fed group and this group had returned to baseline weight by 24-28 weeks.

Thus, it is not yet known whether a reduction in food intake alone is the primary driver of weight loss in bariatric surgery in humans, or whether a malabsorptive component provides an additional or more important element. The mechanisms by which food intake may be reduced are discussed below.

\subsection*{1.4.1.2 Reduced gastric volume}

To some extent, each of the more commonly performed bariatric procedures (LAGB/GB, SG, RYGB) involves a surgical reduction of the gastric volume and thus capacity. Stretch receptors within afferent vagal nerve endings found within the gastric musculature relay information regarding gastric lumen distension to the brain.\textsuperscript{501} As would intuitively be expected, there is evidence of a strong positive relationship between increasing gastric distension and satiety.\textsuperscript{502} Early pioneers of bariatric surgery therefore reasonably proposed that an increase in gastric stretch, induced by restricting gastric volume,
would be an important factor in successful weight loss surgery. However, there are a number of lines of argument that count against this assumption, and suggest that the beneficial effects of gastroplasty may lie outside of the resultant change in gastric volume alone.

The purest comparison to support this argument is when outcomes following GB and SG are examined. GB involves simply volume restriction, whilst SG induces both restriction and alterations in gastric mucosal food contact. Gastric volume is reduced to 15-25ml by modern laparoscopic banding techniques, and it is clear that band malfunction or slippage leading to an increase in gastric volume frequently leads to weight regain.\textsuperscript{503,504,505,506} In contrast, residual gastric volume is considerably greater following SG (80-200ml) and yet weight loss observed following SG is consistently greater than that seen following GB.\textsuperscript{507,426,428} Indeed, as discussed above (see chapter 1.3.2) early to medium term weight outcomes following SG in experienced centres are comparable to those following RYGB, yet the residual gastric volume following open or laparoscopic RYGB is usually less than 30ml. Furthermore, and in contrast to GB, an increase in the gastric volume as a result of dilatation during follow up of SG is uncommon and is not always associated with less favourable weight outcomes.\textsuperscript{508} However, studies exploring the role of sleeve size specifically in weight outcome have produced discordant results. Weiner and colleagues randomised participants to sleeve gastrectomy with a) no calibration of sleeve size, b) use of a 44fr calibration tube, and c) use of a 32fr calibration tube.\textsuperscript{509} Post-operative sleeve volume was greater in participants who had no intra-operative sleeve size calibration. Whilst early post-operative weight loss was similar between groups, participants in group B and C had lost significantly more weight at 2 years of follow up than those in group A. Net weight gain was evident in a minority of participants in group A at 5 years. In contrast a meta-analysis of 10 studies reporting outcomes following SG found no relationship between sleeve volume and weight outcomes.\textsuperscript{510} It has been hypothesized that the site of gastric resection as opposed to residual volume may be the more important factor.\textsuperscript{531} The gastric fundus is the major site of ghrelin secretion, and thus differences in the degree of fundal resection during SG may have an impact on post-operative ghrelin concentrations and thus appetite (see chapter 1.1.2.3.1 and 1.4.2.2).\textsuperscript{510,531}

It remains unclear whether residual gastric pouch size, below an upper threshold, following RYGB is a factor in weight outcomes. RYGB is performed via both open and laparoscopic techniques depending on surgeon preference, although an open procedure is required by some surgeons to fashion a smaller pouch. Studies that have reported on outcomes with both techniques have demonstrated discordant findings. Many studies have shown similar outcomes following laparoscopic RYGB in comparison to open procedures, although it is acknowledged that the technique is significantly more difficult in super
obese patients. Topart and colleagues reported outcomes following laparoscopic RYGB in 107 participants with three years of follow up. A 10-30ml gastric pouch was fashioned during surgery, and pouch dilatation was defined as >50ml at follow up. Weight loss, reported as excess body weight loss, was similar in participants with pouch dilatation versus those who did not, even though some pouches had dilated above 100ml. It should be noted however, that pouch dilation to some degree was evident in most patients during follow up without the use of a Fobi ring. In contrast, other studies have reported an association between pouch size and weight outcomes. Heneghan and colleagues reported an inverse relationship between pouch size and weight loss in 380 patients who underwent endoscopy following laparoscopic RYGB. Stoma size was also reported, and considered normal if <2cm in diameter. Participants were divided into two groups based on weight outcome. Successful weight loss was defined as excess weight loss >50% or a decrease in BMI to ≤30 kg/m². Pouch and stoma size were considered normal in all participants with successful weight loss, but only 28% in those without. Although pouch size, pouch length, pouch volume, and stoma diameter all showed an inverse correlation with excess weight loss, multivariate analysis suggested that only stoma diameter was independently associated with weight regain during follow up. Furthermore, pouch resizing appears to be an effective method of correcting weight loss failure, at least in short term follow up, in patients with pouch dilation following earlier RYGB.

In summary, significant differences in residual gastric volume are expected following GB, SG, and RYGB. However, the between procedure differences do not correlate with predicted weight loss following each procedure, and therefore a reduction in gastric volume alone is unlikely to be a primary factor in weight outcomes. The published literature is not conclusive on whether pouch size following SG and RYGB plays a role in long term weight outcomes for either procedure.

1.4.1.3 Gastric transit

Bariatric surgical procedures that incorporate gastroplasty or other gastric anatomical alterations can be expected to affect gastric kinetics. As noted above, gastric distension is known to correlate with satiety, and a reasonable expectation therefore is that a delay in gastric emptying would be a favourable outcome of bariatric surgery. To support this hypothesis, early studies of gastric transit following successful gastric bypass suggested a delay in gastric emptying of solid food using radionuclide ingestion techniques. However, gastric transit of liquid substances was, in contrast, found to be increased in these studies. This finding is supported by results of an uncontrolled study of seven

88
morbidly obese participants undergoing GB, where gastric transit was assessed using a D-xylose test before and one year following surgery. However, contradictory results have been produced by studies in animal models. Suzuki and colleagues reported delayed gastric emptying following RYGB in a rat model when compared with sham operated pair fed rodents. This finding has been reproduced by this group in a second similar study using D-xylose absorption tests. This group acknowledge that their results contrast with findings in human studies and suggest that their RYGB procedure leads to severance of the gastric-brain vagal connections that regulate autonomic gastrointestinal functions such as peristalsis, thereby effecting gut motility.

In contrast to restrictive procedures such as LAGB and SG, RYGB removes the pyloric sphincter. As an alternative rate limiting anatomical structure is not fashioned, increased gastric transit following RYGB would appear logical. Until recently however, there was a surprising paucity of literature that has specifically examined this assumption. Morinigo and colleagues performed a prospective study of 9 obese individuals who underwent RYGB. Gastric emptying was assessed in six of these participants by means of a paracetemol ingestion test, with plasma paracetemol concentrations measured at regular intervals following ingestion. RYGB was associated with a significant increase in the rate of gastric emptying. A similar technique to measure gastric emptying was employed by Falken and colleagues in a study of 12 obese individuals undergoing RYGB. Gastric emptying, expressed as paracetemol absorption, was twice as fast following surgery when compared with pre-operative assessments, and the rate difference was durable over the 12 months of post-operative follow up. A recent study of participants undergoing RYGB compared with nine healthy controls used an ingested radionuclide technique with scintigraphy to document transit of the tracer. Pouch emptying was more rapid to both food and liquid in the participants who had undergone RYGB. In addition to the above studies assessing gastric transit only, Akkary and colleagues examined whether variations in pouch emptying following RYGB may predict weight outcomes. Four hundred and five participants were recruited for the study and all underwent upper gastrointestinal endoscopy on post-operative day 1 to exclude complications of surgery. Three hundred and four participants were available for follow up at 12 months and all underwent gastric emptying studies again at this stage. Participants were then divided in to group A (normal or enhanced pouch emptying) and group B (slow or no pouch emptying). Participants in group A had a statistically significant additional body weight loss of 3kg following surgery, although it should be noted that substantial weight loss occurred in both groups (50.6 versus 47.3kg). In summary, the few contemporary studies that have sought to address the question of gastric emptying following RYGB generally report more rapid gastric transit time following this procedure. It should also be noted that the reduction in gastric emptying reported by earlier studies did not correlate
with weight loss and it is therefore possible that methodological or study design differences explain the discordancy between historical and contemporary studies.

Despite retention of the pyloric sphincter, the majority of published studies assessing gastric kinetics following SG report an increase in gastric transit, although occasional studies report contradictory results. Melissas and colleagues reported on 23 morbidly obese individuals who underwent SG at a single institution. 11 of the participants underwent studies of gastric transit before surgery and at 6 months follow up using a scintigraphic technique. Gastric emptying was significantly more rapid following surgery with an emptying half time of 47.6 versus 94.3 minutes before surgery. The percentage of food emptied from the stomach at the end of the study period was also significantly greater (75.4 versus 49.2% at 90 minutes). The same group reported outcomes at 24 months in nine of these participants and reported that this effect appears to be durable. Markers of gastric emptying were not significantly different at 24 months when compared to studies at 6 months following surgery. A second study reporting on gastric emptying in 20 obese individuals following SG showed similar results, although assessments were post-operative only and comparison was with a control group of healthy normal weight individuals. Gastric emptying of liquids (13.6 versus 34.9 minutes) and solids (38.3 versus 78 minutes) were both increased in comparison with rates in the control group. Shah and colleagues developed this study design further by studying gastric emptying in 23 individuals with type 2 diabetes who had previously undergone SG, 20 morbidly obese individuals with type 2 diabetes who had not undergone bariatric surgery, and 24 normal weight non-diabetic controls. A scintigraphic technique was employed and demonstrated significantly increased gastric emptying in the SG group compared to both the non-surgical and control groups. Additionally, intestinal transit time was found to be similarly increased by the same technique when compared with the control groups. Recently, Pilone and colleagues have reported consistent findings using a scintigraphic technique to assess gastric emptying in 45 individuals before and after SG. Pre-surgical measurements were compared against a retrospective control group of 20 individuals undergoing gastric emptying studies for other reasons.

An interesting recent study has addressed the mechanisms underlying changes in gastric motility following SG. Dynamic MRI sequences were used to acquire images of gastric transit following the ingestion of water. Participants underwent testing before surgery, and again at six days and six months following the procedure. A more rapid gastric emptying time was again suggested by this technique. This was shown to relate entirely to an accelerated peristalsis in the residual antral component, with aperistalsis observed in the sleeve. In summary, almost all studies assessing gastric transit following SG
have demonstrated a clear decrease in emptying time which appears to result from increased antral peristalsis.

In contrast to RYGB and SG, LAGB/GB does not appear to effect gastric emptying. Three recent prospective uncontrolled studied employing either scintigraphy or paracetemol absorption to assess gastric emptying, reported observations at 3-18 months following GB.\textsuperscript{536,537,538} Of these, one study compared gastric emptying measurements with weight outcomes. No difference between pre-operative and post-operative gastric emptying rates was noted in any study, irrespective of the weight loss achieved. An additional prospective study assessing the use of GB in morbidly obese adolescents again demonstrated no change in gastric emptying following the procedure.\textsuperscript{539}

There appears therefore to be a paradox; bariatric procedures that appear to increase the rate of gastric transit, and therefore intuitively less likely to induce gastric stretch, are associated with the highest and more durable rates of surgical weight loss. Indeed, this apparent contradiction is demonstrated in numerous other non-surgical scenarios where gastric transit is effected, and illustrates the complex relationship between gastric emptying and appetite/satiety. Sibutramine, a centrally acting dopamine-noradrenaline reuptake inhibitor, showed efficacy as a weight loss agent prior to its withdrawal due an apparent increased risk of cardiovascular disease.\textsuperscript{540,541} Exogenously administered versions of endogenous gut hormones have also been shown to have weight loss effects when administered at pharmacological doses (discussed in chapter 1.2.1). Each of these pharmaceutical interventions is associated with delayed gastric emptying, in direct contrast to the more rapid gastric transit seen after RYGB or SG.\textsuperscript{542} Furthermore, the intentional enhancing of gastric emptying through the use of intravenous Erythromycin, a prokinetic macrolide antibiotic, results in a reduced caloric intake during ad libitum eating when compared with a placebo control group.\textsuperscript{543}

As discussed throughout this chapter, bariatric surgery induces weight loss through a number of mechanisms, but it is interesting to note such contrasting effects on gastric transit with different weight loss interventions. Increased gastric transit results in an earlier deliverance of ingested nutrients following eating to the duodenum following SG, and to the jejunum following RYGB. It has been hypothesised that this results in favourable alterations to gut peptide secretion that may explain the apparent discordancy between gastric transit change and weight loss, and this is discussed later in this section (chapter 1.4.2)
It is therefore apparent that a) alterations in gastric transit may affect appetite and satiety and therefore caloric intake, but that this relationship is complex, and that b) the increased gastric transit seen after RYGB and SG is likely to be only a minor contributor to total weight loss.

1.4.1.4 Malabsorption

Whilst less of a factor in the weight loss effects of bariatric surgery than initially assumed, it is clear that malabsorption occurs after both RYGB and BPD but not LAGB or VSG. However, the absorption of macronutrients appears to remain reasonably intact following RYGB; small studies have measured similar absorption of fat, protein, and carbohydrate before and up to 14 months after RYGB.\textsuperscript{544,545} Up regulation of intestinal glucose transports may ameliorate the carbohydrate malabsorption that may otherwise occur following this procedure.\textsuperscript{546} Clinically relevant protein malabsorption is seen only rarely and may necessitate revisional surgery.\textsuperscript{547,548} BPD likely induces a degree of fat malabsorption, and although it is unclear whether this is a factor is the more significant and durable weight loss seen after this procedure than other forms of bariatric surgery.\textsuperscript{396, 549, 550} In contrast, malabsorption of micronutrients including iron, vitamin B12 and D, and calcium is frequently encountered following both before and after RYGB and BPD but does not contribute to weight outcomes.\textsuperscript{551}

1.4.1.5 Eating behaviour

There is some evidence that food choice is effected by bariatric surgery, although the published literature is not conclusive. Animal models present a more objective method of quantifying food choice than studies in humans, as they are less susceptible to the influence of other behavioural or social factors affecting decisions. In general, animal models support a reduced preference for fat intake following RYGB. Zheng and colleagues studied food behaviour in a rat model undergoing RYGB or sham surgery.\textsuperscript{552} Rats were observed for 15 weeks prior to surgery and four months after, and at all times had \textit{ad libitum} access to a low fat (10%) or high fat (60%) liquid solution, and a low and high fat chow. Following surgery, the rats were studied at 2-3 weeks (acute phase of weight loss) and at 16-20 weeks (chronic phase). Rats in the sham surgery group, and an additional no surgical control group, showed high preference for the high fat liquid at each time point (96% preference). There was a slight reduction (86%) in high fat preference in the RYGB group within the acute phase, but a clear and statistically
significant difference (58%) by the chronic phase. Rejection of high fat chow was absolute in those rats who had undergone RYGB at all times following surgery, whilst sham or control rats again demonstrated preference for high fat chow.

A second study by le Roux and colleagues agrees with these findings. Twenty six rats were randomised to RYGB or a sham procedure. Prior to surgery the animals had ad lib access to three equal sized portion of two high fat chows (60% fat) and on normal chow (2% fat). A food preference assessment was conducted at week eight of life (pre-surgery) and at 10 days following surgery. Sham rats maintained similar preferences for each food option before and after surgery, with the low fat chow accounting for 3-5% of total food intake. In contrast, rats that had undergone RYGB showed an increased preference for low fat chow at 10 days from 3.2% to 14% of total diet, whilst reducing their intake of both high fat chows by approximately 40%. The overall intake of food remained the same before and after surgery in the sham group, but reduced by 37% in the RYGB group. In addition, the RYGB animals showed less preference for a fat solution following surgery than the sham animals.

Human studies have provided less clear results, partly because of significant methodological differences between studies. Nonetheless, the majority of studies support that a reduction in preference for fat, substituted by a proportional increase in carbohydrate, is seen following RYGB. Brolin and colleagues performed a prospective study of food intake before and after VBG and RYGB. The choice of surgery modality was based on the pre-operative eating habits of the participant. Caloric intake fell dramatically following surgery (pre-operative caloric intake = 3120 for VBG and 2601 for RYGB) although increased again at each six month post-operative assessment for both groups. However, daily caloric intake at 36 months remained well below baseline at 1753 calories/day for VBG and 1386 for RYGB. Fat intake was significantly reduced at most post-operative assessments for both procedures when compared with pre-operative intake. Whilst not significant, the authors reported that the reduction in fat content was compensated by a small increase in both protein intake (for RYGB) and carbohydrate content (for both procedures). Indeed, at 36 months following RYGB, fat and carbohydrate intake was statistically significantly lower and higher respectively than at the pre-operative assessment.

Most patients who have undergone bariatric surgery can very readily identify a number of food substances that they have learnt to avoid, to avert undesirable outcomes. It is therefore probable that changes in food choice behaviour following bariatric surgery develop partly as a result of symptoms experienced whilst eating, possibly alongside alterations in higher cerebral centres regulating food choice. Indeed, Olbers and colleagues demonstrated the effect food intolerance has on food choice in
a prospective study of participants randomised to RYGB or VSG. Participants who had undergone RYGB consumed a significantly lower daily quantity of fat post-surgery, although the mechanism for this was not examined. In contrast, participants who had undergone VSG restricted the intake of meat and vegetables and increased the intake of energy dense liquid products, an unfavourable phenomenon which has been demonstrated in other studies. A prospective study of a food intolerance questionnaire in participants who underwent either RYGB or AGB showed that increased food intolerance was evident at three months following both procedures, when compared with baseline results in obese and non-obese controls. The questionnaire did not investigate intolerance of specific products. Interestingly, food intolerance scores at 12 months following RYGB were not significantly different again to control scores, whilst participants who had undergone gastric banding had increasing food intolerance over the seven year study period. A second prospective study used an alternative questionnaire that sought to associate specific food products with adverse symptoms. Participants undergoing LAGB, VSG, RYGB, or BPD were assessed at 3-6 months, 6-12 months, or greater than 12 months. Participants who had undergone LAGB had the highest rate of food intolerance at all time periods, and displayed the highest scores of food intolerance for all eight food product categories: red meat, white meat, salad, vegetables, bread rice, pasta, and fish. As with the above study, participants in this study who had undergone VSG, RYGB, or BPD experienced a short term increase in food intolerance, with gradual improvement thereafter. There was no significant difference with respect to tolerance of most food products between procedures, although red meat was better tolerated by participants who had undergone VSG.

Dumping syndrome describes symptoms that result from the ingestion of high osmolar foods including those that are sugar rich, although the mechanism of this effect remains unclarified. It has been assumed that the more rapid deliverance of this food to the intestine as a result of altered anatomy, and the resultant significant fluid shift from the intestinal wall to the lumen, was responsible. However, recent studies suggest that hypersecretion of gastrointestinal peptides in response to this food load stimulate the recognised symptoms of dumping syndrome. Symptoms vary from person to person but include light-headedness, flushing, tachycardia, nausea and vomiting, and diarrhoea which typically occur within 30 minutes of eating. Whilst the syndrome is unpleasant, it is considered a beneficial effect of surgery by many authors due to the positive change in eating behaviour often taken by the patient to avoid episodes. Dumping syndrome occurs in up to 76% of all patients who undergo RYGB, although the longer term frequency is unknown. The syndrome is also seen in patients who undergo BPD, but is not seen in those who undergo GB procedures. The majority of studies have not shown an increased risk of dumping syndrome following gastroplasty procedures.
There is some evidence to suggest that bariatric surgery induces changes in the sensation of taste, which may be a further factor modulating eating behaviour following surgery. 82% of those who underwent RYGB reported subjective changes in taste sensation following surgery, as opposed to 46% of those who had undergone AGB. To support this finding, a small study that assessed the threshold at which participants could detect various taste before and after RYGB, showed an apparent increased acuity for bitter and sour, and saltiness at the expense of sweet tastes. Other studies since have supported this finding, and many surgeons will accordingly counsel pre-operative patients as to the likelihood of this change. A recent study designed to assess taste acuity in rats following gastric bypass, came to same conclusion. However, the group used two bottle choice and lick tests which may not accurately differentiate between taste thresholds and how much the animal prefers one product. Indeed, the degree to which taste thresholds have been reported to change in most studies, falls below conventionally accepted thresholds at which taste perception is altered in healthy humans.

Favourable changes in the “reward” achieved through the consumption of specific food products following bariatric surgery is also suggested by recent research. A lick test can used to assess this in rats although care must be taken to differentiate whether the animal can actually taste the stimuli, a test of taste acuity, rather than like or dislike the food. Several studies have demonstrated a decrease in lick rates for sucrose or sugar in rats following gastric bypass. In humans, use of a questionnaire that assesses hedonistic appetite (i.e. the desire for food in the absence of a physiological need), suggests that gastric bypass may have a favourable reductive effect. Participants who had undergone gastric bypass were compared against a non-obese and an obese control group. Overall, participants who had undergone gastric bypass recorded concentrations of hedonistic appetite of that were not significantly different from the non-obese control group, in contrast to the higher scores seen in the obese controls. As would be expected with such sub conscious food behaviour alterations, changes in the function of the mesolimbic “reward” cerebral pathways have been demonstrated using functional MRI techniques. Ochner and colleagues demonstrated significantly reduced activation of this pathway by high density foodstuffs following gastric bypass, although no control group was employed.

1.4.1.6 Changes in central nervous system energy homeostasis

Given the central role of the hypothalamus in energy homeostasis (chapter 1.1.2.2), it is tempting to conclude that the significant and durable weight loss induced by bariatric surgery must entail
favourable effects on central nervous systems. Indeed, clinical studies exploring the use of bariatric surgery for obesity related to hypothalamic dysfunction have occasionally supported the effects of this intervention under these circumstances. Craniopharyngiomas are predominantly low grade tumours located within the hypothalamus or pituitary sella, and invasion of the tumour itself or surgical intervention frequently leads to hyperphagia and obesity. A meta-analysis in 2013 identified 21 patients with craniopharyngioma undergoing LAGB, VSG, RYGB, or BPD and demonstrated mean weight loss of 20.9kg at 6 months. However, weight loss in other hypothalamic disorders of obesity have been less impressive. Prader-Willi syndrome is a complex genetic disorder resulting in hyperphagia and severe obesity; bariatric surgery results in modest weight loss only (less than 5%) and appear to have a high frequency of weight regain.

Studies in rodents have supported a possible direct effect of bariatric surgery on the hypothalamic circuitry. RYGB/VSG rats have diminished hypothalamic activation during food restriction than non-surgical or sham procedure controls. Furthermore, Aslan and colleagues reported the outcome of LAGB in an adolescent human with complete functional loss of the MC4R gene due to a heterozygote mutation, and consequent severe obesity. Whilst initial weight loss was observed, this individual experienced later weight regain, supporting the hypothesis that some of the longer term favourable effects of bariatric surgery may be mediated by central nervous system changes. Neuroimaging studies using functional magnetic resonance imaging have also suggested relative increases in hypothalamic activity in response to food imagery in obese women in comparison to those who have undergone RYGB. Whilst not matched by BMI, women who had undergone RYGB had similar functional hypothalamic responses to normal weight control women. Whilst few studies have been performed exploring this possibility in more detail, VSG does not appear to directly affect hypothalamic functions in a rodent model. Stefater and colleagues reported no differences in the expression of a number of appetite regulating hypothalamic neuropeptides after VSG, sham VSG, or diet controlled obese rats. Thus, at present, and as a result of a limited literature, there is little strong evidence to suggest a direct effect of bariatric surgery on the hypothalamic centres regulating appetite, although this is question worthy of further study.

1.4.1.7 Changes in energy expenditure

Energy expenditure (EE) is the sum of physical activity and non-resting energy expenditure (PA, 30% of total EE), the thermic effect of food (TEF, 10%) reflecting energy expended during digestion, and resting
energy expenditure (REE) or basal metabolic rate (60%) which is the energy required to maintain physiological activity. In humans, REE increases with weight gain and decreases with weight loss, and has long been postulated as a major factor underlying the presence of an apparent defined body weight set point. The reduction in REE in response to caloric restriction induced weight loss is similar in men and women, and is most apparent early after commencement of weight loss. Furthermore, the reduction in REE appears to vary depending on the intervention used to induce caloric restriction. Therefore, when investigating changes in EE and REE after bariatric surgery, changes should be compared against weight loss matched individuals; the significantly greater weight loss experienced after bariatric surgery makes recruitment of a suitable control group difficult.

The literature on this topic is conflicting however, and reflects the great technical difficulties encountered when attempting to accurately measure energy expenditure. The gold standard method is to measure heat loss during containment in a sealed room, but this technique is limited by the availability of these facilities. Indirect calorimetry instead provides an estimate of EE through measurement of oxygen consumption and carbon dioxide production, but again is impractical outside of research settings. A number of equations have been proposed that estimate EE by considering factors including weight, height, age, gender, and then multiplying predicted REE by a PA coefficient. However, each calculation is validated in specific populations and may not therefore provide accurate estimations of REE in unselected groups.

Studies exploring the effect of bariatric surgery on energy expenditure, perhaps limited by these methodological considerations, have reported contrasting results. Earlier assessments of EE in humans after LAGB and BPD supported a decrease in total EE and REE that was proportional to body weight loss. However, studies in rodents have often demonstrated the opposite effect, and furthermore, that this may be dependent on the bariatric procedure utilised. RYGB increases total energy expenditure in rats when compared against sham operated animals, explained by contributory increase in both REE and TEF. More recently, a number of studies have reported favourable changes in REE in humans following RYGB/BPD but not VBG, suggesting that this may partially explain the differences in weight loss and subsequent weight regain seen after each procedure. Using indirect calorimetry, an increase in TEF and energy expenditure during PA following BPD was reported in 20 participants randomised to either BPD or diet induced weight loss. A second study including six obese females undergoing RYGB showed a decrease in total EE and REE following RYGB. However, TEF increased as did the respiratory quotient when assessed 20 months after surgery. The same group have shown similar results at longer term follow up when comparing seven participants who had
undergone RYGB against seven participants who had undergone VBG; despite matched body composition and weight before and after (nine years) following surgery, an increase in TEF by indirect calorimetry was noted in those who had undergone RYGB and explained the greater total EE when compared to those who had undergone VBG. Dirksen and colleagues recently assessed factors underlying differences in weight outcomes in 33 patients deemed to have either good or bad weight outcomes after RYGB. In contrast to results reported above, differences in energy expenditure in each group were explained by weight loss and did not predict outcomes.

In conclusion, the current evidence supports weight loss associated decreases in total EE after bariatric surgery, but suggests that an increase in TEF may be seen after RYGB and BPD. Further studies are required to confirm this finding, and to clarify the role of this factor in weight loss and the subsequent variation in weight regain seen with different bariatric procedures.

1.4.1.8 Summary of factors that reduce caloric intake (see also chapter 1.5)

It is clear that there are a number of factors that reduce caloric intake following bariatric surgery, although eating behaviour in particular is hard to study. Overall, the available evidence would suggest that bariatric surgery:

- Leads to a reduction in food intake which, as opposed to any malabsorption induced by the procedure, may be the major factor resulting in a net reduction in caloric availability.
- Leads to a reduction in gastric volume, although this alone may not be a major factor determining weight outcomes.
- Increases the rate at which ingested food and liquid transits the stomach (RYGB and SG) and intestine.
- Reduces the preference for high fat (RYGB) and high density calorie food stuffs, reduces the taste acuity for sweet foods, and reduces the cerebral reward available by consuming these products.
- May reduce hypothalamic activity in response to food, but few studies exploring this area have yet been performed.
- Rodent and human studies suggest that RYGB may increase the thermic effect to food, although the role of this effect is as yet unclear.
1.4.2 Gut peptide adaptations following bariatric surgery

Predictably, the release of a number of gut and adipocyte peptides is altered by bariatric surgery (Table 1-6). In this section, I will present the available literature documenting these changes, and conclusions from the available evidence as to the role each plays in weight loss following bariatric surgery. The physiology of each peptide is discussed above (1.1.2.1.1 and 1.1.2.3).

Table 1-6 Summary of gut peptide responses to non-surgical and surgical weight loss

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Obesity</th>
<th>Non-surgical weight loss</th>
<th>After bariatric surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>Proportional to adipose mass</td>
<td>Decreased concentrations</td>
<td>Decreased concentrations</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>Fasting concentrations are decreased. Attenuation of the normal suppression of ghrelin by food intake.</td>
<td>Increased in both fasted and fed state</td>
<td>Increased after LAGB. Conflicting reports after VSG and RYGB</td>
</tr>
<tr>
<td>CCK</td>
<td>Reduced postprandial concentrations</td>
<td>Reduction in post-prandial concentrations below those seen in obesity</td>
<td>Increased post prandial concentrations</td>
</tr>
<tr>
<td>GLP-1</td>
<td>No effect on fasting concentrations. Attenuation of normal post prandial increase.</td>
<td>No clear change</td>
<td>Increased post prandial concentrations after VSG, RYGB, BPD. No change after LAGB. No change in fasting GLP-1 concentrations</td>
</tr>
<tr>
<td>GIP</td>
<td>No effect</td>
<td>Increased post prandial concentrations</td>
<td>Stable or decreased fasting concentrations after RYGB. Most studies report a reduced post prandial response after RYGB. Not affected by LAGB</td>
</tr>
<tr>
<td>PYY</td>
<td>Reduced fasting and post prandial concentrations</td>
<td>Reduction in fasting and post prandial below those seen in obesity</td>
<td>Increased post prandial concentrations after RYGB, VSG, BPD. No change after LAGB. No change in fasting PYY concentrations</td>
</tr>
</tbody>
</table>
1.4.2.1 Leptin

In keeping with non-surgical weight loss, Leptin concentrations fall significantly following bariatric surgery. This has been demonstrated after LAGB,\textsuperscript{602, 603, 604} VSG,\textsuperscript{605, 606, 607} RYGB,\textsuperscript{602, 603, 604, 605, 606, 608, 609, 610} and BPD.\textsuperscript{607, 611} However, it is unclear whether the reduction in leptin following each procedure is simply a reflection of the associated weight loss, or whether there may be procedure specific differences. The decrease in leptin concentrations has been reported to be greater after RYGB than weight matched dietary weight loss,\textsuperscript{602, 610} whilst other studies have reported a greater relative reduction in leptin concentrations after RYGB than after either LAGB or VSG.\textsuperscript{602, 603, 605} Studies in rodents have shown greater reductions in leptin concentrations after VSG in comparison to pair fed animals of matched body weights.\textsuperscript{612} In contrast, other reports have shown no clear differences in the reduction in leptin concentrations after RYGB, VSG, or LAGB.\textsuperscript{604, 606, 613}

Thus, whilst a number of studies support an exaggerated effect of RYGB (and possibly VSG) on the reduction in leptin concentrations, this is not confirmed, and study of this question is difficult due to differing weight loss rates and final weight between procedures. Furthermore, whilst a reduction in leptin with dietary loss is a factor underlying the propensity for weight regain due to increased appetite, weight regain after bariatric surgery is less significant. As discussed above (chapter 1.4.1.1) appetite is reduced and satiety increased after RYGB and VSG in both humans and animal models. It has therefore been proposed that an improvement in hypothalamic leptin sensitivity induced by bariatric surgery may be at play.\textsuperscript{614} However, whilst the sensitivity to infused exogenous leptin is increased in rats after VSG, the expression of hypothalamic leptin responsive genes is unchanged, and a similar improvement in leptin sensitivity is seen after matched caloric reduction weight loss.\textsuperscript{612} Therefore the available evidence currently would suggest that the reduction in leptin following bariatric surgery is a reflection of the associated fat weight loss, and that any improvement in leptin sensitivity is simply a consequence of this weight loss.

1.4.2.2 Ghrelin

The role of changes in Ghrelin concentrations after bariatric surgery as a factor in weight loss remains controversial. As discussed above (chapter 1.1.2.3.1), ghrelin is produced predominantly in the gastric fundus; thus, procedures that either remove the fundus or exclude it from exposure to ingested nutrients may be predicted to reduce circulating ghrelin concentrations. Indeed, multiple studies report a decrease in circulating ghrelin concentrations after SG.\textsuperscript{615, 616, 617, 618} Furthermore, gastric banding results in either no change or an increase in circulating ghrelin, similar to changes after dietary...
induced weight loss. In contrast, the published literature on the effect of RYGB on ghrelin reports variable outcomes; some publications support a reduction of circulating ghrelin concentrations after RYGB, whilst others report no change. Whilst one study showed an early significant reduction in ghrelin after RYGB and VSG, ghrelin concentrations had risen again at three months follow up in those who had undergone RYGB, although remained significantly lower than controls. One possible explanation for this discordancy is differences in surgical practice with respect to the bypassed gastric tissue. However, one study comparing ghrelin concentrations following either standard RYGB or RYGB with resection of the bypassed stomach, showed no significant differences in either circulating ghrelin concentrations or subsequent weight loss.

Furthermore, there are considerable technical difficulties to consider when evaluating studies reporting ghrelin outcomes after bariatric surgery. Whilst methodological concerns are present, of primary importance is the measurement of ghrelin as total ghrelin rather than acylated and des-acylated constituents. As discussed above (chapter 1.1.2.3.1), GOAT mediated acylation of secreted ghrelin is required for ghrelin to bind to the GHSR and exert its actions. Therefore, compensatory increases either in the expression of GOAT or the GHSR could nullify any reductions in secreted ghrelin. To support this concept, some studies have shown no changes or even increased acylated ghrelin specifically after VSG and RYGB. Additionally, VSG results in comparable weight loss in ghrelin knockout and wild type mice. Thus, these data would suggest that ghrelin plays little role in weight loss after bariatric surgery. In contrast, recent studies have reported reductions in acylated ghrelin following RYGB in humans, and furthermore have shown that higher post-surgical fasting total ghrelin predicts weight regain.

In conclusion, the available literature does not conclusively determine whether a reduction in ghrelin following either VSG or RYGB contributes significantly to the weight loss resulting from each of these procedures, and further research is required.

1.4.2.3 Cholecystokinin (CCK)

CCK concentrations following bariatric surgery have been reported in only a handful of studies. Gastrectomy, RYGB, and JIB appear to increase both the post prandial CCK peak and the post prandial AUC CCK. CCK secreting I cells appear to be present in higher numbers in the rat intestine following RYGB, due to hyperplasia of the intestine exposed to nutrients. It is therefore possible that the elevated post prandial CCK concentrations are simply a marker of increased I cell exposure, and may not factor in weight loss outcomes. Indeed, one study comparing participants with good and poor
weight loss after RYGB, reported a more marked post-surgery increase in CCK concentrations in those who had lost less weight.  

1.4.2.4 Glucagon-like peptide-1 (GLP-1)

GLP-1 concentrations rise after bariatric surgery in the post prandial phase, but remain unchanged in the fasting state. This has been demonstrated clearly after RYGB, and BPD. LAGB appears to have little effect on GLP-1 concentrations. Matched weight loss through dietary means does not result in comparable increases in post prandial GLP-1 concentrations, suggesting that the increase in post prandial GLP-1 relates directly to the surgical procedure. However, the mechanism of increased GLP-1 secretion after meals following these procedures is unclear. Two suggested mechanisms have been proposed relating to foregut or hindgut factors. The foregut hypothesis proposes that surgical bypass of a factor integral to the proximal intestine directly leads to an increase in GLP-1 secretion, although no such factor has as yet been identified. The hindgut hypothesis instead proposes that increased distal intestine exposure to nutrients results in increased GLP-1 secretion. The evidence from studies published recently would suggest that a mixture of these factors is more likely to be present. Firstly, and in support of the hindgut hypothesis, an increase in GLP-1 secretion occurs after SG to an extent that may be comparable to RYGB and BPD, suggesting that proximal bypass is not important. Secondly, the rate of gastric pouch emptying and intestinal transit are both positively associated with the rise in post prandial GLP-1 concentrations after bariatric surgery, supporting increased delivery to the distal gut as a factor in GLP-1 secretion. Thirdly, studies in rats and humans have shown an increase in the density of distal gut GLP-1 secreting cells following RYGB.

Nonetheless, the lack of GLP-1 change following LAGB suggests that some degree of proximal gastrointestinal anatomical alteration may still be required to induce the observed changes in GLP-1 secretion. Furthermore, deliverance of nutrients after RYGB into the bypassed gastric remnant in humans does not result in the same increase in post prandial GLP-1 concentrations as when nutrients are delivered via the oral route. Dirksen and colleagues describe a case of a patient with type 2 diabetes, who developed symptoms consistent with a gastrojejunostomy leak on the second day after RYGB. Consequently a percutaneous gastric tube was inserted into the bypassed gastric remnant. Administration of a glucose challenge via the oral route resulted in a five fold greater rise in post prandial GLP-1 secretion when compared with administration via the gastric tube. A second similar case, where post RYGB refractory hyperinsulinaemic hypoglycaemia required gastric remnant feeding
resulted in similar attenuation of the GLP-1 response.\textsuperscript{645} It is therefore clear that the precise mechanisms underlying the increased post prandial GLP-1 response to a meal following bariatric surgery remain to be elucidated.

Irrespective of the mechanism of release, it is currently unclear whether an increase in post-prandial GLP-1 concentrations is an important factor underlying weight loss seen following bariatric surgery. As discussed above (1.2.2) the pharmacological administration of GLP-1 agonists results in modest weight loss in humans. Le Roux and colleagues showed that patients who had lost less weight following RYGB had an attenuated post prandial GLP-1 response when compared with patients who had lost greater amounts of weight.\textsuperscript{659} Furthermore, the administration of a GLP-1 agonist to mice following gastric banding resulted in augmented weight loss; further studies are required to determine whether GLP-1 agonism alone could overcome the differences in weight loss between banding and other bariatric procedures.\textsuperscript{646} However, little research has yet been performed exploring the direct effect of increased post prandial GLP-1 secretion on reduced food intake following bariatric surgery. Furthermore, studies in GLP-1 receptor knockout mice have recently produced surprising results. Knockout mice undergoing either VSG or RYGB lost a comparable amount of weight and maintained this weight loss over the follow up period.\textsuperscript{647,648}

In conclusion, GLP-1 concentrations predictably increase in the post prandial phase following bariatric surgery. However, the currently available literature does not definitively define either the mechanism of this increase, or the role increased GLP-1 concentrations play in weight loss following bariatric surgery.

1.4.2.5 Gastrointestinal glucose dependent peptide (GIP)

Changes in GIP do not appear to be important in weight outcomes following bariatric surgery on the basis that significantly variable GIP responses to surgery have been reported by multiple studies reporting similar effects on weight. Indeed, concentrations appear not to be effected at all by LAGB, whilst fasting concentrations appear unchanged or reduced after RYGB and VSG.\textsuperscript{649,650} Bariatric procedures which bypass the duodenum and jejunum, thereby preventing exposure of the GIP secreting K cells to ingested nutrients, might be expected to produce reduced post prandial GIP responses. Most studies have indeed demonstrated this, whilst pre-operative type 2 diabetes appears to predict this reduction.\textsuperscript{649,651,652,653,654} A small number of studies have reported an exaggerated post prandial GIP response following RYGB.\textsuperscript{655,656}
1.4.2.6 Peptide YY (PYY)

PYY secretion in response to a meal is increased after RYGB, LAGB, and sleeve gastrectomy. In contrast, LAGB does not appear to significantly affect post prandial PYY concentrations, and certainly has less of an effect than RYGB. Fewer reports exploring PYY changes after BPD have been published, but generally support a similar favourable change to that seen with RYGB and VSG. One study reported a greater rise in post-prandial PYY concentrations after BPD when compared with RYGB. With a few exceptions, most studies have shown no differences in fasting PYY concentrations between surgical and non-surgical participants.

The mechanism of increased PYY secretion remains unclear but as with CCK above, may relate to an increased density of PYY secreting cells in the intestine following bariatric surgery. Furthermore, an increase in post-prandial PYY could plausibly explain some of the weight loss effects of bariatric surgery. Morinigo and colleagues showed that an early increase in post-prandial PYY concentrations after RYGB positively predicted weight outcomes at 32 months. In a further study, participants who had lost the most weight had greater increases in post-prandial PYY concentrations than those who had responded poorly to bariatric surgery. Weight regain after initial losses has been associated with an attenuation of increased post-prandial PYY concentrations over time. This favourable change is unlikely to relate to weight loss alone, as post prandial PYY concentrations are significantly greater than those seen in weight matched non-surgical participants achieving weight loss by dietary restriction. In addition, PYY knockout mice lose significantly less early weight after gastric bypass than diet matched wild type littermates.

In conclusion, it is likely that the increase in post-prandial PYY concentrations after RYGB, VSG, and BPD is a factor in the increased satiety observed after these procedures, and contributes to both weight loss and subsequent weight maintenance. Further research will determine the relative contribution of PYY to weight loss and the mechanism of increased PYY secretion.
1.4.3 Gut microbiota

The first attempt at metagenomic sequencing of the microbiome of the human distal gut was performed in 1996 with just one subject. Multiple similar studies have been performed since in participants from different populations and states of health, culminating in the recent Human Microbiome Consortium Study which provided for the first time metagenomic sequencing data of the distal gut microbiota from a large population sample (242 health Western subjects). Bacteroidetes (Bacteroides/Privatella) and Firmicutes (Clostridium/Lactobacillus) species predominate. It therefore became possible for observations to be made regarding the pathogenic role that gut microbiota may play in obesity. An increase in the ratio of Firmicutes to Bacteroides numbers is seen in the distal gut of obese humans compared to those of normal weight; conversely, a relative increase in the population of Bacteroides is seen in when these individuals lose weight. Furthermore, exposure of a normal weight mouse model to a high energy/high fat diet resulted in a demonstrable increase in the Firmicutes to Bacteroides ratio in the distal gut, whilst germ free mice subsequently exposed to this microbiome via faecal transplantation gained significantly more adiposity than germ free mice exposed to the microbiome of mice administered a low fat/plant polysaccharide rich diet. Thus, the constituents of the gut microbiota appear to be response to environmental changes, pathogenic in the development of obesity, and transfer the potential for diet induced adiposity.

Few studies have thus far been performed reporting on the effect of bariatric surgery on the gut microbiome. However, striking similarities in results are noted in both human and rodent studies. SG in humans increased the Bacteroides to Firmicutes ratio in comparison to participants who obtained matched weight loss through a dietary intervention. Li and colleagues documented the expected reduction in the Firmicutes to Bacteroides ratio in non-obese mice undergoing RYGB or sham surgery. However, the post-surgery microbiome was dominated by Proteobacteria, a finding also observed by Zhang and colleagues in human subjects after RYGB. This microbiome has not previously been observed in non-surgical healthy or obese populations. Furthermore, colonization of germ free mice with gut microbiota obtained from mice who had previously undergone RYGB or VBG resulted in reduced fat deposition and a reduction in the utilisation of carbohydrate as an energy source. Finally, the peri and post-operative administration of Proteobacteria probiotics to humans undergoing RYGB resulted in greater weight loss at six and 12 weeks.
1.4.4 Mechanisms underlying the improvements in glucose homeostasis following bariatric surgery

Weight loss by any means results in improved glucose homeostasis. It is therefore evident that many of the mechanisms underlying improvements in dysglycaemia following bariatric surgery are weight loss dependent. However, dysglycaemia improves early after bariatric surgery, and before any measureable weight loss, whilst the bariatric surgery improves diabetes control significantly more effectively than any other current therapeutic option. In the following section I will discuss those factors that are currently proposed to underlie the favourable effects of bariatric surgery on glucose homeostasis.

1.4.4.1 Caloric restriction leads to early improvements in hepatic insulin sensitivity

RYGB improves insulin sensitivity, as measured by HOMA-IR, within four weeks prior to significant weight loss.619,650,683,684 Indeed, a number of studies have shown improvements within the first post-operative week.685,686 Furthermore, insulin sensitivity as measured by the hyperinsulinaemic euglycaemic clamp (HEC), insulin tolerance test, or HOMA-IR is clearly improved from baseline measurements six to 12 months after surgery, by which time substantial weight loss has occurred.687,688,689 In contrast, insulin sensitivity is not changed within four weeks when measured using the HEC.688,690,691 This apparent discordancy may be explained by the differing information provided about insulin resistance by HOMA-IR and the HEC; whilst the HEC primarily reflects peripheral insulin resistance, HOMA-IR is a measure of hepatic insulin sensitivity only.692 HEC can be combined with tracer studies to assess hepatic glucose output, and studies utilising this technique have reported reductions in hepatic glucose production six months or more after RYGB.693,694 However, the current literature reporting specifically on hepatic glucose production in the first few weeks after RYGB is inconclusive. Two studies, reporting changes in hepatic glucose production using an HEC tracer technique at seven days and one month following RYGB, show a reduction in hepatic glucose production without changes in peripheral insulin sensitivity.695,696 However, two further studies reported no change in hepatic or peripheral insulin sensitivity using the same technique at 12 to 20 days after RYGB.594,697 It should be noted however that the number of participants in the study by Camastra et al was only 11, and a trend towards reduced endogenous glucose production (p=0.13) was noted, whilst endogenous glucose production (but not hepatic insulin sensitivity) was reduced at two weeks in the study by de Wijer et al.
Overall, the available evidence would support that hepatic glucose production is reduced and hepatic insulin sensitivity is increased within days/weeks of RYGB, whilst peripheral insulin resistance improves only with weight loss.

It has long been known that non-surgical caloric restriction leads to rapid improvements in glucose homeostasis, often evident prior to weight loss. Henry and colleagues recruited 30 obese individuals with type 2 diabetes and restricted caloric intake to 330 kcal/day for 40 days. Despite steady and progressive weight loss over this period, there was an early improvement in glucose homeostasis reflected by significant decreases in fasting glucose and hepatic glucose production. Indeed, near maximal reductions in both of these parameters were evident after only 10 days of caloric restriction, at which point participants had lost a mean of only 4.6 of the 10.5kg they lost over the 40 day period. Furthermore, a subgroup of participants who were observed during refeeding demonstrated significant early increases in both fasting glucose and hepatic glucose production. A second study compared caloric restriction of 400 or 1000 kcal/day in obese participants with type 2 diabetes. Participants randomised to 400 kcal/day had more significant and early improvements in fasting glucose and insulin sensitivity despite comparable weight loss. Interestingly, when these participants were subsequently provided with 1000 kcal/day, increases in both fasting glucose and insulin resistance above those observed in participants who had been on 1000 kcal/day for the duration of the study were observed. More recently, the mechanism underlying this early response to caloric restriction has been shown to likely relate to a reduction in intrahepatic lipid content (IHL). Peterson and colleagues measured IHL by magnetic resonance spectroscopy in obese participants with type 2 diabetes before and after moderate weight loss (8kg) achieved through a hypocaloric low fat diet. Prior to the intervention the participants had marked increases in both IHL and intramyocellular lipid (IML) content, associated with hepatic and muscle insulin resistance. After eight weeks, IHL content had reduced by 81% and was associated with normalisation of fasting glucose, hepatic glucose production, and hepatic insulin sensitivity. No significant change in peripheral insulin resistance or IML was observed. Other studies have since supported the relationship between IHL and hepatic insulin sensitivity. This phenomenon is utilised clinically in the preparation of patients for abdominal surgery, where a significant reduction in hepatic volume is observed through caloric restriction for two weeks prior to the day of operation. The conclusion from these studies and others is that significant caloric restriction results in an early reduction in IHL and consequently significant improvements in hepatic insulin sensitivity. These improvements occur prior to significant weight loss and are rapidly reversible with an increase in caloric intake.
Patients undergoing bariatric surgery are subjected to a sudden decrease in daily caloric intake that exceeds that utilised in most dietary studies of caloric restriction. It has been calculated that the average person presenting for bariatric surgery would require 3200 kcal per day to maintain their current weight. Whilst daily calorie intake in the first few weeks after RYGB is surprisingly rarely reported, it is likely to total less than 500 kcal/day. Longer follow up studies suggest that daily caloric intake remains around 1500-1800 kcal/day. Could this reduction in caloric intake alone therefore explain the improvements in hepatic insulin sensitivity seen early after RYGB? Lim and colleagues addressed this question in a recent study involving 11 obese participants with type 2 diabetes. Participants were intensively studied at 1, 4 and 8 weeks during supervised caloric restriction of 600 kcal/day. Hepatic glucose production, hepatic insulin sensitivity, and peripheral insulin sensitivity were measured using validated tracer HEC techniques, whilst hepatic and pancreatic triacylglycerol content was measured using magnetic resonance imaging. At one week, IHL had reduced by 30% and was associated with a significant improvement in hepatic insulin sensitivity, such that fasting glucose normalised and hepatic glucose production was comparable to that observed in obese controls. Beta cell function, as measured by first phase and maximal insulin production, normalised over the eight week study period, matched by a gradual reduction in pancreatic lipid content over the same duration. Further work by this group suggests that the reduction in pancreatic triacylglycerol content is not explained simply by whole body fat losses, but instead is specific to individuals with type 2 diabetes.

A number of studies have attempted to assess the role of caloric restriction in the early improvements in hepatic insulin sensitivity observed after RYGB, and have shown similar, worsened, and improved parameters when compared with matched caloric intake. Isbell and colleagues assessed glucose homeostasis at four days in 18 participants undergoing RYGB or a matched very low calorie diet (VLCD, 200-300 kcal/day plus water). 50% of participants had type 2 diabetes. Hepatic insulin sensitivity improved to a similar degree in both groups (25% reduction in HOMA-IR), despite the insulin response to a mixed meal remaining attenuated in both groups. Jackness and colleagues performed a similar study in obese participants with type 2 diabetes randomised to RYGB or a matched very low calorie diet (500 kcal/day). Glucose homeostasis was assessed through the use of the frequently sampled intravenous glucose tolerance test. Similar improvements in insulin resistance (HOMA-IR), insulin sensitivity, the acute insulin response, and the disposition index were observed at 21 days in each group. Lips and colleagues recruited four groups of participants, two with normal glucose tolerance undergoing either GB or RYGB, and two with type 2 diabetes undergoing either RYGB or a matched VLCD. Improvements in glucose homeostasis were similar at three weeks in both groups.
with pre-intervention type 2 diabetes, although were improved after RYGB in comparison to GB in those with pre-intervention normal glucose tolerance. Similar outcomes have been demonstrated in an additional study where the dietary caloric intake was less restrictive. Lingvay and colleagues utilised an alternative study design whereby patients planned for RYGB underwent a pre-operative 10 day period of caloric restriction (identical to that consumed following subsequent RYGB). RYGB was then performed at least six weeks after the VLCD component. All 10 participants had type 2 diabetes. Daily glycaemia, measured by collating frequent capillary glucose readings, was improved during both periods, but to a greater degree during the VLCD component. Improvements in fasting and maximal stimulated glucose during a meal test were similar in both groups. Weight loss was greater during the VLCD period (7.3kg) than during the subsequent RYGB period (4.0kg). It should also be noted that there was a trend towards lower fasting glucose, maximal stimulated glucose, and glucose AUC prior to the RYGB component than prior to the VLCD period, suggesting that improvements during the RYGB period may not have been entirely independent of changes engendered by the VLCD period.

Two studies have shown an improvement in early glucose homeostasis beyond that seen with matched caloric restriction. In contrast to the findings of Lingvay and colleagues, Foo and colleagues reported further improvements in glucose homeostasis after RYGB in participants who had previously undergone VLCD. Eight severely obese participants underwent a six day VLCD (456 kcal/day) prior to RYGB one to three weeks later. A further 24 participants underwent RYGB without prior VLCD. No participants in this study had type 2 diabetes. Insulin resistance, measured by HOMA-IR, was significantly reduced at six days after each intervention, but was 50% lower after RYGB than VLCD. It should be noted that HOMA-IR was also lower at the point of RYGB in those that had previously undergone VLCD when compared with those who had not (4.3 vs. 6.8). Nonetheless, the final HOMA-IR was similar in each group. Peripheral insulin resistance, assessed by an insulin tolerance test, worsened slightly at six days in those who had undergone RYGB in comparison to VLCD. The authors concluded that RYGB resulted in an additional improvement in hepatic insulin sensitivity above that seen after matched caloric restriction alone. Pournaras and colleagues noted similar findings in a study comparing early outcomes in participants with type 2 diabetes undergoing RYGB, GB, or VLCD. A fourth group of obese individuals with normal glucose tolerance undergoing VLCD was used as a control. However, the VLCD in this study allowed considerably greater daily energy intake (1000 kcal/day) than that utilised in others. As noted above, previous studies of non-surgical VLCD have shown a significant difference when participants are restricted to 400 kcal/daily as opposed to 1000 kcal/daily. RYGB resulted in improvements in insulin resistance and production comparable to that evident in normal glucose tolerance controls, which was not observed after GB or VLCD.
In summary, non-surgical caloric restriction to the degree observed after RYGB results in significant improvements in glucose homeostasis within days. A rapid reduction in intrahepatic lipid content, and consequent improved hepatic insulin sensitivity, is likely to be highly important in this phenomenon. Studies comparing RYGB against matched energy intake in humans with type 2 diabetes show similar early improvements in glucose homeostasis. Thus, an improvement in hepatic insulin sensitivity as a result of caloric restriction is likely to explain a significant proportion of the early improves in glucose homeostasis after bariatric surgery. Previous studies have shown that non-surgical VLCD has a greater effect on hepatic insulin sensitivity in those with type 2 diabetes when compared with normal glucose tolerance. Studies that suggest RYGB rapidly improves hepatic insulin sensitivity above and beyond that seen with matched caloric intake either did not include participants with type 2 diabetes, or may be limited by the provision of significantly greater daily energy intake with a VLCD than after surgery.

1.4.4.2 Improving beta cell function is observed early

Insulin secretion in response to a stimulus appears to be improved immediately after RYGB. Studies in participants with normal glucose tolerance or type 2 diabetes show a leftward shift of the insulin profile so that the peak insulin level is increased, whilst the time to peak is reduced. This is evident as early as day three after surgery and reported by many studies within the first post-operative week. Presumably reflective of the simultaneous improvements in hepatic insulin sensitivity (see chapter 1.4.4.1), the total area under the curve for post prandial insulin is reduced in most studies. It should be noted that studies that employed an intravenously administered beta cell stimulant, such as the frequently sampled intravenous glucose tolerance test rather than an oral meal test, reported a more gradual improvement in beta cell function after bariatric surgery. This is consistent with the concept that early improved beta cell function relates significantly to GLP-1 stimulation, whilst intrinsic beta cell function improves days to weeks later (following a reduction intrapancreatic lipid content, see below and Figure 1-6, page 116) and, later still, with weight loss.

As discussed above (see chapter 1.1.3.4), first phase insulin secretion is typically diminished in type 2 diabetes. A number of studies have reported a gradual increase in first phase insulin secretion in the first year after bariatric surgery. As whole body insulin sensitivity improves by that point in relation to weight loss, the disposition index (insulin secretion x insulin sensitivity) is significantly increased in patients with preoperative type 2 diabetes.
The early improvement in insulin secretion after RYGB in response to an oral meal, strongly suggests that this is driven by an equally early increase in post prandial GLP-1 concentrations (see below, chapter 1.4.4.3). However, studies in non-surgical patients has revealed other potential mechanisms. Beta cell function was assessed during the eight week VLCD study described above. First phase insulin secretion and maximal insulin response gradually increased over the study period to concentrations that matched controls with normal glucose tolerance. At a similar rate, pancreatic triacylglycerol content fell from 8.0% to 6.2% (6.0% in controls). Pancreatic triacylglycerol concentrations vary widely in humans with higher concentrations typically seen in those with type 2 diabetes. Furthermore, an increase in pancreatic lipid content appears to precede the development of type 2 diabetes, at least in genetically susceptible rat models. Beta cell exposure to high triacylglycerol/fatty acid concentrations impair beta cell performance. It is therefore possible that this apparent small increase in pancreatic lipid content may explain some of the beta cell dysfunction observed early in type 2 diabetes, and conversely, the reduction in pancreatic lipid content with caloric restriction may explain associated improvements in beta cell function.

In summary, beta cell function improves rapidly after bariatric surgery, firstly with respect to insulin secretion and later with respect to first phase insulin release. The present evidence would suggest that a marked early increase in GLP-1 concentrations underlies the early improvements in beta cell function, facilitated by simultaneous improvements in hepatic insulin sensitivity, whilst a decrease in pancreatic lipid content with caloric restriction and weight loss underlies the more intrinsic improvements observed in later months.

1.4.4.3 Bariatric surgery induces favourable gut peptide alterations

As discussed above (chapter 1.4.2), bariatric surgery results in significant changes in gut peptide concentrations. Improvements in glucose homeostasis resulting from these changes are primarily the consequence of weight dependent mechanisms. In this section, I will therefore focus on the role of GLP-1 in post bariatric surgery improvements in glucose homeostasis.

Type 2 diabetes is associated with an attenuated GLP-1 response to a meal, and this is largely resolved with bariatric surgery. Multiple studies have consistently demonstrated an increase in post prandial GLP-1 concentrations after RYGB, VSG, and BPD but not LAGB (see chapter 1.4.2.4). Importantly, the increase in GLP-1 is evident within days of surgery. More recently the focus has turned to
Chapter 1: Literature review

Attempts to quantify the contribution that increased GLP-1 concentrations play in improved glucose homeostasis following bariatric surgery. Jorgensen and colleagues studied nine participants with type 2 diabetes before, one week after, and three months after RYGB. Two meal tests were performed at each time point, with an infusion of exendin-9 (GLP-1R antagonist) administered during one of the meals. The GLP-1 response to a meal was blunted at baseline, whilst the infusion of exendin-4 did not affect glucose homeostasis prior to surgery. At both one week and three months after surgery, the infusion of exendin-9 was associated with an increased GLP-1 and glucagon response to a meal, and increased post prandial glucose concentrations. Beta cell glucose sensitivity, significantly improved after RYGB, returned to baseline concentrations during an infusion of exendin-9. Very similar findings were reported in a study by Salehi and colleagues, and Shah and colleagues, where participants had undergone RYGB a mean of 5.0 years previously. In addition, Dirksen and colleagues recently described a case where feeding via the bypassed gastric remnant was required early after RYGB (see chapter 1.4.2.4). GLP-1 level were five fold higher during a standardised meal test when feeding was provided via the per oral route in comparison to the bypassed stomach, and beta cell function was more than two fold improved.

In contrast to these findings, Jimenez and colleagues reported a less clear role of endogenous GLP-1 secretion. Twenty three participants with preoperative type 2 diabetes who had undergone SG at least two years previously were recruited; six participants had relapsed type 2 diabetes, whilst 10 and seven participants had achieved remission or partial remission. Participants were well matched at baseline. A standardised mixed meal was performed and demonstrated impaired beta cell function and increased glucagon release in relapsed or partial remission participants in comparison with those who had achieved remission. Fasting, post prandial, and area under the curve values for GLP-1 were not different amongst the groups. However, peak GLP-1 concentrations in each group were significantly higher than observed in a non-surgery control group and higher than reported after VSG in other studies. In a second study, the same group recruited 20 participants, eight of whom had undergone SG at least two years prior to the study, had preoperative type 2 diabetes, and had achieved diabetes remission, six of whom had undergone SG at least two years prior to surgery but had normal glucose tolerance at baseline, and eight of whom comprised a control group of normal weight individuals who had not undergone bariatric surgery. Meal tests with and without exendin-9 infusions were administered. Exendin-9 infusion increased fasting and post prandial glucose concentrations in all three groups, resulted in impaired insulin secretion in the surgical groups, but had minimal effect on overall glucose tolerance. The authors therefore concluded that the increase in post prandial GLP-1
concentrations following SG could not alone explain the persistent improvements in glucose homeostasis seen during follow up.

In conclusion, bariatric surgery results in a predictable post prandial increase in GLP-1 concentrations immediately after surgery and is likely therefore to be a major factor underlying the early improvements in beta cell function.\(^{727}\) The apparent contradictory nature of the studies reported above is likely explained by the differences in time following surgery at which the participants were studied; it is likely that the relative contribution of increased GLP-1 concentrations diminishes with time as improved hepatic sensitivity and peripheral resistance become evident. The exact mechanism underlying the rapid increase in post prandial GLP-1 release after RYGB requires further research. Furthermore, the role of GLP-1 in the longer term maintenance of improved glucose homeostasis after bariatric surgery remission remains unclear.

### 1.4.4.4 Bile acids concentrations are increased by bariatric surgery

Bile acid concentrations are increased after RYGB in both the fasting and post prandial state, but are unchanged by LABG.\(^{728,729,730,731}\) It is unclear whether SG results in bile acid changes; whilst some studies in rodents have suggested increased bile acid concentrations after SG, most human studies report no change.\(^{732,733}\) In humans with type 2 diabetes, greater post-operative increases in bile acid secretion appear to predict diabetes remission.\(^{734}\) Furthermore, fasting bile acids concentrations after RYGB are positively associated with adiponectin and post prandial GLP-1 concentrations, and negatively associated with post prandial glucose concentrations.\(^{728}\) However, in a study of eight participants with pre-operative type 2 diabetes, plasma bile acid concentrations did not correlate with insulin sensitivity during an HEC, insulin response to a meal, or resting energy expenditure. There is circumstantial evidence to support a role of bile acids in a number of favourable metabolic effects of bariatric surgery including lipid and cholesterol metabolism, gut microbiota, and energy metabolism.\(^{735}\)

A number of mechanisms have been proposed to explain the possible favourable effects of increased bile acid concentrations on glucose homeostasis. An increase in post prandial GLP-1 concentrations is a consistent finding after RYGB, as is a positive correlation with increased bile acid concentrations. Bile acids are a substrate for the TGR5 receptor, expressed by GLP-1 secreting intestinal L cells.\(^{736}\) The direct delivery of bile to the distal small intestine in rodents increases local expression of TGR5 and proglucagon genes, and an increase in GLP-1 release.\(^{737,738}\) Study of a mouse model of biliary diversion
from the common bile duct to the mid-distal jejunum showed great weight loss, improved glucose tolerance, greater post prandial GLP-1 increases, and reduced hepatic steatosis when compared with sham surgery littermates.\textsuperscript{739}

An alternative mechanisms relates to a recently identified enterohepatic pathway involving bile acids and fibroblast growth factor 19 (FGF19). FGF19 is produced in the ileum in response to bile acid activation of the farnesoid X receptor (FXR).\textsuperscript{740,741} FGF19 acts through two hepatic receptors to regulate the expression of CYP7A1 which converts cholesterol to bile acids. FGF19 stimulates glycogen synthesis and inhibits gluconeogenesis.\textsuperscript{742} In addition FGF19 appears to augment cerebral insulin independent glucose uptake.\textsuperscript{743} Transgenic mice expressing human FGF19 had improved glucose homeostasis, whilst the administration of FGF15 (mouse equivalent of human FGF19) in mice results in improved glucose tolerance.\textsuperscript{744,745} Thus, whilst the literature is incomplete, the available evidence would support a favourable effect of increasing FGF19 concentrations on glucose homeostasis. FGF19 concentrations are reduced in obese persons with type 2 diabetes but are increased after RYGB.\textsuperscript{734,746}

Irrespective of the mechanism, it remains unclear whether the increase in bile acid and FGF19 concentrations after bariatric surgery contribute to improved glucose homeostasis. Jorgensen and colleagues performed a liquid meal test on 25 participants (13 with type 2 diabetes) before and after RYGB.\textsuperscript{747} As with other studies, hepatic insulin sensitivity was improved at one week, and improvements in post prandial GLP-1 release were evident. However, both fasting and post prandial bile acid and FGF19 concentrations were unchanged immediately after surgery. Fasting and post prandial bile acid and post prandial FGF19 concentrations were increased at three months post-surgery and increased gradually thereafter until 12 months of follow up.

In summary, the majority of studies report and increase in fasting and post prandial bile acid and FGF19 concentrations after RYGB, although there is disagreement as to when these changes become evident. At present there is insufficient evidence to conclude what, if any, role bile acid changes play in glucose homeostasis improvements following bariatric surgery.

1.4.4.5 Intestinal gluconeogenesis

The small intestine is the predominant site of dietary glucose absorption. There is debate as to whether the intestine is also a site of gluconeogenesis, but recent work using mice models would support
Mice with a combined deletion of glucose-6 phosphatase catalytic subunit (G6PC) in the liver and intestine fail to maintain normal glucose concentrations during a fast, whilst mice with a liver specific G6PC deletion are able to do so. In addition, the expression of gluconeogenic enzymes is increased in the intestine in response to fasting in mice with liver specific G6PC deletions. It has been suggested that the intestine may be subject to obesity related insulin resistance as seen in other tissues.

There is therefore interest as to whether alterations in intestinal gluconeogenesis may play a role in the improvements in glucose homeostasis seen after bariatric surgery. Early work provided the rather paradoxical possibility that bariatric surgery may improve glucose homeostasis by enhancing intestinal gluconeogenesis. Troy and colleagues performed either GB or a modified bypass procedure in mice fed a high fat diet, and demonstrated increased intestinal gluconeogenesis, assessed via tracer methods and portal sampling, after bypass but not GB. This was associated with improvements in hepatic insulin sensitivity and a reduction in appetite. The authors postulated that these favourable effects were the consequence of increased portal glucose concentrations resulting from increased intestinal gluconeogenesis, and noted previous studies supporting hypophagia and enhanced whole body glucose disposal after intraportal glucose infusion. Portal ‘sensing’ of glucose concentrations appears to be mediated by GLUT-2 transporters. Furthermore, these favourable effects were not seen in GLUT-2 knockout mice or after portal vein denervation. In addition, intestinal glucose uptake, measured using PET imaging, is increased six months after RYGB and SG and correlates with whole body insulin sensitivity. However, if changes in intestinal gluconeogenesis contribute to improved glucose homeostasis following bariatric surgery, the current evidence would suggest that this is not an early effect. There was no difference in central or portal glucose concentrations before or six days after RYGB in eight obese human participants with pre-operative type 2 diabetes.

Thus, further research is required to quantify the contribution of intestinal gluconeogenesis to glucose control. The current evidence would suggest that improved intestinal gluconeogenesis may contribute to the longer term favourable effects of bariatric surgery on weight loss and glycaemia, but is unlikely to be a major factor underlying early improvements.
1.5 An integrated model explaining weight loss and improved glucose homeostasis after bariatric surgery

It is clear that a number of factors of variable importance underlie the significant improvements in glucose homeostasis observed after bariatric surgery (see Figure 1-6). It is also clear that each of these factors is evident at differing times after surgery, and therefore the contribution of a single factor to overall glucose homeostasis at any one point during follow up may change.

*Figure 1-6* A schematic of the suggested mechanisms explaining the early and significant improvements in glucose homeostasis following RYGB and VSG

With respect to RYGB, the earliest documented change after surgery is an almost immediate improvement in insulin secretion, likely related to a marked increase in the GLP-1 response to a meal. Within days, a significant improvement in hepatic insulin sensitivity is observed which appears to be of a similar magnitude to that observed after matched calorie restriction and is likely to relate to a reduction in intrahepatic lipid. Thus, whilst insulin secretion is enhanced, there is an early reduction in
total insulin secretion after a meal due to improved hepatic insulin sensitivity. First phase insulin release is improved within weeks, and along with other improvements in beta cell function, may relate to a reduction in intrapancreatic lipid. Significant weight loss over the subsequent months results in improvements in peripheral insulin resistance, further enhancing beta cell function. The role of bile acids, FGF19, gut microbiota, and intestinal gluconeogenesis remains unclear but current evidence would suggest that these factors are less likely to contribute to early post-operative changes.

Can we therefore definitively state which early hypothesis (foregut or hindgut) to explain the dramatic effects of bariatric surgery was correct? The clear role of GLP-1 in enhancing beta cell function suggests that structures in the hindgut certainly underlie some of the early improvements in glucose homeostasis. The exact mechanism explaining why post prandial GLP-1 concentrations are increased though remains to be clarified. An increase in L cell density after RYGB may explain the longer term increase in GLP-1 concentrations but could not explain how this response is evident within hours to days of surgery. Whilst VSG is associated with an increase in GLP-1, LAGB is not, and reports of an absence of the increased GLP-1 concentrations after bypassed stomach feeding in patients after RYGB suggest that some anatomical diversion in the proximal gut may be required to engender these effects. Thus, the present evidence does not refute the principle underlying the foregut hypothesis; that a process integral to the proximal gut (secretion of a hormone, digestive processes, etc.) may be the driver behind the rapid increases in post prandial GLP-1 concentrations. Further study is clearly required in this area.

In contrast, the mechanism explaining early improvements in hepatic insulin sensitivity appears clearer. Whilst further study is required, numerous studies have now demonstrated similar early improvements in hepatic insulin sensitivity by caloric restriction alone, and furthermore have related this to reductions in hepatic lipid content.
1.6 Conclusion

Obesity and type 2 diabetes are interlinked conditions that are increasingly prevalent in New Zealand and internationally. Current therapeutic strategies for obesity are minimally effective and often poorly tolerated. Bariatric surgery has emerged as the most effective treatment option for both conditions, either in isolation or combination, but little evidence is available as yet detailing longer term outcomes. As noted above (chapter 1.3.2) there are no randomised data reporting outcomes beyond three years. There is therefore a need for additional data reporting on weight, glycaemic, metabolic, quality of life, and nutritional outcomes to complement the available literature. In chapter 3, I present outcome data from a prospective follow up study of 118 participants with and without dysglycaemia who underwent RYGB at least five years prior to recruitment. A second study in this chapter will address the issue of variable reporting of diabetes outcomes in the bariatric literature.

Significant improvements in our understanding of the mechanisms underlying bariatric surgery induced weight loss and improved glucose homeostasis have occurred recently. However, large gaps in the literature remain, and it is vital for a number of reasons to better understand this process. Firstly, outcomes after bariatric surgery clearly differ from patient to patient. It would be preferable to have better methods for predicting the response to bariatric surgery prior to operation. Secondly, an improved understanding of the exact mechanisms underlying bariatric surgery may allow the development of augmented strategies to facilitate weight loss/diabetes remission in those patients who have initially responded poorly to bariatric surgery. Similarly, weight regain and/or worsening glucose homeostasis is a reasonably common occurrence after an initial good response. An ability to identify the mechanism underlying these changes may allow a stepwise approach with the addition of further pharmaceutical therapy to complement and ensure the durable effect of bariatric surgery. Finally, and perhaps most importantly, an improved understanding of the mechanisms underlying bariatric surgery may enhance our ability to both prevent obesity and type 2 diabetes developing, or to allow the design of pharmaceutical therapies that induce the same significant improvements in weight and glucose homeostasis currently seen only after surgery. In chapter 4, I will present two studies, one exploring the effect of surgery itself on the assessment of glucose homeostasis in the first few post-operative days, and the second providing an initial exploration of the role of gut peptides in the longer term outcomes after bariatric surgery.
2 Chapter two: Methodology

2.1 RYGB surgery

2.2 Measurement of physical characteristics

2.3 Methodology of biochemical characteristics

2.4 Assessment of co-morbid conditions

2.5 Assessment of quality of life measures
2.1 Roux-en-Y gastric bypass surgery

RYGB surgery was performed at Wakefield Hospital by a single surgeon (Professor Richard Stubbs). Extracts from previous publications describing the silastic ring RYGB\textsuperscript{\ref{footnote:65}} and Fobi pouch RYGB\textsuperscript{\ref{footnote:66}} are included below.

Figure 2-1 A schematic to show A) Silastic ring RYGB, and B) Fobi pouch RYGB operations

2.1.1.1 Silastic ring RYGB

Surgery was performed under general anaesthesia with epidural analgesia. An upper midline incision was used. A window into the lesser sac was created adjacent to the lesser curve of the stomach some 9cm from the angle of His, and a passage was created from this point, behind the stomach, to the angle of His. A TA90B stapler (US surgical) was paced between these two points and its position adjusted prior to firing to produce a blind lesser curve stomach pouch approximately 9cm in length and 1.5cm in diameter. A 5.5cm length of 8F silastic rubber tubing was passed circumferentially around the lesser curve pouch some 6cm from the angle of His. This was fixed in place with an internal 2/0 prolene structure. A 40cm Roux loop of jejunum was fashioned with the entero-entero anastomosis being performed with two layers of 2/0 chromic catgut at a convenient point some 20-40cm from the ligament of Treitz. The Roux loop was passed in a retro-colic fashion and anastomosed
side-to-side to the blind end of the gastric pouch just distal to the silastic ring. This anastomosis was made with two layers of 2.0 chromic catgut over a length of 1.5-2.0cm. Mesenteric defects were closed, and cholecystectomy performed if gallstones were present. The abdominal cavity was lavaged with normal saline containing the antibiotic Cefamandole® (Eli Lily), and the abdomen was closed with a mass No.1 nylon suture. The subcutaneous fat layer was vigorously lavaged with the same antibiotic containing saline so as to dislodge all loose fat, and the skin was closed with subcuticular vicryl suture (Johnson & Johnson) and steri-strips. All patients received a single intra-operative vicryl suture. A prophylactic antibiotic, and were commenced on preoperative Fragmin® (Fisons) 2500 units subcutaneously for DVT/PE prophylaxis. The latter was continued postoperatively for 4-5 days. Epidural analgesia was continued postoperatively for 3-4 days. Urinary catheters were not employed, and patients were initially mobilized off the side of the bed 4 hours postoperatively.

2.1.1.2 Fobi pouch/transected RYGB

Fobi pouch was performed under general anaesthesia with epidural analgesia. Through an upper midline incision, a window was produced adjacent to the lesser curvature of the stomach 9cm from the angle of His, and a passage was created to this point behind the stomach, to the angle of His. A TCT-10® linear stapler-cutter (Johnson & Johnson) was positioned between these two points, and its position was adjusted before firing, so as to produce a blind lesser curvature gastric pouch 7-8cm in length and 1.5-2cm in diameter. Firing of the stapler achieves gastric transection, with 2 rows of staples on either side. The staple-line on the bypassed stomach was oversewn with a continuous 2/0 Ethibond suture. A 70cm Roux-loop of jejunum was fashioned, with the entero-entero anastomosis performed with two layers of 2/0 chromic catgut at a convenient place 40-60cm from the ligament of Treitz. The Roux-loop was passed in a retrocolic, retrogastric fashion to lie alongside the newly created lesser curvature pouch, separating this from the oversewn distal stomach. The Roux-loop is sutured to the lesser curvature pouch, in two layers with 2/0 polypropylene (Prolene®) in such a way as to create a serosal patch over a buried staple line. A 6.0cm (for age <50 years) or 6.5cm (for age >50 years) length of 8F silastic rubber tubing was passed circumferentially around the lesser curve pouch 5cm from the angle of His, and defined the size of the pouch above the ring (approximately 10-15ml). This was fixed in pace with an internal 2/0 Prolene suture. The Prolene sutures creating the serosal patch above the ring were continued to a point 1-2cm beyond the silastic ring, at which point a 2-layer end-to-side gastro-jejunal anastomosis 1-1.5cm long was created, after removal of a portion of the
staple-line. The inner layer was fashioned with all coats 2/0 chromic catgut, and the outer seromuscular layer completed with 2/0 Prolene.

Mesenteric defects were closed, and cholecystectomy was performed if gallstones were present. The upper abdominal cavity was lavaged with warm saline and the abdomen was closed with a mass No.1 nylon suture. The subcutaneous fat layer was vigorously lavaged with saline so as to dislodge all loose fat, and skin was closed with subcuticular Vicryl® suture (Johnson & Johnson) and steristrips. All patients received a single intra-operative dose of a prophylactic antibiotic (Usually Cefotetan® 2g), and were commenced on preoperative Clexane® (Aventis) 20mg subcutaneously for DVT/PE prophylaxis. The latter was continued daily after surgery, until discharge. Epidural analgesia was continued postoperatively for 4 days. Urinary catheters were not employed and patients were initially mobilized off the side of the bed 4 hours postoperatively.
2.2 Measurement of physical characteristics

2.2.1 Measurement of body weight parameters

Body weight was measured using calibrated weighing scales in each study. In study 3.1, weight was measured on a TBF 300 Tanita scale throughout the study. The accuracy of the scale was assessed each week by a study nurse using a 10kg weight. Scales were recalibrated if a deviation of +/- 0.1 kg was detected. Participants were instructed to wear minimal clothing, no shoes or socks, and to have an empty bladder. Clothing weight was entered as 300g and weight was recorded to the nearest 10g. In study 4.1 and study 4.2, weight was measured on analog scales located in Wakefield obesity clinic and the surgical ward at Wakefield hospital. Weight was expressed in kilograms (Kg).

Height was measured using a full length stadiometer and expressed in meters. The body mass index was then calculated as:

\[
\text{Body mass index (BMI, kg/m}^2\text{)} = \frac{\text{Weight (kilograms)}}{\text{Height (meters)}^2}
\]

Body weight loss percentage (BWL) was calculated by comparing the BMI before and after the study intervention:

\[
\text{Body weight loss %} = \frac{\text{(BMI (kg/m}^2\text{)) at baseline} - \text{BMI (kg/m}^2\text{) at follow up}}{\text{BMI at baseline}} \times 100
\]
2.2.2 Measurement of blood pressure and heart rate

Blood pressure was obtained indirectly by sphygmomanometry of either the left or the right brachial artery. Participants were asked to sit during the procedure, which was performed after five minutes of rest. The cuff was first inflated to a pressure at which the ipsilateral radial pulse was no longer palpable. The cuff was then released, and reinflated to 20 mmHg above that pressure. The brachial artery was then auscultated with a stethoscope, and the cuff was slowly deflated. The systolic blood pressure (SBP, mmHg) was taken as the pressure at which arterial pulsation first became auscultatable (first Korotkoff phase). The diastolic blood pressure (DBP, mmHg) was taken as the pressure at which the Korotkoff sounds completely disappear (fifth Korotkoff sound). Blood pressure measurements were obtained on three occasions during the physical examination, and mean values were calculated and used in each study.

In addition, the mean arterial pressure (MAP, mmHg) was calculated as:

\[
\text{MAP (mmHg)} = \text{DBP (mmHg)} + \frac{1}{3} (\text{SBP (mmHg)} + \text{DBP (mmHg)})
\]

Hypertension at each study time point was defined as either a systolic blood pressure > 120 mmHg and/or diastolic blood pressure > 80 mmHg, or the current use of anti-hypertensive medication. In addition, hypertension at baseline was defined if the participants reported a previous diagnosis of hypertension.

The heart rate was measured via pulse oximetry over twenty second intervals so as to ensure a stable heart rate was recorded. As with blood pressure, the heart rate was measured on three separate occasions and a mean heart rate was calculated.
2.3 Measurement of biochemical characteristics

2.3.1 Measurement of markers of glucose homeostasis

4ml of venous blood was collected in an EDTA vacutainer for the measurement of HbA1c (mmol/mol) concentrations (Bio-Rad laboratories Pty Ltd, Albany, Auckland, CV 3.7% at 35 mmol/mol and 2.6% at 81 mmol/mol). A separate 6ml of venous blood was obtained using an EDTA vacutainer for the measurement of insulin concentrations. The sample was refrigerated immediately before being centrifuged (2000 rpm for 10 minutes at 4 degrees Celsius). Plasma was then pipetted into two separate 1ml standard tubes, which were both then stored at -80 degrees Celsius. Samples were couriered to the Diabetes and Lipid laboratory, Department of human nutrition, University of Otago, Dunedin under appropriate conditions to maintain integrity. An in house assay was used to report insulin concentrations, with a CV% of <2 for concentrations < 50 pmol/L, and 4% for concentrations ≥50 pmol/L.

Venous glucose was measured following collection with a standard SST vacutainer and analysed at Wellington Regional Hospital laboratory (Roche diagnostics assay, Sandhofer Strasse 116, Mannheim, Germany, CV% <5).

2.3.2 Assessments of insulin sensitivity and insulin secretion

The reference method for calculating whole body insulin resistance is the euglycaemic hyperinsulinaemic clamp (EHC). This technique involves the simultaneous infusion of insulin and glucose. The insulin infusion is commenced at a rate adjusted by body mass. The rate of glucose infusion is thereafter adjusted to maintain plasma glucose concentrations at a predetermined level. Frequent sampling of insulin concentrations during the later steady state phase, provides an index of insulin sensitivity. The EHC is however, time consuming, difficult to perform, and suitable only for supervised research conditions. Therefore, a number of other methods that provide a more obtainable surrogate assessment of glucose homeostasis have been derived. Aside from simply measuring glucose/insulin ratios in the fasting or post prandial state, the Homeostasis Model Assessment (HOMA)
is perhaps the most widely applied such tool. The model requires the sampling of glucose and insulin concentrations in the fasted state, and therefore provides an assessment primarily of hepatic insulin sensitivity. The model was developed on the concept of a hepatic-beta cell feedback loop; in this model, increasing fasting glucose levels (resulting from hepatic gluconeogenesis) provoke a compensatory increase in insulin secretion. Therefore, fasting hyperglycaemia implies diminished insulin sensitivity. This model was adapted by Matthews et al, who reported a set of linear equations describing this relationship, and was then further updated by Levy et al to better account for variations in hepatic and peripheral glucose resistance (HOMA2). This model uses non-linear approximations of insulin sensitivity and presents these as HOMA-%B (beta cell function), HOMA-%S (insulin sensitivity), and HOMA-IR (insulin resistance, or the reciprocal of HOMA-%S). HOMA-%B, and HOMA-%S are comparative percentages against a normal reference population. Thus, HOMA-%B is a surrogate marker of the appropriateness of insulin secretion for a given concentration of glucose, whilst HOMA-%S is a surrogate calculation of the sensitivity of target tissue to insulin.

In this thesis, HOMA-%B, HOMA-%S, and HOMA-IR were calculated using fasting measurements of glucose and insulin as described above, and using the HOMA2 calculator available online.

2.3.3 Diabetes definitions at baseline and follow up

Diabetes status at baseline in each study is reported using the American Diabetes Association (ADA) diagnostic criteria (2015).

- Type 2 diabetes is defined as an HbA1c greater than or equal to 48 mmol/mol, and/or a fasting glucose greater than or equal to 7.0 mmol/L, and/or a 2 hour glucose concentration during a 75g oral glucose tolerance test greater than or equal to 11.1 mmol/L, and/or the ongoing use of glucose lowering medications.

- Prediabetes) is defined as an HbA1c of 39 to 47 mmol/mol inclusively, and/or a fasting glucose of 5.7 to 6.9 mmol/L inclusively, and/or a 2 hour glucose concentration during a 75g oral glucose tolerance test of 7.8 to 11.0 mmol/L inclusively, (providing none of these values exceed the threshold for the definition of type 2 diabetes), and the absence of glucose lowering medication.
Normal glucose homeostasis is defined as an HbA1c less than or equal to 38 mmol/mol, and fasting plasma glucose less than or equal to 5.6 mmol/L, and a 2 hour glucose concentration during a 75g oral glucose tolerance test of less than or equal to 7.7 mmol/L, and the absence of glucose lowering medications.

The ADA criteria for the diagnosis of diabetes differ significantly from those suggested by the New Zealand Society for the Study of Diabetes (NZSSD). The NZSSD criteria consider diabetes to be present in symptomatic individuals if the HbA1c is greater than or equal to 50 mmol/mol, and/or the fasting glucose is greater than or equal to 7.0 mmol/L, and/or a random glucose concentration is greater than or equal to 11.1 mmol/L. A repeat confirmatory test is required in asymptomatic individuals.

Individuals are considered to have normal glucose tolerance if the HbA1c concentration is less than or equal to 40 mmol/mol, and the fasting glucose concentration is less than or equal to 6.0 mmol/L. Individuals with at least one measurement between the thresholds set for normal glucose tolerance and diabetes, are considered to have prediabetes, also termed dysglycaemia or borderline diabetes.

To allow comparison with the international literature, the criteria proposed by the ADA for the diagnosis of diabetes are used in this thesis.

Diabetes status at follow up is reported using the criteria suggested by the ADA specifically for the assessment of diabetes following bariatric surgery.

- **Complete remission**
  HbA1c “in the normal range” and fasting glucose <100mg/dl (5.6 mmol/L) provided that each of these assessments are persistent for at least one year duration, and in the absence of active pharmacologic therapy or ongoing procedures.

- **Partial remission**
  HbA1c<6.5% (48 mmol/L) and fasting glucose 100-125 mg/dl (5.6 – 6.9 mmol/L), provided that each of these assessments were persistent for at least 1 year duration, and in the absence of active pharmacologic therapy or on-going procedures.
Chapter 2: Methodology

- **Persistent diabetes**

  $\text{HbA1c} \geq 6.5\%$ (48 mmol/mol) and/or fasting glucose $\geq 125$ mg/dl (6.9 mmol/L), and/or the ongoing use of active pharmacologic therapy or ongoing procedures.

### 2.3.4 Measurement of hormone concentrations

1ml of venous blood was collected in an EDTA tube for the assessment of Aldosterone. The sample was centrifuged immediately at 4 degrees Celsius on receipt by the laboratory at Wellington Regional Hospital, and transported in a deep frozen state to Endolab, Christchurch. Aldosterone was measured on an immunodiagnostic system (IDS) iSYS automated immunoassay analyser, Tyne and Wear, UK using a two site chemiluminescence assay. The assay has a limit of detection of 102.5 pmol/L and a CV of 8.4% at low concentrations (mean 297.2 pmol/l), 6.2% at medium concentrations (mean 660.5 pmol/l), and 3.5% at high concentrations (mean 1686.1 pmol/L).

1ml of venous blood was collected in an EDTA tube for prolactin concentration measurement (mU/L). The assay used was manufactured by Roche Diagnostics NZ, Mount Wellington, Auckland (CV 2% at 206 mU/L, 2% at 464 mU/L, and 2% at 1229 mU/L).

Measurements of fasting ghrelin, leptin, amylin, and PYY were obtained on samples collected at surgery, on day six following surgery, and again at the follow up assessment at >5 years. Venous blood was immediately centrifuged and plasma was stored at -80 degrees Celsius. 200 microlitre aliquots were created from each sample and sent to the Diabetes and Lipid laboratory, Department of human nutrition, University of Otago, Dunedin for analysis. Samples were couriered under appropriate conditions to maintain integrity. A multiplex assay (Category number HGT-68K, Merck Millipore, Billerica, Massachusetts, 01821 USA) was used to measure levels of each peptide in duplicate in a blinded fashion. Two quality control samples were used in house to assess the precision of each peptide measurement. Fasting ghrelin (coefficient of variance % = 7.4 and 9.6%), fasting leptin (CV% = 1.6 and 6.7), fasting amylin (CV% = 5.0 and 15.9), and fasting PYY (CV% = 8.0 and 16.2) were measured and expressed as pg/mL.
2.3.5 Measurement of other markers

A standard SST vacutainer was used to obtain 1ml of venous blood for the measurement of C reactive protein (CRP) concentrations. The samples were immediately transferred to the laboratory at Wellington Regional Hospital where they were analysed (Roche diagnostics assay, Sandhofer Strasse 116, Mannheim, Germany, CV% <5).

6ml of venous blood was drawn for the measurement of zinc and copper concentrations. A BD navy top vacutainer was used containing K\textsubscript{2} EDTA and a clot activator. Samples were placed immediately into a fridge and centrifuged (2000 rpm for 10 minutes) within 5 minutes of collection. 1ml of plasma was then obtained by pipette and transferred into a 1ml standard tube, which was then frozen at -80 degrees until analysis. An in house assay (Diabetes and Lipid laboratory, Department of human nutrition, University of Otago, Dunedin) was used to measure zinc (CV% = 4.7) and copper (CV% = 2.8) concentrations.

Venous blood for vitamin B12 concentration measurement was obtained using a standard SST vacutainer. The samples were delivered immediately to the laboratory at Wellington regional hospital. An electrochemiluminescence immunoassay (Cobas, Roche diagnostics, Sandhofer Strasse 116, Mannheim, Germany) was used to measure vitamin B12 concentration (CV% = 3.0 to 8.7)

2.3.6 Measurement of urinary markers

Urine was collected and divided into two urine containers for each 24 hour collection. This was necessary as urinary catecholamine and metanephrine concentrations decrease as a result of degradation if they are not stored in an acidified solution. Urinary cortisol concentrations are not affected by degradation to the same extent, and therefore urine can be collected within an empty container. Thus, the actual volume of urine assessed for each hormone was equivalent in volume to a 12 hour urine collection, but was reflective of 24 hour excretion. This issue was overcome by reporting hormonal concentrations as a ratio per mmol of urinary creatinine (i.e. urinary noradrenaline, reported as an absolute level in nmol, was reported as nmol/mmol UCr). Urinary catecholamines (noradrenaline, adrenaline, and dopamine) and metanephrines (normetadrenaline, metadrenaline) were measured using an in house assay (cation exchange/alumina extraction and reverse phase high performance liquid
chromatography with electrochemical detection). The laboratory report inter-assay coefficient of variance of <8% for catecholamines and <10% for metanephrines. Urinary free cortisol concentrations were measured using a Roche assay (Cobas e-601 electrochemiluminescence) with a reported inter-assay coefficient of variation of <5%.

2.4 Assessment of co-morbid conditions

Due to the retrospective nature of this study, data on co-morbid conditions at baseline was limited and predominantly based on patient self reports. A diagnosis of ischaemic heart disease at either baseline or follow up was accepted in the context of angina, evidence of coronary artery disease on angiography (with or without subsequent intervention), or previous myocardial infarction. The prevalence of myocardial infarction was reported separately. A diagnosis of previous stroke was made on the basis of a self reported diagnosis, and corroborated with available medical records. The diagnosis of sleep apnoea, arthritis, gout, depression, and fractures was self reported and corroborated with medical records where available.

2.5 Assessment of quality of life using IWQOL-lite

The impact of weight on quality of life (IWQOL-Lite) questionnaire was used to assess a number of parameters related to quality of life. The questionnaire itself and the scoring system manual are included in Appendix i-8 and Appendix i-9 (pages 360/362) respectively. The questionnaire includes 31 questions covering physical function, self-esteem, sexual life, public distress, and work, and provides a total score. The original IWQOL was a 74 item questionnaire, although this was shortened to the IWQOL-lite format by removing items that did not contribute to the psychometric performance of the test. Psychometric validation was performed using a cohort of nearly 1000 participants who had completed the IWQOL-lite questionnaire in a variety of settings included an outpatient medical weight loss centre, an inpatient intensive treatment centre, during the assessment for and after bariatric surgery, and control groups including community volunteers. Effect sizes were estimated between increasing BMI categories, and effect sizes were calculated longitudinally based on the degree of weight loss.
The questionnaire is undertaken by the participant without oversight by the clinician/researcher. The participant is asked to read each of the 31 questions and assign a response (1= never true, through to 5= always true) to each. Once completed, the clinician/researcher may check to see if a response has been provided to each question, although the scoring system allows absent responses. Participants may decline to answer particular questions because they are deemed either sensitive or not applicable.

A detailed description of the IWQOL-Lite scoring system is included in Appendix i-9, page 362. At least 50% of questions must be answered in each section for that sections score to be included in the total score. The average score in each section is then calculated, and multiplied by the total number of items in that section, which is then rounded to the nearest integer. This ‘raw’ score can then be converted to a more intuitive scaled score of 0 (worst) to 100 (best). The raw score is subtracted from the maximum score for each section, which is then divided by the range of possible scores for each section, and finally multiplied by 100. This method then provides a score out of 100 for each domain. The total score is calculated in exactly the same way, averaging the answers to each item in the questionnaire and dividing by the total number of items to which a response is provided.
3 CHAPTER THREE: CLINICAL STUDIES

RYGB surgery for the treatment of obesity and type 2 diabetes

3.1. Long term metabolic follow up of obese persons with and without dysglycaemia after RYGB
3.2. The application of differing definitions of diabetes outcomes following bariatric surgery
3.1 Long term metabolic follow up of obese persons with and without dysglycaemia undergoing RYGB

3.1.1 Introduction

The prevalence of both type 2 diabetes and obesity is rising at a rapid rate internationally (chapter 1.1.1). Obesity is a strong risk factor for the development of type 2 diabetes, and therefore the prevalence of type 2 diabetes is closely related to that population’s obesity prevalence. In New Zealand, 28.4% of New Zealand adults are obese, whilst 63.8% are overweight (BMI >25 kg/m²). The same report showed that 198,000 adults (5.5%) in New Zealand had diabetes, with men more likely to have diabetes than women (6.3% in males, 4.8% in females). Pacific (9%), Maori (7%), and Asian (6%) adults were all more likely to have diabetes than the national average. Given the asymptomatic nature of early dysglycaemia, it is likely the true prevalence is higher still. 8.3% of the world population had type 2 diabetes in 2011, and this is predicted to increase to approximately 10% by 2040. Furthermore, the financial burden placed on New Zealand’s health resulting from obesity and type 2 diabetes is significant with an annual health care cost attributable to obesity alone of NZ$686 million, or 4.5% of the health budget. Type 2 diabetes presents additional significant healthcare costs, which is expected to increase to NZ$1.8 billion per annum by 2022.

Current non-surgical therapeutic options for the management of both obesity and type 2 diabetes are limited with only a small number of obese patients with type 2 diabetes attaining a normal BMI or glycaemic status following non-surgical interventions (chapter 1.2). Lifestyle changes remains the cornerstone of treatment for both conditions. Dietary changes alone however rarely result in significant weight loss which is sustained over long term follow up. The development of pharmaceutical therapies to induce weight loss has been frustrated by significant drug side effects, whilst the effect of those still available is modest (see Table 1-2). Despite a significant recent increase in medical therapies for the glycaemic and metabolic management of type 2 diabetes, only 50% of patients attain a target HbA1c in population observation studies, and fewer still achieve target levels of glycaemia, bloods pressure, and lipids.
Bariatric surgery was developed initially as a weight loss only therapy (chapter 1.3.1). Four large randomised studies reporting weight outcomes at 12-24 months after bariatric have now been published alongside countless other non-randomised reports in patients with a BMI of ≥35 kg/m² prior to surgery (Table 1-3 and Table 1-4, chapter 1.3.2). A further six large randomised studies have reported outcomes in those with a BMI of ≥27 kg/m². Each study reports body weight loss of between 20 and 34%, with greater weight loss tending to be observed in those with a higher BMI at baseline. However, early in the development of bariatric surgery, it became apparent that significant and early improvements in glucose homeostasis were also observed. A significant number of publications have since reported diabetes outcomes after bariatric surgery, although the quality of study varies (chapter 1.3.3 (page 54)). Twenty publications have reported the prevalence of diabetes resolution after bariatric surgery when compared with an alternative intervention (Table 1-5). Unfortunately, disparity with respect to the definition of diabetes resolution employed in each study makes it difficult to confirm exact expected diabetes outcomes after bariatric surgery, although it is apparent that the effect far exceeds that observed with lifestyle/medical therapy alone. In addition, there is a paucity of higher quality longer term outcome data for both weight and diabetes outcomes. Indeed, no randomised study reported weight outcomes beyond 36 months, whilst Schauer and colleagues have recently reported diabetes outcomes at 36 months, which represents the longest duration of observed follow up in a randomised study against lifestyle therapy alone.

With international guidelines now in agreement that bariatric surgery should be considered at an earlier stage of diabetes, and therefore at a younger age, evidence to justify this approach and to reassure that longer term complications do not develop is of high interest. Particularly, it is important that the complete metabolic consequences of bariatric surgery, including effects on blood pressure and lipid concentrations, are properly understood as the published evidence thus far is not definitive (chapter 1.3.5 and chapter 1.3.7). We therefore determined to report outcomes after bariatric surgery in a cohort of obese individuals with and without type 2 diabetes who had undergone RYGB at least five years previously.
3.1.2 Aims

To assess long term outcomes (greater than five years) in a cohort of individuals following bariatric surgery.

3.1.3 Participants and methods

3.1.3.1 Study overview and design

This was a retrospective non-experimental cohort study of metabolic outcomes in 120 participants who had previously undergone bariatric surgery at least five years prior to recruitment for this study. All patients who had undergone bariatric surgery at Wakefield obesity clinic at least 5 years prior to commencement of the study were identified from a database and invited to attend for an interview. Invitation was by letter, with further attempts to contact potential participants by telephone. Baseline data were collected before surgery and stored in a database. These data were extracted for the participants included in this study. Weight, height, and anthropometric data were measured or collected during the interview and compared with baseline values. Markers of glucose homeostasis were measured on blood samples taken immediately prior to surgery and at a follow-up at least five years after surgery. Diabetes outcomes are reported using a number of commonly utilised definitions within the published literature. Micronutrient status of Vitamin B12, zinc and copper were determined to assess post-operative adequacy. A validated quality of life score was used to assess participant’s wellbeing at follow up.

A universal trial number (UTN) was allocated (U1111-1130-1613). The study was registered in advance with the Australian New Zealand Clinical Trials Registry (ANZCTR) and allocated the registration number ACTRN12612000505808.

The study was approved by the New Zealand multiregional Health and Disability Ethics Commission (HDEC) in June 2012 (Appendix i-1, page 335). The study approval number was MEC/11/04/040. Approval was sought from the hospital Maori research group, and received after recommendations were accepted (Appendix i-2 and Appendix i-3, page 336).
3.1.3.2 Study Participants

Study participants were 120 patients who had undergone bariatric surgery at least five years before the commencement of this study, and had consented to participation.

Inclusion criteria

- Bariatric surgery performed at Wakefield Obesity Clinic by a single surgeon at least five years before assessment (chapter 2.1, page 120)
- Willing to attend for an interview, physical examination, and blood sample collection.

Exclusion criteria

- Further bariatric surgery, either revision or repair, performed since original procedure and within five years of study commencement
- Initial surgery performed for other medical conditions. e.g. cancer

3.1.3.3 Methods

This study used data previously collected pre-operatively as the baseline. Prospective data were collected at a follow up appointment conducted at least five years after surgery. The participant characteristics were recorded as part of the admission for gastric bypass surgery and obtained by review of the clinical records for that admission. Additional data were extracted from a database maintained by Wakefield Obesity Clinic. These data were: weight, height and BMI, blood markers of glucose homeostasis (fasting glucose, fasting insulin, and HbA1c) and lipid measurements (total cholesterol, HDL, LDL, triglycerides), and blood pressure (chapter 2.1 and 2.3). Most participants had a standard 75g oral glucose tolerance test performed prior operation as this was the accepted contemporary practice for the diagnosis of diabetes.
Potential participants were invited by letter (Appendix I-4, page 339) to attend for an interview and examination at our research unit, with those who did not respond to the initial letter receiving an additional phone call to invite participation. An appointment was arranged for those who did wish to participate, at which the study was discussed in detail and informed consent obtained (Appendix I-6, page 341). The study design initially included the recruitment of a control group of participants who had considered bariatric surgery, but had not eventually undergone the procedure for various reasons. A letter of invite (Appendix I-5, page 340) was also sent to these potential participants, but unfortunately no participant responded favourably to the letter. The decision was therefore taken to abandon this aspect of the study and report outcomes as a retrospective non experimental cohort study instead.

The interview proceeded through the use of a standardised questionnaire (Appendix I-7, page 349) and was conducted by either the author or a research nurse. In addition, participants were asked to complete a quality of life questionnaire directed specifically at issues around obesity (Appendix I-8 (360) and Appendix I-9 (362)). A brief physical examination was then performed to measure weight, height, neck, waist, and hip circumference measurements, heart rate and blood pressure (see chapter 2.2.1, page 123, and chapter 2.2.2, page 124). Fasting blood samples and a mid stream spot urine collection were obtained (chapter 2.3, page 125). The American Diabetes Association criteria for the diagnosis of diabetes were applied to define glycaemic status at baseline and during follow up (chapter 2.3, page 125).

Information on co-morbidities at baseline was collected by the surgical team at admission for gastric bypass surgery, and was not checked against other medical records. The prevalence of each co-morbid condition is based on a confirmed diagnosis of a clinical event (e.g. myocardial infarction indicating ischaemic heart disease) rather than a positive screening test (e.g. exercise treadmill).
3.1.4 Outcomes following RYGB surgery

3.1.4.1 General baseline characteristics

The study included 120 participants who had undergone bariatric surgery at least five years ago, although two who had undergone revision surgery were excluded. The mean (SD) age of those included in this analysis was 47.5 (10.7) and 57.5 (11.3) years at baseline and follow up respectively, and displayed normal distribution. Ninety (76%) of the participants were female, and the mean (SD) duration of follow up after bariatric surgery was 10.2 (6.1) years.

Table 3-1 Baseline characteristics of the study participants

<table>
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<th>N=118</th>
<th>Mean (SD)</th>
<th>IQR</th>
<th>Minimum</th>
<th>Maximum</th>
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</table>
3.1.4.2 Type of bariatric surgery performed (Table 3-2)

Ninety-nine (84%) of participants underwent a transected RYGB (tRYGB) which became the bariatric procedure of choice at Wakefield Obesity Clinic in the year 2000. The mean (SD) age at surgery for this procedure was 48.1 (10.9) and the mean (SD) duration of follow up was 7.8 (2.5) years (Table ii-1, 363). Thus, the mean (SD) age of participants at the follow up assessment was 55.9 (11.2) years.

<table>
<thead>
<tr>
<th>Surgical procedure</th>
<th>N/118 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transected Roux-en-Y Gastric Bypass</td>
<td>99 (84)</td>
</tr>
<tr>
<td>Silastic ring RYGB</td>
<td>13 (11)</td>
</tr>
<tr>
<td>Vertical banded gastroplasty</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Gastric bypass</td>
<td>5 (4)</td>
</tr>
</tbody>
</table>

Thirteen (11%) of the participants underwent a silastic ring RYGB (sRYGB), performed between 1988 and 2000, with a mean (SD) age at surgery of 47.0 (9.0) years. Given that this procedure predated the tRYGB the mean (SD) duration of follow up was 18.4 (2.9) years and the mean (SD) age of participants at the follow up assessment was 65.4 (9.9) years. There was no clear difference in age at operation between participants who underwent tRYGB and sRYGB; estimated difference in age (years) 1.14 years (95% CI -5.1 to 7.4, p=0.71). However, participants who had undergone a sRYGB were predictably both older (estimated difference 9.6 years (95% CI 3.0 to 16.0, p=0.004) and had a longer duration of follow up (estimated difference 10.6 years (95% CI 9.2 to 12.1, p<0.001) to those who had undergone tRYGB. A further one (0.8%) and 5 (4%) participants underwent vertical banded gastroplasty or gastric bypass surgery respectively. Baseline data for these groups are presented in Table ii-1 (363).
### 3.1.4.3 Smoking status, alcohol use and employment status at follow up

Data on current smoking status at baseline were not available for this study. Forty-five (38%) of participants were either current smokers at the follow up appointment (seven (6%)) or were ex-smokers (38 (32%)) (see Table 3-3). The mean (SD) number of pack years of smoking was 21.4 (25.1) in those who had previously stopped smoking, and 20.6 (11.9) who were current smokers. Sixty-six (56%) of participants in this study had never smoked.

<table>
<thead>
<tr>
<th>Status</th>
<th>N (%)</th>
<th>Mean (SD)</th>
<th>IQR</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>66 (56)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex</td>
<td>38 (32)</td>
<td>21.4 (25.1)</td>
<td>25.5</td>
<td>1.0</td>
<td>120.0</td>
</tr>
<tr>
<td>Current</td>
<td>7 (6)</td>
<td>20.6 (11.9)</td>
<td>20.0</td>
<td>5.0</td>
<td>40.0</td>
</tr>
<tr>
<td><strong>Alcohol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>40 (34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex</td>
<td>39 (33)</td>
<td>10.2 (13.2)</td>
<td>12.0</td>
<td>1.0</td>
<td>60.0</td>
</tr>
<tr>
<td>Current</td>
<td>32 (27)</td>
<td>7.7 (8.6)</td>
<td>8.0</td>
<td>1.0</td>
<td>33.6</td>
</tr>
<tr>
<td><strong>Employment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed at baseline</td>
<td>94 (80)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed at follow up</td>
<td>71 (60)</td>
<td>37.0 (17.2)</td>
<td>7.0</td>
<td>2.5</td>
<td>80.0</td>
</tr>
</tbody>
</table>

Forty (34%) of participants did not drink alcohol, whilst 39 (33%) had consumed alcohol previously but no longer did (Table 3-3). Baseline data on alcohol use prior to surgery was not available, and therefore no formal analysis can be performed on the timing of alcohol intake cessation. However, most participants who reported previous alcohol use stopped drinking alcohol at the time of surgery. The mean (SD) number of self-reported units per week in those who reported previous but not current alcohol use was 10.2 (13.2).

Thirty-two (27%) of participants reported regular alcohol intake at the follow up interview, with a mean (SD) intake of 7.7 (8.6) units per week. Thus, the weekly alcohol intake of participants who
continued to consume alcohol following bariatric surgery was less than the previous intake of those who stopped alcohol intake following surgery (Current users mean (SD) 7.7 (8.6) units per week, ex users mean (SD) 10.2 (13.2) units per week; estimated difference (95% CI) 2.47 (-2.95 to 7.88) units per week, P=0.37).

Ninety-four (80%) of participants were in active employment at baseline although data on employment type and hours per week of work were not available (table 4-4). Seventy one (60%) participants were in active employment at the time of the follow up visit. The mean (SD) hours of work per week was 37.0 (17.2) with a range of 2.5 to 80.0 hours.

Smoking status, alcohol history, and employment history of participants based on type of bariatric procedure are presented in Table ii-2 (364).
3.1.4.4 Weight at baseline and follow up

All participants had data on weight available at both baseline and follow up. The mean (SD) weight at baseline in all participants was 128.8 (26.8) kg with a mean BMI (kg/m$^2$) of 46.6 (8.6), whilst the mean (SD) weight at follow up in all participants was 90.3 (21.5) kg with a mean (SD) BMI of 32.7 (7.0) kg/m$^2$ (Table 3-4). Frequency histograms of weight and BMI at baseline and follow up in all participants demonstrated right skewed distribution, and Shapiro-Wilk testing failed to reject the null hypotheses (Figure ii-1 and Figure ii-2, and Table ii-3 and Table ii-4 (365-366)). The distribution of weight and BMI at baseline and follow up was normalised through logarithmic transformation. Box plots to show weight and BMI at baseline and follow up in all participants and those who underwent tRYGB and sRYGB are presented in Figure 3-1 (145).

Each participant in this study had lost weight over the period of follow up (Figure 3-2 (146)). The mean (SD) body weight loss % in all participants, those who had undergone tRYGB, and those who had undergone sRYGB was 29.6 (10.7), 30.3 (10.5), and 25.7 (10.3) % respectively. The mean (SD) reduction in weight in all participants, those who had undergone tRYGB, and those who had undergone sRYGB was 38.5 (17.4), 39.4 (16.6), and 34.3 (21.2) kg respectively. The mean (SD) reduction in BMI in all participants, those who had undergone tRYGB, and those who had undergone sRYGB was 14.0 (6.3), 14.2 (6.1), and 12.7 (7.6) kg/m$^2$ respectively.

Statistically significant reductions in weight and BMI were evident at follow up for all participants and those who had undergone tRYGB; estimated differences between baseline and follow up weight and BMI are presented in Table 3-4. Change in weight (and thus body weight loss %) and BMI, displayed normal distribution for all participants and those who had undergone tRYGB (Figure ii-3 (367)).
Table 3-4  Weight (kg) and BMI (Kg/m$^2$) at baseline and follow up for all participants and those undergoing tRYGB

<table>
<thead>
<tr>
<th></th>
<th>n=118</th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>Follow up</td>
<td>Paired T test *</td>
<td>Equivalence</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>IQR</td>
<td>Min/Max</td>
<td>Mean (SD)</td>
<td>IQR</td>
<td>Min/Max</td>
<td>Est. Diff</td>
<td>95% CI</td>
<td>P value</td>
<td>Mean ratio</td>
</tr>
<tr>
<td>All participants (n=118)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>128.8 (26.8)</td>
<td>36.0</td>
<td>83.0/202.0</td>
<td>90.3 (21.5)</td>
<td>31.7</td>
<td>47.9/171.0</td>
<td>0.36</td>
<td>0.33 to 0.39</td>
<td>&lt;0.001</td>
<td>1.43</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>46.6 (8.6)</td>
<td>11.8</td>
<td>33.0/74.9</td>
<td>32.7 (7.0)</td>
<td>9.0</td>
<td>19.4/51.5</td>
<td>0.36</td>
<td>0.33 to 0.39</td>
<td>&lt;0.001</td>
<td>1.43</td>
</tr>
<tr>
<td>Transected RYGB (N=98)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>129.4 (26.8)</td>
<td>40.4</td>
<td>83.0/202.0</td>
<td>90.0 (22.6)</td>
<td>34.7</td>
<td>47.9/171.0</td>
<td>0.37</td>
<td>0.34 to 0.40</td>
<td>&lt;0.001</td>
<td>1.45</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>46.4 (8.6)</td>
<td>12.4</td>
<td>33.0/73.6</td>
<td>32.2 (7.2)</td>
<td>9.1</td>
<td>19.4/51.5</td>
<td>0.37</td>
<td>0.34 to 0.40</td>
<td>&lt;0.001</td>
<td>1.45</td>
</tr>
</tbody>
</table>

*Paired t test performed following logarithmic transformation
Figure 3-1  Box plots showing weight (kg, left column) and BMI (kg/m\(^2\), right column) at baseline and after at least 5 years of follow up after a) all bariatric procedures, b) tRYGB, and c) sRYGB.
Figure 3.2  Bar chart to show body weight loss (%) in all 118 participants.
3.1.4.4.1 Prediction of weight loss using baseline variables

To assess whether the degree of obesity at baseline affected weight loss outcomes, participants were stratified according to the World Health Organisation classification of obesity (Table 3-5). An additional category of class 4 obesity (super-obese) was added for this analysis and includes participants with a BMI of greater than or equal to 50.0 kg/m².

Table 3-5 World Health Organisation classification of obesity, with the numbers of participants in each category at baseline and follow up

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Classification</th>
<th>Baseline (%)</th>
<th>Follow up (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5</td>
<td>Underweight</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>18.5 – 24.9</td>
<td>Normal weight</td>
<td>0 (0)</td>
<td>14 (12)</td>
</tr>
<tr>
<td>25.0 – 29.9</td>
<td>Overweight</td>
<td>0 (0)</td>
<td>33 (28)</td>
</tr>
<tr>
<td>30.0 – 34.9</td>
<td>Class 1 obesity</td>
<td>8 (7)</td>
<td>37 (31)</td>
</tr>
<tr>
<td>35.0 – 39.9</td>
<td>Class 2 obesity</td>
<td>18 (15)</td>
<td>15 (13)</td>
</tr>
<tr>
<td>40.0 – 49.9</td>
<td>Class 3 obesity</td>
<td>56 (47)</td>
<td>18 (15)</td>
</tr>
<tr>
<td>≥ 50.0</td>
<td>Class 4 obesity</td>
<td>36 (30)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

Using this classification 8/118 (7%) participants had class 1 obesity at baseline, 18/118 (15%) had class 2 obesity, 56/118 (47%) had class 3 obesity, and 36/118 (30%) had class 4 obesity. The baseline and follow up characteristics of participants, stratified by obesity classification at baseline, are presented in Table ii-5 (368).
At the follow up assessment 14/118 (12%) of participants had achieved a normal weight (18.5 – 24.9 kg/m²) according to the WHO of obesity (Figure 3-3). A further 33 (28%) were overweight, 36 (31%) had class 1 obesity, 15 (13%) had class 2 obesity, 18 (15%) had class 3 obesity, and 2 (2%) had class 4 obesity. Both participants with class 4 obesity had class 4 obesity at baseline and both participants had lost weight (body weight loss of 2.4% and 31.4%).

Of the 8 (7%) of participants with class 1 obesity at baseline, 3 (38%) and 4 (50%) had improved to normal weight and overweight respectively, whilst 1 (13%) remained with class 1 obesity (Table 3-6). 18 (15%) of participants had class 2 obesity at baseline, with 4 (22%), 10 (56%), and 3 (17%) of participants improving to normal weight and overweight respectively, whilst 3 (17%) and 1 (6%) remained with class 1 and class 2 obesity. The majority of participants (57 (48%)) had class 3 obesity at baseline. Seven (12%) of these improved to normal weight and 15 (26%) to overweight following surgery, whilst 25 (46%), 7 (12%), and 2 (4%) remained with class 1, class 2, and class 3 obesity.

**Figure 3-3** Pie charts to show percentage of participants within each WHO class of obesity at a) baseline, and b) follow up
respectively. Thirty six (30%) of participants were super-obese at baseline (class 4 obesity). Two (6%) of these participants were the only participants in the study cohort who remained with class 4 obesity at follow up. A further 16 (44%) had class 3 obesity, whilst 7 (19%) of participants improved to both class 1 and class 2 obesity. Only 4 (11%) of those with class 4 obesity at baseline improved to overweight at follow up, and none of these participants had a normal body weight. Cross tabulation of obesity classification at baseline and follow up is shown in Table 3-6.

<table>
<thead>
<tr>
<th>N=118</th>
<th>Obesity classification at follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NW</td>
</tr>
<tr>
<td>Obesity classification at baseline</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
</tr>
</tbody>
</table>

When stratified by obesity classification at baseline, and thus by BMI, and indirectly weight, an incremental increase in the baseline BMI or weight was associated with an incremental increase in the weight classification at follow up (Figure 3-4). Furthermore, there was an incremental increase in the body weight loss base on weight classification at baseline.
Figure 3-4  Boxplots showing a) weight at baseline, b) BMI at baseline, and c) body weight loss (%) for each category of obesity classification at follow up or baseline. NW=normal weight, OW=overweight
Therefore, an analysis of the relationships between weight and BMI at baseline and follow up was performed. To assess whether change in BMI following bariatric surgery can be predicted at baseline, univariate and multivariate regression analysis was performed. Variables included in this analysis were age at operation, gender, BMI at baseline, weight at baseline, diabetes status and markers of glucose homeostasis, lipid status and lipid profile, and blood pressure status. Coefficients calculated from regression modelling are presented in Table ii-6 (370).

Linear regression established that BMI (kg/m^2) at baseline predicts change in BMI over the study period (r=0.58, f=62.5, p<0.001), and accounted for 33% of the change in BMI (Figure 3-5). The regression equation was:

\[
\text{Change in BMI (kg/m}^2\text{)} = -6.23 + (0.43 \times \text{BMI at baseline (kg)})
\]

Acknowledging that weight is a requisite component of BMI, weight (kg) at baseline was also an independent predictor of the change in BMI during follow up (r=0.49, f=37.5, p<0.001), accounting for 24% of the change in BMI (Figure 3-5). The regression equation was:

\[
\text{Change in BMI (kg/m}^2\text{)} = -1.03 + (0.12 \times \text{weight at baseline (kg)})
\]
Figure 3-5  Regression variable plot for a) BMI (kg/m²) at baseline, and b) weight at baseline against change in BMI (kg/m²)

Furthermore, baseline weight and BMI also predicted final BMI (kg/m²). BMI (kg/m²) (R=0.69, F=107.1, p<0.001) and, weight (R=0.59, F=60.6, p<0.001), at baseline (Figure 3-6). BMI at baseline accounted for 48% of the variation in final BMI (kg/m²) whilst weight at baseline accounted for 34%. The regression equations were:

Final BMI (kg/m²) = 6.23 + (0.57 * BMI (kg/m²) at baseline)
Final BMI (kg/m²) = 12.8 + (0.15 * weight (kg) at baseline)

Figure 3-6  Regression variable plots to show a) BMI (kg/m²) at baseline, and b) weight (kg) at baseline, against final BMI (kg/m²)
With respect to other continuous independent baseline variables, HOMA-IR and total cholesterol (mmol/L) also predicted change in BMI using linear regression. HOMA-IR showed mild correlation with change in BMI ($f=4.2, p<0.04$) and accounted for only 4% of the change in BMI. The regression equation was:

$$\text{Change in BMI (kg/m}^2) = 11.0 + (0.97 \times \text{HOMA-IR})$$

Total cholesterol also demonstrated mild correlation with change in BMI ($f=4.0, p=0.04$) and accounted for only 3% of change in BMI. The regression equation was:

$$\text{Change in BMI (kg/m}^2) = 21.3 - (1.3 \times \text{total cholesterol (mmol/L)})$$

Both categorical variables used in this analysis predicted change in BMI over the study period. Diabetes status at baseline showed mild correlation ($f=5.5, p=0.02$), but accounted for only 4% of change in BMI. The regression equation was:

$$\text{Change in BMI (kg/m}^2) = 12.2 + (1.7 \times \text{ADA status})$$

where ADA status is expressed as 0=normal glucose tolerance, 1= prediabetes, 2 = type 2 diabetes. Hypertension at baseline (0=normal blood pressure, 1 = hypertension) showed mild correlation ($f=5.8, p=0.02$), but accounted for only 4% of the change in BMI over the study period. The regression equation was:

$$\text{Change in BMI (kg/m}^2) = 10.7 + (4.1 \times \text{Hypertension status})$$

Regression variable boxplots for models including the above two categorical variables are shown in Figure 3-7.
Multivariate regression analysis was then performed to explore whether use of a combination of baseline measured variables could better predict the change in BMI (kg/m$^2$) following surgery than any one variable alone. Given the sample size of 118 participants, a maximum of six variables could be used in a multivariate model.

An optimal model was obtained when BMI at baseline, age at baseline, diabetes status at baseline, and hypertension status at baseline were included (Table 3-7). The change in BMI (kg/m$^2$) following surgery was predicted by this model, $F(4,103)=18.1$, $p<0.001$, $R^2=0.41$, although explained only 39% of the total variation in BMI change. Furthermore, of all the independent variables, only BMI at baseline added statistically significantly to the prediction, $p<0.05$. The addition of gender to the list of included independent variables had minimal effect on performance ($F(5, 102) = 14.6$, $p<0.001$, $R^2=0.42$).
Table 3-7  Multivariate regression analysis incorporating BMI at baseline and the listed independent variables to predict change in BMI (kg/m$^2$). Table a presents the model summary and table b presents the coefficients.

### a)

<table>
<thead>
<tr>
<th>Model summary</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>R2</td>
</tr>
<tr>
<td>0.643</td>
<td>0.413</td>
</tr>
</tbody>
</table>

### b)

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Unstandardised coefficients</th>
<th>Standardised coefficients</th>
<th>T</th>
<th>P value</th>
<th>95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>β</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>-11.0</td>
<td>-3.0</td>
<td>0.004</td>
<td>-18.4 to -3.7</td>
<td></td>
</tr>
<tr>
<td>Age at operation</td>
<td>0.05</td>
<td>0.09</td>
<td>1.0</td>
<td>0.31</td>
<td>-0.05 to 0.16</td>
</tr>
<tr>
<td>Hypertension at operation</td>
<td>2.60</td>
<td>0.14</td>
<td>1.85</td>
<td>0.07</td>
<td>-0.19 to 5.38</td>
</tr>
<tr>
<td>ADA classification at baseline</td>
<td>0.58</td>
<td>0.07</td>
<td>0.84</td>
<td>0.40</td>
<td>-0.78 to 1.9</td>
</tr>
<tr>
<td>BMI (kg/m$^2$) at baseline</td>
<td>0.42</td>
<td>0.59</td>
<td>7.6</td>
<td>&lt;0.001</td>
<td>0.31 to 0.53</td>
</tr>
</tbody>
</table>
3.1.4.4.2 Prediction of weight loss using additional follow up variables

To assess whether additional variables not available at baseline may affect weight loss following RYGB, additional regression analyses were performed. Linear regression established that age at follow up (years), duration of follow up (years) and diabetes status at follow up could not predict change in BMI over the study period (Table 3-8). To support the conclusion that duration of follow up does not predict change in BMI following RYGB, a scatterplot showed no clear relationship (Figure 3-8).

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>ANOVA</th>
<th>Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>p value</td>
</tr>
<tr>
<td>Age at follow up (years)</td>
<td>0.29</td>
<td>0.9</td>
</tr>
<tr>
<td>Duration of follow up (years)</td>
<td>3.0</td>
<td>0.08</td>
</tr>
<tr>
<td>Diabetes status at follow up</td>
<td>0.31</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Figure 3-8 Scatter plot to show duration of follow up (years) against change in BMI (kg/m²)

$r^2 = 0.02$
3.1.4.4.3 Comparison of outcomes stratified by duration of outcomes

To further explore the relationship between duration of follow up and weight outcomes, outcomes in those with 5.0 to <10.0 years of follow up were compared against those with greater or equal than 10.0 years of follow up. The mean (SD) duration of follow up in all 118 participants was 10.1 (6.0) years. Eighty one (69%) of participants had a follow up duration of between 5.0 and 10.0 years (mean (SD) 6.9 (1.4) years), whilst 37 (31%) of participants had a follow up duration of greater than 10 years (mean (SD) 17.3 (6.1) years, maximum 30.6 years) (Table ii-7 (371)). Furthermore, BMI data at 1 and 2 years following surgery was available in 76 (92%) and 17 (46%) of those with the shorter or longer duration of follow up respectively. All 81 (100%) participants with 5.0 to less than 10.0 years of follow up had undergone tRYGB. Seventeen (46%) of those with greater than or equal to 10 years of follow up had undergone tRYGB, with a further 14 (38%) undergoing sRYGB, one undergoing vertical banded gastroplasty, and the remaining five (14%) having undergone gastric bypass.

The mean (SD) age at operation and follow up in those with 5.0 to less than 10.0 years of follow up was 48.1 (11.2) and 54.9 (11.3) years, whilst the mean (SD) age at operation and follow up in those with great than or equal to 10.0 years of follow up was 46.3 (8.9) and 63.6 (8.2) years respectively. The two groups were not clearly different with respect to age at operation (estimated difference 1.72 years (95% CI -2.4 to 5.9, p=0.4)), although those with a longer duration of follow up were predictably significantly older at the follow up assessment (estimated difference 8.7 years (95% CI 4.6 to 12.8, p=0.001).

The mean (SD) BMI at baseline in those with less than or ≥10.0 years of follow up was 47.3 (8.8) and 45.2 (8.1) kg/m$^2$, and at follow up was 32.6 (7.4) and 32.9 (6.4) kg/m$^2$ (Figure 3-9). There was no clear difference in baseline or follow up BMI between the groups. The estimated difference in baseline BMI was 2.02 kg/m$^2$ (0.04 (95% CI 0.01 to 0.17, p=0.25, equivalent to a mean ratio of 1.04 (95% CI 1.01 to 1.19). The estimated difference in follow up BMI was 0.3 kg/m$^2$ (0.01 (95% CI -0.07 to 0.1), p=0.74, equivalent to a mean ratio of 1. 01 (95% CI -1.08 to 1.11). The mean (SD) absolute reduction in BMI (kg/m$^2$) during the study period was 14.7 (6.3) kg/m$^2$ for those with 5.0 to 10.0 years of follow up, and 12.3 (6.0) kg/m$^2$ for those with greater than 10 years of follow up; estimated difference 2.3 kg/m$^2$ (95% CI -0.1 to 4.8, p= 0.06).
Figure 3-9 Boxplots showing a) BMI change (kg/m\(^2\)), and b) body weight loss (%) for all participants, and those with <10 years or ≥10 years of follow up
3.1.4.5 Glycaemic status at baseline and follow up

The distribution of data for fasting glucose, HbA1c, fasting insulin, and HOMA-IR at baseline and follow up was right skewed as demonstrated by inspection of histograms (Figure ii-4 (372)) and assessment using the Shapiro-Wilk test (Table ii-8 (373)). Box plots to each variable at baseline and follow up are presented in Figure 3-10, and illustrate outlying results. Logarithmic transformation of all the data resulted in a better approximation of normal distribution allowing parametric analysis (Figure ii-5(374)). Furthermore, logarithmic transformation of the change in each variable from baseline to follow up also resulted in a better approximation of normal distribution (Figure ii-6 (375)).

Figure 3-10 Box plots to show a) fasting glucose, b) HbA1c, c) fasting insulin, and d) HOMA-IR at baseline and follow up
Participants were classified as having normal glucose tolerance, prediabetes, or overt type 2 diabetes at baseline and follow up as per criteria described above. Table 3-9 presents the frequency of each diagnosis using the ADA criteria for assessing diabetes outcomes following bariatric surgery. Thus, the percentage of participants with normal glucose tolerance at baseline was 25% when those where a diagnosis was not available from baseline data were excluded. Using the same method, 37.5% participants had prediabetes at baseline, whilst 37.5% of participants had type 2 diabetes at baseline. At follow up, 58 participants had normal glucose tolerance (53.7% of those whose glycaemic status could be assessed), whilst 38 (35.2%) and 12 (11.1%) had prediabetes and type 2 diabetes respectively (Table 3-9) when the 10 (8.5% of whole cohort) in whom a diagnosis at follow up was not available were excluded.

Table 3-9 Frequency of participants with each category of glucose tolerance using diagnostic criteria suggested by the ADA. Absolute (calculated from the whole cohort) and valid (calculated just using participants where a diagnosis was available) percentages are presented.

<table>
<thead>
<tr>
<th>Category</th>
<th>Baseline</th>
<th></th>
<th>Follow up</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/118</td>
<td>%</td>
<td>Valid %</td>
<td>n/118</td>
</tr>
<tr>
<td>Normal glucose tolerance</td>
<td>28</td>
<td>23.7</td>
<td>25.0</td>
<td>58</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>42</td>
<td>35.6</td>
<td>37.5</td>
<td>38</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>42</td>
<td>35.6</td>
<td>37.5</td>
<td>12</td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
<td>5.1</td>
<td>N/A</td>
<td>10</td>
</tr>
</tbody>
</table>

Participants that had data available at both baseline and follow up were included in an analysis to compare the means, following appropriate logarithmic transformation where required. Results are presented in Table 3-10. Comparison of the means using a paired T test is also presented.
Table 3-10 Baseline and follow up characteristics and markers of glycaemic status for all participants at baseline. A paired T test is shown.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow up</th>
<th>Paired T test *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Mean (SD)</td>
<td>IQR</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>105 (89)</td>
<td>6.16 (2.1)</td>
<td>1.75</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>92 (78)</td>
<td>47.1 (14.7)</td>
<td>16.0</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>94 (80)</td>
<td>159.3 (89.6)</td>
<td>110.3</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>83 (70)</td>
<td>2.84 (1.34)</td>
<td>2.1</td>
</tr>
<tr>
<td>HOMA-%B</td>
<td>83 (70)</td>
<td>147.6 (63.1)</td>
<td>85.9</td>
</tr>
<tr>
<td>HOMA-%S</td>
<td>83 (70)</td>
<td>45.2 (25.3)</td>
<td>30.0</td>
</tr>
</tbody>
</table>

*p values for BMI, fasting glucose, HbA1c, fasting insulin, and HOMA following logarithmic transformation
Twenty-four (20%) participants were using oral glucose lowering therapy at baseline, whilst six (5%) of these were also using insulin therapy. The mean (SD) duration of treatment with oral glucose lowering therapy was 8.9 (5.2) years, and the mean (SD) duration of treatment with insulin therapy was 4.8 (3.3) years. All participants on either oral glucose lowering therapy or insulin had type 2 diabetes at baseline by definition.

When the whole cohort were considered, the mean (SD) fasting glucose at baseline and follow up were 6.16 (2.1) and 5.00 (1.20) mmol/L respectively; estimated difference 1.18 mmol/L (95% CI 0.83 to 1.54, p<0.001) (Table 3-10). The corresponding mean (SD) HbA1c measurements were 47.1 (14.7) and 39.6 (8.2) mmol/mol respectively (estimated difference 7.5 mmol/mol, p<0.001), whilst those for fasting insulin were 159.3 (89.6) and 47.5 (22.8) pmol/L respectively (estimated difference 117.7 pmol/L, p<0.001). The mean (SD) HOMA-IR at baseline was 2.84 (1.34) and 0.92 (0.40) at follow up; estimated difference 2.0, p<0.001. Thus, the mean concentrations of insulin and HOMA-IR normalised over the follow up period, whilst the mean diabetes status using ADA criteria improved from type 2 diabetes to prediabetes.

The mean (SD) age at operation for those with normal glucose tolerance was 40.9 (11.0) with a mean (SD) duration of follow up of 10.2 (4.7) years and thus a mean (SD) age at follow up of 51.0 (12.4) years. The respective values for those with prediabetes were 48.0 (9.6), 8.7 (4.3) and 56.6 (10.6). The estimated difference (95% CI) between age at baseline in those with normal glucose tolerance and prediabetes was 7.1 (2.2 to 12.1) years, P=0.005. The estimated difference (95% CI) between duration of follow up in those with normal glucose tolerance and prediabetes was 1.5 (-0.7 to 3.7) years, P=0.2), whilst the estimated difference (95% CI) between age at follow up was 5.7 (-0.1 to 11.1) years, P=0.05).

The mean (SD) age at operation for those with type 2 diabetes was 52.8 (8.2) with a mean (SD) duration of follow up of 9.1 (4.9) years and thus a mean (SD) age at follow up of 62.0 (8.7) years. The estimated difference (95% CI) between age at baseline in those with normal glucose tolerance and type 2 diabetes was 12.0 (7.4 to 16.6) years, p<0.01), whilst the estimated difference (95% CI) between those with prediabetes and type 2 diabetes was 4.9 (1.0 to 8.7) years, P=0.01). The estimated difference (95% CI) between duration of follow up in those with normal glucose tolerance and type 2 diabetes was 1.1 (-1.3 to 3.4) years, p=0.4), whilst the estimated difference (95% CI) between those with prediabetes and type 2 diabetes was 0.4 (-2.4 to 1.6) years, P=0.7). The estimated difference (95% CI) between age at follow up in those with normal glucose tolerance and type 2 diabetes was 10.9
Figure 3-11  Boxplots to show change in each variable over the follow up period. Box plots are categorised by ADA diagnosis at baseline (0= normal glucose tolerance, 1= prediabetes, 2= type 2 diabetes).
years (5.9 to 15.9) years, p<0.01), whilst the estimated difference (95% CI) between those with prediabetes and type 2 diabetes was 5.3 (1.1 to 9.5) years, P=0.01).

Thus, participants with normal glucose tolerance at baseline were younger and had a longer duration of follow up than participants with either prediabetes or type 2 diabetes. Additionally, those with normal glucose tolerance were significantly younger at follow up than those with type 2 diabetes, but were not clearly different from those with prediabetes. Participants with prediabetes at baseline were younger at both baseline and follow up than those with type 2 diabetes. However, the duration of follow up was similar in these two groups.

Eight of the 95 (79%) of participants with a fasting insulin concentration available at baseline had concentrations within the normal reference range (<60 pmol/L). Six of these participants were categorised as having prediabetes by the ADA criteria and the remaining two were deemed to have normal glucose tolerance. The mean (SD) fasting insulin concentration in those with normal glucose tolerance was 110.1 (52.1) pmol/L whilst the mean (SD) fasting insulin concentration in those with prediabetes was 142.3 (87.2); estimated difference 32.2 pmol/L (95% CI -15.3 to 79.0, P=0.18). The mean (SD) fasting insulin concentration in those with type 2 diabetes at baseline was 200.8 (89.2) pmol/L; estimated difference (95%) against normal glucose tolerance 90.7 pmol/L (41.3 to 140.4) pmol/L, P=0.01; estimated different (95%) against those with prediabetes 58.5 pmol/L (19.0 to 98.1), P=0.04. The mean (SD) HOMA-IR scores at baseline for participants with normal glucose tolerance, prediabetes, and type 2 diabetes were 1.98 (0.91), 2.61 (1.22), and 3.63 (1.33) respectively. The estimated difference (95% CI) between HOMA-IR at baseline in those with normal glucose tolerance and prediabetes was 0.63 (-0.05 to 1.3, p=0.68), 1.65 (0.9 to 2.4, p<0.01) between those with normal glucose tolerance and type 2 diabetes, and 1.01 (0.4 to 1.6, p=0.002 between those with prediabetes and type 2 diabetes.

Thus, participants were increasingly hyperinsulinaemic with each deteriorating category of glycaemic status, and those with type 2 diabetes had statistically significant higher fasting insulin concentrations at baseline than those with normal glucose tolerance. In addition, participants with type 2 diabetes at baseline were significantly more insulin resistant at baseline than those with normal glucose tolerance and prediabetes.
One hundred and two (85%) of participants had a complete set of glycaemic data at both baseline and follow up time points, and could therefore be included in an analysis on diabetes outcomes (Table 3-11). Note that the ADA criteria for the assessment of diabetes following bariatric surgery are intended to apply only to those people with a diagnosis of dysglycaemia prior to surgery; however, the diabetes status at follow up was not altered by use of the ADA diagnostic criteria instead.

Of the 26 participants with normal glucose tolerance at baseline, twenty-one remained with normal glucose tolerance and five had progressed to prediabetes (Table 3-11). None of these 26 participants developed type 2 diabetes during the period of follow up. Forty participants had prediabetes at baseline, with twenty-five (63%) having normal glucose tolerance at follow up after surgery. A further 14 (35%) participants remained with prediabetes, whilst one participant had progressed to type 2 diabetes at follow up. Thirty six participants had type 2 diabetes prior to surgery. Of these, nine (25%) of participants had normal glucose tolerance at follow up, 17 (47%) had prediabetes, and 10 (28%) remained with type 2 diabetes.

Table 3-11 Cross tabulation of ADA diagnosis at baseline against ADA diagnosis at follow up of the 102 available participants

<table>
<thead>
<tr>
<th>ADA Diagnosis at baseline</th>
<th>ADA diagnosis at follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NGT</td>
</tr>
<tr>
<td>ADA Diagnosis at baseline</td>
<td></td>
</tr>
<tr>
<td>NGT</td>
<td>21</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>25</td>
</tr>
<tr>
<td>T2DM</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
</tr>
</tbody>
</table>
3.1.4.5.1 Glycaemic outcomes in those with normal glucose tolerance at baseline

28 participants had normal glucose tolerance at baseline and 26 of these participants had sufficient data at follow up to comment on diabetes status outcome (Table 3-11 (page 165)). 23 (82%) of these participants underwent a transected RYGB whilst five (18%) underwent a silastic ring RYGB (Table 3-12). 21 (81%) of these participants remained with normal glucose tolerance at follow up whilst 5 (19%) had progressed to prediabetes. Baseline data for all participants with normal glucose tolerance at operation is presented in Table 3-13.

Table 3-12 Type of bariatric surgery performed in those with normal glucose tolerance at baseline

<table>
<thead>
<tr>
<th></th>
<th>N=28</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transected Roux-en-Y Gastric Bypass</td>
<td>23 (82)</td>
<td></td>
</tr>
<tr>
<td>Silastic ring RYGB</td>
<td>5 (18)</td>
<td></td>
</tr>
</tbody>
</table>

Fasting glucose concentrations did not differ significantly at either baseline or follow up between those with normal glucose tolerance at follow up and those with prediabetes (estimated difference 0.3 mmol/L for baseline glucose (95% CI -0.13 to 0.75, P=0.16) and 0.3 mmol/L for follow up glucose (95% CI -0.07 to 0.7, p=0.15) despite fasting glucose concentrations being a factor that defines glycaemic status. The maximum fasting glucose concentration in those with prediabetes was 5.4 mmol/L, whilst the ADA criteria accept a glucose of less than 5.6 mmol/L for the criteria of normal glucose tolerance. In contrast, whilst HbA1c values at baseline were similar between those with normal glucose tolerance and prediabetes at baseline (estimated difference 0.6 mmol/mol (95% CI -4.9 to 3.8, p=0.8)), HbA1c concentrations at follow up in those with prediabetes were clearly higher than those with normal glucose tolerance (estimated difference 5.7 mmol/mol (95% CI 3.1 to 8.3, p<0.001). The minimum HbA1c value at follow up in those with prediabetes was 37 mmol/mol and thus entirely explained the differences in glycaemic status. Thus change in HbA1c (following logarithmic transformation) over the study period is used as the dependent variable in regression analysis below.
Table 3-13  Baseline and follow up characteristics and markers of glycaemic status for participants with normal glucose tolerance at baseline. A paired T test is shown.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow up</th>
<th>Paired T test *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Mean (SD)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Normal glucose tolerance (n=28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>28 (100)</td>
<td>40.8 (11.0)</td>
<td>28 (100)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28 (100)</td>
<td>45.1 (6.7)</td>
<td>28 (100)</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>26 (93)</td>
<td>4.83 (0.44)</td>
<td>26 (93)</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>19 (68)</td>
<td>35.0 (2.7)</td>
<td>19 (68)</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>18 (65)</td>
<td>106.7 (51.5)</td>
<td>18 (65)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>16 (57)</td>
<td>2.02 (0.93)</td>
<td>16 (57)</td>
</tr>
<tr>
<td>HOMA-%B</td>
<td>16 (57)</td>
<td>172.9 (50.9)</td>
<td>16 (57)</td>
</tr>
<tr>
<td>HOMA-%S</td>
<td>16 (57)</td>
<td>60.8 (30.5)</td>
<td>16 (57)</td>
</tr>
</tbody>
</table>

* p values for BMI, fasting glucose, HbA1c, fasting insulin, and HOMA following logarithmic transformation
Fasting insulin concentrations were not clearly different at either baseline or follow up in those with normal glucose tolerance or those with prediabetes (estimated difference 28.1 pmol/L for baseline insulin (95% CI -106.7 to 50.4, P=0.5) and 2.7 pmol/L for follow up insulin (95% CI -17.2 to 11.9, p=0.7). Given the absence of differences in the other dependent factor (fasting glucose), calculations of HOMA-IR, HOMA-%B, and HOMA-%S were also not clearly different at either baseline or follow up in either group.

The mean (SD) age at operation of those who remained with normal glucose tolerance during the study period was 41.8 (11.7) years and 37.6 (9.9) years in those who progressed to prediabetes during follow up. The mean (SD) duration of follow up was also similar in the two groups with 9.8 (4.4) and 12.8 (6.5) years of follow up for those with normal glucose tolerance and prediabetes respectively. Consequently, the age at follow up was not clearly different between the two groups (mean (SD) of 51.5 (12.3) years in those with normal glucose tolerance at follow up and 50.4 (16.0) years in those with prediabetes (estimated difference 3.1 years (95% CI -12.2 to 14.54), p=0.87).

BMI at baseline and follow up were similar irrespective of whether normal glucose tolerance or prediabetes were evident at follow up (mean (SD) 44.3 (7.0) kg/m² in those who remained with normal glucose tolerance and 46.4 (5.7) kg/m² in those who progressed to prediabetes; estimated difference 2.1 kg/m² (95% CI -4.9 to 9.1, p=0.5). Likewise, participants had obtained a very similar BMI at follow up irrespective of glycaemic outcome with a mean (SD) BMI of 32.1 (7.6) kg/m² in those who remained with normal glucose tolerance and 34.2 (7.8) kg/m² in those with prediabetes. Mean (SD) Body weight loss (%) was similar in both groups at follow up at 27.9 (8.8) % in those with normal glucose tolerance at follow up, and 26.8 (10.0) % in those with prediabetes (estimated difference 1.1% (95% CI -8.2 to 10.3, p=0.8).

Univariate regression analysis was performed to assess whether any variable could predict diabetes status outcome in those participants with normal glucose tolerance at baseline. As n=28, multivariate analysis was not appropriate. With the exception of HbA1c at follow up (not relevant as the groups were defined by this marker alone as above) only HbA1c at baseline (r=0.65, f=12.3, p=0.003) and follow up (r=0.8, f=29.2, p<0.001) predicted the change in HbA1c over the study period at follow up and accounted for 39% and 61% of the observed variation respectively. The regression equations were:
Chapter 3: Clinical outcomes after RYGB

\[
\text{Change in LnHbA1c (mmol/mol)} = -3.8 + (1.1 \times \text{Ln(x) HbA1c (mmol/mol) at baseline})
\]

\[
\text{Change in LnHbA1c (mmol/mol)} = 3.7 + (-1.0 \times \text{Ln(x) HbA1c (mmol/mol) at follow up})
\]

Table 3-14 Univariate regression analyses outcomes for baseline variables (independent) against the change in logarithmic transformed HbA1c over the study period (dependent variables) in participants with normal glucose tolerance at baseline

<table>
<thead>
<tr>
<th>Independent variable *</th>
<th>Constant</th>
<th>Independent variable</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at operation (years)</td>
<td>-0.02</td>
<td>0.001</td>
<td>0.7</td>
</tr>
<tr>
<td>Age at follow up (years)</td>
<td>-0.005</td>
<td>0.001</td>
<td>0.8</td>
</tr>
<tr>
<td>Duration of follow up (years)</td>
<td>0.09</td>
<td>-0.007</td>
<td>0.5</td>
</tr>
<tr>
<td>BMI at baseline (kg/m2)</td>
<td>-0.5</td>
<td>0.15</td>
<td>0.4</td>
</tr>
<tr>
<td>BMI at follow up (kg/m2)</td>
<td>-0.16</td>
<td>0.06</td>
<td>0.7</td>
</tr>
<tr>
<td>Change in BMI (kg/m2)</td>
<td>-0.06</td>
<td>0.03</td>
<td>0.7</td>
</tr>
<tr>
<td>Fasting glucose at baseline (mmol/L)</td>
<td>-0.05</td>
<td>0.04</td>
<td>0.9</td>
</tr>
<tr>
<td>Fasting glucose at follow up (mmol/L)</td>
<td>-0.02</td>
<td>0.03</td>
<td>0.95</td>
</tr>
<tr>
<td>HbA1c at baseline (mmol/mol)</td>
<td>-3.8</td>
<td>1.1</td>
<td>0.003</td>
</tr>
<tr>
<td>HbA1c at follow up (mmol/mol)</td>
<td>3.7</td>
<td>-1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting insulin at baseline (pmol/L)</td>
<td>-0.19</td>
<td>0.05</td>
<td>0.5</td>
</tr>
<tr>
<td>Fasting insulin at follow up (pmol/L)</td>
<td>-0.3</td>
<td>0.09</td>
<td>0.3</td>
</tr>
<tr>
<td>HOMA-IR at baseline</td>
<td>-0.01</td>
<td>0.05</td>
<td>0.5</td>
</tr>
<tr>
<td>HOMA-IR at follow up</td>
<td>0.05</td>
<td>0.09</td>
<td>0.5</td>
</tr>
</tbody>
</table>

* following logarithmic transformation for fasting glucose, HbA1c, insulin, and HOMA-IR
3.1.4.5.2 Diabetes outcomes in those with prediabetes at baseline

42 participants had prediabetes, and 40 of these had sufficient data to categorise diabetes status at baseline and follow up. 37 (88%) participants had undergone transected RYGB whilst the remaining 5 (12%) participants had undergone silastic ring RYGB. Descriptive data for this group are presented in Table 3-16.

<table>
<thead>
<tr>
<th>Type of bariatric surgery performed in those with prediabetes at baseline</th>
<th>N=42</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transected Roux-en-Y Gastric Bypass</td>
<td>37 (88)</td>
<td></td>
</tr>
<tr>
<td>Silastic ring RYGB</td>
<td>5 (12)</td>
<td></td>
</tr>
</tbody>
</table>

The mean (SD) duration of follow up in this group was 8.7 (4.3) years (minimum 5.1, maximum 22.2 years). Twenty-five (63%) of these participants had an improvement in glucose tolerance to normal concentrations at follow up. 14 (35%) remained with prediabetes, whilst one (2%) had progressed to type 2 diabetes. In keeping with the ADA definitions for diabetes status following bariatric surgery, no participant within this group used diabetes medications at follow up.

As with those with normal glucose tolerance at baseline, fasting glucose concentrations in those with prediabetes at baseline did not differ significantly at either baseline or follow up between those who had improved to normal glucose tolerance at follow up and those who remained with prediabetes (estimated difference 0.1 mmol/L for baseline glucose (95% CI -0.3 to 0.52, P=0.6) and -0.09 mmol/L for follow up glucose (95% CI -0.2 to 0.35, p=0.5). The maximum fasting glucose concentration at follow up in those with prediabetes was 5.5 mmol/L which falls below the threshold of 5.6 mmol/L set by the ADA as a definition of prediabetes.
Table 3-16 Baseline and follow up characteristics and markers of glycaemic status for participants with prediabetes at baseline. A paired T test is shown.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow up</th>
<th>Paired T test *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Mean (SD)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Prediabetes (n=42)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>42 (100)</td>
<td>48.0 (9.6)</td>
<td>42 (100)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>42 (100)</td>
<td>46.3 (9.1)</td>
<td>42 (100)</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>40(95)</td>
<td>5.47 (0.64)</td>
<td>40(95)</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>33 (79)</td>
<td>40.3 (3.3)</td>
<td>33 (79)</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>30 (71)</td>
<td>154.8 (91.7)</td>
<td>25</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>25 (60)</td>
<td>2.91 (1.25)</td>
<td>25 (60)</td>
</tr>
<tr>
<td>HOMA-%B</td>
<td>25 (60)</td>
<td>171.7 (65.5)</td>
<td>25 (60)</td>
</tr>
<tr>
<td>HOMA-%S</td>
<td>25 (60)</td>
<td>42.0 (21.5)</td>
<td>25 (60)</td>
</tr>
</tbody>
</table>

*p values for BMI, fasting glucose, HbA1c, fasting insulin, and HOMA following logarithmic transformation*
Hba1c values at follow up were clearly different between the groups as expected and, as with those with normal glucose tolerance at baseline, was the sole determinant of glycaemic status. In contrast, HbA1c values at baseline in those participants with prediabetes before surgery were higher in those who had remained with prediabetes at the follow up appointment, than those who had improved to normal glucose tolerance. The mean (SD) HbA1c at baseline was 39.2 (3.4) and 42.1 (2.3) mmol/mol in those with normal glucose tolerance and prediabetes at follow up respectively (estimated difference 2.92 mmol/mol (95% CI 0.7 to 5.1 to 5.41, p=0.01).

Fasting insulin concentrations were not clearly different at either baseline or follow up in those with normal glucose tolerance or those with prediabetes (estimated difference 24.4 pmol/L for baseline insulin (95% CI -42.7 to 91.4, P=0.5) and 9.5 pmol/L for follow up insulin (95% CI -4.9 to 24.0, p=0.2). Given the absence of differences in the other dependent factor (fasting glucose), calculations of HOMA-IR, HOMA-%B, and HOMA-%S were also not clearly different at either baseline or follow up in either group. The mean (SD) HOMA-%S at baseline and follow up in those who had normal glucose tolerance was 45.4% (24.7) and 141.5% (50.7) respectively, whilst the mean (SD) at the same time points who those who remained with prediabetes at follow up was 43.8 (23.1) and 106.9 (42.4). The estimated difference in HOMA-%S at follow up between the two groups was 34.6 (95% CI 2.3 to 71.6) although this did not reach statistical significance (p=0.07). Beta cell steady state function, as assessed by HOMA-%B, was increased in all those with prediabetes at baseline, and normalised in both groups at follow up (mean (SD) 88.0% (20.4) in those who obtained normal glucose tolerance and 112.3 (37.4) in those who remained with prediabetes; estimated difference 15.2% (95% CI -2.67 to 33.1, p=0.09).

Thus, the major determinant of the differences in glucose homeostasis, as assessed using the HOMA model, in those with preoperative prediabetes was an improvement in insulin sensitivity to concentrations greater than the population normal control average. As illustrated by both the fall in fasting insulin concentrations and HOMA-%B in this cohort, this allowed normalisation of preoperative hyperinsulinaemia.

There was no difference in the age at operation of participants who obtained normal glucose tolerance versus those who remained with prediabetes (estimated difference 3.1 years (95% CI -3.2 to 9.5, p=0.3). However, participants who obtained normal glucose tolerance had a significantly longer duration of follow up (mean (SD) 9.5 (4.4) versus 6.7 (1.4) years, estimated difference 2.8 years (95% CI 0.3 to 5.3, p=0.03)) than those who remained with prediabetes; consequently, participants with normal glucose tolerance at follow up were older at that point (mean (SD) 58.2 (10.5) versus 52.3
estimated difference 5.9 years (95% CI -1.1 to 13.0) although this was not statistically significant (p=0.1).

BMI at baseline and follow up were similar irrespective of whether normal glucose tolerance or pre diabetes were evident at follow up. The mean (SD) BMI at baseline for those who obtained normal glucose tolerance was 46.7 (9.9) kg/m2 and 45.3 (7.8) kg/m2 in those who remained with pre diabetes (estimated difference 1.3 kg/m2 (95% CI -4.9 to 7.6, p=0.7). The mean (SD) BMI at follow up was 31.6 (7.1) kg/m2 in those who remained with normal glucose tolerance and 31.6 (8.2) kg/m2 in those with pre diabetes; estimated difference 0.03 kg for baseline weight (95% CI -5.1 to 5.0, P=1.0). Mean (SD) Body weight loss (%) at follow up was slightly greater in both groups than that seen in those with preoperative normal glucose tolerance, at 30.2 (10.9) % in those with normal glucose tolerance at follow up, and 30.9 (10.9) % in those with pre diabetes. However, there was no clear difference between those with pre diabetes at baseline and normal or pre diabetes at follow up (estimated difference 0.71% (95% CI -5.74 to 7.15, p=0.83).

Univariate regression analysis was performed to assess whether any variable could predict the change in HbA1c over the follow up period in those participants with pre diabetes at baseline (Table 3-17). HbA1c at follow up was the sole differentiator of the groups (as above) and therefore follow up values were not considered. HbA1c at baseline did however predict the change in HbA1c and therefore diabetes status at follow up (r=0.4, f=4.5, p=0.04), although accounted for only 10% of the variance in HbA1c change. Fasting glucose at baseline also predicted the change in HbA1c over the study period (r=0.43, f=6.8, p=0.01) and accounted for 16% of the total variation. Regression plots are shown in Figure 3-12, and the regression equations were:

\[
\text{Change in HbA1c (mmol/mol)} = -1.4 + (0.4 \times \text{Ln(x)} \text{HbA1c (mmol/mol) at baseline})
\]

\[
\text{Change in HbA1c (mmol/mol)} = -0.5 + (0.35 \times \text{Ln(x) fasting glucose (mmol/L) at baseline})
\]
Table 3-17  Univariate regression analyses outcomes for baseline variables (independent) against diabetes status at the follow up assessment (dependent variables) in participants with prediabetes at baseline

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Constant</th>
<th>Independent variable</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at operation (years)</td>
<td>0.07</td>
<td>&lt;0.001</td>
<td>0.9</td>
</tr>
<tr>
<td>Age at follow up (years)</td>
<td>0.07</td>
<td>&lt;0.001</td>
<td>0.9</td>
</tr>
<tr>
<td>Duration of follow up (years)</td>
<td>0.07</td>
<td>&lt;0.001</td>
<td>1.0</td>
</tr>
<tr>
<td>BMI at baseline (kg/m2)</td>
<td>-0.68</td>
<td>0.2</td>
<td>0.05</td>
</tr>
<tr>
<td>BMI at follow up (kg/m2)</td>
<td>-0.08</td>
<td>0.05</td>
<td>0.6</td>
</tr>
<tr>
<td>Change in BMI (kg/m2)</td>
<td>-0.06</td>
<td>0.05</td>
<td>0.08</td>
</tr>
<tr>
<td>Fasting glucose at baseline (mmol/L)</td>
<td>-0.52</td>
<td>0.35</td>
<td>0.01</td>
</tr>
<tr>
<td>Fasting glucose at follow up (mmol/L)</td>
<td>0.5</td>
<td>-0.27</td>
<td>0.2</td>
</tr>
<tr>
<td>HbA1c at baseline (mmol/mol)</td>
<td>-1.4</td>
<td>0.4</td>
<td>0.04</td>
</tr>
<tr>
<td>HbA1c at follow up (mmol/mol)</td>
<td>2.2</td>
<td>-0.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting insulin at baseline (pmol/L)</td>
<td>-0.03</td>
<td>0.02</td>
<td>0.25</td>
</tr>
<tr>
<td>Fasting insulin at follow up (pmol/L)</td>
<td>0.19</td>
<td>-0.03</td>
<td>0.4</td>
</tr>
<tr>
<td>HOMA-IR at baseline</td>
<td>-0.01</td>
<td>0.09</td>
<td>0.03</td>
</tr>
<tr>
<td>HOMA-IR at follow up</td>
<td>0.06</td>
<td>-0.1</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* following logarithmic transformation for fasting glucose, HbA1c, insulin, and HOMA-IR

HOMA-IR at baseline predicted the change in HbA1c over the study period (r=0.41, f=5.6, p=0.03) and accounted for 14% of the observed variation. The regression equation was:

\[
\text{Change in HbA1c (mmol/mol)} = -0.014 + (0.09 \times \text{HOMA-IR at baseline})
\]
Multivariate regression analysis was then performed with models restricted to include only two independent variables as n=40. An optimal model included baseline concentrations of HbA1c and fasting glucose as shown in Table 3-18. The change in HbA1c over the follow up period was predicted...
by this model ($F(2,30)=5.0, P=0.01$) but explained only 20% of the total variation in the observed change in HbA1c.

Table 3-18 Multivariate regression analysis incorporating baseline values of HbA1c and fasting glucose (following logarithmic transformation) to predict the change in HbA1c over the follow up period in participants with prediabetes at baseline. Table a presents the model summary and table b presents the coefficients

<table>
<thead>
<tr>
<th>Model summary</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R$</td>
<td>$R^2$</td>
</tr>
<tr>
<td>0.50</td>
<td>0.25</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Unstandardised coefficients</th>
<th>Standardised coefficients</th>
<th>$T$</th>
<th>$P$ value</th>
<th>95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-1.55</td>
<td>0.65</td>
<td>-2.38</td>
<td>0.02</td>
<td>-2.9 to -0.2</td>
</tr>
<tr>
<td>Baseline HbA1c (mmol/mol)</td>
<td>0.30</td>
<td>0.18</td>
<td>0.27</td>
<td>1.67</td>
<td>0.1</td>
</tr>
<tr>
<td>Baseline fasting glucose (mmol/L)</td>
<td>0.30</td>
<td>0.13</td>
<td>0.36</td>
<td>2.23</td>
<td>0.03</td>
</tr>
</tbody>
</table>

A receiver operator curve was constructed to further assess the use of baseline HbA1c in those with prediabetes as a predictor of glycaemic outcome at follow up (Figure 3-13). The attached table presents coordinates of this curve and shows that an HbA1c of >39.5 mmol/mol at baseline (and ≤47 mmol/mol given the limitations of criteria for prediabetes) was 92% sensitive for persistent prediabetes at follow up, but only 50% specific. An HbA1c of >40.5 mmol/mol at baseline was 85% sensitive and 65% specific for persistent prediabetes at the follow up assessment.
Figure 3-13  Receiver operator curve (ROC) and coordinates for HbA1c at baseline to predict persistent prediabetes at follow up

<table>
<thead>
<tr>
<th>Positive if Greater Than or Equal To (HbA1c (mmol/mol))</th>
<th>Sensitivity</th>
<th>1 - Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>32.0</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>33.5</td>
<td>1.000</td>
<td>.900</td>
</tr>
<tr>
<td>35.0</td>
<td>1.000</td>
<td>.850</td>
</tr>
<tr>
<td>37.0</td>
<td>1.000</td>
<td>.750</td>
</tr>
<tr>
<td>38.5</td>
<td>1.000</td>
<td>.650</td>
</tr>
<tr>
<td>39.5</td>
<td>.923</td>
<td>.500</td>
</tr>
<tr>
<td>40.5</td>
<td>.846</td>
<td>.350</td>
</tr>
<tr>
<td>41.5</td>
<td>.308</td>
<td>.250</td>
</tr>
<tr>
<td>42.5</td>
<td>.308</td>
<td>.150</td>
</tr>
<tr>
<td>43.5</td>
<td>.308</td>
<td>.100</td>
</tr>
<tr>
<td>44.5</td>
<td>.231</td>
<td>.050</td>
</tr>
<tr>
<td>45.5</td>
<td>.154</td>
<td>.000</td>
</tr>
<tr>
<td>47.0</td>
<td>.000</td>
<td>.000</td>
</tr>
</tbody>
</table>
3.1.4.5.3  Diabetes outcomes in those with type 2 diabetes at baseline

42 participants had type 2 diabetes at baseline, 36 (86%) of participants had sufficient data available to categorise diabetes status at baseline and follow up. 38 (92%) of the participants had undergone transected RYGB whilst three (5%) and one (2%) participant had undergone silastic ring RYGB and gastric bypass respectively (Table 3-19). Descriptive data for this group are presented in Table 3-20.

Table 3-19  Type of bariatric surgery performed in those with Type 2 diabetes at baseline

<table>
<thead>
<tr>
<th>Type of bariatric surgery performed</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transected Roux-en-Y Gastric Bypass</td>
<td>38 (92)</td>
</tr>
<tr>
<td>Silastic ring RYGB</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Gastric bypass</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

The mean (SD) age at operation and follow up was 52.8 (8.24) and 61.6 (8.4) respectively, resulting in a mean (SD) of 8.8 (4.6) years). 26 (72%) of these participants had an improvement in glucose tolerance to either normal glucose tolerance (9 participants (25%)) or prediabetes (17 participants (47%)) at follow up. 10 participants (28%) remained with type 2 diabetes at follow up.

It is important to note that 24/42 participants in this analysis were using diabetes medications at baseline with six of those participants using insulin therapy. Two (34%) participants with type 2 diabetes at baseline but normal glucose tolerance at follow up were using oral diabetes medications at the time of surgery, with the remainder using dietary methods only. 11/17 (65%) of those with prediabetes at follow up were using oral diabetes medications at baseline, and one of these participants was also using insulin therapy. 10/11 (91%) of those with persistent type 2 diabetes at follow up were using oral diabetes medications at baseline, and four of these participants were also using insulin therapy. Furthermore, 5/11 (42%) of those with persistent type 2 diabetes at follow up remained on diabetes medications (four using metformin, one additionally using a
Table 3-20  Baseline and follow up characteristics and markers of glycaemic status for participants with type 2 diabetes at baseline. A paired T test is shown.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow up</th>
<th>Paired T test *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Mean (SD)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Type 2 diabetes (n=42)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>42 (100)</td>
<td>52.8 (8.2)</td>
<td>42 (100)</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>42 (100)</td>
<td>48.2 (9.5)</td>
<td>42 (100)</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>32 (77)</td>
<td>8.08 (2.71)</td>
<td>32 (77)</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>31 (75)</td>
<td>61.7 (15.9)</td>
<td>31 (75)</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>29 (71)</td>
<td>200.8 (89.2)</td>
<td>29 (71)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>20 (48)</td>
<td>3.73 (1.42)</td>
<td>20 (48)</td>
</tr>
<tr>
<td>HOMA-%B</td>
<td>20 (48)</td>
<td>109.6 (54.1)</td>
<td>20 (48)</td>
</tr>
<tr>
<td>HOMA-%S</td>
<td>20 (48)</td>
<td>32.3 (17.1)</td>
<td>20 (48)</td>
</tr>
</tbody>
</table>

*p values for BMI, fasting glucose, HbA1c, fasting insulin, and HOMA following logarithmic transformation
sulphonylurea, and one on insulin therapy). By definition, none of the participants with normal glucose tolerance or prediabetes at follow up were using diabetes medications. In those with persistent type 2 diabetes at follow up only, the mean (SD) number of medications at follow up was 0.6 (0.73).

Table 3-21  Independent T test analysis to compare age at diagnosis and duration of diabetes prior to surgery in participants with type 2 diabetes at baseline and either prediabetes or type 2 diabetes at follow up

<table>
<thead>
<tr>
<th></th>
<th>ADA diagnosis at follow up</th>
<th>Independent T test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prediabetes (n=17)</td>
<td>Type 2 diabetes (n=12)</td>
</tr>
<tr>
<td>n (%)</td>
<td>Mean (SD)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Age of diagnosis (years)</td>
<td>15 (87)</td>
<td>44.7 (10.1)</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>15 (87)</td>
<td>9.5 (7.9)</td>
</tr>
</tbody>
</table>

A diagnosis of type 2 diabetes was made during the assessments for surgery in 4/42 participants, whilst 10/42 participants had not received a diagnosis of type 2 diabetes prior to surgery from their usual health practitioner, despite confirmatory biochemistry. Thus, 28 participants were questioned about duration of diabetes prior to surgery. The mean (SD) duration of diabetes in all those with type 2 diabetes at baseline was 9.1 (7.0) years (minimum = 0 (i.e. informed of diagnosis during assessment for surgery, maximum = 23 years). The mean (SD) age of diabetes diagnosis was 43.2 (9.7) years (minimum 20.0, maximum 61.0). There was no apparent difference in either the age of onset, or duration prior to surgery, of diabetes in those who improved to prediabetes at follow up or remained with type 2 diabetes (Table 3-21).
Chapter 3: Clinical outcomes after RYGB

Univariate regression analysis was performed to assess whether any variable could predict the change in HbA1c over the follow up period in those participants with type 2 diabetes at baseline (Table 3-22). HbA1c at follow up was the key differentiator of the groups (as above) and therefore is irrelevant in this analysis. Fasting glucose, HbA1c, fasting insulin, and HOMA-IR (all following logarithmic transformation) at baseline did however predict the change in HbA1c and therefore diabetes status at follow up. Fasting glucose predicted the change in HbA1c \( (r=0.58, f=12.2, p=0.002) \) and accounted for 31% of the observed variation in this outcome. HbA1c predicted the change in HbA1c \( (r=0.56, f=13.3, p=0.001) \) and accounted for the 29% of the variation. Fasting insulin and HOMA-IR \( (r=0.43, f=6.4, p=0.02; \text{ and } r=0.47, f=5.9, p=0.03) \) accounted for 16 and 18% of the variation respectively. Regression plots are shown in Figure 3-14, and the regression equations were:

\[
\text{Change in HbA1c (mmol/mol)} = -0.49 + (0.38 \times \ln(x) \text{ fasting glucose (mmol/L) at baseline})
\]

\[
\text{Change in HbA1c (mmol/mol)} = -1.6 + (0.47 \times \ln(x) \text{ HbA1c (mmol/mol) at baseline})
\]

\[
\text{Change in HbA1c (mmol/mol)} = -0.77 + (0.21 \times \ln(x) \text{ fasting insulin (pmol/L) at baseline})
\]

\[
\text{Change in HbA1c (mmol/mol)} = -0.03 + (0.26 \times \ln(x) \text{ HOMA-IR at baseline})
\]

Furthermore, the change in BMI following RYGB also predicted the change in HbA1c \( (r=0.43, f=6.4, p=0.02) \) and accounted for 15% of the observed variation. The regression equation was:

\[
\text{Change in HbA1c (mmol/mol)} = -0.13 + (0.17 \times \ln(x) \text{ BMI (kg/m}^2\text{)})
\]

Thus, univariate regression modelling predicts that, in participants with pre-operative type 2 diabetes, the change in HbA1c over the follow up period will be greater with a greater baseline fasting glucose, HbA1c, fasting insulin, and HOMA-IR, and in those who lose a greater amount of weight following surgery. Duration of diabetes prior to surgery or the age at which diabetes was diagnosed did not predict glycaemic outcomes.
Table 3-22  Univariate regression analyses outcomes for baseline variables (independent) against change in HbA1c over the follow up period (dependent variables) in participants with type 2 diabetes at baseline

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Constant</th>
<th>Independent variable</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at operation (years)</td>
<td>0.55</td>
<td>-0.005</td>
<td>0.3</td>
</tr>
<tr>
<td>Age at follow up (years)</td>
<td>0.52</td>
<td>-0.003</td>
<td>0.4</td>
</tr>
<tr>
<td>Duration of follow up (years)</td>
<td>0.3</td>
<td>0.008</td>
<td>0.6</td>
</tr>
<tr>
<td>BMI at baseline (kg/m2)</td>
<td>-1.0</td>
<td>0.4</td>
<td>0.07</td>
</tr>
<tr>
<td>BMI at follow up (kg/m2)</td>
<td>-0.19</td>
<td>0.14</td>
<td>0.5</td>
</tr>
<tr>
<td>Change in BMI (kg/m2)</td>
<td>-0.13</td>
<td>0.17</td>
<td>0.02</td>
</tr>
<tr>
<td>Fasting glucose at baseline (mmol/L)</td>
<td>-0.49</td>
<td>0.38</td>
<td>0.002</td>
</tr>
<tr>
<td>Fasting glucose at follow up (mmol/L)</td>
<td>0.45</td>
<td>-0.08</td>
<td>0.6</td>
</tr>
<tr>
<td>HbA1c at baseline (mmol/mol)</td>
<td>-1.59</td>
<td>0.5</td>
<td>0.001</td>
</tr>
<tr>
<td>HbA1c at follow up (mmol/mol)</td>
<td>1.4</td>
<td>-0.29</td>
<td>0.09</td>
</tr>
<tr>
<td>Fasting insulin at baseline (pmol/L)</td>
<td>-0.77</td>
<td>0.21</td>
<td>0.02</td>
</tr>
<tr>
<td>Fasting insulin at follow up (pmol/L)</td>
<td>0.61</td>
<td>-0.078</td>
<td>0.3</td>
</tr>
<tr>
<td>HOMA-IR at baseline</td>
<td>-0.03</td>
<td>0.26</td>
<td>0.03</td>
</tr>
<tr>
<td>HOMA-IR at follow up</td>
<td>0.3</td>
<td>-0.13</td>
<td>0.3</td>
</tr>
<tr>
<td>Age at diagnosis of diabetes</td>
<td>0.45</td>
<td>-0.003</td>
<td>0.5</td>
</tr>
<tr>
<td>Duration of diabetes pre surgery</td>
<td>0.331</td>
<td>-0.001</td>
<td>0.9</td>
</tr>
</tbody>
</table>

* following logarithmic transformation for fasting glucose, HbA1c, insulin, and HOMA-IR
Figure 3-14 Regression variable plots for a) Ln(x) fasting glucose at baseline, b) Ln(x) HbA1c at baseline, c) Ln(x) fasting insulin at baseline, and d) Ln(x) HOMA-IR at baseline, against change in HbA1c over the follow up period.

Multivariate regression analysis was then performed with models restricted to include only two independent variables as n=36. The optimal model included the change in BMI (kg/m\(^2\)) over the follow up period, and either the baseline fasting glucose (mmol/L, model A, Table 3-23) or the baseline HbA1c (mmol/mol, model B, Table 3-24). The change in HbA1c over the follow up period was predicted by model A (F(2,23)=14.1, P<0.001, r=0.74, r\(^2\)=0.55) and explained 51% of the total variation in the observed change in HbA1c. The change in HbA1c over the follow up period was predicted by model B (F(2,28)=12.2, P<0.001, r=0.68, r\(^2\)=0.47) and explained 43% of the total variation in the observed change in HbA1c.
Table 3-23  Multivariate regression analysis incorporating baseline values of fasting glucose (following logarithmic transformation) and the change in BMI following surgery, to predict the change in HbA1c over the follow up period in participants with type 2 diabetes at baseline. Table a presents the model summary and table b presents the coefficients.

<table>
<thead>
<tr>
<th>Model summary</th>
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<tbody>
<tr>
<td>R</td>
<td>R^2</td>
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<tr>
<td>0.74</td>
<td>0.55</td>
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</table>

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Unstandardised coefficients</th>
<th>Standardised coefficients</th>
<th>T</th>
<th>P value</th>
<th>95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-0.96</td>
<td>0.24</td>
<td>-4.01</td>
<td>&lt;0.001</td>
<td>-1.45 to -0.47</td>
</tr>
<tr>
<td>Baseline fasting glucose (mmol/L)</td>
<td>0.37</td>
<td>0.09</td>
<td>0.56</td>
<td>4.04</td>
<td>0.001 0.18 to 0.56</td>
</tr>
<tr>
<td>Change in BMI (kg/m^2) over follow up</td>
<td>0.2</td>
<td>0.06</td>
<td>0.46</td>
<td>3.31</td>
<td>0.003 0.07 to 0.32</td>
</tr>
</tbody>
</table>

Table 3-24  Multivariate regression analysis incorporating baseline values of HbA1c (following logarithmic transformation) and the change in BMI following surgery, to predict the change in HbA1c over the follow up period in participants with type 2 diabetes at baseline. Table a presents the model summary and table b presents the coefficients.

<table>
<thead>
<tr>
<th>Model summary</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>R^2</td>
</tr>
<tr>
<td>0.68</td>
<td>0.47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Unstandardised coefficients</th>
<th>Standardised coefficients</th>
<th>T</th>
<th>P value</th>
<th>95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-1.9</td>
<td>0.48</td>
<td>-3.9</td>
<td>&lt;0.001</td>
<td>-2.9 to – 0.9</td>
</tr>
<tr>
<td>Baseline HbA1c (mmol/mol)</td>
<td>0.44</td>
<td>0.12</td>
<td>0.53</td>
<td>3.9</td>
<td>0.001 0.21 to 0.68</td>
</tr>
<tr>
<td>Change in BMI (kg/m^2) over follow up</td>
<td>0.15</td>
<td>0.06</td>
<td>0.39</td>
<td>2.8</td>
<td>0.009 0.04 to 0.27</td>
</tr>
</tbody>
</table>
Receiver operator curves were constructed to further assess the use of baseline fasting glucose and HbA1c values in those with type 2 diabetes as a predictor of glycaemic outcome at follow up (Figure 3-15). A fasting glucose of greater than or equal to 8.15 mmol/L at baseline was 75% sensitive and 73% specific for persistent type 2 diabetes at follow-up. Alternatively, a fasting glucose of ≥9.70 mmol/L was only 62.5% sensitive for persistent type 2 diabetes at follow up, but 90% specific. An HbA1c of greater than or equal to 62 mmol/mol at baseline was 87.5% sensitive for persistent type 2 diabetes at follow up, and 78.3% specific. Alternatively, and HbA1c of ≥66.5 mmol/mol was 75% sensitive but 91.3% specific for persistent type 2 diabetes. Conversely, 80% specificity for normal glucose tolerance in those with type 2 diabetes at baseline was not reached until a fasting glucose and HbA1c threshold of 10.25 mmol/L and 89.5 mmol respectively, rendering the clinical use of this tool for predicting diabetes resolution limited.

Figure 3-15 Receiver operator curves (ROC) and coordinates for a and c) Fasting glucose (mmol/L) and b and d) HbA1c (mmol/mol) at baseline in participants with type 2 diabetes, as a predictor of persistent type 2 diabetes status at follow up
c) Fasting glucose (mmol/L) greater than

<table>
<thead>
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<th>Fasting glucose (mmol/L) greater than</th>
<th>Sensitivity</th>
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</thead>
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<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>4.7000</td>
<td>1.000</td>
<td>.955</td>
</tr>
<tr>
<td>5.2500</td>
<td>1.000</td>
<td>.909</td>
</tr>
<tr>
<td>5.4500</td>
<td>1.000</td>
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<tr>
<td>7.1000</td>
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<td>7.4000</td>
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d) HbA1c (mmol/mol) greater than

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<th>1 - Specificity</th>
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<td>.000</td>
</tr>
<tr>
<td>100.0000</td>
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<td>.000</td>
</tr>
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</table>
3.1.4.6 Blood pressure at baseline and follow up

Data for systolic, diastolic and mean arterial blood pressure at baseline and follow up were normally distributed as demonstrated by inspection of histograms (Figure ii-7 (377)) and assessment using the Shapiro-Wilk test (Table ii-9 (377)). Furthermore, the change from baseline to follow up of each of these variables also displayed normal distribution (Figure ii-8 (378)). Thus, parametric models were used for comparison of the data at baseline and follow up. Box plots of systolic, diastolic, and mean arterial blood pressure are at baseline and follow up in all participants and those with hypertension at baseline are presented in Figure 3-16.

Figure 3-16 Box plots to show a) systolic blood pressure, b) diastolic blood pressure, and c) mean arterial pressure at baseline and follow up, in (left column) all participants, and (right column) those with hypertension at baseline.
The mean (SD) systolic and diastolic blood pressure at baseline was 141.9 (20.7) mmHg and 81.9 (12.1) mmHg respectively, whilst the mean (SD) SBP and DBP at follow up was 129.8 (21.4) and 78.7 (10.2) mmHg respectively. The mean arterial pressure (MAP) at baseline was 101.9 (13.9) mmHg, and 95.7 (12.7) mmHg at follow up.

Systolic blood pressure (SBP) was significantly lower at follow up when compared to baseline measurements (Figure 3-16 and Table 3-25). The mean (SD) SBP at baseline was 141.9 (20.7) and 129.8 (21.4) mmHg at follow up; estimated difference 11.3 mmHg (95% CI 7.3 to 15.4, p<0.001). Predictably the mean (SD) systolic blood pressure at baseline was higher (146.6 (18.6) mmHg) when only those with hypertension (n=96) were considered, but a similar reduction in blood pressure at follow up was noted (mean (SD) SBP at follow up 133.9 (21.3) mmHg; estimated difference 12.7 mmHg (95% CI 8.1 to 17.3, p<0.001).

Diastolic blood pressure (DBP) was also significantly reduced at follow up in those with and without hypertension at baseline (Figure 3-16 and Table 3-25). The mean (SD) DBP at baseline in all participants was 81.9 (12.1) mmHg, and at follow up was 78.7 (10.2) mmHg; estimated difference 3.1 mmHg (95% CI 0.5 to 5.7, p=0.02). The mean (SD) DBP in those with hypertension at baseline (n=96) was 84.0 (11.5) mmHg, and at follow up was 80.0 (10.1) mmHg; estimated difference 4.0 mmHg (95% CI 1.2 to 6.7, p=0.006). Predictably, similar results were therefore noted when comparisons were made of mean arterial blood pressure (MAP) at baseline and follow up. The estimated reduction in MAP in all participants was 7.9 mmHg (95% CI 4.0 to 11.8, p<0.001), whilst the estimated reduction in those with hypertension at baseline was 7.0 mmHg (95% CI 4.0 to 9.9, p<0.001).
Table 3-25  Descriptive blood pressure data for all participants and those with hypertension at baseline and follow up. Results of a paired T test are shown.

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<th>Baseline</th>
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<th>Follow up (&gt;5 years)</th>
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<td>IQR</td>
<td>Min/Max</td>
<td>Mean (SD)</td>
<td>IQR</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td><strong>n=118</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Systolic blood pressure</td>
<td>141.9 (20.7)</td>
<td>30.0</td>
<td>100.0/200.0</td>
<td>129.8 (21.4)</td>
<td>25.1</td>
</tr>
<tr>
<td>(mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>81.9 (12.1)</td>
<td>13.5</td>
<td>50.0/120.0</td>
<td>78.7 (10.2)</td>
<td>12.7</td>
</tr>
<tr>
<td>(mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>101.9 (13.9)</td>
<td>15.3</td>
<td>66.7/133.3</td>
<td>95.7 (12.7)</td>
<td>15.6</td>
</tr>
<tr>
<td>(mmHg)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Number of blood pressure</td>
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<td>1.0</td>
<td>0/3</td>
<td>0.36 (0.56)</td>
<td>1.0</td>
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<td></td>
</tr>
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<td><strong>Hypertension at baseline (n=96)</strong></td>
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</tr>
<tr>
<td>Systolic blood pressure</td>
<td>146.7 (18.5)</td>
<td>24.8</td>
<td>104.0/200.0</td>
<td>133.9 (20.9)</td>
<td>23.0</td>
</tr>
<tr>
<td>(mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>84.0 (11.5)</td>
<td>17.0</td>
<td>63.0/120.0</td>
<td>80.0 (10.3)</td>
<td>13.6</td>
</tr>
<tr>
<td>(mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>104.9 (12.5)</td>
<td>17.0</td>
<td>77.3/133.3</td>
<td>98.0 (12.4)</td>
<td>16.9</td>
</tr>
<tr>
<td>(mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of blood pressure</td>
<td>0.86 (0.90)</td>
<td>1.0</td>
<td>0/3</td>
<td>0.40 (0.60)</td>
<td>1.0</td>
</tr>
<tr>
<td>medications</td>
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</tbody>
</table>

Chapter 3: Clinical outcomes after RYGB
Participants used fewer anti-hypertensive medications at follow up than at baseline. When all participants were considered, the mean (SD) number of anti-hypertensive medications used was 0.7 (0.9) and 0.36 (0.56) at baseline and follow up respectively; estimated difference 0.35 (95% CI 0.19 to 0.50, p<0.001). The reduction was greater still in those with hypertension at baseline with an estimated difference of 0.47 (95% CI 0.29 to 0.65, p<0.001).

In contrast to participants with hypertension at baseline, there were no clear changes following surgery in those with normotension at baseline (n=15). The estimated difference in SBP was a reduction of 3.7 mmHg (95% CI -4.1 to 11.5, p=0.32) from baseline to follow up, whilst DBP was slightly higher at follow up than at baseline; estimated difference 1.69 mmHg (95% CI -5.5 to 8.8, p=0.62). MAP measurements were very similar at both time points; estimated difference 0.1 mmHg (95% CI -6.6 to 6.8, p=0.97). Four (27%) of these participants developed hypertension by the study criteria during the period of follow up; two on the basis of blood pressure thresholds, and two who were using anti-hypertensive medication (both beta blockers).

Regression analysis was performed to explore relationships between the change in blood pressure following surgery and measured baseline variables. An initial analysis to assess whether baseline variables predict blood pressure outcomes included age at operation and follow up, gender, diabetes status and markers of glucose homeostasis, and did not reveal any relationship with the change in systolic, diastolic, or mean arterial pressure during follow up. Linear regression established that systolic, diastolic, and mean arterial blood pressure at baseline all predict the change in systolic, diastolic, and mean arterial blood pressure at follow up (Table ii-10 (379)). The duration of follow up since surgery predicted the change in diastolic blood pressure over the follow up period (r= 0.3, f=9.2, p=0.003) although accounted for only 8% of the variation in this outcome. The blood pressure status (normotensive versus hypertensive), number of blood pressure medications, duration of hypertension, and duration of treated hypertension at baseline did not relate to change in systolic, diastolic, or mean arterial blood pressure. Results pertaining to mean arterial blood pressure are thus discussed in more detail.

The systolic, diastolic, and mean arterial blood pressure at baseline each predicted mean arterial blood pressure at follow up ((r=0.46, f=24.7, p<0.001), (r=0.58, f=47.1, P<0.001), (r=0.56, f=43.1, p<0.001), and accounted for 20, 33, and 31% of the variance in mean arterial blood pressure at follow up respectively (Figure 3-17). The regression equations were:
Mean arterial blood pressure (mmHg) at follow up

\[
\text{Mean arterial blood pressure} = 35.4 + (-0.3 \times \text{Systolic blood pressure at baseline}) \\
= 46.1 + (-0.5 \times \text{Diastolic blood pressure at baseline}) \\
= 48.5 + (-0.6 \times \text{Mean arterial blood pressure})
\]

Figure 3-17  Regression variable plots for a) systolic blood pressure (mmHg), b) diastolic blood pressure (mmHg), and c) mean arterial blood pressure at baseline (mmHg), against the change in mean arterial blood pressure (mmHg) at follow up.
Thus, the degree of change in mean arterial blood pressure increased with increasing systolic, diastolic, and mean arterial blood pressure at baseline.

Multivariate regression analysis was then performed to assess whether a model including multiple independent variables could better predict the mean arterial blood pressure at follow up than any one independent variable alone. As with previous analysis, a multivariate model was restricted to a maximum of six independent variables (n=118). An optimal model was obtained by including mean arterial blood pressure (mmHg), the number of blood pressure medications used at baseline, and the duration of hypertension prior to surgery (Table 3-26). The change in mean arterial blood pressure at follow up was predicted by this model (F(3,36)=9.6, P<0.001, r=0.67, r²=0.45) and explained 40% of the total variation in mean arterial blood pressure. However, only the mean arterial blood pressure at baseline added significantly to the prediction, p<0.05, and therefore it is unlikely that the other independent variables (duration of hypertension prior to surgery and number of blood pressure medications at baseline) contribute. Furthermore, inclusion of any of these additional independent variables available only at follow up did not add to the multivariate model.

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Unstandardised coefficients</th>
<th>Standardised coefficients</th>
<th>T</th>
<th>P value</th>
<th>95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>61.4</td>
<td>14.4</td>
<td>4.3</td>
<td>&lt;0.001</td>
<td>32.2 to 90.6</td>
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<tr>
<td>Systolic blood pressure at baseline (mmHg)</td>
<td>-0.65</td>
<td>0.13</td>
<td>-0.65</td>
<td>-5.2</td>
<td>-0.9 to -0.4</td>
</tr>
<tr>
<td>Hypertension duration prior to surgery (years)</td>
<td>0.06</td>
<td>0.2</td>
<td>0.04</td>
<td>0.8</td>
<td>-0.4 to 0.51</td>
</tr>
<tr>
<td>Number of blood pressure medications used at baseline</td>
<td>2.85</td>
<td>3.7</td>
<td>0.1</td>
<td>0.78</td>
<td>-4.6 to 10.3</td>
</tr>
</tbody>
</table>
3.1.4.6.1 Stratification by blood pressure status at follow up

Whilst statistically significant reductions in systolic, diastolic, and mean arterial blood pressure were evident in all participants and those with hypertension at baseline, this did not translate into change in the blood pressure status of most participants. Of the 15 participants with normotension at baseline, 11 (73%) remained with normotension at follow up, whilst 4 (27%) had developed hypertension (Table 3-27). Ninety-three participants with hypertension at baseline had adequate information to categorise at both baseline and follow up. Of these, 19 (20%) had improved to normotension, whilst 74 (80%) remained with hypertension.

Table 3-27 Cross tabulation of blood pressure status at baseline against Blood pressure status at follow up

<table>
<thead>
<tr>
<th>Blood pressure status at follow up</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotension</td>
<td>30</td>
</tr>
<tr>
<td>Hypertension</td>
<td>78</td>
</tr>
<tr>
<td>Total</td>
<td>108</td>
</tr>
</tbody>
</table>

However, the 74 participants with persistent hypertension at follow up had better controlled hypertension than at baseline. The mean (SD) number of anti-hypertensive medications used by this group at baseline was 0.96 (0.87) and had fallen to 0.51 (0.62) at follow up; estimated difference 0.45 (95% CI 0.25 to 0.64, p<0.001). Furthermore, a reduction in SDP was evident with a mean (SD) of 149.7 (19.0) and 139.9 (19.5) mmHg at baseline and follow up respectively; estimated difference 9.8 mmHg (95% CI 4.4 to 15.3, p=0.001). Despite similar DBP measurements at baseline and follow up (estimated difference 2.0 mmHg (95% CI -1.2 to 5.2, p=0.22), this translated into a significant reduction in MAP with a mean (SD) measurement of 106.7 (13.1) and 102.0 (10.5) mmHg at baseline and follow up respectively; estimated difference 4.7 mmHg (1.2 to 8.1, p=0.01).
Duration of hypertension prior to surgery and duration of treatment with anti-hypertensive agents prior to surgery did not appear to predict blood pressure status outcomes. Forty-eight participants with hypertension at baseline (50%) also had information on duration of hypertension prior to surgery. Twenty-eight (58%) had received a diagnosis of hypertension within 10 years of surgery (mean (SD) 3.1 (2.9) years), whilst 20 (42%) had had hypertension for 10 years or longer prior to surgery (mean (SD) 19.2 (7.0) years) (Table 3-28). Three (12%) participants with less than 10 years of hypertension pre-surgery were normotensive at the follow-up appointment, in comparison to 1 (5%) of those with greater than 10 years of hypertension. Conversely, 25 (88%) of those with less than 10 years of hypertension were normotensive at the follow-up appointment in comparison to 19 (95%) of those with the longer duration of hypertension. The absence of any relationship between duration of hypertension prior to surgery and blood pressure status at follow-up was supported by regression analysis (R=0.15, F=1.1, p=0.3).

<table>
<thead>
<tr>
<th>N=48</th>
<th>Blood pressure status at follow up</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normotension</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Duration of hypertension before surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 years</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>≥10 years</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>44</td>
</tr>
</tbody>
</table>

Forty (42%) of participants with hypertension at baseline had information on the duration of hypertension treatment prior to surgery; this duration was slightly less than the mean duration of hypertension (estimated difference 1.1 more years since hypertension diagnosis than commencement of treatment (95% CI 0.02 to 2.2, p=0.05). Twenty-one (53%) had commenced treatment for
hypertension within 10 years of surgery (mean (SD) 3.0 (3.1) years), whilst 19 (47%) had had hypertension treatment for 10 years or longer prior to surgery (17.4 (6.3) years) (table 4-x). One (5%) participant in each group had normotension at the follow up assessment, whilst 20 and 19 (both 95%) of those with less than or more than 10 years of treatment respectively had persistent hypertension at follow up. Again, the absence of any relationship between duration of hypertension prior to surgery and blood pressure status at follow up was supported by regression analysis (R=0.02, F=0.1, p=0.9).

Table 3-29 Cross tabulation of the duration of hypertension treatment prior to surgery against blood pressure status at follow up

<table>
<thead>
<tr>
<th>Duration of hypertension treatment before surgery</th>
<th>Blood pressure status at follow up</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 years</td>
<td>Normotension</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>21</td>
</tr>
<tr>
<td>≥10 years</td>
<td>Normotension</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40</td>
</tr>
</tbody>
</table>

Furthermore, there were no clear differences when the mean systolic, diastolic and arterial pressure at follow up were compared in those with differing durations of hypertension, or differing durations of hypertension treatment prior to surgery. With respect to duration of hypertension, the estimated difference in mean systolic blood pressure between those with less than 10 years of hypertension prior to surgery, or greater than or equal to 10 years was 9.5 mmHg (95% CI -22.3 to 3.3, p=0.14). The estimated difference in mean diastolic blood pressure was 0.1 mmHg (95% CI -5.1 to 5.3, p=0.96), whilst the estimated difference in mean arterial pressure was 3.1 mmHg (95% CI -10.0 to 3.8, p=0.4). With respect to the duration of hypertension treatment prior to surgery, the estimated difference in mean systolic blood pressure between those with less than 10 years of hypertension treatment prior to surgery, or greater than or equal to 10 years was 10.7 mmHg (95% CI -24.7 to 3.3, p=0.13).
estimated difference in mean diastolic blood pressure was 0.3 mmHg (95% CI -6.1 to 5.5, p=0.93), whilst the estimated difference in mean arterial pressure was 3.7 mmHg (95% CI -11.3 to 3.8, p=0.3).

The number of medications used to control hypertension at baseline, did appear to relate to blood pressure status at follow up. Ninety-three participants had a record of both the medication use at baseline and adequate data to categorise blood pressure status at follow up (Table 3-30). Of these 19 (20%) had improved to normotension at follow up, and of these participants, 14 (74%) were not using anti-hypertensive medication at baseline.

Table 3-30  Cross tabulation of the duration of the number of anti-hypertensive medications used at baseline against blood pressure status at follow up

<table>
<thead>
<tr>
<th>Number of anti-hypertensive medications used at baseline</th>
<th>Blood pressure status at follow up</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normotension</td>
<td>Hypertension</td>
</tr>
<tr>
<td>0</td>
<td>14</td>
<td>26</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>74</td>
</tr>
</tbody>
</table>

As only 5 participants used 3 medications at baseline, further meaningful analysis including this group was not possible. However, in support of the hypothesis that the number of medications required at baseline may predict blood pressure outcomes after surgery, the median systolic and mean arterial pressure increased with each incremental increase in the number of medications used (figures 4-x).
3.1.4.7 Lipids at baseline and follow up

Ninety-two (78%) of participants had data on baseline total cholesterol, HDL (and therefore cholesterol to HDL ratios), LDL, and Triglyceride concentrations available. Data for total cholesterol and LDL concentrations at baseline and follow up, and the change from baseline to follow up, were normally distributed as demonstrated by inspection of histograms (Figure ii-9 (380) and Figure ii-11 (382)) and assessment using the Sharpiro-Wilk test (Table ii-11 (381)). Thus, parametric models were used for analysis of the change from baseline to follow up. Data for HDL and triglyceride concentrations showed right skew as shown in Figure ii-9 (380). Logarithmic transformation resulted in normal distribution of this data (Figure ii-10 (381) and Table ii-12 (382)), allowing parametric analysis.

Seventy two (61%) denied a previous diagnosis of dyslipidaemia at baseline, whilst 38 (34%) had previously received a diagnosis of dyslipidaemia or were using lipid lowering therapy at baseline. Of those with a known diagnosis of dyslipidaemia at baseline, 29 (76%) of participants had information on the duration of dyslipidaemia, with a mean (SD) duration of 5.0 (4.8) years. Nineteen (50%) of those with a previous diagnosis of dyslipidaemia reported the use of a lipid lowering medication at baseline. Only 19/118 (16%) of participants reported the use of lipid lowering therapy at baseline. A similar number (18/118 (15%) were using lipid lowering therapy at follow up, and no participants was using more than one agent. The estimated difference in number of lipid lowering therapies used at baseline and follow up was 0.008 (95% CI -0.06 to 0.07, p=0.8) (Table 3-31).

The mean (SD) fasting total cholesterol, HDL, LDL, and triglycerides concentration at baseline were 5.40 (0.99), 1.33 (0.34), 3.20 (0.97), and 1.82 (1.02) mmol/L respectively (Table 3-31 and Figure 3-18). The mean (SD) total cholesterol to HDL ratio was 4.25 (1.13) mmHg. 84 (71%) of participants had data at both baseline and follow up. LDL concentrations were significantly lower at follow up than at baseline. The mean (SD) LDL concentration at baseline was 3.24 (0.93) and 2.80 (0.81) mmol/L at follow up; estimated difference 0.43 mmol/L (0.21 to 0.65, p<0.001). Additionally, HDL concentrations were significantly increased at follow up in comparison to baseline, resulting in significant improvements in the cholesterol to HDL ratio. The mean (SD) HDL at baseline and follow up was 1.33 (0.34) and 1.91 (0.54) mmol/L respectively; estimated difference 0.58 mmol/L (p<0.001 after logarithmic transformation).
### Table 3-31  Descriptive lipid data for all participants at baseline and follow up. Results of a paired T test are shown.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow up (&gt;5 years)</th>
<th>Paired T test for Estimated difference *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (SD)</td>
<td>IQR</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>92</td>
<td>5.40 (0.99)</td>
<td>1.42</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>92</td>
<td>1.33 (0.34)</td>
<td>1.71</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>92</td>
<td>3.24 (0.93)</td>
<td>1.41</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>92</td>
<td>1.82 (1.02)</td>
<td>0.95</td>
</tr>
<tr>
<td>Cholesterol:HDL ratio</td>
<td>92</td>
<td>4.25 (1.13)</td>
<td>1.48</td>
</tr>
<tr>
<td>Number of lipid lowering medications</td>
<td>118</td>
<td>0.16 (0.37)</td>
<td>0.0</td>
</tr>
</tbody>
</table>

* Paired T tests for HDL and Triglycerides report logarithmic transformed data to better approximate normal distribution.
The estimated difference in mean total cholesterol to HDL ratio was 1.3 mmol/L (95% CI 1.04 to 1.56, P<0.001). Thus, whilst the mean total cholesterol concentration was lower at follow up when compared to baseline measurements, the estimated difference was not statistically significant (Table 3-31 and Figure 3-18).

A significant reduction in fasting triglyceride concentrations was noted. The mean (SD) triglyceride concentration at baseline and follow up was 1.82 (1.02) and 1.13 (0.42) mmol/L respectively; estimated difference 0.69 (p<0.001 after logarithmic transformation).

Each of these relationships persisted when only those participants not on cholesterol lowering therapy at either baseline or follow up were included in the analysis (n=67) as presented in Table ii-13 (383).
Univariate and multivariate analysis was performed to explore relationships between the change in lipid concentrations following surgery and other measured variables. An initial analysis did not reveal any association between the change in LDL, HDL, or Triglyceride concentrations and age at operation, gender, BMI at baseline, diabetes status and markers of glucose homeostasis (fasting glucose, HbA1c, fasting insulin, and HOMA-IR), and blood pressure status and concentrations (Table ii-14 (384)). Additionally, there was no evident association between lipid markers and change in markers of glucose homeostasis from baseline to follow up.

LDL level at baseline predicted the change in LDL over the follow up period \( (r=0.66, f=63.6, p<0.001) \), and accounted for 43% of this variation (Table ii-14 (384)). This finding persisted when only those participants not using cholesterol lowering therapy at baseline or follow up were considered. Furthermore, in this group the change in LDL was also predicted by BMI at follow up \( (r=0.31, f=7.0, p=0.01) \), the percentage change in body weight over the study period \( (r=0.38, f=11.1, p=0.001) \), although each variable accounted for only 8 and 13% of the variability in LDL change respectively. HDL level at baseline did not however predict the change in HDL over the study period, but was predicted by BMI at follow up \( (r=0.31, f=9.1, p=0.003) \). Triglyceride level at baseline predicted the change in triglyceride concentrations over the follow up period \( (r=0.92, f=429.8, p<0.001) \), and accounted for 84% of this variation. HDL level at baseline also predicted change in triglycerides over the follow up study \( (r=0.37, f=13.1, p=0.001) \), and accounted for 13% of the total variation in triglyceride change. Change in triglycerides was independent of BMI at baseline or follow up, or the change in body weight during the follow up period.

Duration of follow up predicted change in LDL (mmol/L) and HDL (mmol/L) from baseline to follow up \( (r=0.27, f=6.5, p=0.01) \) and \( (r=0.27, f=6.63, p=0.01) \) respectively, suggesting that an increase in the duration of follow up since surgery was associated with a reduction in LDL concentrations and an increase in HDL concentrations (Table ii-14 (384) and Figure 3-19). The regression equations were:

\[
\text{Change in LDL (mmol/L)} = -0.43 + (0.11 \times \text{duration of follow up (years)}
\]

\[
\text{Change in HDL (mmol/L)} = 0.2 + (0.05 \times \text{duration of follow up (years)}
\]
Of the 38 participants who had previously received a diagnosis of dyslipidaemia or were using lipid lowering therapy at baseline, 29 (76%) were able to confirm the duration of this diagnosis. The mean (SD) duration of dyslipidaemia in this group was 5.0 (4.8) years (range 0.0 to 17.0 years), and thirteen (34%) of these participants were able to confirm the duration of lipid lowering therapy prior to surgery (mean (SD) 6.5 (3.7) years (range 1.0 to 14.0 years)).

The duration of dyslipidaemia prior to surgery (years) predicted both the change in LDL (r=0.42, f=4.6, p=0.04) and change in HDL (r=0.58, f=11.6, p=0.002), and accounted for 14% and 31% respectively of the variation in each (Table ii-14 (384) and Figure 3-20). Change in triglyceride concentrations was not predicted by duration of dyslipidaemia. Thus, the change in LDL from baseline to follow up reduced with an increasing duration of preoperative dyslipidaemia, whilst the change in HDL increased with time. The regression equations were:

\[
\text{Change in LDL (mmol/L)} = 0.94 + (-0.14 \times \text{Duration of dyslipidaemia (years)})
\]

\[
\text{Change in HDL (mmol/L)} = 0.32 + (0.05 \times \text{Duration of dyslipidaemia (years)}).
\]
To explore whether the duration of dyslipidaemia prior to surgery predicts lipid outcomes following surgery, variables of interest in these two groups were compared using an independent T test (Table ii-15 (385)). The two groups were of a similar mean age at baseline and follow up (estimated difference 1.7 years at baseline (95% CI -5.3 to 8.7, p=0.6), and 1.6 years at follow up (95% CI -5.7 to 8.9, p=0.7). Thus the mean duration of follow up was also similar with an estimated difference of 0.1 years (95% CI -1.9 to 2.1, p=0.9). Whilst participants with the longer duration of dyslipidaemia were lighter at baseline and follow up, this did not translate in to a clear statistical difference. The estimated difference, after logarithmic transformation, between mean BMI at baseline was 0.05 (95% CI -0.1 to 0.2, p=0.5; equivalent to a mean ratio of 1.05 (95% CI 0.9 to 1.22)). The estimated difference between mean BMI at follow up was 0.08 (95% CI -0.05 to 0.1, p=0.3; equivalent to a mean ratio of 1.08 (95% CI 0.95 to 1.10)). Mean (SD) body weight loss (%) over the 7.6 years of follow up was similar in each group at 28.0 (9.1) % in those with less than five years of diagnosed dyslipidaemia prior to surgery, and 29.8 (12.6) % in those with five or more years; estimated difference 1.8% (95% CI -10.2 to 6.5, p=0.7). Participants with five or more years of dyslipidaemia did however use more lipid lowering therapy (estimated difference 0.4 (95% CI 0.1 to 0.8, p=0.02) than participants with less than five years of follow up; ten out of fourteen (71%) of those with the longer duration of dyslipidaemia were on lipid lowering therapy at baseline, in comparison to 4/15 (27%) of the second group. Thus, with the exception of medication use, the two groups were similar in character and further study to explore the relationship between preoperative duration of dyslipidaemia and change in LDL and HDL concentrations following surgery is justified.


3.1.4.8 Other co-morbidities at baseline and follow up

Table 3-32 below presents data on other co-morbidities reported by participants at baseline and follow up. Outcomes represent events that occurred either prior to surgery (baseline) or between surgery and the follow up assessment (follow up). Outcomes of McNemar’s test to assess differences in the proportion of participants with each diagnosis at each time point are shown.

Table 3-32 Frequency of co-morbid conditions at baseline and follow up. Results of McNemar’s test to compare categorical variables are reported.

<table>
<thead>
<tr>
<th>Co-morbidity</th>
<th>Baseline (%)</th>
<th>Follow up (%)</th>
<th>McNemar’s test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic heart disease</td>
<td>9 (8)</td>
<td>6 (5)</td>
<td>0.55</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3 (3)</td>
<td>0 (0)</td>
<td>0.25</td>
</tr>
<tr>
<td>Coronary artery bypass graft</td>
<td>4 (4)</td>
<td>0 (0)</td>
<td>0.13</td>
</tr>
<tr>
<td>Stroke</td>
<td>3 (3)</td>
<td>1 (1)</td>
<td>0.63</td>
</tr>
<tr>
<td>Depression</td>
<td>32 (27)</td>
<td>23 (20)</td>
<td>0.08</td>
</tr>
<tr>
<td>Arthritis</td>
<td>39 (34)</td>
<td>51 (44)</td>
<td>0.052</td>
</tr>
<tr>
<td>Sleep apnoea</td>
<td>39 (34)</td>
<td>5 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gout</td>
<td>12 (10)</td>
<td>4 (4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>58 (49)</td>
<td>5 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Osteoporotic fracture</td>
<td>11 (9)</td>
<td>11 (9)</td>
<td>1.0</td>
</tr>
</tbody>
</table>
3.1.4.8.1  Ischaemic heart disease

Eight (7%) participants had an established diagnosis of ischaemic heart disease at baseline, three (3%) of whom had previously suffered a myocardial infarction, and four (4%) of whom had previously undergone coronary artery bypass graft surgery. Six (5%) further participants developed ischaemic heart disease during the period of follow up, although no further myocardial infarctions were reported, and no participant underwent coronary artery bypass graft surgery during this period. McNemar’s test determined there was no clear difference in the frequency of ischaemic heart disease or related co-morbid conditions at baseline and follow up (p=0.55).

3.1.4.8.2  Stroke

Three (3%) of participants had suffered a stroke prior to acceptance for surgery. A further participant suffered a stroke between surgery and the follow up assessment. McNemar’s test determined there was no clear difference in the frequency of stroke at baseline and follow up (p=0.63).

3.1.4.8.3  Depression

Thirty two (27%) participants had a diagnosis of depression at baseline. Depression had resolved by the follow up assessment in 18 (15%) of these participants, but was persistent in 14 (12%). A further nine (8%) participants developed depression between surgery and the follow up assessment. Seventy-seven (65%) of participants had never received a diagnosis of depression. Twenty three (20%) of participants reported a current diagnosis of depression at the follow up assessment. McNemar’s test determined that there was a trend towards a reduction in the frequency of depression after gastric bypass surgery although this did not reach statistical significance (p=0.08).

Univariate regression analysis did not suggest any relationship between BMI and the likelihood of depression at baseline (r=0.08, f=0.7, p=0.4), or any relationship between either the degree of weight loss over the study period and depression (r=0.04, f=0.2, p=0.7) or the BMI at follow up and depression (r=0.09, f=0.8, p=0.4). The presence of diabetes did not appear to increase the risk of depression at either time points by regression analysis (r=0.05, p=0.6 at baseline, r=0.14,
p=0.2 at follow up). Indeed, none of the participants with type 2 diabetes at the follow up appointment reported a diagnosis of depression, whilst four (31%) participants experienced resolution of depression, a percentage which exceed that seen in those with normal glucose tolerance (14%) and prediabetes (14%) at follow up.

3.1.4.8.4 Arthritis

Thirty nine (34%) participants reported a diagnosis of arthritis at baseline, which resolved following surgery in ten (10%) participants. Arthritis was still evident at the follow up assessment in the remaining 29 (24%) of participants, and a further 22 (19%) participants had developed arthritis during the period of follow up. McNemar’s test determined that there was an increase in the frequency of arthritis after gastric bypass surgery (p=0.052).

3.1.4.8.5 Sleep Apnoea

Sleep apnoea was common at baseline, with 39 (34%) of participants reporting either the use of nocturnal positive pressure ventilation therapy at baseline, or a previous diagnosis of sleep apnoea. Sleep apnoea resolved following surgery in 34 (87%) of these participants and was persistent in 5 (13%). One (1%) participant developed sleep apnoea between surgery and the follow up assessment. McNemar’s test determined that there was a significant reduction in the frequency of sleep apnoea after gastric bypass surgery (p<0.001).

3.1.4.8.6 Gout

Twelve (10%) participants reported a previous diagnosis of gout at the time of surgery. This resolved following surgery in 11 (92%), whilst three (3%) participants developed gout between surgery and the follow up assessment. McNemar’s test determined that there was a clear difference reduction in the frequency of gout in this cohort from baseline to follow up (p=0.003).
3.1.4.8.7 Cholecystectomy

Fifty-seven (48%) participants had undergone a cholecystectomy at baseline. In twenty of these participants, cholecystectomy was performed at the same time as gastric bypass, due to the perceived risk of post-operative cholelithiasis resulting from expected significant weight loss. Thirty-seven participants had undergone cholecystectomy prior to gastric bypass. Five (8% of those who had not undergone cholecystectomy by the time of gastric bypass surgery) participants subsequently underwent cholecystectomy between baseline and the follow up assessment. McNemar’s test determined that there was a clear difference in the proportion of participants at each time point eligible for cholecystectomy who had undergone this procedure (p<0.001). When only participants who had already undergone cholecystectomy at baseline (i.e. the procedure was not prophylactic) were compared to those who subsequently underwent cholecystectomy following gastric bypass were considered, McNemar’s test determined that there was still a clear difference reduction in the frequency of cholecystectomy in this cohort from baseline to follow up (p<0.001).

When only those participants who had not undergone cholecystectomy prior to or at baseline were considered, five (8%) participants required cholecystectomy by the time of the follow up assessment, whilst 56 (92%) did not. The small numbers limit the likelihood of statistically significant differences being confirmed, but interesting trends are noted. Participants who required subsequent cholecystectomy tended to be older at follow up than those who did not (Figure 3-21). The mean (SD) age at follow up in those who underwent cholecystectomy was 61.4 (11.3) years and 55.5 (11.8) years in those who did not; estimated difference 5.9 years (95% CI -5.1 to 17.0, p=0.3). As the age at baseline was similar in both groups, there was an increase in the duration of follow up in those who subsequently underwent cholecystectomy (16.8 (12.4) years versus 9.4 (5.8) years respectively; estimated difference 7.4 years (95% CI 1.3 to 13.4, p=0.02) (Figure 3-21). However, the confidence intervals for this calculation are considerable, and the range of duration of follow up was similar in each group (5.1 to 29.5 years in those who did subsequently undergo cholecystectomy, and 5.2 to 30.6 years in those who did). There were no clear differences in this cohort with respect to weight/BMI at baseline and follow up, or total body weight loss when those who underwent cholecystectomy subsequent to gastric bypass and those who did not were considered. However, despite similar weight and BMI at baseline, participants who required cholecystectomy following gastric bypass showed a trend towards less
weight loss during the follow up period and consequently a higher weight and BMI at follow up. The mean (SD) weight at follow up was 97.7 (25.3) kg in those who subsequently underwent cholecystectomy and 93.0 (22.4) kg in those who did not; estimated difference when logarithmic transformed data used 0.05 (95% CI -0.2 to 0.3, p=0.6), equivalent to a mean ratio of 1.05 (95% CI 0.81 to 1.35). The mean (SD) BMI at follow up was 36.8 (9.4) kg/m\(^2\) in those who subsequently underwent cholecystectomy and 32.9 (6.9) kg/m\(^2\) in those who did not; estimated difference when logarithmic transformed data used 0.1 (95% CI -0.1 to 0.3, p=0.3), equivalent to a mean ratio of 1.11 (95% CI 0.9 to 1.35). The mean (SD) body weight loss (%) at follow up was 24.6 (13.4) kg/m\(^2\) in those who subsequently underwent cholecystectomy and 28.9 (11.1) kg/m\(^2\) in those who did not; estimated difference 4.3% (95% CI -6.2 to 14.8, p=0.4).

Figure 3-21  Boxplots to show a) age at follow up, b) duration of follow up, c) BMI at follow up (kg/m\(^2\)), and d) body weight loss (%) at follow up (n=56)
3.1.4.8.8 Osteoporotic fractures

There was no clear difference in the frequency of osteoporotic related fracture before or after gastric bypass surgery in this cohort. Eleven (9%) participants had suffered a fracture related to osteoporosis prior to surgery, and 11 (9%) participants suffered an osteoporotic fracture between baseline and the follow up assessment.

3.1.4.8.9 Nephropathy

13/103 (13%) of participants had nephropathy at the follow up visit. The mean (SD) microalbuminuria to creatinine ratio was 24.2 (42.8) in those with elevated ratios (range 3.0 to 152.7). Similar data was not obtained at baseline and therefore a comparative analysis is not possible. The microalbumin to creatinine ratio at follow up was not predicted by body weight loss (r=0.1, f=1.1, p=0.3).
3.1.4.9 Micronutrient status, intake, and multivitamin use at follow up

One hundred and nine (92%) of participants reported current use of multivitamin tablets at the follow up appointment, whilst nine (8%) of participants acknowledged that they never took multivitamin supplementation. Those participants who did not take multivitamin tablets had a significantly longer duration of follow up than those who did; mean (SD) 17.0 (8.5) years versus 9.5 (5.5) years, estimated difference 7.5 years (95% CI 3.6 to 11.4, \(p<0.001\)). There were no other clear differences in age or post-surgery outcomes between these two groups.

Of the 109 participants who took regular multivitamin tablets, 94 (86%) took multivitamin tablets on a daily basis, and 10 (9%) took tablets at least four times per week (Figure 3-22). Two (2%) participants took tablets weekly but less than at least four times per week, and three (3%) participants took tablets irregularly.

![Use of multivitamin supplements in participants who reported regular use (n=109)](image-url)
Fifty three (45%) participants were prescribed regular vitamin B12 injections at the time of follow up. There were no clear differences in age or weight outcomes between those who took B12 injections and those who didn’t. Participants who received regular B12 injections had a longer duration of follow up (mean (SD) 11.4 (6.8) years) than those who didn’t (9.1 (5.2) years); estimated difference 2.3 years (95% CI 0.2 to 4.5, p=0.04). However, the range of duration of follow up was large and similar in each group (5.1 to 29.9 years, and 5.1 to 30.6 years) raising doubt as to significance of this finding.

Table 3-33  Descriptive data for vitamin B12, zinc, and copper concentrations in all participants at the follow up assessment

<table>
<thead>
<tr>
<th></th>
<th>Normal reference range</th>
<th>n (%)</th>
<th>Mean (SD)</th>
<th>IQR</th>
<th>Min/Max</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All participants (n=118)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B12 (pmol/L)</td>
<td>170 to 800</td>
<td>100 (85)</td>
<td>491.2 (411.5)</td>
<td>527.3</td>
<td>90.0/1476.0</td>
</tr>
<tr>
<td>Zinc (µg/dL)</td>
<td>68.0 to 149.0</td>
<td>109 (92)</td>
<td>68.3 (10.5)</td>
<td>11.6</td>
<td>47.5/116.0</td>
</tr>
<tr>
<td>Copper (µg/dL)</td>
<td>63.7 to 140.12</td>
<td>109 (92)</td>
<td>104.8 (22.4)</td>
<td>24.9</td>
<td>54.7/143.9</td>
</tr>
</tbody>
</table>

The mean (SD) vitamin B12 concentration at follow up in all participants was 491.2 (411.5) pmol/L (Table 3-33). The distribution of vitamin B12 concentrations was not normal (Figure ii-12 (386)), and was not normalised by logarithmic transformation. Therefore, the Mann-Whitney test was applied to estimate the differences in mean vitamin B12 concentration between participants receiving vitamin B12 injections and those who were not. The mean (SD) vitamin B12 concentration was significantly greater in those participants receiving regular vitamin B12 injections (n=53) at 701.6 (457.0) pmol/L, in comparison to 338.9 (296.0) pmol/L in those participants who were not (n=47), (U=584.0, p<0.001).
Thirteen participants (13% of participants with available data) had a vitamin B12 concentration below the reference range at follow up (range 90 to 167.0 pmol/L). Two of these participants were receiving vitamin B12 injections at the time of measurement, whilst 11 were not. Thus, 36/47 (77%) of these participants had concentrations of vitamin B12 within the normal reference range despite an absence of supplementation, at a mean (SD) duration of follow up of 9.1 (5.2) years. Conversely, 21 participants had vitamin B12 concentrations above the normal reference range. Fourteen of these participants were receiving vitamin B12 supplementation, but seven had obtained these concentrations in the absence of supplementation. Analysis of boxplots of vitamin B12 concentrations stratified by frequency of use of oral multivitamin supplementation does not discount the possibility that vitamin B12 concentrations may have been increased by regular supplementation (Figure 3-23), although the analysis is limited by small numbers in each category. However, regression analysis after logarithmic transformation did not support a relationship between dietary B12 intake at follow up and vitamin B12 concentrations in those not on supplementation (r=0.09, f=0.4 p=0.5).
The mean (SD) zinc concentration at follow up in all participants was 68.3 (10.5) µg/dL (Table 3-33). The distribution of zinc concentrations was left skewed, but was normalised through logarithmic transformation (Figure ii-13 (386)). An assessment of normality using the Kolmogorov-Smirnov test returned a statistic of 0.72, where $p>0.2$.

The mean (SD) zinc concentration was similar in those participants receiving multivitamin supplementation ($n=100$, 68.5 (10.8) µg/dL), to those participants who were not ($n=9$, 65.8 (6.6) µg/dL); estimated difference after logarithmic transformation 0.03 µg/dL (95% CI -0.07 to 0.14, $p=0.5$), equivalent to a mean ratio of 1.03 (0.93 to 1.15). 53 (49%) of the 109 participants with an available measurement, had a zinc concentration below the published reference range (108.5 µg/dl ±2 standard deviations). Univariate regression analysis suggested that the dietary intake of zinc at the follow up assessment did not relate to zinc concentrations (after logarithmic transformation, $r=0.1$, $f=2.1$, $p=0.15$). Furthermore, there was no evident change in zinc concentration at follow up when participants were stratified by the frequency of multivitamin tablet use (Figure 3-24), suggesting that multivitamin administration is unable to correct the zinc deficiency. Zinc concentration at follow up did not relate to age, BMI, or body weight loss % at follow up.

![Figure 3-24 Boxplots to show zinc concentrations in those participants receiving multivitamin supplementation at follow up, stratified by frequency of use](image-url)
The mean (SD) copper concentration at follow up in all participants was 104.8 (22.4) µmol/L in the 109 participants with a measurement available at follow up (Table 3-33). One outlying participant had a total copper concentration of 243.8 µg/dl, 100.0 µg/dl (170%) greater than any other measured concentration. This value was therefore not included in the following analysis. The distribution of zinc concentrations was normally distributed (Kolmogorov-Smirnov test statistic = 0.52, p>0.2, Figure ii-14 (387)).

The mean (SD) copper concentration was similar in those participants receiving multivitamin supplementation (n=99, 104.0 (18.0) µg/dl), to those participants who were not (n=9, 98.7 (18.7) µg/dl); estimated difference 5.3 µg/dl (95% CI -7.2 to 17.7, p=0.4), and there was no evident change in copper concentration at follow up when participants were stratified by the frequency of multivitamin tablet use (Figure 3-25). Furthermore, dietary copper intake did not clearly relate to copper concentrations (r=0.17, f=3.0, p=0.09). Only one participant had a copper concentration at follow up that fell below the reported reference ranges. Copper concentration at follow up did not relate to age, BMI, or body weight loss % at follow up.

Figure 3-25  Boxplots to show copper concentrations in those participants receiving multivitamin supplementation at follow up, stratified by frequency of use

![Boxplots to show copper concentrations in those participants receiving multivitamin supplementation at follow up, stratified by frequency of use](image)
3.1.4.10 Symptoms related to gastric bypass surgery

Participants were questioned as to the presence of a number of symptoms known to be associated with RYGB. 57/116 (49%) of participants reported having experienced dumping syndrome which occurred at a mean (SD) of 16.8 (22.8) minutes after eating (maximum = 60 minutes). 32/48 (67%) participants reported frequent vomiting after meals, whilst 13/48 (27%) reported post prandial indigestion. 20/48 (42%) of participants reported a change in bowel habit since RYGB. The presence of dumping syndrome, frequent vomiting, indigestion, or altered bowel habit did not predict body weight loss during the study by linear regression analysis, and did not appear to negatively impact on high participant satisfaction following RYGB (see chapter 3.1.4.11.2).

Participants were less likely to derive enjoyment from eating following RYGB (see Table 3-34). At baseline, 46/48 (96%) of participants stated that they always enjoyed food, with the remaining two (4%) stating that they never enjoyed food. At follow up, 28/46 (61%) of those who enjoyed food at baseline felt they still derived enjoyment from eating, although 17 (37%) stated that they occasionally didn’t enjoy food, and one (2%) stated they now never enjoyed food. Of the two participants who never enjoyed food at baseline, only one participant improved to occasional enjoyment at follow up. It is should be noted that these data were obtained at follow up only and not prior to surgery.

Table 3-34  Crosstabulation to show the enjoyment of food at baseline and follow up. 1=Always enjoyed eating, 2=occasionally enjoyed eating, 3-never enjoyed eating

<table>
<thead>
<tr>
<th></th>
<th>Follow up</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Baseline</td>
<td>1</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>18</td>
</tr>
</tbody>
</table>
3.1.4.11 Patient satisfaction and quality of life

Participants were provided with two questions during the interview to assess their satisfaction with the outcomes of gastric bypass surgery. The first questioned their satisfaction with the obtained weight following surgery. The second question asked whether the participant felt any beneficial effects from surgery they may have experienced outweighed any negative effects that were likely attributable to surgery.

3.1.4.11.1 Weight satisfaction following surgery

Participants were asked to select from one to five to represent their satisfaction with obtained weight following gastric bypass surgery, one representing “very unsatisfied” through to five representing “very satisfied”. The frequency of each option in this cohort is presented in Figure 3-26.

Figure 3-26  Frequency of selection of each weight satisfaction option chosen by participants
One participant declined to answer the question. Forty-four (37%) of participants were unsatisfied with their achieved weight at follow up; 14 (12%) of these were very unsatisfied, whilst 30 (25%) were unsatisfied. Thirteen (11%) participants expressed indifference as to their obtained weight loss, whilst 60 (51%) of participants were either satisfied (43 (36%) participants) or very satisfied (17 (14%) with the obtained weight loss.

Boxplots were constructed to explore whether participants’ weight satisfaction at follow up could be associated with one or more clear predictive variables at either baseline or follow up (Figure 3-27). There were no clear differences in age at operation or follow up, or weight/BMI at operation in those who selected differing weight satisfaction scores at follow up. However, as would be predicted, weight and BMI at follow up were both clearly associated with the weight satisfaction score chosen by the participant. To quantify these differences, participants who had selected either “unsatisfied” or “satisfied” were compared using an independent T test. The mean (SD) weight at follow up in participants who were “unsatisfied” with their weight was 99.7 (24.8) kg, whilst the mean (SD) weight in those who were “satisfied” was 85.6 (15.3) kg; estimated difference when logarithmic transformed data was used 0.13 (95% CI 0.03 to 0.24, p=0.005), equivalent to a mean ratio of 1.14 (95% CI 1.03 to 1.27). The difference was greater still when those who were “very unsatisfied” and “very satisfied” were compared; mean (SD) weight at follow up 100.1 (26.7) versus 75.4 (17.1) kg; estimated difference following logarithmic transformation 0.3 (95% 0.07 to 0.5, p=0.008), equivalent to a mean ratio of 1.35 (95% 1.07 to 1.65).

Similarly, the mean (SD) BMI at follow up in participants who were “unsatisfied” with their weight was 36.1 (6.5) kg/m², whilst the mean (SD) BMI in those who were “satisfied” was 30.6 (4.9) kg/m²; estimated difference when logarithmic transformed data was used 0.16 (95% CI 0.08 to 0.24, p<0.001), equivalent to a mean ratio of 1.17 (95% CI 1.08 to 1.27). Again, the difference was greater still when those who were “very unsatisfied” and “very satisfied” were compared; mean (SD) BMI at follow up 38.1 (10.0) versus 26.5 (3.9) kg/m²; estimated difference following logarithmic transformation 0.34 (95% 0.17 to 0.5, p<0.001), equivalent to a mean ratio of 1.4 (95% 1.18 to 1.65).
Figure 3-27  Boxplots to show a) weight at baseline, b) BMI at baseline, c) weight at follow up, d) BMI at follow up, e) and body weight loss (%), and f) duration of follow up (years) stratified by participants selection of weight satisfaction at the follow up assessment.
Thus, body weight loss (%) during the period of follow up was also closely associated with the weight satisfaction score chosen by participants. The mean (SD) body weight loss (%) in those who selected “unsatisfied” was 22.5 (9.1) %, and 32.4 (8.8) % in those who were “satisfied” with their achieved weight. The estimated difference was 9.9% (95% CI 5.7 to 14.1, $P<0.001$).

A trend towards increasing weight satisfaction score and decreasing duration of follow up was suggested by examination of box plots (Figure 3-27). This approached statistical significance when participants were grouped into those who were “unsatisfied” (both “very unsatisfied” and “unsatisfied”) and those were “satisfied” (similarly grouped). The mean (SD) duration of follow up in those who were “unsatisfied” was 11.1 (6.4) years and 8.9 (4.8) years in those who were “satisfied”; estimated difference 2.13 years (95% CI -0.05 to 4.3, $P=0.06$).

Participant’s choice of weight satisfaction score did not appear to associate with the likelihood of depression. Table 3-35 shows cross tabulation of the frequency of depression for each weight satisfaction score, and demonstrates no logical trend with change in weight satisfaction score.

<table>
<thead>
<tr>
<th>Depression at follow up</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>94</td>
</tr>
<tr>
<td>Yes</td>
<td>22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight satisfaction score (%)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>14</td>
<td>30</td>
<td>13</td>
<td>43</td>
<td>16</td>
<td>116</td>
</tr>
</tbody>
</table>

Table 3-35  Cross tabulation of frequency of depression at follow up against weight satisfaction score
3.1.4.11.2 Do the benefits of surgery outweigh the negatives?

Forty seven participants (40%) were additionally asked whether they felt the benefits they may have received from undergoing gastric bypass surgery outweighed any negative effects they may have suffered as a consequence of this intervention. Forty five (96%) participants responded positively, whilst only two (4%) participants felt that the net effect of gastric bypass on their health and circumstances was negative.

One of these participants did not lose substantial weight following gastric bypass (BMI at baseline 52.8 kg/m\(^2\) and 51.5 kg/m\(^2\) at follow up) and indeed, remained with class 4 obesity. The other participants had lost a substantial amount of weight (BMI 45.0 kg/m\(^2\) at baseline and 24.7 kg/m\(^2\) at follow up) resulting in an improvement from class 3 obesity to normal weight at follow up. However, this participant remained troubled by frequent vomiting, indigestion, and an adverse change in bowel habit, as well as symptoms related to pre and post meal hypoglycaemia and dumping syndrome. In addition, this participant suffered from depression at baseline which had not resolved during the period of follow up. Both participants had normal glucose tolerance at baseline and follow up.
3.1.4.11.3 Quality of life assessments after RYGB surgery

The impact of weight on quality of life (IWQOL-Lite) questionnaire (see chapter 2.4 and Appendix i-8/Appendix i-9, page360) was used to assess a number of parameters related to quality of life. In the following section, each section of this questionnaire is analysed individually, prior to reporting of participant’s scores, associations with weight and weight loss, and relationships to outcomes in validated cohorts. Participants were asked to choose one of five options that best applied to them in the past week (1 – never true, 2 rarely true, 3 – sometimes true, 4 – usually true, 5 – always true). Neither participant who had undergone revision surgery was included in this analysis. The frequency of each option along with the mean score is presented in Table ii-16 (388), whilst the mean score for each section expressed as a percentage is presented in Table 3-36

Physical function (11 questions)

115 (98%) answered all 11 questions in this section, with the exception of one participant who elected not to answer question 9. The mean (SD) score in the physical function domain was 18.9 (7.8).

Self-esteem (7 questions)

115 (98%) participants answered all seven questions in this section. The mean (SD) score in the physical function domain was 13.8 (7.7).

Sexual life (4 questions)

14 (14%) participants elected not to provide answers to questions in this section. The other 104 (86%) participants provided answers to each question. The mean (SD) score in the physical function domain was 8.5 (8.5).
Public distress (5 questions)

110 (92%) participants provided answers to all questions in this section, with the exception of two participants who elected not to provide answers to question 4 and 5. The mean (SD) score in the physical function domain was 7.6 (4.2).

Work

110 (92%) of participants provided answers to question one and two of this section, with the exception of three participants who declined to answer question 3 and two participants who elected not to answer question 4. The mean (SD) score in the physical function domain was 6.1 (5.2).

Table 3-36  IWQOL-lite % scores for each domain

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>Mean (SD)</th>
<th>95% confidence interval</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants (n=118)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical function</td>
<td>114 (97)</td>
<td>82.4 (17.4)</td>
<td>79.1 to 85.6</td>
<td>13.6</td>
<td>100.0</td>
</tr>
<tr>
<td>Self esteem</td>
<td>113 (96)</td>
<td>77.1 (25.8)</td>
<td>72.3 to 81.9</td>
<td>0.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Sexual life</td>
<td>101 (86)</td>
<td>85.6 (21.5)</td>
<td>81.4 to 89.9</td>
<td>0.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Public distress</td>
<td>108 (92)</td>
<td>87.6 (20.1)</td>
<td>83.8 to 91.4</td>
<td>10.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Work</td>
<td>105 (89)</td>
<td>92.7 (13.2)</td>
<td>90.1 to 95.2</td>
<td>43.8</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>97 (82)</td>
<td>84.6 (16.5)</td>
<td>81.3 to 88.0</td>
<td>26.6</td>
<td>100.0</td>
</tr>
</tbody>
</table>
3.1.4.11.4  Association of IWQOL-lite score with BMI at follow up

Figure 3-28 shows IWQOL-lite scores for each domain stratified by BMI at follow up. Validated reference data for the IWQOL-lite in non-surgical cohorts (n=11,640) of differing BMI are available. Table ii-17 (390) presents this data and similar data for this cohort when stratified by the same BMI categories.

An incremental reduction in % score in each domain was noted with increasing obesity classification (and therefore BMI) at follow up, with the exception of sexual life score. Participants who had obtained normal weight or were overweight by classification generally reported scores of greater than 90% in each domain.

Participants who had achieved a normal weight (BMI 18.0 to 24.9 kg/m²) by the follow up assessment, had similar IWQOL-lite scores in each domain to reference controls who were of a similar weight but had not undergone bariatric surgery (Table ii-17 (390)). In contrast, overweight or obese participants who had undergone bariatric surgery had higher scores in each domain than those of similar BMI who had not undergone surgery. The estimated differences were statistically significant with respect to physical function and total scores in each of the obesity strata from overweight to class 3 obesity. Self-esteem scores were higher in those who had previously undergone bariatric surgery and had achieved overweight or class 1 obesity by follow up, when compared to non-surgical reference controls of a similar BMI. However, there were no clear differences in self-esteem scores in those who remained with class 2 or greater obesity at follow up and non-surgical controls.

Statistically significant higher sexual life scores were noted in those who were overweight or had class 2 obesity at follow up in comparison with the reference population. However, this finding should be interpreted with caution as the confidence intervals on these estimations are broad, and differences were not noted in the other weight categories. Surgical participants who had been overweight at follow up had statistically higher public distress scores than non-surgical controls, although both groups scored in excess of 95%. There were no other clear differences in public distress between the groups. Work scores were clearly better in those who had undergone surgery in each BMI category, with the exception of class 2 obesity.
Figure 3-28  Boxplots to show IWQOL-lite % scores for a) physical function, b) self-esteem, c) sexual life, d) public distress, e) work, and f) total score, stratified by obesity classification at follow up (NW = normal weight, 18.0 to 24.9 kg/m², OW = overweight, 25.0 to 29.9, class 1 = 30.0 to 34.9, class 2 = 35.0 to 39.9, class 3 > 40.0).
Moderate, but highly statistical significant relationships were noted between participants score in each IWQOL-lite domain and the BMI (kg/m\(^2\)) at follow up (Table 3-37). An inverse relationship was noted such that reducing BMI was associated with higher IWQOL-lite scores in each domain. However, inspection of regression variable plots suggested that the apparent relationship between sexual life and work scores, and BMI may be weaker than suggested by calculations of Pearson’s coefficient (Figure ii-15 (392)). Weaker, but statistically significant, relationships were noted between body weight loss by the follow up assessment and scores for physical function, self-esteem, public distress, work, and total score, such that greater body weight loss was associated with higher scores in each of these domain. There was no evident relationship between body weight loss and sex life score.

### Table 3-37  Bivariate correlation using Pearson’s coefficient to show relationships between BMI and body weight loss, and scores in each IWQOL-lite domain

<table>
<thead>
<tr>
<th></th>
<th>Against BMI at follow up (kg/m(^2))</th>
<th>Against body weight loss (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>R</td>
</tr>
<tr>
<td>Physical function</td>
<td>114</td>
<td>-0.52</td>
</tr>
<tr>
<td>Self esteem</td>
<td>113</td>
<td>-0.58</td>
</tr>
<tr>
<td>Sexual life</td>
<td>101</td>
<td>-0.36</td>
</tr>
<tr>
<td>Public distress</td>
<td>108</td>
<td>-0.58</td>
</tr>
<tr>
<td>Work</td>
<td>105</td>
<td>-0.50</td>
</tr>
<tr>
<td>Total</td>
<td>97</td>
<td>-0.63</td>
</tr>
</tbody>
</table>
3.1.4.11.5 Relationship between IWQOL-lite scores and other variables

There was no clear relationship between IWQOL-lite score at the follow up assessment and age at follow up, duration of follow up, or a diagnosis of depression at follow up or baseline.

Diabetes status at follow up appeared to relate to physical function score on the IWQOL-lite questionnaire, but did not relate to any other domain. The mean (SD) physical function score at follow up for the 35 participants with normal glucose tolerance at follow up was 87.3 (13.6) %, whilst the mean (SD) score for those with prediabetes (n=55) and type 2 diabetes (n=15) was 83.1 (17.1) and 69.1 (17.7)% respectively; estimated difference compared to those with normal glucose tolerance was 14.0% (4.0 to 24.0, p=0.007) for those with prediabetes, and 18.2% (8.9 to 27.4, p<0.001) for those with type 2 diabetes. Furthermore, Pearson’s correlation coefficient for physical function score % against HbA1c at follow up was r=-0.36, p<0.001, n=106, suggesting a weak but statistically significant relationship, whilst the incremental reduction in score with each strata of glycaemic status also supports a true relationship.

3.1.4.12 Comparison of study cohort with non-recruited surgical controls

Approximately 850 people who had undergone bariatric surgery at the Wakefield obesity clinic were appropriate for recruitment to this study. 120 (14.1%) were recruited at study close. The study is therefore potentially limited by selection bias. To assess this, three analyses were performed. Firstly, the baseline characteristics of the 118 recruits were compared against the baseline characteristics of the non-recruited 1114 persons who underwent bariatric surgery through Wakefield obesity clinic. Secondly, outcomes in both populations in those with available data at 1 and 2 years (n=684) were compared. Thirdly, a similar analysis comparing the recruited cohort against potential recruits who specifically declined participation in the study was performed. Table ii-18 (393) shows relevant baseline characteristics of the 118 recruited persons and the 1114 potential recruits who did not participate in the study. Figure 3-29 shows box plots comparing baseline characteristics of both populations.
Figure 3.29  Box plots to show a) age (years), b) weight (kg), c) BMI (kg/m²), d) fasting glucose (mmol/L), e) HbA1c (mmol/mol), f) mean arterial blood pressure (mmHg), at baseline of the recruited (n=118) and non-recruited populations (n=1114)
3.1.5 Discussion

Outcomes from randomised studies have confirmed bariatric surgery to be a superior therapeutic option to lifestyle and/or medical therapy over follow up to 3 years, for weight loss and glycaemic control in the management of obesity and type 2 diabetes. This study was proposed to provide data on longer term weight, glycaemic, and metabolic follow up outcomes after RYGB, and adds to the increasing body of literature reporting on longer term outcomes. Furthermore, the study provides reassurances that the weight and diabetes related effects of RYGB are durable over many years follow up and does not raise new concerns about significant longer term complications. Each outcome of the study is discussed in more detail below.

3.1.5.1 Weight outcomes

Every participant in this cohort lost weight after RYGB, and maintained a lower weight than documented at baseline throughout the follow up period. The mean body weight loss in this cohort was 29.6% at a mean of 10 years of follow up, which is comparable to that observed after RYGB in the randomised studies reporting 1-3 year follow up outcomes noted in chapter 1.3.2. However, it should be noted that the majority (61% of cohort) of patients remained obese at follow up with a mean BMI of 32.7 kg/m². Only 12% attained a normal weight (BMI 18.5 to 24.9 kg/m²) whilst 28% were overweight at follow up (25.0 to 29.9 kg/m²). As seen with other measurements, this reduction in BMI is clinically relevant and not just of cosmetic value. A metaanalysis including studies reporting hazard ratios for all cause mortality based on BMI showed that subjects who were obese had a higher hazard ratio than those who were not (1.18, CI 1.12 – 1.25). However, closer inspection of the obese group revealed interesting differences. Whilst those with grade 2 or 3 obesity had a significantly higher risk of mortality (HR 1.29, CI 1.18 to 1.41, p<0.05) than those of normal weight, subjects with grade 1 obesity (BMI 30-34.9 kg/m²) had a risk that was not clearly different (0.95, CI 0.88-1.01). Furthermore, those subjects who were overweight had a significantly lower hazard risk for all-cause mortality than those who were either of normal weight or were obese (0.94, CI 0.91-0.96). We can not of course confirm that these results are conferrable to subjects after a reduction in BMI induced by bariatric surgery, although these data illustrate that attaining normal weight may not be the optimal therapeutic goal. Further research is required to determine whether attainment of a particular BMI category after bariatric surgery conveys additional benefit.
Amount of weight lost after RYGB was predicted by BMI at baseline, and increased with increasing baseline BMI. However, differences in body weight loss between groups stratified by BMI at baseline was not great, such that final BMI also increased with increasing baseline BMI. BMI at baseline alone explained 33% of the variation in subsequent change in BMI over the study period, and multivariate modelling added little value. Other studies have reported conflicting outcomes with respect to the prediction of weight loss from baseline BMI. Consistent with our data, some studies have reported greater weight loss with increasing baseline BMI.\textsuperscript{771,772} Inge and colleagues reported little difference in body weight loss in adolescents undergoing RYGB based on baseline BMI but, as in our study, reported increasing BMI at follow up with increasing BMI at baseline.\textsuperscript{773} However, a large number of studies have reported an apparent negative relationship between increasing BMI at baseline and subsequent weight loss.\textsuperscript{774,775,776} It is likely however, that this relates to the differing definitions of weight loss used in the bariatric literature, as each of these studies reported excess weight loss. The absolute weight loss was greater with increasing BMI in a number of these studies.\textsuperscript{774} It is perhaps unsurprising that heavier patients lost less excess weight after surgery, as, given that excess weight increases in proportion to increasing BMI, the same absolute reduction in weight would be interpreted as less excess weight loss. Our data are therefore consistent with the likelihood that weight loss after RYGB is similar between populations of differing baseline BMI.

These data suggest that weight loss following RYGB is durable, at least over the average of 10 years of follow up provided by this study. Regression analysis and bivariate analysis did not suggest increasing weight regain over time. The participants with a shorter duration of follow up, 5 to <10 as opposed to >10 years, were slightly heavier at baseline although this did not reach statistical significance. This likely relates to an increasing acceptance of super-obese surgical candidates as the surgical programme developed. Consistent with the above findings, these participants lost slightly more weight than those with the longer duration of follow up. This suggested difference though is likely to relate to differences in early weight loss, rather than reflect differences in weight regain or total loss. When only those participants with BMI data at 2 years were considered, weight regain between the 2 year and the greater than 5 year assessment was not clearly different; the mean (SD) 3.0 (3.9) kg/m\textsuperscript{2} in those with <10.0 years of follow up and 3.4 (5.8) kg/m\textsuperscript{2} in those with >10 years of follow up; estimated difference 0.4 kg/m\textsuperscript{2} (95% CI -1.8 to 2.7, \(p=0.7\)). Thus, participants with the shorter duration of follow up had lost more weight (BMI) by the follow up assessment, but were heavier at baseline and had a similar BMI to those with a longer duration of follow up at the follow up assessment. Weight regain after the early period of extreme weight loss was similar in both groups.
In addition to the arguments presented above to support the durable effect of RYGB on weight loss, body weight loss was similar in each of two studies reporting outcomes at more than five years after RYGB presented in chapter 1.3.3.3.3 (Table 1-5), and selected from the large number of published outcome studies for their superior quality. Whilst these two studies are presented above to illustrate glycaemic outcomes, weight outcomes were also reported with body weight loss at 6 years of 27.7% in the study by Adams and colleagues, and body weight loss at 10 years of 25% in the study by Sjostrom and colleagues. However, it should be acknowledged that some weight regain was observed in both of these studies from nadir weight loss at 12 to 24 months. Longitudinal data from randomised controlled studies are needed to comment firstly on whether this a genuine trend, and secondly, whether the rate of weight gain over that period exceeds that seen in the control group, as weight gain with advancing age is to some degree expected.  

3.1.5.2 Diabetes outcomes

RYGB had favourable effects on glucose homeostasis and diabetes in this study. Fasting concentrations of glucose and insulin, and assessments of HbA1c and HOMA-IR fell significantly after surgery in the majority of participants. Indeed, the mean concentrations of insulin and HOMA-IR normalised over the follow up period, whilst the mean diabetes status using ADA criteria improved from type 2 diabetes to prediabetes.

81% of participants undergoing bariatric surgery with normal glucose tolerance at baseline remained with normal glucose tolerance at follow up, whilst 19% of participants had developed prediabetes during that time period. With the exception of HbA1c at baseline, no plausible measured variable at baseline predicted glycaemic outcome in this group, and furthermore classical risk factors for prediabetes including BMI at follow up or the degree of body weight loss did not differentiate the groups.

In those with prediabetes at baseline, twenty-five (63%) participants had an improvement in glucose tolerance to normal concentrations at follow up, 14 (35%) remained with prediabetes, whilst one (2%) had progressed to type 2 diabetes at a mean duration of follow up of 8.7 years. HbA1c and fasting glucose at baseline appear to predict diabetes outcome in this group, such that a higher HbA1c and/or fasting glucose at baseline is associated with a greater reduction in HbA1c over the follow up period.
Increasing baseline HOMA-IR also predicted a lower reduction in HbA1c over the study period. Whilst not reaching statistical significance, these data suggest that body weight loss may be a factor underlying glycaemic improvements after surgery. There was no clear additional associations between glycaemic outcome and classical risk factors for prediabetes. The improvement in glucose homeostasis in both groups was primarily the result of an improvement in insulin sensitivity as assessed by HOMA modelling.

Nine (25%) and 17 (47%) of participants with preoperative type 2 diabetes had improved to normal glucose tolerance and prediabetes respectively, whilst 10 (28%) remained with type 2 diabetes at a mean (SD) duration of follow up of 8.8 (4.6) years. Fasting glucose, HbA1c, fasting insulin, and HOMA-IR at baseline all appear to predict likelihood of persistent type 2 diabetes, whilst age at diagnosis and duration of type 2 diabetes did not. Increasing body weight loss after surgery appears to predict a higher likelihood of resolution of type 2 diabetes at follow-up. As well as improvements in fasting glucose and HbA1c, those participants who remained with type 2 diabetes also required less medications following surgery, suggesting that overall glycaemic control was improved despite persistent type 2 diabetes. A multivariate regression model employing body weight loss after surgery and either baseline fasting glucose or HbA1c, accounted for approximately 50% of the observed variation in the change in HbA1c following surgery. Both fasting glucose and HbA1c at baseline appear to be useful tools with which to predict persistent type 2 diabetes at follow up with optimal sensitivity/specificity of 75/73% and 87.5/78.3% respectively. However, these markers are less helpful when predicting diabetes resolution. Given the known progressive natural history of diabetes it is notable that duration of follow up did not appear to predict diabetes status at follow up irrespective of the diabetes status at baseline. This might suggest that RYGB fundamentally changes the underlying pathogenic mechanism of type 2 diabetes.

These outcomes are similar to those reported in other studies of bariatric surgery, despite a significantly longer duration of follow up (chapter 1.3.3.3). As discussed in chapter 3.2 however, the comparison of published studies is significantly limited by the use of highly variable definitions of diabetes, both at baseline and follow up. As in multiple other studies, body weight loss appears to be an important factor underlying the likelihood of glycaemic improvements after RYGB. This relationship was less apparent in those with either normal glucose tolerance or prediabetes at baseline, although a similar trend was suggested in those with prediabetes. Furthermore, these data are consistent with the published literature in supporting that improved glycaemic outcomes following bariatric surgery in patients with type 2 diabetes at baseline are predicted by better glycaemic control prior to
surgery.\textsuperscript{440,443,446} Interestingly however, and in contrast to other studies,\textsuperscript{443,445,446,447} there was no apparent relationship between glycaemic outcomes and either the age at which the participant underwent RYGB, or the duration of diabetes prior to surgery. This is of clinical interest and would be a point of difference between this study and similar studies. Duration of diabetes is generally taken as a surrogate of likelihood of beta cell failure, and should therefore intuitively predict glycaemic outcomes. It is possible this finding relates to the duration of follow up at which diabetes outcomes are reported. Each of the studies above reported outcomes within 24 months as opposed to 10 years as in our study. Perhaps these factors better predict early improvements in glycaemic control, whereas weight loss predominates in longer term observations? Longitudinal studies reporting these measurements in the same participants would be required to address this apparent discrepancy. The diabetes outcomes were similar in each study, and therefore this alone is unlikely to confound this assessment.

3.1.5.3 Blood pressure and lipid outcomes

Systolic, diastolic, mean arterial blood pressure were all reduced significantly at follow up when all participants or those with baseline hypertension were considered. There was no clear change in blood pressure in those participants with normal blood pressure at baseline. However, the majority of participants with baseline hypertension remained hypertensive at follow up, although required fewer medications. Most,\textsuperscript{396,412,778} but not all studies,\textsuperscript{402} have reported similar outcomes after RYGB. Indeed recent meta-analyses concluded that bariatric surgery resulted in a 0.52 (0.42 to 0.64) risk reduction for a diagnosis of hypertension at 12 to 24 months in those with hypertension at baseline, which remained stable up until five years.\textsuperscript{779,780} However, it must be acknowledged that this cohort did not have optimised blood pressure control at baseline. Twenty six participants with measured hypertension at baseline were not using anti-hypertensive medications, whilst a further 28 and 17 participants were using only one or two anti-hypertensive medications respectively. Therefore, the effect size of bariatric surgery on hypertension in this study may be over estimated.

Blood pressure improvements over the study were associated with baseline blood pressure measurement, such that greater reductions in mean arterial pressure were observed with increasing mean arterial pressure at baseline. However, within the entire cohort, blood pressure outcomes were not associated with weight or diabetes outcomes, or with the duration of hypertension prior to surgery.
or medication use at baseline. Furthermore, the duration of follow up did not predict any blood pressure outcomes. Whilst surprisingly few studies have reported factors predicting blood pressure outcomes after bariatric surgery, it is clear that in non-surgical studies weight loss is favourable. A systematic review of randomised trials reporting weight outcomes after dietary interventions suggested that each kilogram of body weight loss predicts a 1 mmHg reduction in diastolic blood pressure.\textsuperscript{781} A more recent systematic review supported the favourable effect of weight loss alone on both systolic and diastolic blood pressure, although reported a lower effect size.\textsuperscript{782} Therefore, the lack of any association between body weight loss and blood pressure outcomes in this study is unexpected. It is possible however, that this may be explained by the confounding effects of anti-hypertensive medication use. When only those participants not using anti-hypertensive medication at baseline or follow up, with or without hypertension at either time point (n=47) were considered, increasing body weight loss was associated with an increasing reduction in mean arterial pressure (R=0.33, F=5.6, p=0.02) at follow up. Furthermore, and perhaps consistent with the conclusions of Neter and colleagues,\textsuperscript{781} this association was predominantly attributable to the relationship between increasing body weight loss and increasing reductions in diastolic blood pressure (r=0.3, f=5.4, p=0.02). It has also been suggested that the improvement in blood pressure markers after bariatric surgery may relate to an improvement in renal function, although our study was not designed to assess this.\textsuperscript{783}

Concentrations of LDL, HDL, and triglycerides were reduced significantly at follow up in this cohort, and support the findings in multiple other studies.\textsuperscript{396,402,403,784,785} However, the number of lipid lowering agents per participant was not altered. As with blood pressure, this finding most likely reflects the sub-optimal medical management of participants prior to referral for surgery; 85% of participants were not using lipid lowering medication at baseline. In contrast to the findings of others (see chapter 1.3.7), the change in LDL over the study period was predicted by body weight loss (r=0.38, f=11.1, p=0.001) and the change in BMI (r=0.3, f=6.3, p=0.02) when only those participants not using lipid lowering therapy at either time point were considered (n=66). This suggests that the beneficial effects of RYGB on LDL concentrations are to some extent weight related, but this study is of course not able to comment on the possibility that the effect of RYGB may be greater than other bariatric surgery procedures.

Changes in each lipid concentration was associated body weight loss over the course of the study. Surprisingly however, both the change in LDL and HDL concentrations over the study period appeared to be associated with the duration of follow up. However, these relationships were both weak (r\textsuperscript{2}=0.07 for LDL and HDL) and account for only 6% of the variation seen in change in both. Furthermore,
stratification of the study population into those with less or more than 10 years of follow up did not support this finding. The mean (SD) LDL at baseline in those with <10 years and ≥10 years of follow up was 3.14 (0.92) and 3.65 (0.91) mmol/L respectively (estimated difference 0.5 mmol/L (95% CI 0.02 to 1.0, p=0.04), whilst the mean (SD) LDL at follow up was 2.80 (0.79) and 2.79 (0.85) mmol/L (estimated difference 0.01 mmol/L (95% CI -0.3 to 0.3, p=0.91). Thus, the difference in the change in LDL in these two groups (estimated difference 0.36 mmol/L (95% CI -0.17 to 0.9, p=0.18) is likely to be explained by the higher baseline LDL in those with a longer duration of follow up. The mean (SD) HDL at baseline in those with < 10 years and ≥ 10 years of follow up was 1.32 (0.33) and 1.37 (0.39) mmol/L respectively, whilst the mean (SD) HDL at follow up was 1.85 (0.48) and 2.02 (0.64) mmol/L. Following logarithmic transformation, there was no clear difference at either baseline (estimated difference 0.05 mmol/L, p=0.7 following logarithmic transformation) or follow up (estimated difference 0.17 mmol/L, p=0.2 after logarithmic transformation). Finally, when only participants not using lipid lowering therapy at any point during the study were considered (n=66), there was no clear relationship between duration of follow up and change in LDL (r=0.15, p=0.2). An apparent relationship with the change in HDL remained however, with a slight increase in the increase in HDL with increasing duration of follow up (r=0.33, f=7.8, p=0.007). This was not explained by coincidental differences in HDL at baseline for differing durations of follow up.

3.1.5.4 Co-morbidity outcomes

There was no clear difference in the frequency of cardiac events or stroke before or after surgery in this study. However, event numbers for both were small with only nine (8%) of participants having established ischaemic heart disease at baseline, and only three (3%) having had a stroke. However, no patient in this study suffered a myocardial infarction or underwent invasive coronary interventions following bariatric surgery. This study is therefore unable to contribute significantly to the literature indicating the effects of bariatric surgery on these outcomes. However, the small number of events is not particular to this study and is reported in most bariatric follow up studies, likely because surgical candidates are, by selection, at a relatively low risk for cardiovascular events at baseline. A similar phenomenon has been observed in studies exploring medical therapy for type 2 diabetes. Earlier published studies were unable to confirm the cardiovascular benefits of medical interventions in patients with type 2 diabetes because event rates were low. More recent studies, specifically
recruiting only participants considered to be at high risk of cardiovascular events, have still failed to clearly show the benefits of medical intervention, which may only become evident after extended follow up. As presented in chapter 1.3.6, large systematic reviews and meta-analyses have been required to clearly demonstrate the cardiovascular benefits of bariatric surgery.

Both obesity and type 2 diabetes are established risk factors for the development of depression. It is likely that these relationships are bidirectional, with evidence that depression is both a consequence and a cause of obesity and type 2 diabetes. However, the relationship between BMI and depression may not linear. Whilst some studies have reported an increasing likelihood of depression with increasing obesity, other studies have reported a U shaped curve, with higher rates of depression in the underweight and obese when compared with normal weight individuals. As the prevalence of obesity and type 2 diabetes is naturally very high in those seeking bariatric surgery, numerous studies have confirmed a high prevalence of depression in this context. Thus, it is expected that the prevalence of depression at baseline in this cohort may exceed that seen in healthy sample populations. The study was not designed to test this hypothesis, but a high prevalence within the cohort was observed. In contrast to studies noted above, our data did not show a relationship between BMI at baseline or glycaemic status and the likelihood of depression, which may be explained by both the small cohort numbers and the fact that the presence of depression was assessed purely on the basis of simple questioning during the interview. Use of a more robust depression assessment may have yielded different results.

Nonetheless, the frequency of depression was significantly reduced in this cohort following gastric bypass surgery. This is consistent with findings of numerous similar studies following bariatric surgery. However, the likelihood of depression at follow up did not appear to relate to weight, BMI, body weight loss, or the presence of diabetes. Furthermore, the presence of depression at baseline did not predict outcomes after bariatric surgery. These findings are surprising, and may relate again to the dichotomous definition of depression (yes or no) utilised in this study rather than a tool that quantified depressive symptoms. Certainly, the severity of depression at baseline has been shown to predict subsequent weight loss in other studies, whilst body weight loss has been shown to predict improvement in depressive symptoms. An alternative explanation for this apparent discordancy, is that the relationship between these measures changes with the duration of follow-up. Perhaps factors other than body weight loss develop greater importance as predictors of depressive symptoms once a number of years since surgery have elapsed? Unfortunately, the data obtained from this study cannot
answer this question, and a longitudinal study utilising a detailed depression assessment tool would be required.

The frequency of gout was significantly reduced in this cohort following gastric bypass. Of the 12 participants who reported a diagnosis of previous gout at baseline, only one of these reported further attacks after bariatric surgery. Gout is strongly associated with hyperuricaemia, which is itself associated with obesity. A number of studies have now demonstrated clinically significant reductions in uric acid levels following bariatric surgery. Furthermore, because of the uricosuric effect of hyperglycaemia, subjects without type 2 diabetes tend to have higher concentrations of uric acid than those with. Despite this, reductions in uric acid have been demonstrated in both diabetic and non diabetic populations following bariatric surgery. A recent study in Auckland demonstrated significant reductions in uric acid following laparoscopic sleeve gastrectomy in participants with type 2 diabetes, with and without a diagnosis of gout at baseline. In non-surgical populations, there is a relationship between the frequency of gout attacks and the level of serum uric acid, in that increasing levels predict more frequent episodes. Furthermore, lowering of serum uric acid by pharmaceutical means reduces the frequency of episodes. There is as yet, little published evidence to demonstrate the clinical effect of the reduced serum uric acid concentrations induced by bariatric surgery, although based on these non-surgical findings, it may be reasonable to consider these changes favourable. In addition, hyperuricaemia has been associated with a number of other adverse medical conditions including cardiovascular mortality. Nonetheless, bariatric surgery appears to increase the risk of gout attacks in the early post-operative period, presumably as a consequence of renal dysfunction, fasting, or rapid weight loss. Consistent with this, three further participants in this study without a history of gout at baseline, reported at least one episode of gout after surgery. Further work is therefore required to describe the clinical effect of bariatric surgery induced lowering of uric acid levels.

The frequency of arthritis was significantly greater after gastric bypass surgery than before. However, univariate regression analysis determined that age at either baseline or follow up strongly predicted the likelihood of arthritis at that time point (r=0.36, f=17.3, p<0.001 at baseline, and r=0.33, f=14.6, p<0.001) but was not predicted by the duration of follow up (r=0.02, f=0.06, p=0.8), suggesting that the apparent increase in frequency of arthritis is the result of an increase in age. Furthermore, neither BMI at baseline (r=0.07, p=0.5) or at follow up (r=0.09, p=0.3) predicted the likelihood of arthritis, nor did the change in body weight over the study period (r<0.01, p=0.9), supporting the hypothesis that the apparent increase in the prevalence of arthritis is independent of surgery. Consistent with this,
musculoskeletal complaints have been reported to decrease following bariatric surgery when assessed with specialist tools.\textsuperscript{816,817}

Obstructive sleep apnoea and sleep dysfunction is common in bariatric surgery candidates, and frequently unrecognised.\textsuperscript{818} Both surgical and non-surgical weight loss has been shown to be effective in reducing the severity of sleep apnoea.\textsuperscript{819} In this study, sleep apnoea was common at baseline, and was significantly reduced following gastric bypass, although it is acknowledged that sleep apnoea was not diagnosed through the use of appropriate sleep studies in this study. Participants who remained with sleep apnoea at follow up were significantly heavier at follow up than those who did not, and had experienced less body weight loss. The five participants with sleep apnoea at the follow up assessment were significantly heavier at both baseline and follow up than those who had never received a diagnosis of sleep apnoea, or had resolution of sleep apnoea with gastric bypass surgery. The mean (SD) BMI at baseline was 46.2 and 55.4 kg/m\textsuperscript{2} for those without sleep apnoea and with sleep apnoea at follow up respectively; estimated difference 9.2 kg/m\textsuperscript{2} (p=0.03 after logarithmic transformation). The mean (SD) BMI at follow up was 32.3 and 41.2 kg/m\textsuperscript{2} for those without sleep apnoea and with sleep apnoea at follow up respectively; estimated difference 8.9 kg/m\textsuperscript{2} (p=0.02 following logarithmic transformation). Thus, participants with sleep apnoea at follow up also had a lower mean body weight loss after gastric bypass than those who did not have sleep apnoea although this difference was not statistically significant; mean (SD) body weight loss (%) 25.0 versus 29.7% respectively; estimated difference 4.72% (95% CI -5.0 to 14.5, p=0.4). Furthermore, univariate regression analysis established that the final BMI (kg/m\textsuperscript{2}) predicted the likelihood of sleep apnoea at that time point (r=0.3, f=8.1, p=0.005) but accounted for only 6% of the variation seen.

Cholecystectomy was performed in twenty (17%) participants during gastric bypass as a prophylactic procedure. Allowing for this, the frequency of cholecystectomy was significantly reduced following gastric bypass. Cholecystectomy was required in 8% of participants following gastric bypass. There were no clear baseline factors that predicted the requirement for cholecystectomy following gastric bypass.
3.1.5.5 Micronutrient status

Bariatric surgery can be predicted to cause alterations in the absorption and availability of minerals and micronutrients. Vitamin B12 absorption requires the release of the vitamin from food, regulated by R protein and pancreatic proteases, the production of gastric intrinsic factor which binds to vitamin B12, and an intact intestinal mucosa to allow absorption. Dysfunction in any of these areas may result in vitamin B12 deficiency. Whilst vitamin B12 concentrations were predictably lower in those participants not receiving vitamin B12 supplementation, only 13% of all participants had vitamin B12 concentrations below the reported reference range. Eleven (85%) of these participants were not receiving regular vitamin B12 injections, although the remaining 36 participants not receiving supplementation had normal concentrations of vitamin B12. Thus, 23% of participants not using vitamin B12 supplementation were deficient. A compensatory effect on vitamin B12 concentrations through oral supplementation appears unlikely given the lack of relationship with dietary intake. These data are in keeping with findings in other studies where vitamin B12 deficiency prevalence rates of between zero and 37% have been observed at 12 to 48 months of follow up. Furthermore, vitamin B12 deficiency is common in the general population at approximately 5%, and is more common in the context of type 2 diabetes, particularly when Metformin is used. Indeed, Hauesler and colleagues recently reported a 19% prevalence of vitamin B12 deficiency in New Zealanders with type 2 diabetes using metformin, although the cut-off used to define deficiency was slightly higher in that study than this. Therefore, deficiency rates after RYGB may not differ significantly from the background expected prevalence rates in populations that are likely to be considered for surgery. Nonetheless, it would be reasonable to continue to recommend the measurement and, where necessary, supplementation of vitamin B12, as deficiency is associated with severe clinical consequences.

Zinc deficiency is common in the obese general population, and has been associated with alopecia, hypogonadism, impaired neuropsychological performance, and skin disorders. In addition to an increased likelihood of zinc deficiency at baseline, oral zinc intake is likely to decline following surgery as zinc rich foods including meat and fish, may be less desirable. Zinc is primarily absorbed in the small intestine, and therefore intestinal bypass through bariatric surgery may further reduce availability. Therefore, a high prevalence of zinc deficiency is expected after bariatric surgery. Indeed, 49% of participants in this study had zinc deficiency at follow up. Only a handful of studies have reported the frequency of zinc deficiency after bariatric surgery, but are consistent with our data, showing prevalence rates of between 12 and 68%. BPD appears to be more likely to cause
zinc deficiency than RYGB. In our study, oral multivitamin supplementation neither prevented zinc deficiency, nor had an effect on zinc concentrations, consistent with findings by others.  

As the small intestine appears to be the major site of dietary copper absorption, concerns as to the potential for copper deficiency following bariatric surgery have reasonably been raised. Indeed, a number of case reports of severe copper deficiency resulting in neurological and haematological dysfunction have been published. The prevalence of copper deficiency following RYGB has been reported in only a few cohorts, with prevalence rates of between four and 15%. In contrast, the prevalence following BPD appears to be higher. The prevalence of copper deficiency at long term follow up after RYGB in our study was only 1%, using the same thresholds to define deficiency as used in the above studies. The majority of participants in this cohort had normal concentrations of copper at follow up, whilst oral multivitamin supplementation does not appear to effect copper concentrations. It is therefore possible, that the exact length of bypassed small intestine has a bearing on the likelihood of copper deficiency during long term follow up. Furthermore, whilst the prevalence of copper deficiency in the general population is not known, a prevalence of 1% after RYGB surgery may not be significantly different.

3.1.5.6 Quality of life and patient satisfaction

Whilst it is tempting to consider only weight, diabetes, and metabolic measures as important outcomes after bariatric surgery, it would be wrong to neglect the impact on quality of life, which may be tied to one or more of the weight/metabolic outcomes. Obesity is known to severely impact upon quality of life as a consequence of physical disability, an increased risk of co-morbid conditions, and, not least, because of discrimination. Obese patients are less likely to perceive their health as being excellent, and appear to report poor health on more days than non obese persons. Thus, the effect of bariatric surgery should be judged by improvements in obesity related quality life as well as more standard measures.

In this study, quality of life was assessed through the use of the IWQOL-lite questionnaire (Appendix i-8, page 360), validated in many populations including subjects who had previously undergone bariatric surgery. Quality of life, assessed through five domains, was judged to be higher by overweight or obese
participants in our study who had undergone RYGB, than by referenced control non-surgical populations matched to BMI category. These differences were significant for physical function and total scores. BMI, and to a lesser extent body weight loss, correlated with participant’s physical function, self-esteem, public distress, work, and total percentage scores on the IWQOL-lite test. Sexual life did not correlate with either outcome. Physical function score appeared to correlate with glycaemic status at follow up.

These conclusions are consistent with the findings of other studies. A recent systematic review including over 9,000 participants from 72 studies calculated that the average effect of bariatric surgery on quality of life was significantly positive (average effect size 0.88 (95% 0.80 to 0.96)). The analysis included studies of all bariatric procedures, and whilst the authors identified a greater favourable effect on quality of life by combined restrictive/malabsorptive procedures when compared with restriction alone, this was not statistically significant. As with our data, the time after surgery at which quality of life was assessed did not appear to predict quality of life either, supporting the durable effect of bariatric on quality of life. The effect on physical markers of quality of life appears to be greater than that on mental markers, consistent with our data where the difference in reported physical function between post-surgical participants and controls was statistically significant.

In summary, RYGB appears to have a favourable effect on quality of life, particularly physical quality of life, which is closely related to the obtained weight loss and final achieved BMI.

3.1.5.7 Study limitations

This study has a number of limitations. The conclusions that can be derived from a retrospective non-experimental cohort study are limited, and the quality of evidence is poorer than would have been obtained from a randomised study. Unfortunately the retrospective nature of this study precluded randomisation. Furthermore, the initial study design incorporated a control group of participants who were referred or self referred for bariatric surgery but did not undergo the procedure. This study design would have been inherently biased as patients may not have undergone surgery because of factors that would have directly determined longer outcomes. For example, patients with existing heart disease or those with very poorly controlled glycaemic control, and therefore presenting a more significant anaesthetic and operative risk, may not have been referred for surgery in the first place. Furthermore,
they may have very reasonably been declined for surgery by the operating surgeon. After commencing recruitment for this study, it quickly became apparent that no control group participant invited to partake in the study was willing to do so. Thus, on the basis that the initial proposed study design was inherently limited, and recruitment of a suitable control group was not proceeding as planned, we decided to abandon this study design and report outcomes only in those who had undergone bariatric surgery.

RYGB was provided in a private capacity, which may have introduced further selection bias and make the outcomes of this study less relevant to the general population. At the time that the participants in this study underwent surgery, bariatric surgery was provided in the private sector only which would likely result in less standardisation of patient selection. It is possible that this factor resulted in an ethnicity bias within the cohort, as Maori in particular were under represented in comparison to the local population.

As the study was conducted retrospectively, data collection at baseline was limited to that which seemed most relevant at the time it was collected and did not always include the parameters collected at follow up. For example, no record of smoking history was recorded at baseline. Likewise, quality of life data was not obtained prior to surgery for a comparative analysis with similar data at follow up. Furthermore, documentation of the prevalence of co-morbid conditions at both baseline and follow up was obtained primarily by questioning participants as to their clinical history and was not confirmed via medical records. However, the major outcomes of the study were quantitative, with complete data available at baseline and follow up. Furthermore, blood samples obtained at baseline in this study were analysed in a number of regional laboratories over a period of 30 years. It is therefore not possible to comment specifically as to whether any significant differences in assay methodology used by these laboratories would impact on the comparability of biochemical markers at baseline and follow up. However, all samples were analysed within a suitably accredited laboratory and it is unlikely that significant variation would occur that might effect the interpretation of this dataset.

Recruitment numbers for this study were fewer than expected. Approximately 900 participants were suitable for inclusion in this study, with 120 recruited at study completion. Numerous reasons were provided by potential participants as to their decision not to participate, including relocation out of region, dissatisfaction with outcomes, and being unable to provide the time. However, the majority of potential participants not recruited for this study simply declined to respond to the study invite or to subsequent phone calls. Indeed, only 31 people specifically declined to participate, 24 of which had
data within the original surgical database. There was no difference in age at operation, weight and BMI at operation, blood pressure parameters at operation, or markers of fasting glucose, HbA1c, and total cholesterol between these 24 people and the recruited participants at baseline, one, or two years. Whilst the low recruitment numbers are not ideal, it should be noted that the cohort was larger than all the randomised studies reporting weight outcomes presented in chapter 1.3.2 and comparable in size to most of those that reported diabetes outcomes (chapter 1.3.3).

Nonetheless, the possibility that the recruited cohort may not be representative of the entire possible cohort should be entertained. To address this question, the recruited population was compared against non-recruited controls (chapter 3.1.4.12). The recruited study population were older at operation than the non-recruited population of patients who had undergone bariatric surgery at Wakefield obesity clinic; estimated difference 3.7 years (95% CI 1.7 to 5.8, p<0.001). There is no clear explanation as to why this difference occurred. The inclusion criteria for the study stipulated participants should be 18 years or older, but only three people in the non-recruited cohort were younger than this cut off. Age at operation was not shown to predict any study outcome in a positive or negative fashion, and it is unclear whether this apparent selection bias will have affected the legitimacy of the study. The recruited population and non-recruited population were otherwise not clearly different at baseline. Furthermore, there was no clear difference between outcomes at one and two years after surgery in the recruited group and those in the non-recruited group (n=684), when weight, BMI, blood pressure parameters, and concentrations of fasting glucose, HbA1c, and total cholesterol were compared (Table ii-19 (394)). Thus, there is no clear evidence to suggest significant selection bias with respect to the recruited population, when compared with those who underwent surgery but were not recruited.
3.1.6 Conclusion

In this study, longer term outcomes after RYGB are reported in 118 obese participants with or without type 2 diabetes. These data support the published literature on shorter term outcomes, and suggest that these effects are durable over extended follow up. Each participant lost weight after surgery, and the majority achieved improvements in markers of glucose homeostasis, blood pressure, and lipids. Outcomes with respect to diabetes status were similar or better than those in the published literature despite a significantly longer duration of follow up. Despite a high prevalence of persistent symptoms directly related to RYGB, patient satisfaction is extremely high and quality of life is improved. Micronutrient deficiencies do not appear to be a significant factor after RYGB in this context, although more active measures should be taken during follow up to prevent zinc deficiency.

In summary, this study supports the conclusion that bariatric surgery is an effective and durable treatment for obesity, type 2 diabetes, and the multitude of complications that frequently result from both disorders.
3.2 The application of differing definitions of diabetes outcomes following bariatric surgery

3.2.1 Introduction

Obesity and Type 2 diabetes are major health issues worldwide with high prevalence in Westernised countries, and an alarming increase in incidence in developing countries (chapter 1.1.1).\textsuperscript{2,3,4,842,843} Whilst diet and lifestyle modification remain the cornerstone of weight management, no single strategy for achieving sustained clinically important weight loss in obese individuals has been identified, with weight regain following periods of weight loss frequently observed.\textsuperscript{844,845,846,847} Many studies have demonstrated weight loss of the order 10\% of body weight, often with improvements in metabolic and cardiovascular parameters. However, even with this degree of weight loss, morbidly obese individuals with established type 2 diabetes remain obese and still require antidiabetic medication.

Bariatric surgery has emerged as the most effective treatment for obesity and type 2 diabetes and results in significant improvements in glycaemic dysfunction in most patients. Diabetes outcomes following bariatric surgery are of significant clinical interest, and accurate representation of the likelihood of diabetes remission is important when discussing surgery with potential patients. Reported diabetes outcomes are, however, likely to be highly variable depending on the definitions used to classify resolution and partial resolution.

Buchwald and colleagues published a large meta-analysis of studies assessing glycaemic outcome following RYGB and concluded that diabetes remission was seen in 78.1\% of patients.\textsuperscript{433} Diabetes resolution in this analysis was defined as an HbA1C of <6.0\% (42 mmol/mol) or a fasting blood glucose of <100 mg/dl (5.6 mmol/L) off diabetes medications. More recently, two randomised controlled trials have been published, each using a further disparate definition of diabetes outcome. Schauer and colleagues performed a randomized, non-blinded, single-centre trial, comparing intensive medical therapy alone versus medical therapy plus RYGB surgery or sleeve gastrectomy in 150 obese patients with uncontrolled type 2 diabetes.\textsuperscript{415} The primary endpoint was the proportion of patients with and HbA1c of <6.0\% (42 mmol/mol) at 12 months post-surgery with or without the use of diabetes medications.
medications. 50 subjects underwent RYGB surgery and the primary endpoint was reached in 42% of patients (as opposed to 12% in the non-surgical arm (p=0.002), with no patient requiring ongoing diabetes medications. Mingrone and colleagues performed a single-centre, non-blinded, randomized, controlled trial comparing conventional medical therapy alone versus medical therapy plus RYGB surgery or biliopancreatic diversion in 60 patients with type 2 diabetes of at least 5 years duration and an elevated BMI (>35 kg/m$^2$). Remission of diabetes was defined as a fasting plasma glucose level of less than 100 mg per decilitre (5.6 mmol per litre) and an HbA1c level of less than 6.5% (47 mmol/mol) for at least 1 year without active pharmacologic therapy. At 2 years follow up, 75% of patients who had undergone RYGB surgery had achieved diabetes remission as opposed to none in the non-surgical arm (p<0.001). Further studies by Adams et al and Ikramuddin et al have used further disparate definitions of diabetes outcome.\(^\text{422,412}\)

In light of this inconsistency The American Diabetes Association (ADA) has released a consensus statement providing recommendations on the definition of glycaemic outcomes post bariatric surgery.\(^\text{848}\) This suggested the use of the terms “partial remission” (HbA1C≤6.5% (47 mmol/L), fasting glucose 100-125 mg/dl (5.6 – 6.9 mmol/L)), and complete remission (HbA1c “in the normal range”, fasting glucose <100mg/dl (5.6 mmol/L)) provided that each of these assessments were persistent for at least 1 year duration, and in the absence of active pharmacologic therapy or ongoing procedures. Additionally, the ADA defined prolonged remission as the thresholds required for satisfaction of complete remission, maintained for at least 5 years.

To assess the effect of the use of disparate definitions of diabetes outcomes following bariatric surgery, we assessed diabetes outcomes in participants with pre-operative dysglycaemia who had undergone RYGB at least 5 years ago. This cohort was a subgroup from a larger surgical follow up study (chapter 3.1). Each of the definitions described above was applied to this cohort.
3.2.2 Aims

To assess of the application of various published definitions of diabetes outcomes following bariatric surgery, to a cohort of participants with dysglycaemia at baseline who had undergone gastric bypass surgery at least five years ago.

3.2.3 Participants and methods

3.2.3.1 Study overview and design

This was a retrospective non-experimental cohort study of glycaemic outcomes in 84 participants who had previously undergone RYGB, were participating in a long term follow up study (chapter 3.1), and had dysglycaemia (prediabetes or type 2 diabetes, see chapter 2.3.3, page 126) before surgery. Markers of glucose homeostasis were measured on blood samples taken immediately prior to surgery and at a follow-up at least five years after surgery. Diabetes outcomes are reported using a number of commonly utilised definitions within the published literature.

Inclusion criteria

- Gastric bypass surgery performed at least five years before assessment
- BMI $\geq 30$kg/m2 at baseline
- Dysglycaemia at baseline based on American Diabetes Association classifications 2015:
  - Prediabetes (one or more of the following)
    - Fasting plasma glucose 5.7 to 6.9 mmol/L
    - 2 hour glucose during a 75g oral glucose tolerance test of 7.8 to 11.0 mmol/L
    - HbA1c 39 to 47 mmol/mol (5.7 to 6.4%)
  - Type 2 diabetes
Fasting plasma glucose ≥ 7.0 mmol/L
2 hour glucose during a 75g oral glucose tolerance test ≥ 11.1 mmol/L
HbA1c ≥ 48 mmol/mol (6.5%)

- Dysglycaemia on the basis of current use of oral glucose lowering therapy or insulin treatment.
- Complete complement of biochemical results available at baseline to categorise diabetes status

Exclusion criteria

- Further bariatric surgery (either revision or repair) performed since original procedure

3.2.3.2 Methods

The study design and protocol for the bariatric follow up study is described in chapter 2 and chapter 3. Diabetes outcome definitions were extracted from the manuscript of the included studies and are reported in detail below (see 3.2.4.2 and Table 3-48). Limitations encountered when applying each definition are noted in the discussion.
3.2.4 Results

The study included 84 participants who had undergone gastric bypass surgery at least five years ago, and had participated in the bariatric follow up study described elsewhere (chapter 3.1). The mean (SD) age of those included in this analysis was 50.4 (9.2) and 59.3 (10.0) years at baseline and follow up respectively. Sixty-one (73.7%) of the participants were female, and the mean (SD) duration of follow up after gastric bypass was 8.9 (4.6) years.

<table>
<thead>
<tr>
<th>Table 3-38 Baseline characteristics of the study participants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n=93</strong></td>
</tr>
<tr>
<td>Age at operation (years)</td>
</tr>
<tr>
<td>Age at follow up (years)</td>
</tr>
<tr>
<td>Duration of follow up (years)</td>
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<tr>
<td>Pre-operative BMI (kg/m2)</td>
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<tr>
<td>BMI (kg/m2) at follow up</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Female</td>
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<tr>
<td>Male</td>
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<tr>
<td>Chinese</td>
</tr>
<tr>
<td>Other/Not stated</td>
</tr>
<tr>
<td>Current smoker</td>
</tr>
<tr>
<td>Ex-smoker</td>
</tr>
<tr>
<td>Current alcohol user</td>
</tr>
<tr>
<td>In current employment</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Cigarette pack years</td>
</tr>
<tr>
<td>Alcohol units (per week)</td>
</tr>
<tr>
<td>Hours of work (per week)</td>
</tr>
</tbody>
</table>
3.2.4.1 Diabetes assessments at baseline and follow up

At baseline, forty-two (50%) of the participants had prediabetes before surgery, and forty-two (50%) had type 2 diabetes. Frequency histograms to demonstrate the distribution of each variable along with results of Shapiro-Wilk testing are shown in Figure iii-1 (396) and Table iii-1 (397). The distribution of each variable showed right skew at baseline and follow up, due to outlying results, identified by boxplots (Figure 3-30). Logarithmic transformation improved the distribution (Figure iii-2 (397)) allowing parametric analysis. Boxplots to show change in each variable over the study period are shown in Figure 3-30. A summary of diabetes assessment data is presented in Table 3-39.

Figure 3-30 Box plots showing a) fasting glucose (mmol/L), b) HbA1c (mmol/mol), c) fasting insulin (units/L), d) HOMA-IR, e) HOMA-%B, and f) HOMA-%S at baseline and after 5 years of follow up.
23 participants with type 2 diabetes used oral glucose lowering therapy (27% of whole dysglycaemic cohort and 59% of those with type 2 diabetes), whilst six used insulin therapy (7% of whole cohort, and 14% of those with type 2 diabetes).

Baseline and follow up fasting glucose was 6.62 (2.2) and 5.13 (1.33) mmol/l respectively, resulting in a mean fasting glucose at follow up within the normal population reference range (<6.1 mmol/L). The estimated difference was 1.55 mmol/L (95% CI 1.09 to 2.00, p<0.001 after logarithmic transformation). Mean HbA1c declined by a clinically significant degree following surgery. Baseline and follow up fasting HbA1c was 49.0 (14.7) and 40.3 (8.5) mmol/mol respectively. Thus, the mean HbA1c level of the cohort reduced from a level diagnostic of type 2 diabetes, to a level consistent with prediabetes. The estimated difference in HbA1c was 9.5 mmol/mol (95% CI 6.7 to 12.2, p<0.001 after logarithmic transformation).

Baseline and follow up fasting insulin was 175.4 (98.2) and 48.6 (20.8) pmol/L respectively; estimated difference 132.7 pmol/L (95% CI 107.2 to 157.3, p<0.001 after logarithmic transformation). HOMA-IR improved following surgery; the result of favourable changes in both beta cell function and insulin sensitivity. The estimated difference was 2.3 (95% CI 1.9 to 2.7, p<0.001). By definition, no participant with prediabetes used glucose lowering medication.

3.2.4.2 Diabetes outcomes utilising different definitions

Diabetes outcomes are reported below for all participants, for those with prediabetes/prediabetes before surgery only, and for those with type 2 diabetes before surgery. The definition of diabetes outcomes are those used in recently published studies of bariatric surgery for persons with type 2 diabetes. Where provided, definitions are used to categorise participants at follow up into those with resolution of diabetes, those with partial resolution, and those with type 2 diabetes. It should be noted that only two participants with prediabetes/prediabetes at baseline had progressed to type 2 diabetes at follow up, and that this was only when two of the included eight definitions were applied. Results using each definition are compared against those achieved when using the criteria suggested by the American diabetes association for the assessment of diabetes status following bariatric surgery.
Table 3-39  Baseline diabetes and follow up characteristics of the study participants stratified by diabetes status. Results of a paired T test are shown.

|                         | N (%), n | Baseline | | Follow up | | Paired T test * | | 95% CI | | P value |
|-------------------------|----------|----------|----------|----------|----------|----------|----------|----------|
|                         |          | Mean (SD) | IQR   | Min/Max | Mean (SD) | IQR   | Min/Max | Estimated difference | 95% CI | |
| All participants (n=84) |          |          |        |         |          |        |         |                      |        | <0.001|
| Age (years)             | 84 (100) | 50.4 (9.2) | 13.6   | 27.9/68.5 | 59.3 (10.0) | 14.7   | 34.0/78.1 | 8.9 | 7.9 to 9.9 | <0.001|
| Follow up duration (years) | 84 (100) | N/A | N/A | N/A | 8.9 (4.6) | 4.3 | 5.1/29.9 | N/A | N/A | N/A |
| BMI (kg/m2)             | 84 (100) | 47.2 (9.3) | 12.6 | 33.0/74.9 | 32.2 (6.7) | 7.7 | 19.4/50.5 | 15.0 | 13.6 to 16.4 | <0.001|
| Fasting glucose (mmol/L) | 78 (93) | 6.62 (2.2) | 2.25 | 3.90/13.90 | 5.11 (1.33) | 0.8 | 3.80/13.50 | 1.55 | 1.09 to 2.00 | <0.001|
| HbA1c (mmol/mol)        | 72 (86) | 50.5 (16.0) | 16.0 | 33/99 | 41.1 (8.7) | 6.8 | 28/83 | 9.5 | 6.7 to 12.2 | <0.001|
| Insulin (pmol/L)        | 71 (85) | 174.5 (93.9) | 109.0 | 5.26/482.0 | 50.3 (24.8) | 24.8 | 6.1/164.9 | 132.7 | 107.2 to 157.3 | <0.001|
| HOMA-IR                 | 61 (73) | 3.1 (1.3) | 1.9 | 0.9/6.5 | 0.98 (0.4) | 0.47 | 0.4/2.8 | 2.3 | 1.9 to 2.7 | <0.001|
| Prediabetes (n=42)      |          |          |        |         |          |        |         |                      |        | <0.001|
| Age (years)             | 42 (100) | 48.0 (9.6) | 12.2 | 27.9/68.5 | 56.6 (10.6) | 14.2 | 34.0/78.0 | 8.7 | 7.3 to 10.0 | <0.001|
| Duration of follow up (years) | 42 (100) | N/A | N/A | N/A | 8.7 (4.3) | 4.0 | 5.1/22.2 | N/A | N/A | <0.001|
# Chapter 3: Clinical outcomes after RYGB

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>Baseline</th>
<th>Follow up</th>
<th>Paired T test *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean (SD)</td>
<td>IQR</td>
<td>Min/Max</td>
</tr>
<tr>
<td><strong>BMI (kg/m2)</strong></td>
<td>42 (100)</td>
<td>46.3 (9.1)</td>
<td>12.6</td>
<td>33.9/74.9</td>
</tr>
<tr>
<td><strong>Fasting glucose (mmol/L)</strong></td>
<td>42 (100)</td>
<td>5.45 (0.7)</td>
<td>1.0</td>
<td>3.90/6.90</td>
</tr>
<tr>
<td><strong>HbA1c (mmol/mol)</strong></td>
<td>35 (83)</td>
<td>40.5 (3.3)</td>
<td>4.0</td>
<td>33.0/46.0</td>
</tr>
<tr>
<td><strong>Insulin (pmol/L)</strong></td>
<td>36 (86)</td>
<td>148.9 (92.4)</td>
<td>108.8</td>
<td>5.3/473.0</td>
</tr>
<tr>
<td><strong>HOMA-IR</strong></td>
<td>33 (79)</td>
<td>2.73 (1.2)</td>
<td>1.71</td>
<td>0.91/5.92</td>
</tr>
</tbody>
</table>

**Type 2 diabetes (n=42)**

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>Baseline</th>
<th>Follow up</th>
<th>Paired T test *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>42 (100)</td>
<td>52.8 (8.2)</td>
<td>12.7</td>
<td>33.2/65.2</td>
</tr>
<tr>
<td><strong>Duration of follow up (years)</strong></td>
<td>42 (100)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>BMI (kg/m2)</strong></td>
<td>42 (100)</td>
<td>48.2 (9.5)</td>
<td>13.5</td>
<td>33.0/73.6</td>
</tr>
<tr>
<td><strong>Fasting glucose (mmol/L)</strong></td>
<td>36 (86)</td>
<td>8.00 (2.6)</td>
<td>2.92</td>
<td>4.30/13.90</td>
</tr>
<tr>
<td><strong>HbA1c (mmol/mol)</strong></td>
<td>37 (88)</td>
<td>60.0 (15.4)</td>
<td>15.0</td>
<td>38/99</td>
</tr>
<tr>
<td><strong>Insulin (pmol/L)</strong></td>
<td>35 (83)</td>
<td>200.8 (89.2)</td>
<td>114.0</td>
<td>66.0/482.0</td>
</tr>
<tr>
<td><strong>HOMA-IR</strong></td>
<td>28 (67)</td>
<td>3.63 (1.33)</td>
<td>2.2</td>
<td>1.18/6.54</td>
</tr>
</tbody>
</table>

* Paired T test after logarithmic transformation (fasting glucose, HbA1c, fasting insulin, HOMA-IR)
3.2.4.2.1 ADA suggested definitions for diabetes outcomes after bariatric surgery

As noted above, the American Diabetes Association (ADA) has released a consensus statement providing recommendations on the definition of glycaemic outcomes post bariatric surgery. These criteria define “partial remission” as an HbA1c ≤ 6.5% (47 mmol/L), and/or a fasting glucose of 100-125 mg/dl (5.6 – 6.9 mmol/L), and complete remission as an HbA1c “in the normal range”, and a fasting glucose concentration of <100mg/dl (5.6 mmol/L) provided that each of these assessments were persistent for at least 1 year duration, and in the absence of active pharmacologic therapy or ongoing procedures. Prolonged remission is satisfaction of complete remission criteria maintained for at least 5 years. The ‘normal range’ HbA1c is not clearly defined in this statement but is assumed to represent the upper limit of normal in the ADA criteria for the diagnosis of diabetes (<39 mmol/mol). For unclear reasons, the ADA stipulate that a fasting glucose level of less than or equal to 5.6 mmol/L is required as a component of the criteria for “normal” glucose homeostasis, but that the fasting glucose level must be less than 5.6 mmol/L as a component of the criteria for diabetes resolution following bariatric surgery. This simple difference resulted in one participant being categorised as having achieved diabetes resolution when the ADA diagnosis criteria were applied, but with partial resolution when the ADA criteria post bariatric surgery were used.

Table 3-40 Diabetes outcomes using definitions as defined by the ADA criteria for diabetes outcomes following bariatric surgery. Complete remission = HbA1c ≤ 38 mmol/mol, and fasting glucose < 5.6 mmol/L, and the absence of glucose lowering medications. Partial remission = HbA1c 39-47 mmol/mol and/or fasting glucose 5.7 to 6.9 mmol/L, in the absence of glucose lowering medications.

<table>
<thead>
<tr>
<th>N=76</th>
<th>N</th>
<th>Complete remission (%)</th>
<th>Partial remission (%)</th>
<th>Residual type 2 diabetes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>76</td>
<td>34 (45)</td>
<td>31 (41)</td>
<td>11 (14)</td>
</tr>
<tr>
<td>Prediabetes before surgery</td>
<td>40</td>
<td>25 (63)</td>
<td>14 (35)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Type 2 diabetes before surgery</td>
<td>36</td>
<td>9 (25)</td>
<td>17 (47)</td>
<td>10 (28)</td>
</tr>
</tbody>
</table>
When the ADA criteria for the assessment of diabetes outcomes after bariatric surgery are applied 34 (45%) and 31 (41%) of all participants with dysglycaemia at baseline were in complete remission or partial remission respectively at follow up, with type 2 diabetes evident in only 11 (14%) (Table 3-40). In those with type 2 diabetes at baseline, 26 (72%) had improved to either normal glucose tolerance or prediabetes at follow up, whilst 10 (28%) remained with type 2 diabetes.

3.2.4.2.2 New Zealand Society for the Study of Diabetes (NZZSD) criteria for diabetes diagnosis

Type 2 diabetes is defined as an HbA1c greater than or equal to 50 mmol/mol, and/or a fasting glucose of great than or equal to 7.0 mmol/L, and/or the ongoing use of glucose lowering medications. Prediabetes (prediabetes) is defined as an HbA1c less than or equal to 49 mmol/mol, and fasting glucose less than or equal to 6.9 mmol/L (with one or both of these being above the threshold defining normal glucose homeostasis), and the absence of glucose lowering medication, and is used here as a definition of partial resolution. Normal glucose homeostasis is defined as an HbA1c less than or equal to 40 mmol/mol, and fasting plasma glucose less than or equal to 6.0 mmol/L, and the absence of glucose lowering medications, and is used here as the definition of diabetes resolution.

Using these criteria, 57 (67%) of the total cohort were in diabetes remission at the greater than five year follow up assessment, whilst 19 (22%) and 9 (11%) had partial resolution or persistent type 2 diabetes respectively (Table 3-41). Diabetes resolution was achieved in all but six participants who had prediabetes before surgery (44/50 (88%), whilst no participant with pre surgery prediabetes progressed to type 2 diabetes. In those with preoperative type 2 diabetes, 27 (77%) had improved to either normal glucose tolerance (13 (37%)) or prediabetes (14 (40%)) at follow up, whilst 8 (23%) participants remained with type 2 diabetes.
### Table 3-41 Diabetes outcomes using definitions as defined by the NZSSD. Normal (resolution) = HbA1c ≤ 40 mmol/mol, and fasting glucose ≤ 6.0 mmol/L, and the absence of glucose lowering medications. Prediabetes (Partial resolution) = HbA1c ≤ 49 mmol/L and/or fasting glucose ≤ 6.9 mmol/L (but one or both being above the threshold for resolution), and the absence of glucose lowering medications. Type 2 diabetes = HbA1c ≥ 50 mmol/L and/or fasting glucose ≥ 7.0 mmol/L, and/or the ongoing use of glucose lowering medications.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Resolution (%)</th>
<th>Partial resolution (%)</th>
<th>Residual type 2 diabetes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>78</td>
<td>49 (63)</td>
<td>20 (26)</td>
<td>9 (12)</td>
</tr>
<tr>
<td>Prediabetes before surgery</td>
<td>40</td>
<td>34 (85)</td>
<td>5 (13)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Type 2 diabetes before surgery</td>
<td>38</td>
<td>15 (40)</td>
<td>15 (40)</td>
<td>8 (20)</td>
</tr>
</tbody>
</table>

Diabetes status differed significantly when outcomes with the ADA criteria and NZSSD diagnostic criteria were applied. For the entire cohort, 13 (17%) fewer participants were deemed to have achieved complete remission by the ADA criteria, 9 (22%) more participants were deemed to have prediabetes at follow up, and 2 (5%) more patients had type 2 diabetes. One participant deemed to have progressed to type 2 diabetes from prediabetes by the ADA criteria, was considered to remain with prediabetes by the NZSSD criteria given an HbA1c of 48 mmol/mol. Nine additional participants with prediabetes at baseline were considered to remain with prediabetes at follow up by the ADA criteria, but have achieved resolution when the NZSSD diagnostic criteria were applied, each as a consequence of the difference HbA1c values used in each definition and entirely independent of fasting glucose concentrations.

An additional two participants with type 2 diabetes at baseline, were considered to have residual type 2 diabetes at follow up by the ADA criteria when compared to the NZSSD criteria (10 (28%) and 8 (20%) respectively). A further two participants with type 2 diabetes at baseline were considered to have partial remission at follow up by the ADA criteria, but normal values by the NZSSD diagnostic criteria. Again, this difference was entirely attributable the lower HbA1c thresholds stipulated by the ADA criteria; participants deemed to have persistent type 2 diabetes each had an HbA1c at follow up of between 48 and 49 mmol/L, whilst those deemed to have prediabetes rather than normalisation had values of 40 mmol/mol.
3.2.4.2.3  American Diabetes Association (ADA) criteria for diabetes diagnosis

The ADA suggest slightly different criteria for the diagnosis of type 2 diabetes to those suggested for assessing diabetes status following bariatric surgery. A diagnosis of type 2 diabetes is defined as an HbA1c greater than or equal to 48 mmol/mol, and/or a fasting glucose of greater than or equal to 7.0 mmol/L, and/or the ongoing use of glucose lowering medications. Prediabetes is defined as an HbA1c less than or equal to 47 mmol/mol, and fasting glucose less than or equal to 6.9 mmol/L (with one or both of these being above the threshold defining normal glucose homeostasis), and the absence of glucose lowering medication, and is used here as a definition of partial resolution. Normal glucose homeostasis is defined as an HbA1c less than or equal to 38 mmol/mol, and fasting plasma glucose less than or equal to 5.6 mmol/L, and the absence of glucose lowering medications, and is used here as the definition of diabetes resolution.

Using these criteria, 35 (46%) of the total cohort were in diabetes remission at the greater than five year follow up assessment, whilst 30 (40%) and 11 (15%) had partial resolution or persistent type 2 diabetes respectively (Table 3-42). Only one participant was reclassified when the ADA diagnosis as opposed to assessment post bariatric surgery criteria were applied. As noted above, the ADA diagnosis criteria accept a fasting glucose of 5.6 mmol/L or less as consistent with normal glucose tolerance, whilst the post bariatric surgery criteria require that the fasting glucose be less than 5.6 mmol/L. One participant had a fasting glucose of 5.6 mmol/L, and HbA1c of 36 mmol/mol, and was not using diabetes medication at follow up, thereby being classified as in diabetes remission by the diagnosis criteria but with only partial remission by the post bariatric surgery criteria.

3.2.4.2.4  Buchwald et al criteria for diabetes outcomes

Diabetes resolution in this meta-analysis was defined as an HbA1C of < 42 mmol/mol or a fasting blood glucose of < 5.6 mmol/L, in the absence of glucose lowering medications. Partial resolution was defined as a reduction in the number or dose of glucose lowering medications, or a fasting glucose level of 5.6 to 6.9 mmol/L. Interestingly, the authors chose not to include an HbA1c threshold in the definition of partial remission. Those participants who did not meet either of these criteria were classified into ‘unchanged’ and ‘worsened’ categories. Full information on glucose lowering medication dose at baseline was not available for this study and is therefore not considered in this analysis.
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Table 3-42  Diabetes outcomes using definitions as defined by the ADA. Normal (resolution) = HbA1c ≤ 38 mmol/mol, and fasting glucose ≤ 5.6 mmol/L, and the absence of glucose lowering medications. Prediabetes (Partial resolution) = HbA1c ≤ 47 mmol/L and/or fasting glucose ≤ 6.9 mmol/L (but one or both being above the threshold for resolution), and the absence of glucose lowering medications. Type 2 diabetes = HbA1c ≥ 48 mmol/L and/or fasting glucose ≥ 7.0 mmol/L, and/or the ongoing use of glucose lowering medications.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Resolution (%)</th>
<th>Partial resolution (%)</th>
<th>Residual type 2 diabetes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>76</td>
<td>35 (46)</td>
<td>30 (40)</td>
<td>11 (15)</td>
</tr>
<tr>
<td>Prediabetes before surgery</td>
<td>40</td>
<td>25 (63)</td>
<td>14 (35)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Type 2 diabetes before surgery</td>
<td>36</td>
<td>10 (28)</td>
<td>16 (44)</td>
<td>10 (28)</td>
</tr>
</tbody>
</table>

Table 3-43  Diabetes outcomes using definitions as defined meta-analysis by Buchwald et al. Resolution = HbA1c < 42 mmol/mol, or fasting glucose < 5.6 mmol/L, and the absence of glucose lowering medications. Partial resolution = fasting glucose 5.6 to 6.9 mmol/L, or a reduction in dose or number of glucose lowering medications (not considered in this analysis).

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Resolution (%)</th>
<th>Partial resolution (%)</th>
<th>Residual type 2 diabetes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>78</td>
<td>65 (83)</td>
<td>9 (12)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Prediabetes before surgery</td>
<td>40</td>
<td>39 (98)</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Type 2 diabetes before surgery</td>
<td>38</td>
<td>26 (68)</td>
<td>9 (24)</td>
<td>3 (8)</td>
</tr>
</tbody>
</table>
The acceptance of either an HbA1c or fasting glucose level below a threshold resulted in quite marked differences in outcomes when the criteria employed by Buchwald and colleagues were used and when all other included definitions were used (Table 3-43 and Table 3-48), and resulted in the inclusion of two additional participants who had fasting glucose concentrations only obtained. When all 78 participants with dysglycaemia at baseline were considered, use of the ADA criteria rather than the Buchwald criteria resulted in 31 (40%) fewer participants deemed to have achieved complete remission, 22 (28%) more participants having prediabetes at follow up, and 7 (8%) more participants having type 2 diabetes. All 14 (35%) participants with prediabetes at baseline and considered to have achieved partial resolution only by the ADA criteria, were considered to have achieved diabetes resolution using the Buchwald criteria because of a fasting glucose <5.6 mmol/L despite an HbA1c > 42 mmol/mol. The one participant considered to have progressed from prediabetes to type 2 diabetes by the ADA criteria was considered to have remained with prediabetes by the Buchwald criteria, as a result of the higher fasting glucose thresholds employed by the Buchwald criteria.

The differences were just as striking in those with type 2 diabetes at baseline, although each of the nine (25%) of participants considered to have achieved complete remission by the ADA criteria had also done so when the Buchwald criteria were applied. The two additional participants who could be included in this analysis using the Buchwald criteria both had type 2 diabetes at baseline and had both achieved complete remission at follow up. 2 participants with partial remission at follow up by the ADA criteria were also considered to have achieved partial remission by the Buchwald criteria, whilst the remaining 15 (43%) were considered to have achieved complete remission. In each case, the discrepancy was entirely attributable to the Buchwald criteria not considering HbA1c for the diagnosis of partial remission. Of the 10 participants with type 2 diabetes at baseline and considered to remain with type 2 diabetes at follow up by the ADA criteria, 2 (6%) were considered to have achieved complete remission by the Buchwald criteria, 5 (14%) had achieved partial resolution, and only 3 (8%) were also considered to remain with type 2 diabetes.

In addition to the clear differences in obtained results with the more flexible criteria applied by Buchwald, the authors also included a reduction in dose or number of glucose lowering medications as a criteria that independently confirmed partial resolution; the above analysis is not able to include this criteria, but it is likely that reported diabetes outcomes would be improved further if this criteria were included.
3.2.4.2.5 Schauer et al criteria for diabetes outcomes

The primary outcome in this study was defined as an HbA1c less than or equal to 42 mmol/mol, with or without the ongoing use of glucose lowering medications. Fasting glucose concentrations were not considered in analysis of the primary outcome. The authors used the term glycaemic control in place of diabetes resolution. Thresholds for partial responses were not defined. Thus, for the purpose of this analysis, failure to achieve the primary outcome was considered to represent persistent dysglycaemia, but this could not be further divided into those with partial remission or persistent type 2 diabetes.

53 (70%) of participants with dysglycaemia at baseline achieved the primary end point at follow up (Table 3-44). For the entire cohort of 76 participants with dysglycaemia at baseline, use of the ADA criteria rather than the Schauer criteria resulted in 19 (25%) fewer participants deemed to have achieved complete remission at follow up, and instead remaining with dysglycaemia. In those with prediabetes at baseline, 36 (90%) of participants had achieved the primary end point at follow up, whilst 4 (10%) remained with dysglycaemia. The criteria were completely concordant with the ADA criteria with respect to the 25 (63%) of participants who were considered to have improved to normal glucose tolerance. However, use of the Schauer criteria resulted in a further 11 (28%) participants with prediabetes at baseline and normal glucose tolerance at follow up. In each of these cases, the difference was entirely attributable to higher threshold of HbA1c accepted by the Schauer criteria to represent normal glucose tolerance. Three of the four participants with prediabetes at baseline, and considered to remain with dysglycaemia at follow up by the Schauer criteria, had achieved partial remission according to the ADA criteria, whilst one had progressed to type 2 diabetes by the ADA criteria.

In those with type 2 diabetes at baseline, 17 (47%) of participants would be considered to have achieved the primary endpoint at follow up whilst 19 (53%) would be considered to remain with dysglycaemia. Again, the criteria were entirely concordant with results using the ADA criteria with respect to the 9 (25%) of participants who were considered to have improved to normal glucose tolerance by the ADA criteria. 6 (17%) additional participants (17 (47%) in total) were deemed to have complete resolution of diabetes at follow up by the Schauer criteria and partial resolution only by the ADA criteria. Given that fasting glucose was not included in the definition utilised by Schauer, this discordancy was predominantly the result of the differing HbA1c thresholds set by each criteria. Each of the 6
participants in this group had an HbA1c at follow up of between 39 and 42 mmol/mol, although one participant with an HbA1c of 36 mmol/mol had a fasting glucose of 5.6 mmol/L resulting in a diagnosis of prediabetes (partial remission). The criteria were again concordant with respect to the 10 participants with type 2 diabetes at baseline considered to remain with type 2 diabetes at follow up by the ADA criteria. Each of these participants did not achieve the primary objective by the Schauer criteria and therefore had persistent dysglycaemia.

Table 3-44  Diabetes outcomes using definitions as defined by Schauer et al. Glycaemic control = HbA1c ≤ 42 mmol/mol, with or without the use of glucose lowering medications.

<table>
<thead>
<tr>
<th></th>
<th>Primary endpoint achieved (%)</th>
<th>Primary endpoint not achieved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>76</td>
<td>53 (70)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23 (30)</td>
</tr>
<tr>
<td>Prediabetes before surgery</td>
<td>40</td>
<td>36 (90)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 (10)</td>
</tr>
<tr>
<td>Type 2 diabetes before surgery</td>
<td>36</td>
<td>17 (47)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19 (53)</td>
</tr>
</tbody>
</table>

3.2.4.2.6  Mingrone et al criteria for diabetes outcomes

The primary outcome in this study was defined as an HbA1c less than 47 mmol/mol, and a fasting plasma glucose of less than 5.6 mmol/L, and the absence of glucose lowering medications. The authors used the term diabetes remission if the primary endpoint was achieved. Thresholds for partial responses were not defined. As with the analysis of the Schauer definition above, failure to achieve the primary outcome was therefore considered to represent persistent dysglycaemia, but could not be further divided into those with partial remission or persistent type 2 diabetes.

58 (76%) of participants with dysglycaemia at baseline achieved the primary end point at follow up, whilst 18 (24%) remained with dysglycaemia (Table 3-45). For the entire cohort of 76 participants with
dysglycaemia at baseline, use of the ADA criteria rather than the Mingrone criteria resulted in 24 (32%) fewer participants deemed to have achieved complete remission at follow up, each of these participants remaining with dysglycaemia.

In those with prediabetes at baseline, 39 (98%) of participants had achieved the primary end point at follow up, whilst only one (2%) remained with dysglycaemia. All 40 of participants with prediabetes at baseline and either complete remission (25 (63%)) or partial remission 14 (35%) by the ADA criteria had achieved the primary endpoint used by Mingrone and colleagues. The participant considered to have progressed to type 2 diabetes from this group by the ADA criteria was also considered to have persistent dysglycaemia by the Mingrone criteria. In each of these cases, the difference was entirely attributable to higher threshold of HbA1c accepted by the Mingrone criteria to represent normal glucose tolerance.

<table>
<thead>
<tr>
<th>N=76</th>
<th>N</th>
<th>Primary endpoint achieved (%)</th>
<th>Primary endpoint not achieved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>76</td>
<td>58 (76)</td>
<td>18 (24)</td>
</tr>
<tr>
<td>Prediabetes before surgery</td>
<td>40</td>
<td>39 (98)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Type 2 diabetes before surgery</td>
<td>36</td>
<td>19 (53)</td>
<td>17 (47)</td>
</tr>
</tbody>
</table>

In those with type 2 diabetes at baseline, 19 (53%) of participants would be considered to have achieved the primary endpoint at follow up whilst 17 (47%) would be considered to remain with dysglycaemia. All 9 (25%) of participants considered to have achieved complete remission or partial remission by the ADA criteria, had achieved the primary objective set by Mingrone and colleagues. A further 10 (28%) of participants, considered to have achieved partial remission by the ADA criteria, had achieved the primary objective. Each of the 11 participants in this group had an HbA1c at follow up of between 39
and 42 mmol/mol, although one additional participant with an HbA1c of 36 mmol/mol had a fasting glucose of 5.6 mmol/L resulting in a diagnosis of prediabetes (partial remission). The criteria were entirely concordant with respect to the 10 (28%) participants with type 2 diabetes at baseline considered to remain with type 2 diabetes at follow up by the ADA criteria.

3.2.4.2.7 Adams et al criteria for diabetes outcomes

Like Schauer and Mingrone, Adams defined a primary endpoint which was equated to diabetes remission. The primary endpoint was a fasting glucose level of < 126mg/dl (7.0 mmol/L) and/or an HbA1c level < 6.5% (47 mmol/mol), in the absence of glucose lowering medications. The authors categorised those participants who failed to achieve the primary endpoint as remaining with type 2 diabetes. No thresholds for partial remission were defined. Two additional participants were included in this study given the authors acceptance of either an HbA1c or fasting glucose value in isolation to decide diabetes status.

Table 3-46 Diabetes outcomes using definitions as defined meta-analysis by Adams et al. Type 2 diabetes defined as a fasting glucose ≥ 126mg/dl (7.0 mmol/L) and/or and HbA1c level ≥ 6.5% (47 mmol/mol), or the use of glucose lowering medications.

<table>
<thead>
<tr>
<th></th>
<th>N=78</th>
<th>Primary endpoint not achieved (%)</th>
<th>Primary endpoint achieved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>78</td>
<td>64 (82)</td>
<td>14 (18)</td>
</tr>
<tr>
<td>Prediabetes before surgery</td>
<td>40</td>
<td>39 (98)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Type 2 diabetes before surgery</td>
<td>38</td>
<td>25 (66)</td>
<td>13 (34)</td>
</tr>
</tbody>
</table>

64 (82%) of participants with dysglycaemia at baseline had achieved the primary end point at follow up (Table 3-46). When all 78 participants with dysglycaemia at baseline were considered, use of the ADA criteria rather than the Adams criteria resulted in 30 (37%) fewer participants deemed to have achieved
complete remission at follow up. In those with prediabetes at baseline, 39 (98%) of participants had achieved the primary end point at follow up, whilst only 1 (2%) remained with dysglycaemia. Thus, all 25 (63%) of participants who were considered to have improved to normal glucose tolerance by the ADA criteria and all 14 (35%) who had achieved partial remission, had achieved the primary endpoint. The only participant with prediabetes at baseline deemed not to have achieved the primary end point at follow had progressed to type 2 diabetes by the ADA criteria. The maximum fasting glucose level at follow up in those with prediabetes at baseline was 5.8 mmol/L, far below the threshold defined by Adams for the primary endpoint. Therefore, the different diabetes status in the 14 (35%) of participants with discordant results was explained entirely by different HbA1c thresholds.

In those with type 2 diabetes at baseline, 25 (66%) of participants would be considered to have achieved the primary endpoint if the Adams criteria were applied to this cohort, and 13 (34%) would be considered to remain with dysglycaemia. As with the NZSSD diagnosis criteria and those defined by Buchwald, Schauer, and Mingrone, the criteria were entirely concordant with results using the ADA criteria with respect to the 9 (25%) of participants who were considered to have improved to normal glucose tolerance by the ADA criteria. 16 (41%) additional participants (25 (66%) in total) were deemed to have complete resolution of diabetes at follow up by the Adams criteria and partial resolution only by the ADA criteria, including both participants unable to be clarified by the ADA criteria. Thus, all of the participants with type 2 diabetes at baseline deemed to have achieved either diabetes remission or partial remission by the ADA criteria would be considered in diabetes remission if the Adams criteria were applied. The maximum fasting glucose level in this group was 6.2 mmol/L, again far below the defined threshold, and thus attributing every discrepant outcome to the differing HbA1c thresholds. Each of the 25 participants in this group had an HbA1c at follow up of between 32 and 46 mmol/mol. As with other utilised criteria, the Adams criteria were entirely concordant with the ADA criteria with respect to the 10 participants with type 2 diabetes at baseline considered to remain with type 2 diabetes at follow up by the ADA criteria, although, as above the criteria suggested by Adams did not allow consideration of partial remission.

3.2.4.2.8 Ikramuddin et al criteria for diabetes outcomes

Type 2 diabetes was defined as a fasting glucose ≥ 126mg/dl (7.0 mmol/L) and/or and HbA1c level ≥ 6.5% (47 mmol/mol), or the use of glucose lowering medications. However, the study authors elected
to reported a primary composite outcome of HbA1c <7.0% (53 mmol/mol), serum LDL < 100 mg/dl, and a systolic blood pressure of < 130 mmHg. Neither fasting glucose level nor the use of diabetes medications was considered for the primary outcome. They acknowledge that this does not adequately define diabetes resolution, but employed the definition as a clinically useful indicator of the efficacy of surgery in patients with type 2 diabetes. For the purposes of this analysis, only the HbA1c value at follow up was considered.

Accordingly, a significantly higher percentage of participants achieved the primary endpoint when this definition was employed than when any other definition of diabetes outcome included in this analysis was used (Table 3-47). When all 76 included participants were considered, 70 (92%) were considered to have achieved the glycaemic primary end point and only 6 (8%) were considered to remain with type 2 diabetes. Every participant (40/40) with prediabetes at baseline had achieved the primary endpoint; the one participant considered to have progressed to type 2 diabetes by most other included definitions was instead defined as having achieved the diabetes endpoint despite an HbA1c at follow up of 50 mmol/mol. Thus, this definition defined 15 (37%) further participants with prediabetes at baseline as having diabetes resolution at follow up than when the ADA criteria were applied to same cohort. Given that the HbA1c value was the only considered diabetes outcome, each of the 5 (14%) of participants with type 2 diabetes at baseline, and considered to have persistent type 2 diabetes at follow up by the ADA criteria had an HbA1c in excess of 55 mmol/L. Two participants with type 2 diabetes at baseline, and not considered to remain with type 2 diabetes at follow up, remained on diabetes medications.

Table 3-47  Diabetes outcomes using definitions as defined meta-analysis by Ikramuddin et al. Primary outcome = HbA1c < 53 mmol/mol.

<table>
<thead>
<tr>
<th></th>
<th>N=76</th>
<th>N</th>
<th>Primary endpoint achieved (%)</th>
<th>Primary end point not achieved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>76</td>
<td>70  (92)</td>
<td>6 (8)</td>
<td></td>
</tr>
<tr>
<td>Prediabetes before surgery</td>
<td>40</td>
<td>40  (100)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes before surgery</td>
<td>36</td>
<td>31  (86)</td>
<td>5 (14)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3-48  Diabetes outcomes using definitions as defined by each included study. Participants are categorised by diabetes status before surgery (All, prediabetes, or Type 2 diabetes) and by diabetes status at the follow up assessment at greater than 5 years

<table>
<thead>
<tr>
<th>Study/Definition</th>
<th>Definitions</th>
<th>Diabetes status at baseline</th>
<th>Diabetes status at follow up (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resolution</td>
<td>All</td>
<td>Prediabetes</td>
</tr>
<tr>
<td>ADA criteria for outcomes following bariatric surgery</td>
<td>HbA1c ≤ 38 mmol/mol, and fasting glucose &lt; 5.6 mmol/L, and the absence of glucose lowering medications.</td>
<td>R</td>
<td>PR</td>
</tr>
<tr>
<td></td>
<td>HbA1c 39-47 mmol/mol and/or fasting glucose 5.7 to 6.9 mmol/L, in the absence of glucose lowering medications</td>
<td>45</td>
<td>41</td>
</tr>
<tr>
<td>NZSSD criteria for the diagnosis of type 2 diabetes</td>
<td>HbA1c ≤ 40 mmol/mol, and fasting glucose ≤ 6.0 mmol/L, and the absence of glucose lowering medications.¹</td>
<td>63</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>HbA1c ≤ 49 mmol/L and/or fasting glucose ≤ 6.9 mmol/L (but one or both being above the threshold for resolution), and the absence of glucose lowering medications.²</td>
<td>46</td>
<td>40</td>
</tr>
<tr>
<td>ADA criteria for the diagnosis of type 2 diabetes</td>
<td>HbA1c ≤ 38 mmol/mol, and fasting glucose ≤ 5.6 mmol/L, and the absence of glucose lowering medications.</td>
<td>R</td>
<td>PR</td>
</tr>
<tr>
<td></td>
<td>HbA1c ≤ 47 mmol/L and/or fasting glucose ≤ 6.9 mmol/L (but one or both being above the threshold for resolution), and the absence of glucose lowering medications.</td>
<td>46</td>
<td>40</td>
</tr>
</tbody>
</table>

R = Diabetes resolution, PR = Diabetes partial remission, T2DM = Type 2 diabetes mellitus at follow up. ¹Definitions derived from the NZSSD and ADA criteria for the diagnosis of type 2 diabetes use normal concentrations as evidence of diabetes resolution, and concentrations diagnostic of prediabetes or prediabetes as evidence of partial resolution.
## Chapter 3: Long term outcomes after RYGB

### Study/Definition

<table>
<thead>
<tr>
<th>Study/Definition</th>
<th>Definitions</th>
<th>Resolution</th>
<th>Partial resolution</th>
<th>Diabetes status at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R</td>
</tr>
<tr>
<td>Buchwald et al</td>
<td>HbA1c &lt; 42 mmol/mol, or fasting glucose &lt; 5.6 mmol/L, and the absence of glucose lowering medications.</td>
<td>Fasting glucose 5.6 to 6.9 mmol/L, or a reduction in dose or number of glucose lowering medications (not considered in this analysis)</td>
<td></td>
<td>83</td>
</tr>
<tr>
<td>Schauer et al</td>
<td>HbA1c ≤ 42 mmol/mol, with or without the use of glucose lowering medications.</td>
<td>Not provided</td>
<td></td>
<td>70</td>
</tr>
<tr>
<td>Mingrone et al</td>
<td>HbA1c &lt; 47 mmol/mol, and fasting glucose &lt; 5.6 mmol/L, in the absence of glucose lowering medications.</td>
<td>Not provided</td>
<td></td>
<td>76</td>
</tr>
<tr>
<td>Adams et al</td>
<td>HbA1c ≤ 46 mmol/mol and fasting glucose ≤ 6.9 mmol/L, in the absence of glucose lowering medications.</td>
<td>Not provided</td>
<td></td>
<td>82</td>
</tr>
<tr>
<td>Ikramuddin et al</td>
<td>HbA1c &lt; 53 mmol/mol</td>
<td>Not provided</td>
<td></td>
<td>92</td>
</tr>
</tbody>
</table>

R = Diabetes resolution, PR = Diabetes partial remission, T2DM = Type 2 diabetes mellitus at follow up.

Definitions derived from the NZSSD and ADA criteria for the diagnosis of type 2 diabetes use normal concentrations as evidence of diabetes resolution, and concentrations diagnostic of prediabetes or prediabetes as evidence of partial resolution.
3.2.5 Discussion

Use of these seven criteria, when compared to those suggested by the ADA for the assessment of diabetes outcomes after surgery, produced significant variability. The definition associated with the best outcomes following surgery was that used by Ikramuddin with complete remission seen in 92% of participants with dysglycaemia at baseline, and 86% of participants with type 2 diabetes at baseline in the bariatric follow up study had this definition been used. The definition associated with the poorest outcomes following bariatric surgery was by some distance the criteria suggested by the ADA for the assessment of diabetes outcomes following bariatric surgery. This was true for each status of glucose tolerance at baseline. The number of participants with dysglycaemia at baseline who would be considered to have achieved diabetes resolution at follow up when the criteria defined by Ikramuddin were applied was two fold higher than the number when the ADA criteria were applied. When only those with type 2 diabetes at baseline were considered, this difference was even greater with over a three fold difference in the numbers achieving diabetes resolution when the Ikramuddin and ADA criteria were applied. Comparisons with the definitions employed by the NSZSSD, Schauer, Mingrone, and Buchwald produce similar findings with a 1.4, 1.6, 1.7, and 1.8 fold greater number of all participants considered to have achieved diabetes remission respectively, when compared with the ADA criteria.

The variation was not as significant when those with persistent type 2 diabetes at follow up were considered, although the differences are still of importance. Again, the ADA criteria were the most stringent in this respect with 28% of participants with type 2 diabetes at baseline remaining with type 2 diabetes at follow up. The other definitions that provided thresholds for partial remission as well as complete remission produced 1.4 and 3.5 fold fewer patients with persistent type 2 diabetes using the NZSSD and Buchwald criteria respectively. With respect to the Schauer and Mingrone definitions, this variability is reduced to some extent by considering the absence of a partial remission category in the definitions employed by the authors. If one assumes that achieving the primary endpoint in these studies is equivalent to the combined numbers of complete remission and partial resolution, then the relative ratios are instead 1.4 and 1.5 fold fewer participants with type 2 diabetes achieving this endpoint with the Mingrone and Schauer criteria respectively than when the ADA criteria are applied. If instead one assumes that failure to achieve the primary endpoint is equivalent to the combined numbers of partial resolution and persistent type 2 diabetes then the relative ratios are greater at 1.4
and 1.6 fold fewer participants failing to achieve the primary endpoint with the Schauer and Mingrone criteria respectively than when the ADA criteria are applied.

The provocative paper by Pories et al in 1995 suggested that bariatric surgery may be the most effective currently available therapy for inducing remission of type 2 diabetes. This suggestion has since been proved correct with the publication of large randomised interventional studies comparing diabetes outcomes following bariatric surgery against those of optimal lifestyle/medical management. The significant improvements in glucose metabolism following bariatric surgery frequently results in individuals being able to stop all antidiabetic medications, including many of those who required insulin pre-operatively. However, a closer inspection of this literature suggests that the diabetes related outcomes and endpoints are reported in a diverse fashion, such that comparisons of outcomes from individual studies involving different surgical procedures may be rendered meaningless.

Each of these authors of the studies included in this analysis used differing definitions of glycaemic outcomes (Table 3-48) although similarities were predictably present. It is clear that the HbA1c threshold is the major determinant of diabetes outcome when each of these definitions is applied. Indeed, the criteria employed by Mingrone et al and those proposed by the ADA as definitions for diabetes outcomes following bariatric surgery differ only in terms of the HbA1c threshold. Both criteria stipulate that the fasting glucose level should be less than 5.6 mmol/L for diabetes resolution, and both require that this is achieved in the absence of glucose lowering medication. However, whilst the Mingrone criteria accept an HbA1c of less than 48 mmol/mol as evidence of diabetes resolution, the ADA suggest that an HbA1c of less than 39 mmol/mol should be the threshold. This single difference resulted in a two fold increase in the prevalence of failure to achieve resolution (24% versus 55%) in all participants in the study, and over a 50% reduction in the number of participants with type 2 diabetes at baseline who achieved diabetes resolution at five years of follow up (53% versus 25%). In contrast, a significant difference in the fasting glucose threshold alone had a much smaller effect on the frequency of different diabetes outcomes. For example, the definitions employed by Mingrone et al and Adams et al both required that the HbA1c level should be less than 48 mmol/mol and that the participant should not be using glucose lowering medication. However, Mingrone et al required a fasting glucose of less than 5.6 mmol/L whilst Adams et al used a much higher threshold of 6.9 mmol/L. Despite this clear difference, the outcomes when both definitions were employed were generally similar, and identical in the participants with prediabetes at baseline. Four percent more participants achieved diabetes resolution when the Adams criteria were applied (82% versus 76%), and 30% more
of those with pre-existing type 2 diabetes failed to achieve diabetes resolution at follow up when the Mingrone criteria were applied (47% versus 34%).

It is accepted that many of the authors of the included studies do not intend to imply that the stipulated diabetes outcome equates to resolution or remission, and that they are simply trying to demonstrate clinically relevant effects of bariatric surgery. Nonetheless, an increasing proportion of patients undergoing bariatric surgery will have pre-existing type 2 diabetes, and are likely to place a high priority on the question of whether they can expect their diabetes to be ‘cured’. It is therefore suggested that, irrespective of whether other diabetes outcomes are also presented, it is preferable that any study reporting on diabetes outcomes following bariatric surgery also include outcomes based on standardised criteria defining resolution and partial resolution.

However, the use of the terms ‘cure’, ‘resolved’ or ‘remission’ in this context is controversial for a number of reasons. Firstly, the diagnosis of diabetes itself is not dichotomous; rather thresholds for disease have been defined on the basis of risk of complications (micro and macro vascular disease). It is not known if these thresholds remain true in a post RYGB surgery population, and therefore, it is unknown what glycaemic thresholds are acceptable to define as optimal targets post-surgery. Secondly, use of the term “cure” for a chronic disease mediated predominantly by lifestyle may not be helpful in encouraging longer term compliance to favourable dietary and exercise strategies. Furthermore, progressive decline, albeit potentially reversible, in pancreatic beta cell function over time is considered characteristic of type 2 diabetes by some and it remains unclear whether bariatric surgery alters this process.

This study had a number of limitations, predominantly with the ability to entirely apply the definitions utilised in the included studies. Firstly, limited information was available on the specifics of glucose lowering therapy at follow up in our cohort. Data only on the class of glucose lowering medication was collected, and not data on dose or whether the dose had changed following surgery. Buchwald et al accepted a reduction in the dose or number of glucose lowering medications as evidence for improvement post bariatric surgery, and indeed, had this information been available for this analysis, it is highly likely that the outcomes would be further improved when applying the Buchwald definitions. In addition, many of the studies stipulated that the biochemical criteria required to categorise each participant (fasting glucose and HbA1c) should be persistent over a period of 12 months or more. In particular, the studies by Schauer et al and Mingrone et al were of a prospective nature and therefore the authors were able to collect data at numerous time points and comment on the persistency of their
findings. The follow up data for this study was collected as part of a larger bariatric follow up study (chapter 3.1), where each participant was invited to attend for one follow up assessment. Additional data collected on a different day or at a different time to assess persistency was therefore not available for this analysis. Whilst this is certainly a limitation when extrapolating diabetes outcomes in this cohort against others in the published literature, it is not likely that it significantly affected the outcomes of this particular analysis, as the limitation would of course effect each employed definition. A further similar limitation is that both the NZSSD and ADA criteria for the diagnosis of diabetes require that a repeat confirmatory test be performed unless the patient has clear symptoms of hyperglycaemia. With the exception of the small number of participants with type 2 diabetes at the follow up assessment, none of the remainder of participants would be expected to have symptoms of hyperglycaemia and therefore confirmatory testing would almost certainly be required in a real world setting. Again, whilst this limitation is acknowledged, each definition here would be affected to a similar extent and it is therefore unlikely that this limitation would have a significant effect on the analysis.
3.2.6 Conclusion

RYGB has emerged as the preferred bariatric procedure for the treatment of obesity related type 2 diabetes (chapter 1.3). Further research is required into the long term effects of this procedure on glycaemic, metabolic and nutritional outcomes before the exact role of surgery in the management of type 2 diabetes can be clarified. This needs to include greater understanding of the exact mechanisms by which RYGB improves glucose metabolism, focusing on specific effects in the pancreatic beta cell, liver, gut and adipose tissue. The present analysis highlights the need for the use of one consistent set of definitions of glycaemic outcomes following bariatric surgery to allow comparisons between studies, and facilitate research into post bariatric surgery micro and macro vascular outcomes. Failure to conform to one set of definitions is likely to result in striking differences in reported diabetes outcomes in published studies. Accurate data on diabetes outcomes is vital to allow appropriate pre-operative patient counselling on expected benefits of bariatric surgery for those with established type 2 diabetes. Nonetheless, further long term data are required before the term diabetes resolution can be confidently applied, as it remains unclear whether a period of protracted hyperglycaemia, even if corrected by bariatric surgery, leaves the patient with a residual increased long term risk of diabetes related complications. Until that data is available, it would seem prudent to continue micro and macro vascular complication surveillance in those with pre-existing type 2 diabetes even after restoration of normal glucose homeostasis by bariatric surgery.
Chapter 4: Mechanistic studies

Mechanisms underlying improvements in glucose homeostasis and weight following RYGB

4.1. The perioperative stress response to RYGB

4.2. Fasting gut peptides following gastric bypass surgery and weight outcomes
4.1 The perioperative stress response to RYGB

4.1.1 Introduction

Bariatric surgery results in improvements in glucose homeostasis in a high proportion of those with pre-operative type 2 diabetes. As discussed in chapter 1.4.4, improvements are observed rapidly following surgery, with numerous studies documenting improvements in both beta cell function and insulin sensitivity within two to seven days. Improvements in insulin sensitivity, related particularly to reduced hepatic insulin resistance, are evident within a similar timeframe after non-surgical caloric restriction. However, most studies reporting the physiological effects of non-surgical very low caloric restriction have shown later improvements in beta cell function improvement after four to eight weeks.

It is therefore of great interest to clarify the physiological changes engendered by bariatric surgery, and in particular, how these changes may relate to the early and specific improvements in glucose homeostasis observed following surgery. However, studies addressing this question may be inherently flawed if the surgery itself results in transient changes that affect the adequacy of tools used to measure markers of glucose homeostasis. For example, when reporting on early physiological changes after bariatric surgery, one would need to account for the temporary effects of post-surgery inflammation which may have both positive and negative effects on glucose homeostasis.

Surgery of any nature is known to induce a stress response, although the degree and characteristics of this response are dependent on both nature of the surgery and characteristics of the person undergoing surgery. This stress response involves both hormonal and metabolic components, and is induced by a number of factors that are beyond the scope of this work but discussed elsewhere. Increased secretion of a number of anterior pituitary hormones underlies a significant proportion of this response. Adrenocorticotropin (ACTH) concentrations rise rapidly after incision, remain elevated for hours after surgery, and are less responsive to usual negative cortisol feedback than in the physiological state. Consequently, plasma cortisol concentrations rise, often greater than four fold above those observed in healthy individuals. Growth hormone (GH) and prolactin concentrations rise in response to surgery under general anaesthesia, although the increase...
in GH occurs later after incision than observed with ACTH.\textsuperscript{852,856,857} The peak prolactin level after surgery is reduced under epidural rather than general anaesthesia, and is also related to the invasiveness of the procedure.\textsuperscript{856,857} In addition to the anterior pituitary response to surgery, increased secretion of a number of other hormones contributes to the stress response to surgery. Aldosterone, the major mineralocorticoid and regulator of resting blood pressure, increases markedly after surgery as a result of both an increase in renin concentrations and a response to elevated ACTH concentrations.\textsuperscript{858,859} Adrenaline concentrations are also increased early after surgical incision, although noradrenaline levels have been reported to be unchanged in some studies.\textsuperscript{855,860} Along with the invasiveness of the surgery, anaesthetic management has been associated with the degree to which each of these hormones changes in the perioperative period.\textsuperscript{853} Most studies have shown a return to baseline values within 24 hours of uncomplicated surgery.\textsuperscript{853,855}

The net consequence of the hormonal response is an increase in catabolism of stored carbohydrate, fat, and protein; it has been postulated that this response evolved to allow survival without feeding, allowing injured animals to recuperate.\textsuperscript{850} Increased concentrations of cortisol, catecholamines, and GH stimulate enhanced lipolysis, converting stored triglycerides to glycerol and fatty acids, whilst also stimulating hepatic glycogenolysis and gluconeogenesis.\textsuperscript{861} In addition, these hormones increase peripheral insulin resistance so that insulin-stimulated glucose uptake in skeletal muscle and other tissues is reduced.\textsuperscript{862,863} Furthermore, insulin secretion appears to be impaired in the perioperative state as a result of both the adrenergic response to surgery and the effect of general anaesthesia.\textsuperscript{864,865,866} Thus, a rise in glucose in the perioperative period is to some extent predicted, and is dependent on the invasiveness of the surgery.

This pilot study was therefore designed to assess the effect of open RYGB surgery on concentrations of a number of hormonal and metabolic markers of the stress responses to surgery, and to provoke further work on whether these changes are likely to affect the integrity of tests used to assess early changes in glucose homeostasis.
4.1.2 Aims

To characterise hormonal and related metabolic stress responses of obese patients to RYGB surgery.

4.1.3 Participants and methods

4.1.3.1 Study overview and design

This was a non-experimental prospective cohort study of obese patients after open RYGB surgery. Blood and urine samples were taken immediately before surgery and then daily for six days after surgery to assess hormonal and related stress responses.

4.1.3.2 Study participants

A convenience sample of eight participants, accepted as suitable for RYGB surgery after consultation with a bariatric surgeon, gave independent consent for this study.

Inclusion Criteria

- Assessed as suitable for RYGB surgery
- BMI >35 kg/m² before surgery

Exclusion criteria

- Medication use which could potentially interfere with the assessment of cortisol, catecholamine or prolactin concentrations
4.1.3.3 Methods

All participants gave written informed consent to participate in the study. A New Zealand National Health and Disability Ethics Committee (HDEC) screening questionnaire was completed, and confirmed that the observational nature of this study meant that a full ethics review was not required. The HCEC screening questions and response is presented in appendix iv (page 399).

4.1.3.4 Protocol

Participants were assessed for a total of six days, from the day before surgery and then daily for a further five days after operation. Fasting blood and urine samples were collected daily for the measurements described below.

1. 24 hour urine collections were obtained as described in chapter 2.3.6 (page 129). On the day before surgery (Day = -1) participants collected all urine passed after voiding and discarding urine at 0800 hours. Participants arrived at the surgical hospital at 1400. At this time all collected urine volume was measured and then divided into 2 equal volume aliquots. One aliquot was then placed into a bottle containing an acidified solution, and the other aliquot into an empty bottle (see biochemistry analysis below for rationale). Urine collections were then continued over the next 18 hours to complete a 24 hour collection with equal aliquots placed in each container.

2. Participants remained seated from 1400 until 1430 at which point venepuncture was performed and baseline blood samples acquired. Seating before venepuncture is recommended for optimal measurement of aldosterone and prolactin concentrations as per local laboratory guidelines. Seated blood pressure and heart rate measurements were then obtained as described in chapter 2.2.2 (page 124).

3. RYGB was performed on day 0 as described in chapter 2.1 (page 120). The second daily urine collection was commenced as the procedure began and was continued until 0800 on the first post-operative day (day=1). As surgery would commence between 0800 and 1100, the urine collection for day varied from a 21 to a 24 hour collection. As discussed in chapter 2.3.6 (page
129), this variation was accounted for by the use of measures of concentration rather than absolute urinary hormone concentrations. A blood sample (day=0) was taken from a central venous line placed as per routine care during surgery within 30 minutes of completion of surgery.

4. Thereafter, from the first post-operative day until the fifth post-operative day, 24 hour urine collections were started and stopped at 0800, and a blood sample was taken from the central venous line at 0800 with the patient fasted.

5. After the fifth post-operative day the central line was removed and the participant was discharged.

All participants received routine postoperative care. The only additional component was a 24 hour urine collection at baseline and daily collection over the five days, and the aspiration of an extra 20mls blood each day for research rather than clinical purposes.

4.1.3.5 Biochemical and clinical observations

Blood and urine sampling was performed and analysed as per methods discussed in chapter 2.3 (page 125). Blood pressure and heart rate measurements were obtained on daily basis as described in chapter 2.2.2 (page 124).
4.1.3.6 Sample size

There are no published data on the stress hormone response to open RYGB surgery to use as estimates of the variance of these measurements in this particular group of patients. Data from this study will provide these estimates to allow sample size calculations for future research. The number of potential participants was also limited by the number of patients undergoing gastric bypass at Wakefield hospital within the six month study period and all such patients were invited to participate in this study. Two people declined to participate in the study.

4.1.3.7 Statistical analysis

Hormone and other blood derived measurements are summarised by simple data descriptors including mean, standard deviation, and quartiles, as well as plots. Comparisons use paired t-tests of the difference of each reading from the baseline reading with associated estimates of the mean difference and appropriate confidence intervals.

Box-plots representing median, 25% and 75% quartiles, and maximum/minimum values are used to illustrate change in each measured variable over the study period. Outliers greater than 1.5 times the interquartile range are indicated by a circle, whilst those greater than 3.0 times the interquartile range are indicated by an asterisk.
4.1.4 Results

The characteristics of the eight participants are shown in Table 4-1. Three of the participants had type 2 diabetes; one of these participants used insulin therapy pre-operatively, one used oral hypoglycaemic agents, and the third used dietary methods only to control diabetes. Five participants used antihypertensive agents prior to surgery. All diabetes and blood pressure medications were stopped at surgery as per clinical protocols. No participant used medication that precluded participation in the study.

Table 4-1  Demographic and biochemical indices of the eight participants assessed on day−1

<table>
<thead>
<tr>
<th>N=8 unless specified</th>
<th>Mean (SD)</th>
<th>IQR</th>
<th>Min/Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.0 (13.9)</td>
<td>21.8</td>
<td>24/66</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>50.7 (6.4)</td>
<td>12.5</td>
<td>42.6/59.8</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>79.0 (11.1)</td>
<td>21</td>
<td>66/96</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>132.5 (17.2)</td>
<td>33</td>
<td>110/158</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>81.9 (11.4)</td>
<td>23</td>
<td>66/96</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mmHg)</td>
<td>98.8 (11.7)</td>
<td>21.2</td>
<td>86.0/113.3</td>
</tr>
<tr>
<td>Urinary noradrenaline (nmol/mmolUCr/24hr)</td>
<td>35.4 (30.7)</td>
<td>26.7</td>
<td>8.3/105.2</td>
</tr>
<tr>
<td>Urinary adrenaline (nmol/mmolUCr/24hr)</td>
<td>2.7 (2.5)</td>
<td>2.1</td>
<td>0.7/8.6</td>
</tr>
<tr>
<td>Urinary dopamine (nmol/mmolUCr/24hr)</td>
<td>194.1 (114.0)</td>
<td>112.1</td>
<td>93.4/448.6</td>
</tr>
<tr>
<td>Urinary normetadrenaline (μmol/mmolUCr/24hr)</td>
<td>0.25 (0.23)</td>
<td>0.2</td>
<td>0.07/0.8</td>
</tr>
<tr>
<td>Urinary metadrenaline (μmol/mmolUCr/24hr)</td>
<td>0.04 (0.03)</td>
<td>0.09</td>
<td>0.03/0.3</td>
</tr>
<tr>
<td>Urinary free cortisol (nmol/mmolUCr/24hr)</td>
<td>5.14 (3.05)</td>
<td>4.0</td>
<td>2.4/11.5</td>
</tr>
<tr>
<td>Prolactin (U/L)</td>
<td>341.3 (186.2)</td>
<td>237.3</td>
<td>183.0/741.0</td>
</tr>
<tr>
<td>Serum Aldosterone (pmol/L) (N=7)</td>
<td>108.9 (31.8)</td>
<td>45.0</td>
<td>49.0/140.0</td>
</tr>
<tr>
<td>Insulin (U/L) (N=6)</td>
<td>329.7 (151.3)</td>
<td>160.0</td>
<td>230.0/630.0</td>
</tr>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>7.7 (3.2)</td>
<td>5.4</td>
<td>3.8/13.3</td>
</tr>
<tr>
<td>CRP (U/L) (N=6)</td>
<td>6.2 (2.6)</td>
<td>5.3</td>
<td>4.0/10.0</td>
</tr>
</tbody>
</table>
4.1.4.1 Heart rate and blood pressure

Mean heart rate fell early following surgery (Figure 4-1 and Table 4-2). The nadir was a mean (SD) of 67.3 (10.9) bpm on day 2. The estimated difference (95% CI) from baseline was 11.8 (1.3 to 22.3), P=0.03. From day 3 to day 6 the mean heart rate was similar to that at baseline (day -1).

Mean arterial pressure fell at day 1 at mean (SD) 83.9 (5.9) mmHg (Figure 4-2 and Table 4-2). The estimated difference (95% CI) from baseline was 14.8 (7.1 to 22.5) mmHg, P=0.03. From day 2 to day 6 mean arterial pressure was similar to that at baseline (day -1). The decline in mean arterial pressure at day 1 was the result of a fall both in systolic blood pressure, baseline mean (SD) 132.5 (17.2) compared to day 1 116.1 (7.4) and diastolic blood pressure, baseline mean (SD) 81.9 (11.4) mmHg compared to day 1, 67.9 (8.0) (Table 4-2). The estimated systolic and diastolic difference (95% CI) from baseline was 16.4 (3.6 to 29.1) mmHg, P=0.02, and 14.0 (5.7-22.3) mmHg, P=0.005 respectively. From day 2 to day 6 both systolic and diastolic blood pressures increased to concentrations similar to or above those measured at baseline, although participants were no longer on anti-hypertensive treatment.

Figure 4-1  Box-plots showing heart rate (beats per minute) from baseline (day=-1) to post-operative day=6.
Chapter 4: Mechanistic studies

Figure 4-2  Box-plot showing mean arterial blood pressure (mmHg) from baseline (day=-1) to post-operative
day=6.

Table 4-2  Mean (standard deviations) of the daily measurements of heart rate (bpm), systolic blood pressure
(mmHg), diastolic blood pressure (mmHg), and mean arterial pressure (mmHg)

<table>
<thead>
<tr>
<th>N=8</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day of Study</td>
<td>-1</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>79 (11.1)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>132.5 (17.2)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>81.9 (11.4)</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mmHg)</td>
<td>98.7 (11.7)</td>
</tr>
</tbody>
</table>
4.1.4.2 Urinary catecholamine studies (Figure 4-3 and Table 4-3)

Urinary adrenaline excretion increased immediately after surgery when compared with baseline concentrations (Baseline mean (SD) 2.69 (2.53) nmol/mmolUCr/24hr, day 0, 5.65 (2.61) nmol/mmolUCr/24hr; estimated difference (95% CI) 2.96 (-0.19 to 5.94), nmol/mmolUCr/24 hr, P=0.051). Consequently there was also an increase in urinary metadrenaline, baseline mean (SD) 0.04 (0.027) umol/mmolUCr/24hr, day 0 mean (SD) 0.082 (0.08) umol/mmolUCr/24hr; estimated difference (95% CI) 0.042 (-0.03 to 0.12), P=0.23. Thereafter, adrenaline and metadrenaline concentrations were not significantly different from baseline studies. Urinary noradrenaline, normetadrenaline and dopamine concentrations were not significantly different from baseline throughout the study period.

Figure 4-3 Box-plots for daily measurements of a) urinary noradrenaline (nmol/mmolUCr/24hr), b) urinary normetadrenaline (umol/mmolUCr/24hr), c) urinary adrenaline (nmol/mmolUCr/24hr), d) urinary metadrenaline (umol/mmolUCr/24hr), and e) urinary dopamine (nmol/mmolUCr/24hr).
Chapter 4: Mechanistic studies

b)

![Box plot of Urinary Noradrenaline (umol/mmolCr/24hr) by Day of study]

Day of study

-1 0 1 2 3 4 5

Urine Noradrenaline (umol/mmolCr/24hr)

0.0 0.2 0.4 0.6 0.8

*3


c)

![Box plot of Urinary Adrenaline (nmol/mmolCr/24hr) by Day of study]

Day of study

-1 0 1 2 3 4 5

Urine Adrenaline (nmol/mmolCr/24hr)

0 2 4 6 8

*2

Q7

Q2

Q1

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d) Urinary metadrenaline (umol/mmolUClr (24hr))

![Graph showing urinary metadrenaline levels by day of study]

- Day of study: -1, 0, 1, 2, 3, 4, 5
- Values range from 0.00 to 0.30 umol/mmolUClr (24hr)

e) Urinary Dopamine (nmol/mmolUClr (24hr))

![Graph showing urinary Dopamine levels by day of study]

- Day of study: -1, 0, 1, 2, 3, 4, 5
- Values range from 0 to 500 nmol/mmolUClr (24hr)

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4.1.4.3 Urinary steroid studies (Figure 4-4 and Table 4-3)

Urinary free cortisol excretion increased immediately after surgery when compared with baseline (day -1 mean (SD) 5.14 (3.05) nmol/mmolUCr/24hr, day 0 mean (SD) 23.26 (13.6) nmol/mmolUCr/24hr; estimated difference (95% CI) 18.2 (6.2 to 30.1), nmol/mmolUCr/24 hr, P=0.009). Thereafter, urinary free cortisol concentrations were not significantly different from baseline.

Figure 4-4 Box-plots for daily measurements of Urinary free cortisol (nmol/mmolUCr/24hr).
4.1.4.4 Prolactin and aldosterone

Prolactin markedly rose on the day of operation (day -1 mean (SD) 341.3 (186.2) mU/L, day 0 mean (SD) 1801.2 (779.0) mU/L; estimated difference (95% CI) 1460.1 (883.6 to 2036.6) mU/L, P=0.001). The prolactin level remained different from baseline until the 3rd post-operative day (day 3 mean (SD) 714.4 (510.3) mU/L; estimated difference (95% CI) to day -1, 373.1 (90.3-836.5) mU/L, p=0.10. Thereafter, prolactin was not significantly different from baseline values.

4.1.4.4 Prolactin and aldosterone
Serum Aldosterone increased on the day of operation when compared with baseline (day -1 mean (SD) 108.9 (31.8) pmol/L, day 0 mean (SD) 532.2 (349.2) pmol/L; estimated difference (95% CI) 509.8 (143.6 to 876.0) pmol/L, P=0.02) but was thereafter similar to baseline concentrations.

Figure 4.5 Box-plots for daily measurements of a) prolactin (mU/L) and b) serum aldosterone (pmol/L).
4.1.4.5 C-reactive protein (Figure 4-6 and Table 4-5)

CRP increased from baseline concentrations on day 1 (day -1 mean (SD) 6.2 (2.6) mg/L, day 1 mean (SD) 70.3 (29.8) mg/L; estimated difference (95% CI) 64.2 (33.6 to 94.7) mg/L, P=0.003). Thereafter, concentrations remained elevated when compared to baseline from study day 1 through to study day 6 (Table 4-5).

Figure 4-6  Box-plots for daily measurements of C-reactive peptide (mg/L).

Table 4-5 Mean (standard deviations) of the daily measurement of CRP (mg/L). Point estimates and confidence intervals are against baseline (day -1) measurements
4.1.4.6 Markers of glucose homeostasis

4.1.4.7

4.1.4.8 Figure 4-7 and Table 4-6)

One participants plasma insulin result at baseline was excluded from analysis as an unexpected outlier (participant 5, fasting insulin 1625 pmol/L, not on exogenous insulin treatment), on the basis that an analysis of pre-operative fasting insulin concentrations in 94 participants in a separate study undergoing gastric bypass showed a mean of 159.3 pmol/L (standard deviation 89.6), and a maximum value of 482.0 pmol/L, suggesting that the participant was not truly fasted.

Fasting plasma glucose increased significantly on the day of operation (day -1 mean (SD) 7.73 (3.2) mmol/L, day 0 mean (SD) 11.1 (3.4) mmol/L; estimated difference (95% CI) 3.39 (1.89 to 4.88) mmol/L, P=0.001). A daily fall in glucose concentrations was evident thereafter, such that fasting plasma glucose was significantly less than baseline concentrations by day 5 (mean (SD) 4.93 (1.8) mmol/L; estimated difference (95% CI) from baseline = -2.78 (-4.9 to 0.6), p=0.020).

Unfortunately, only four participants had insulin concentrations measured on day 0 samples. A comparison between day -1 and day 0 insulin concentrations was therefore not performed. Thereafter, fasting insulin concentrations were not different from baseline on days one and two. From day three insulin remained significantly lower than baseline concentrations (day 3 mean (SD) 145.7 (42.4) units/L; estimated difference (95% CI compared with baseline, N=6) -184.0 (-326.4 to -41.6) units/L, p=0.021).

HOMA-IR (see chapter Error! Reference source not found.) declined following surgery, such that a statistically significant reduction from baseline was evident by day 3 (N=5, day -1 mean (SD) 4.98 (1.0), day 3 mean (SD) 2.57 (0.6); estimated difference (95% CI) -2.41 (-4.3 to -0.5), p=0.02). Thereafter, HOMA-IR remained significantly reduced from baseline on each study day (estimated difference -3.2 to 4.0, p<0.02). Indeed, HOMA-IR fell below the generally accepted threshold indicating clinically significant insulin resistance (2.0) on day 5 and day 6 (mean (SD) 1.32 (1.0) and 1.6 (0.8) respectively, N=7 for both study days). The improvements in HOMA-IR were predominantly the result of a trend towards increased insulin sensitivity (HOMA-%S) as opposed to beta cell function (HOMA-%B), with HOMA-%S different from baseline by day 4 (N=5, day -1 mean (SD) 20.7 (3.7), day 4 mean (SD) 56.7 (11.8); estimated difference (95% CI) 36.0 (22.3 to 49.7), p=0.002).
Figure 4-7 Box-plots for daily measurements of a) glucose (mmol/L), and b) Insulin (mU/L), and calculations of c) HOMA-IR, d) HOMA-%B, and e) HOMA-%S as described in chapter 2.
Chapter 4: Mechanistic studies

c)

![Box plot showing HOMA-IR variation over different days of study.]

- Day 1 to Day 6 shows a decrease in HOMA-IR.
- The box plot indicates a trend with more variability on Day 1 and a consistent lower value from Day 2 onwards.


d)

![Box plot showing HOMA-%B variation over different days of study.]

- Day 1 to Day 6 shows a decrease in HOMA-%B.
- The box plot indicates a trend with more variability on Day 1 and a consistent lower value from Day 2 onwards.

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Table 4-6  Mean (standard deviations) of the daily measurements of glucose (mmol/L) and insulin (units/L), and related calculations of HOMA-%S, HOMA-%B, and HOMA-IR.

<table>
<thead>
<tr>
<th>Day of Study</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Glucose (mmol/L)</td>
<td>Insulin (units/L)</td>
<td>HOMA-%S</td>
<td>HOMA-%B</td>
<td>HOMA-IR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td>7.73 (3.21)</td>
<td>514.71 (508.7)</td>
<td>20.70 (3.68)</td>
<td>245.96 (148.1)</td>
<td>4.98 (1.03)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11.11 (3.44)</td>
<td>121.33 (72.51)</td>
<td>48.13 (28.50)</td>
<td>46.2 (35.28)</td>
<td>2.67 (1.35)</td>
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<td></td>
</tr>
<tr>
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<td>7.56 (1.35)</td>
<td>248.75 (123.2)</td>
<td>30.90 (22.59)</td>
<td>123.53 (51.12)</td>
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<td>2</td>
<td>7.61 (2.15)</td>
<td>193.63 (83.24)</td>
<td>32.89 (18.42)</td>
<td>128.53 (74.0)</td>
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<td>4</td>
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<td>106.63 (46.97)</td>
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<td>131.26 (63.3)</td>
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<tr>
<td>5</td>
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<td>72.13 (54.17)</td>
<td>106.03 (62.29)</td>
<td>134.5 (67.56)</td>
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<td>6</td>
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<td>1.59 (0.84)</td>
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</table>
Figure 4-8  Hormonal concentrations on each study day expressed as a ratio against baseline values (i.e. study day 1 urinary noradrenaline ratio = study day 1 mean urinary noradrenaline/baseline mean urinary noradrenaline level). Asterisks = p<0.05 versus baseline versus baseline.
4.1.5 Discussion

RYGB results in early improvements in glucose homeostasis in participants with and without dysglycaemia, as measured by venous glucose concentrations, HOMA-IR, insulin secretion, the frequent sampled intravenous glucose tolerance test, and an oral meal test (see chapter 1.4.4, page 106). In contrast, insulin sensitivity is not improved within four weeks of surgery when assessed using the hyperinsulinaemic euglycaemic clamp technique. Understanding the mechanisms underlying these early favourable changes are fundamental to understanding both the mechanisms driving dysglycaemia in this population, and considering other non-surgical approaches that target similar mechanisms.

Glucose homeostasis in this early post-operative period may be influenced by transient physiological effects of the surgery itself, and therefore techniques employed to assess glucose homeostasis at this time may provide misleading results. As discussed in chapter 1.4 and 1.5, the current accepted model is that significant caloric restriction engendered by surgery is the primary driver of early favourable changes in glucose homeostasis. Definitive studies to test this hypothesis remain to be conducted, and would best be performed by comparing early changes in glucose homeostasis in matched participants undergoing RYGB or matched caloric restriction. However, such a study would be inherently flawed if results obtained from techniques employed to assess glucose homeostasis were not comparable between the groups because of specific and transient effects of surgery. This study was therefore designed to report the perioperative hormonal and metabolic response to open RYGB surgery, and thus allow consideration of these responses when assessing glucose homeostasis.

4.1.5.1 Aldosterone and prolactin

Aldosterone and prolactin concentrations rose significantly on the day of operation. Aldosterone concentrations were not significantly different from baseline on day one, whilst prolactin concentrations remained significantly higher than baseline values from day zero until day three.

Major surgery results in sodium retention, a phenomenon recognised over 70 years ago. On the basis that sodium retention may be a physiological response to hypovolaemia, independent of blood loss and instead the consequence of the redistribution of extracellular fluid, the post-operative administration of isotonic saline in large volumes was standard practice for many years. The
availability of a reliable technique for measuring aldosterone concentrations in the 1970s lead to research exploring whether increased aldosterone secretion in response to surgery may explain the observed sodium retention. However, whilst aldosterone secretion increases rapidly following surgery, the resultant venous concentration has been shown to be directly related to dietary salt intake in the early post-operative period, thereby indicating a physiological rather than autonomous response. Furthermore, sodium retention occurred in participants even after aldosterone concentrations had returned to baseline, indicating that aldosterone was not the primary driver of this phenomenon. Nonetheless, an increase in aldosterone concentrations has been demonstrated following many other surgical procedures in numerous studies. There is little published longitudinal data on aldosterone concentrations beyond the first few post-operative hours. However, as in this study, other studies have also suggested that the rise in aldosterone concentrations is brief, with normal concentrations observed within 24 hours of surgery.

It is well established that prolactin concentrations rise in response to surgery, and that levels may be five fold greater than those observed at baseline. The mechanism underlying this rise may be multifactorial; the administration of dopamine antagonists enhances the rise in prolactin during apprehensive stress, but blunts the post-operative rise suggesting that additional mechanisms other than dopamine release regulate prolactin secretion in this context. As with aldosterone, there is little published data on the duration of prolactin rise following surgery. In one study, prolactin levels had returned to preoperative concentrations or below by 24 hours in the majority of 79 patients with resectable colon cancer, having risen by between 167% and 379% within the first two post-operative hours. A second study reporting perioperative prolactin concentrations in otherwise healthy individuals undergoing cholecystectomy, demonstrated that the peak prolactin concentration was measured 30 minutes after incision. Thus, the significant rise and degree of elevation in prolactin concentrations observed immediately after surgery in this study is consistent with the published literature. However, in contrast to aldosterone concentrations, prolactin concentrations remained significantly greater than baseline until the third post-operative day, albeit within or only slightly above the published reference ranges. A number of confounding factors may explain this apparent discrepancy. Firstly, the act of venepuncture or apprehension around this procedure frequently results in a small rise in prolactin concentrations in healthy individuals, and can be marked in some patients. Whilst venous blood was taken from a centrally placed venous catheter during this study and did therefore not cause pain, participant anxiety during this procedure cannot be excluded. In contrast to the studies reported above, the collection of blood samples beyond the first 24 hours after surgery may
be more susceptible to this phenomenon than those collected during the early recovery phase when patients may be partially sedated due to residual effects of anaesthesia.

Secondly, pain and discomfort, is a stimulant for prolactin release and it is possible therefore that the mildly elevated prolactin concentrations observed on days one to three may result in part from residual surgical discomfort. Further longitudinal data on prolactin concentrations beyond the first 24 hour post-operative period in other surgical settings would be required to test this hypothesis. Furthermore, it is likely that one or more pharmaceutical agents used in the peri-operative period (anaesthesia, analgesia, etc.) may have affected the production of prolactin. Opiate based analgesic agents have diffuse inhibitory effects on anterior pituitary output, reducing the secretion of growth hormone, adrenocorticotrophin, thyroid stimulating hormone, and the gonadotrophins, but are also associated with hyperprolactinaemia. It is likely that this is mediated by antagonistic activity at the dopamine receptor. Dopamine antagonists are commonly co-administered with opiate analgesia due to their anti-emetic properties, and further stimulate prolactin release. All participants in this study received appropriate post-operative analgesia care, with regular and as required opiate based treatment. Anti-nausea medication was provided as required.

In contrast to above potential confounders, starvation has been shown to produce no change or a fall in prolactin concentrations in humans and rats in most studies. Participants caloric intake fell significantly following RYGB, and whilst pre-operative caloric intake was not formally measured in this study, from previous analysis in those undergoing the same procedure, it is likely that daily caloric intake in the early post-operative period would have equated to as little as 10% of that consumed daily prior to surgery. Thus, there are a number of factors not related to surgical trauma itself that may have increased or decreased prolactin concentrations in the early post-operative period.

4.1.5.2 Urinary Catecholamines and cortisol

Urinary free cortisol concentrations were significantly increased on the day of surgery when compared to baseline measurements, but were also not significantly different thereafter during the study period.

An acute rise in catecholamine concentrations however has been documented following numerous surgical procedures including endoscopic sinus surgery, hysterectomy, abdominal aortic aneurysm surgery, and upper abdominal surgery. In this study, Urinary adrenaline concentrations were
significantly elevated on the day of surgery, when compared with baseline concentrations. Consequently, the major metabolite of adrenaline, urinary metadrenaline, was also elevated on day 0 although this was not statistically significant. Urinary noradrenaline, normetadrenaline, and dopamine levels did not significantly change during the study period. Peak urinary adrenaline concentrations were similar to those observed in other studies, although the absence of a rise in urinary noradrenaline concentrations is not. However, there were no clear differences between any of the urinary concentrations from day one onwards when compared with baseline.

A number of studies have reported on changes in cortisol concentrations and physiology in the perioperative period. Free cortisol concentrations increase during surgery or immediately after surgery, although total serum cortisol concentrations may not be elevated until the first few hours after surgery. This phenomenon may be explained by the effect of anaesthesia on cortisol physiology, as the capacity of albumin to bind cortisol is significantly reduced by systemic anaesthetic agents. Thus, general anaesthesia appears to result in higher perioperative cortisol rises than local anaesthesia, even when the same procedure is performed. In this study, an expected transient rise in urinary free cortisol excretion was evident on day 0 with a 4 fold elevation in cortisol concentrations when compared to baseline. Whilst urinary free cortisol levels remained higher than baseline on day one, this finding was not statistically significant and may be explained by one outlying result. After exclusion of this outlying result on post-operative day 1 (urinary free cortisol = 41.11 nmol/mmolUCr, the mean of remainder of day 1 results = 5.78 nmol/mmolUCr), the mean urinary free cortisol concentration on day 1 was not clearly different from baseline (5.78 ± 4.41 nmol/mmolUCr vs. 5.14 ± 2.12 nmol/mmolUCr, P=0.84). Nonetheless, a conservative conclusion is that urinary free cortisol excretion returned to baseline concentrations by day 2 following open RYGB surgery.

4.1.5.3 C-reactive protein

C-reactive protein (CRP) is produced by hepatocytes in response to circulating interleukin-6, and binds to damaged or apoptotic cells to facilitate immune clearance. Consequently, the measurement of CRP concentrations is used widely in clinical practice as a surrogate marker of inflammation or infection. A large amount of published data supports a longer term reduction in CRP concentrations following bariatric surgery, with the change in CRP at follow up associated with the degree of weight loss. There is far less published data reporting change in CRP concentrations in the immediate post-operative period, and even less data to investigate any difference in procedural
technique. Open gastrectomy does appear to be associated with a greater post-operative rise in CRP concentrations than observed after laparoscopic gastrectomy in the context of gastric cancer, but this procedure does not involve the additional surgical manipulations performed during RYGB. A literature review identified only one published study specifically reporting early changes in CRP following bariatric surgery, although the primary aim of the study was to explore relationships between CRP concentrations and post-operative complications. 410 participants undergoing RYGB were included in the study if CRP concentrations had been measured at least once between the day prior to surgery and the seventh post-operative day. The mean CRP concentration pre surgery was 7 (4-12) mg/L in both those participants who developed post-operative complications and those who did not, whilst the peak mean CRP concentration (129 (80-199) mg/L) was noted on day two. Concentrations in both groups fell thereafter but remained higher at day seven (mean 61 (35-105) mg/L) than at baseline. A CRP concentration of >229 mg/L was found to be 53% sensitive and 91% specific for any of a number of specified post-operative complications, and 100% sensitive for intestinal anastomotic leaks.

In this study, CRP concentrations at baseline were similar (mean (SD) 6.2 (2.6) to those observed in the earlier study, with a similar trend in changes in CRP thereafter, albeit with lower mean concentrations at each time point. Specifically, the peak mean (SD) CRP concentration was 78.4 (48.2) mg/L observed on the second post-operative day, whilst the mean concentration on post-operative day 6 was 29.4 (17.4) mg/L.

4.1.5.4 Glucose homeostasis and Insulin

As noted in a large number of other studies exploring early changes in glucose homeostasis after bariatric surgery (see chapter 1.3.3.1, page 54), improvements in glucose homeostasis were evident in participants by the sixth post-operative day. Furthermore, fasting insulin concentrations were significantly lower than pre-surgery levels by the third post-operative day, whilst the mean fasting glucose concentration had fallen from the impaired fasting glucose level to normal glucose tolerance by day three, with fasting glucose concentrations significantly lower than pre surgery measurements from day five onwards. Consequently, and acknowledging the limitations of the HOMA assessment in this acute context, insulin sensitivity (HOMA-%S) had returned to population mean levels (106%) by the fifth post-operative day in comparison to clearly reduced insulin sensitivity (20% of population mean) at the pre surgery assessment.
4.1.5.5 Direct effects of measured hormonal/metabolic markers on glucose homeostasis

As presented in chapter 1.4.4 (page 106), caloric restriction is likely to explain a significant proportion of the early improvements in glucose homeostasis observed after bariatric surgery, as similar improvements are observed after non-surgical caloric restriction. Furthermore, the data supports that this improvement can be mostly explained by an improvement in hepatic insulin sensitivity which is evident within days of bariatric surgery, with peripheral insulin resistance improving only after weight loss. This conclusion draws on data from a large number of studies utilising a number of techniques to estimate parameters of glucose homeostasis within the first few post-operative days. However, as discussed above, a number of hormonal and metabolic responses to surgery appear evident after RYGB, and whilst these responses are transient, it is important to consider the direct impact these changes may have on assessments of glucose homeostasis performed within the first few days.

The renin-angiotensin-aldosterone system appears to influence a number of aspects of glucose homeostasis, although the overall effect is modest. Angiotensin II increases insulin resistance in tissues by interfering with post receptor insulin signalling. Consequently, the clinical use of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) results in improved peripheral glucose disposal. Furthermore, it is likely that both angiotensin and aldosterone directly impair insulin release. To support these findings, two recent large randomized studies showed an increased likelihood of improvement to normal glucose tolerance in participants with impaired glucose tolerance treated with either ACE or ARB therapy. However, with the exception of the day of surgery, aldosterone concentrations were not clearly different after surgery when compared to pre-operative measurements in this study. Thus, this potential confounder would need consideration only in the context of assessments on the day of surgery itself. Furthermore, the physiological effects described above may not appear with such short lived exposure to aldosterone.

Cortisol induces whole body insulin resistance at supraphysiological concentrations. Furthermore, hypercortisolaemia impairs glucose effectiveness, a physiological mechanism whereby hyperglycaemia itself suppressed further endogenous glucose release and improves glucose uptake. This is not surprising as both endogenous and exogenously derived hypercortisolaemia results in dysglycaemia in clinical settings. Both insulin resistance and reduced glucose effectiveness are evident during acute hypercortisolaemia in healthy individuals suggesting these effects are rapid in onset. Thus, the transient elevation in cortisol concentrations, measured as urinary free cortisol, observed early after RYGB in this study may potentially impact on the accuracy of assessments of glucose homeostasis.
during this period. Furthermore, non-surgical severe caloric restriction results in a gradual reduction in plasma and urinary cortisol concentrations in obese individuals, attributed to a reduction in cortisol binding globulin production and normalisation of hepatic handling of cortisol. It would therefore be important to consider this potential confounder in a study comparing surgical and non-surgical matched caloric restriction on glucose homeostasis, particularly within the first two days after surgery.

The association between glucose homeostasis and inflammation is complex. Hyperglycaemia is evident in previously healthy individuals during acute inflammatory responses, for example during infection, primarily as a result of increased hepatic gluconeogenesis. This effect is mediated by activation of the adrenergic system, counter regulatory hormonal responses, and cytokine production, and augmented by the increased supply of gluconeogenic substrates related to the infection response. Furthermore, inflammation markedly increases insulin peripheral resistance, despite promoting insulin independent glucose uptake, an effect which appears to be mediated by several cytokines including TNF-α. Whilst interleukin-6, the primary regulator of CRP production, has also been implicated in this process, the data is contradictory. The observation that interleukin-6 concentrations rise rapidly during exercise in healthy individuals is counterintuitive to the concept of this cytokine primarily exerting an insulin resistance effect. Indeed, studies in humans, as opposed to mice, have suggested that interleukin-6 has no measurable effect on hepatic, and actually decreases circulating insulin concentrations in humans with type 2 diabetes. Circulating interleukin-6 has been shown to either have no effect on peripheral glucose uptake or increase glucose uptake in adipocytes in other studies.

It is clear that the relationship between glucose homeostasis and inflammation remains to be fully elucidated, but is quite plausible that glucose homeostasis in the very early post-operative period is affected in both a positive and negative fashion by surgical inflammation. As CRP concentrations appear to remain elevated until at least the sixth or seventh post-operative day, this should be borne in mind when assessing glucose homeostasis early after bariatric surgery. Of particular relevance may be assessments of peripheral insulin resistance using the euglycaemic hyperinsulinaemic clamp. In general, studies reporting changes in insulin resistance following RYGB/SG using the EHC technique, have noted improvements only after 6-12 months and not within four weeks. Further longitudinal research is therefore required to ensure that this apparent phenomenon, integral to the current understanding of the mechanisms underlying the early improvements in glucose homeostasis.
following bariatric surgery, is not simply related to the confounding effect of a persistent post-operative inflammatory response.

### 4.1.5.6 Study limitations

This pilot study provides early data on the expected hormonal and metabolic response to open RYGB surgery. There are however a number of limitations to consider. Firstly, the number of participants in the study was low, and limited by the availability of people meeting the inclusion criteria during the study period. The range of each measured parameter and standard deviations of the calculated mean were wide. In addition, the study is more susceptible to error introduced by outliers, all of which increase the likelihood that the conclusions drawn from this data may be revised with a larger dataset. Ideally, a further study would be performed to confirm these findings, with the number of participants selected based on power calculations using this data.

Secondly, the conclusions from this study can be applied only to open RYGB surgery. Bariatric surgery is a frequently used over-riding term in clinical and research areas, and may reference one of a number of different surgical techniques. Furthermore, it is likely that the stress response may differ between open and laparoscopic surgery as observed in gastrectomy performed for gastric cancer.\textsuperscript{901,902} To the best of my knowledge, no study has yet compared the early stress response to open versus laparoscopic bariatric surgery. Indeed, even when a surgical technique used by two differing surgeons appears to be similar in name, it is expected that there may still be intersurgeon variation with respect to time of procedure, anaesthesia regimen, etc. It would be reasonable to suggest that other research groups wishing to assess accurately changes in glucose homeostasis early after a bariatric surgical procedure, compared against non-surgical caloric restriction, should initially study the stress response expected immediately after that particular procedure.

Failure to document a clear catecholamine response following RYGB may be a limitation of the methodology of this study. To better reflect the overall excretion of catecholamines we elected to use urinary collection measurements rather than plasma measurements. Plasma catecholamine measurements are not routinely used in clinical practice due to the significant fluctuations seen in normal physiological states; plasma metadrenaline studies are preferred as this reflects an average excretion of catecholamines via their metabolites over a period of time. Urinary studies, whilst cumbersome to perform, have the advantage of also reflecting average excretion over a period of 24
hours and are therefore less susceptible to error in most clinical scenarios. Had we elected to measure plasma catecholamines in this study, it is plausible that we may have documented shorter duration transient elevations in plasma adrenaline, noradrenaline, or dopamine which have not been detected by means of a method that reflects a longer period of excretion. However, this limitation does not detract from the conclusion that can be made from this study; the average excretion of catecholamines and metanephrines does not appear to differ from baseline from the first post-operative day following RYGB surgery, and therefore will not interfere with interpretation of measurements of glucose metabolism and insulin sensitivity.

In this study, CRP was measured as a surrogate of the inflammatory response, which in reality involves a multitude of physiological peptides including cytokines. As discussed above, it is likely that each of these cytokines has a direct role within this inflammatory response, and therefore it may have been of interest to additionally measure changes in the concentrations of these cytokines. As noted above, both Interleukin-6 and TNF-α play a clear role in the inflammatory and may have direct influence over glucose homeostasis. Whilst not possible with this small dataset, a larger study population may allow the estimation of the relative contribution of inflammatory markers to early changes in glucose homeostasis following bariatric surgery.
4.1.6 Conclusion

Open RYGB surgery results in a transient elevation in concentrations of prolactin, aldosterone, urinary adrenaline and metadrenaline, and urinary free cortisol that appear to return to baseline concentrations by post-operative day 3. Conversely, CRP, as a surrogate of inflammation, remains elevated for at least the first 6 days following RYGB surgery. This study supports the assumption that studies assessing glucose homeostasis performed on or after day 4 following RYGB, are not likely to be affected by stress response hormones but may be influenced by an on-going inflammatory response. This finding will need consideration in future studies comparing early changes in glucose homeostasis following RYGB when compared with non-surgical control groups.
4.2 Fasting gut peptides following gastric bypass surgery and weight outcomes

4.2.1 Introduction

Caloric restriction, such that energy expenditure exceeds intake, results in weight loss whether this is achieved by surgical or non-surgical mechanisms.\textsuperscript{324,327} However, the durability of this effect differs significantly between these two interventions. Bariatric surgery tends to result in rapid weight loss with maximal weight loss observed within 24 months.\textsuperscript{394,396,397,402} Longer term follow up studies have suggested that many of those who have undergone bariatric surgery experience some weight regain thereafter, but this is usually minimal with significant reductions maintained (see chapter 3.1).\textsuperscript{427,428} In contrast, weight regain after non-surgical caloric restriction is common,\textsuperscript{924,925} although there is some evidence to suggest this is less likely after very low calorie interventions or following rapid early weight loss.\textsuperscript{926} Indeed, successful weight loss maintenance, defined as 10\% initial body weight loss maintained for 12 months, was achieved by only 21\% of participants in one highly intensive interventional study.\textsuperscript{927}

How then can we explain these differing longer term outcomes if the primary effect of each intervention is caloric restriction? Recently the concept that regulatory physiological mechanisms may “defend against weight loss” after dietary caloric restriction has received much attention, in recognition of the observation that energy homeostasis may actually favour weight gain in humans.\textsuperscript{928,929,930} Whilst detailed research is required to clarify this phenomenon, it is likely that it involves interactions between persistent adipocyte hyperplasia,\textsuperscript{931} adipose tissue cytokines, adipocyte and gut hormones,\textsuperscript{928} appetite regulation,\textsuperscript{932,933} and changes in energy expenditure.\textsuperscript{934,935} Furthermore, this combination of factors appear to be initiated rapidly after the commencement of caloric restriction, prior to weight loss, and are independent of actual body energy stores.\textsuperscript{928} Weight loss induced changes in adipocyte and gut peptides favour weight regain, and appear to persist after the period of initial weight loss.\textsuperscript{501,936}

As discussed in chapter 1.4.1 and 1.4.2, bariatric surgery appears to induce a durable reduction in caloric intake which is related to reduced food intake, changes in digestive tract transit, altered food behaviour, and favourable alterations in gut peptides involved in energy homeostasis. However, most of the evidence to support these potential mechanisms is derived from either short term studies in animal models, or from early follow up in clinical studies in humans undergoing bariatric surgery. This
study was designed as an initial exploration of whether differences in adipocyte and gut hormones at long term follow up after RYGB correlate with weight outcomes, and therefore whether differences in the longer term hormonal adaptation to surgical and non-surgical weight loss may explain discrepancies in weight regain between these two interventions.

4.2.2 Aims

To assess fasting gut peptide concentrations during long term follow up after gastric bypass surgery, and describe any associations with weight outcomes

4.2.3 Participants and methods

4.2.3.1 Study overview and design

This was a retrospective non-experimental cohort study of fasting gut peptides in 25 participants who had undergone gastric bypass at least five years before their latest measurements. Fasting gut peptide concentrations were measured on blood samples taken immediately prior to surgery, at six days after surgery, and at a follow-up at least five years after surgery. As historical stored samples were used in this study, with only fasting plasma samples available, an assessment of post prandial changes in the concentrations of measured gut peptides was not possible.

4.2.3.2 Study Participants

Study participants were 25 patients who had gastric bypass surgery at least five years previously, and had participated in the bariatric follow up study described elsewhere (Chapter 3.1), and were selected from this larger cohort because of the availability of historical blood samples for analysis.
Inclusion criteria

- RYGB performed at least five years before assessment
- BMI ≥30kg/m2 at baseline
- Stored blood samples available for analysis from immediately prior to surgery and day 6

Exclusion criteria

- Further bariatric surgery (either revision or repair) performed since original procedure
- Missing blood samples results from either baseline and/or six days after the bariatric surgery.

4.2.3.3 Methods

This study used data previously collected for the pre-operation time point, and collected prospective data as part of the bariatric follow up study discussed elsewhere (chapter 3.1, pages 134-243). In addition, data collected at 1 and 2 years following surgery for each participant as part of a separate study were used. The participant characteristics were recorded as part of the admission for gastric bypass surgery and obtained by review of the clinical records for that admission. These data were: Weight, height and BMI, and blood markers of glucose homeostasis (fasting glucose, fasting insulin, and HbA1c). Most participants had a standard oral glucose tolerance test (75g OGTT) performed prior to their operation as this was the accepted contemporary practice for the assessment of diabetes. These measurements were repeated one and two years after surgery, and these data were obtained from a review of the participant’s clinical records, and from a database maintained by Wakefield Obesity Clinic.

In addition to the routine blood samples taken for the pre-operative and post-operative assessments, further fasting blood samples were collected into EDTA collection tubes before surgery, six days after surgery and at the follow up assessment at least five years after surgery. Samples were immediately centrifuged (3000 revolutions per minute, for 10 minutes at room temperature) and plasma then extracted. Aliquots of 200 microlitres were then stored in a freezer at -80 degrees Celsius until analysis.
4.2.3.4 Biochemical analysis

Glucose and Insulin concentrations and HbA1c were measured at the biochemistry Laboratory at Wellington Regional Hospital, Wellington, NZ (chapter 2.3, page 125). Inter-assay CV was <5% for glucose, 2% for insulin values < 50 pmol/L and 4% for those > 50 pmol/L.

As discussed in chapter 2.3.4 (page 128) fasting gut peptides (ghrelin, leptin, polypeptide YY, and amylin) were measured using a multiplex kit (Product HGT-68K, Merck Millipore, Billerica, Massachusetts, USA) in the Department of Nutrition laboratory, University of Otago, Dunedin. Fasting ghrelin (coefficient of variance % = 7.4 and 9.6%), fasting leptin (CV% = 1.6 and 6.7), fasting amylin (CV% = 5.0 and 15.9), and fasting PYY (CV% = 8.0 and 16.2) were measured and expressed as pg/mL.

4.2.3.5 Statistical analysis

Simple data descriptions are used for the anthropometric measurements and expressed as mean and standard deviation (SD) or other appropriate summaries. The data distributions of the peptide concentrations, including change from baseline, were examined with plots (histograms and box-plots), and by formal tests to assess whether they were normally distributed. A logarithm transformation was also examined to assess whether skew data could be better analysed on that scale of measurement. Wilcoxon signed rank test was used to assess variables where normality assumptions for analyses were poorly met. Pearson’s correlation coefficient was used to assess the strength of linear association between variables. Linear regression analysis was used to further explore this association.
4.2.4 Results

The mean (SD) age of those included in this analysis was 45.1 (12.5) and 52.2 (12.8) years at baseline and follow up respectively (Table 4-7). Nineteen (76%) of the participants were female, and the mean (SD) duration of follow up after gastric bypass was 7.0 (1.3) years.

Table 4-7  Baseline characteristics of the study participants

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The distribution of data for weight, BMI, fasting glucose, HbA1c, fasting insulin, and HOMA-IR at baseline and follow up was right skewed as demonstrated by inspection of histograms (Figure v-1 (403) and Figure v-3 (405)). Box plots to show BMI at baseline and during follow up are presented in Figure 4-9, and illustrate outlying results. With the exception of HOMA-IR data, logarithmic transformation of all the data resulted in a better approximation of normal distribution allowing parametric analysis (Figure v-1 (403) and Figure v-3 (405)).
4.2.4.1 Body weight change

Every participant in the study lost weight following gastric bypass surgery. The mean (SD) BMI at baseline was 45.4 (7.8) kg/m², and the minimum BMI at one to two years of follow up was 29.0 (6.5) kg/m². The mean (SD) BMI after at least five years of follow was 33.1 (8.5) kg/m² (figure 4-1 and table 4-2). This translates into relative body weight loss from baseline of 26.9% at latest follow up. The change in BMI from baseline to minimum, and from minimum to the final follow up was normally distributed (Figure v-2 (404)).

Figure 4-9 Box plot showing body mass index (BMI, kg/m²) at surgery, at one to two years (minimum), and at the greater than 5 year follow up assessment
4.2.4.2  Diabetes at baseline and outcomes

Twenty four (96%) participants had sufficient data available to define glycaemic status (ADA criteria) at baseline and final follow up (Table 4-8). Nineteen (76%) participants had abnormal glucose homeostasis at baseline. Of these, thirteen participants had prediabetes, whilst the remaining six had overt type 2 diabetes. Three participants used insulin to control diabetes, one used oral glucose lowering agents, and two used dietary and lifestyle methods only. At assessment at greater than five years, three participants remained with type 2 diabetes, and a further participant had prediabetes. Each of the participants with residual type 2 diabetes had required insulin treatment before surgery; two of these participants managed their diabetes through lifestyle and dietary means only at follow up, whilst one participant required oral glucose lowering medication. The one participant with residual prediabetes had type 2 diabetes before surgery and used oral glucose lowering therapy. All participants with either prediabetes or diet/lifestyle controlled type 2 diabetes before surgery, had normal glucose assessments at the greater than five year follow up visit. No participant progressed to either abnormal glucose tolerance or type 2 diabetes during the study period.

Table 4-8  Cross tabulation to show glycaemic status at baseline against glycaemic status at the final follow up assessment. The ADA criteria for the diagnosis of diabetes, and the assessment of diabetes following bariatric surgery are applied.

<table>
<thead>
<tr>
<th>ADA criteria at baseline</th>
<th>ADA criteria at final follow up</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NGT</td>
<td>Prediabetes</td>
</tr>
<tr>
<td>N=24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADA criteria at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGT</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Type 2 DM</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>13</td>
</tr>
</tbody>
</table>

No participant progressed to either abnormal glucose tolerance or type 2 diabetes during the study period.
4.2.4.3 Fasting gut peptide concentrations

Full data descriptions for fasting gut peptide concentrations prior to surgery, on day six after surgery, and at the greater than five year follow up assessment are reported below in Table 4-9 to Table 4-12. Results of each hormone studied are discussed below. Histograms were used to assess data distributions (Figure v-4 (408) to Figure v-7 (411)). With the exception of baseline leptin and amylin concentrations, and PYY measured at greater than five years, the remaining data had right skew distributions which were more symmetric after a natural logarithm transformation (Table v-1 (407)).

Table 4-9 Descriptive statistics for fasting leptin concentrations before surgery, at day six after surgery, and at the greater than five year assessment

<table>
<thead>
<tr>
<th>Leptin (pg/ml)</th>
<th>Baseline</th>
<th>Day 6</th>
<th>&gt;5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>29,943.8</td>
<td>9,936.0</td>
<td>10,608.3</td>
</tr>
<tr>
<td>Standard error of the mean</td>
<td>3,357.3</td>
<td>1,593.2</td>
<td>1,626.5</td>
</tr>
<tr>
<td>95% CI (upper)</td>
<td>36,888.8</td>
<td>13,224.4</td>
<td>13,965.1</td>
</tr>
<tr>
<td>95% CI (lower)</td>
<td>22,998.7</td>
<td>6,647.6</td>
<td>7,251.4</td>
</tr>
<tr>
<td>Median</td>
<td>27,322.1</td>
<td>7,120.4</td>
<td>9,405.3</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>16,447.2</td>
<td>7,966.5</td>
<td>8,132.3</td>
</tr>
<tr>
<td>Minimum</td>
<td>5,247.2</td>
<td>1,755.6</td>
<td>1,040.6</td>
</tr>
<tr>
<td>Maximum</td>
<td>79,680.9</td>
<td>34,999.7</td>
<td>29,174.5</td>
</tr>
<tr>
<td>Range</td>
<td>74,433.6</td>
<td>33,244.1</td>
<td>28,133.9</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>16,252.9</td>
<td>9,782.0</td>
<td>12,168.6</td>
</tr>
</tbody>
</table>

Table 4-10 Descriptive statistics for fasting ghrelin concentrations before surgery, at day six after surgery, and at the greater than five year assessment

<table>
<thead>
<tr>
<th>Ghrelin (pg/ml)</th>
<th>Baseline</th>
<th>Day 6</th>
<th>&gt;5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>20.64</td>
<td>21.24</td>
<td>18.54</td>
</tr>
<tr>
<td>Standard error of the mean</td>
<td>0.97</td>
<td>0.98</td>
<td>0.61</td>
</tr>
<tr>
<td>95% CI (upper)</td>
<td>22.65</td>
<td>23.23</td>
<td>19.81</td>
</tr>
<tr>
<td>95% CI (lower)</td>
<td>18.64</td>
<td>19.21</td>
<td>17.28</td>
</tr>
<tr>
<td>Median</td>
<td>19.90</td>
<td>18.96</td>
<td>18.10</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>4.86</td>
<td>4.92</td>
<td>3.06</td>
</tr>
<tr>
<td>Minimum</td>
<td>13.90</td>
<td>16.12</td>
<td>14.77</td>
</tr>
<tr>
<td>Maximum</td>
<td>33.59</td>
<td>32.68</td>
<td>25.42</td>
</tr>
<tr>
<td>Range</td>
<td>19.69</td>
<td>16.56</td>
<td>10.65</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>4.41</td>
<td>7.36</td>
<td>4.94</td>
</tr>
</tbody>
</table>
### Chapter 4: Mechanistic studies

#### Table 4-11 Descriptive statistics for fasting PYY concentrations before surgery, at day six after surgery, and at the greater than five year assessment

<table>
<thead>
<tr>
<th>PYY (pg/ml)</th>
<th>Baseline</th>
<th>Day 6</th>
<th>&gt;5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>242.5</td>
<td>213.1</td>
<td>181.5</td>
</tr>
<tr>
<td>Standard error of the mean</td>
<td>41.1</td>
<td>32.9</td>
<td>14.0</td>
</tr>
<tr>
<td>95% CI (upper)</td>
<td>335.4</td>
<td>284.8</td>
<td>210.9</td>
</tr>
<tr>
<td>95% CI (lower)</td>
<td>149.6</td>
<td>141.4</td>
<td>152.1</td>
</tr>
<tr>
<td>Median</td>
<td>200.9</td>
<td>168.4</td>
<td>164.8</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>129.9</td>
<td>118.6</td>
<td>60.9</td>
</tr>
<tr>
<td>Minimum</td>
<td>102.5</td>
<td>116.22</td>
<td>97.7</td>
</tr>
<tr>
<td>Maximum</td>
<td>545.1</td>
<td>576.7</td>
<td>341.6</td>
</tr>
<tr>
<td>Range</td>
<td>442.6</td>
<td>460.5</td>
<td>243.9</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>151.9</td>
<td>92.8</td>
<td>80.8</td>
</tr>
</tbody>
</table>

#### Table 4-12 Descriptive statistics for fasting Amylin concentrations before surgery, at day six after surgery, and at the greater than five year assessment

<table>
<thead>
<tr>
<th>Amylin (pg/ml)</th>
<th>Baseline</th>
<th>Day 6</th>
<th>&gt;5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>40.22</td>
<td>34.68</td>
<td>37.01</td>
</tr>
<tr>
<td>Standard error of the mean</td>
<td>0.97</td>
<td>0.98</td>
<td>1.15</td>
</tr>
<tr>
<td>95% CI (upper)</td>
<td>42.23</td>
<td>36.70</td>
<td>39.37</td>
</tr>
<tr>
<td>95% CI (lower)</td>
<td>38.22</td>
<td>32.65</td>
<td>34.64</td>
</tr>
<tr>
<td>Median</td>
<td>39.16</td>
<td>34.13</td>
<td>36.1</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>4.86</td>
<td>4.91</td>
<td>5.74</td>
</tr>
<tr>
<td>Minimum</td>
<td>30.32</td>
<td>28.91</td>
<td>29.99</td>
</tr>
<tr>
<td>Maximum</td>
<td>55.89</td>
<td>47.47</td>
<td>61.63</td>
</tr>
<tr>
<td>Range</td>
<td>25.57</td>
<td>18.56</td>
<td>31.64</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>5.79</td>
<td>6.70</td>
<td>4.59</td>
</tr>
</tbody>
</table>

#### Table 4-13 Mean and standard error of each measured fasting gut peptide at each study time point. P values illustrate comparison with baseline data

<table>
<thead>
<tr>
<th>Gut peptide</th>
<th>Study time point</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Day 6</td>
<td>Final follow up</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
<td>P value</td>
<td>Mean (SE)</td>
</tr>
<tr>
<td>Leptin (pg/ml)</td>
<td>29,943.8 (3,357.3)</td>
<td>9,936.0 (1,593.2)</td>
<td>&lt;0.001</td>
<td>10,608.3 (1,626.5)</td>
</tr>
<tr>
<td>Ghrelin (pg/ml)</td>
<td>20.64 (0.97)</td>
<td>21.24 (0.98)</td>
<td>0.5</td>
<td>18.54 (0.61)</td>
</tr>
<tr>
<td>PYY (pg/ml)</td>
<td>242.5 (41.1)</td>
<td>213.1 (32.9)</td>
<td>0.3</td>
<td>181.5 (14.0)</td>
</tr>
<tr>
<td>Amylin (pg/ml)</td>
<td>40.2 (0.97)</td>
<td>34.7 (0.98)</td>
<td>&lt;0.001</td>
<td>37.0 (1.15)</td>
</tr>
</tbody>
</table>
4.2.4.4 Leptin

Leptin values decreased from the sixth day after surgery. As shown in Table 4-9 and Figure 4-10 fasting leptin decreased from 29,943.8 to 9,936.0 pg/ml after six days, estimated difference after logarithmic transformation (n=24): -1.23 (95% CI -0.9 to -1.6, p<0.001), equivalent to a mean ratio of -0.29 (95% CI 0.41 to 0.2). The mean fasting leptin after five years follow up was 10,608.3 pg/ml, estimated difference after logarithmic transformation from baseline -1.28 (95% CI -0.9 to -1.7, P<0.001), equivalent to a mean ratio of 0.28 (95% CI 0.41 to 0.18), and from day 6, 0.01 (95% CI -0.3 to 0.3, P=0.9) equivalent to a mean ratio of 1.01 (95% CI 0.74 to 1.35).

4.2.4.5 Ghrelin

Ghrelin concentrations were not clearly different from baseline at the day 6 assessment, but there was a significant further reduction in ghrelin concentrations at the final follow up assessment (Table 4-10 and Figure 4-10). Baseline and day six mean fasting ghrelin was 20.64 (4.86) and 21.24 (4.92) pg/ml respectively (estimated difference after logarithmic transformation (95% CI) 0.03 (-0.1 to 0.06) pg/ml, P=0.5), equivalent to a mean ratio of 1.03 (95% CI -1.11 to 1.06). The mean fasting ghrelin after five years follow up was 18.54 (3.06) pg/ml, (estimated difference after logarithmic transformation from baseline (95% CI) -0.1 (-0.01 to 0.2) pg/ml, P=0.04), equivalent to a mean ratio of -1.11 (95% CI 1.01 to 1.22).

4.2.4.6 PYY

PYY concentrations were not clearly different from baseline at either follow up assessment (Table 4-11 and Figure 4-10). Baseline and day six mean fasting PYY was 242.5 (129.9) and 213.1 (118.6) pg/ml respectively (estimated difference after logarithmic transformation (95% CI) -0.08 (-0.07 to 0.2) pg/ml, P=0.3, N=9), equivalent to a mean ratio of -1.08 (95% CI -0.93 to 1.22). The mean fasting PYY after five years follow up was 181.5 (60.9) pg/ml, (estimated difference (95% CI) -0.14 (-0.2 to 0.4) pg/ml, P=0.4, N=10), equivalent to a mean ratio of -1.15 (95% CI -1.22 to 1.49).
4.2.4.7 Amylin

Amylin values decreased from the sixth day after surgery (Table 4-12 and Figure 4-10). Baseline mean fasting amylin decreased from 40.22 (4.86) to 34.68 (4.91) pg/ml after six days, estimated difference after logarithmic transformation (n=25): 0.15 (95% CI 0.09 to 0.21, p=<0.001), equivalent to a mean ratio of 1.16 (95% CI 1.09 to 1.23). The mean fasting amylin after five years of follow up remained lower than baseline concentrations at 37.01 (5.74) pg/ml (estimated difference after logarithmic transformation from baseline (n=25) -0.09 (95% CI -0.14 to -0.03), p=<0.01, equivalent to a mean ratio of -1.09 95% CI -1.15 to -1.03), but were increased in comparison to concentrations at day six (estimated difference after logarithmic transformation (n=25): 0.06 (95% CI 0.01 to 0.12), p=0.02, equivalent to a mean ratio of 1.06 (95% CI 1.01 to 1.13).

Figure 4-10  Box plots showing fasting concentrations of a) leptin (pg/ml), b) ghrelin (pg/ml), c) PYY (pg/ml), and d) amylin (pg/ml) at each time point
4.2.4.8 Regression analysis

To explore relationships between concentrations of fasting gut peptides and BMI, regression analysis was performed. Absolute concentrations and change in level of each gut peptide were employed as independent variables, whilst absolute BMI at each study point and the change in BMI between study points were employed as dependent variables.

4.2.4.8.1 Leptin

Neither fasting leptin at baseline (n=25, r=0.26, f=1.6, p=0.2) or final follow up (n=25, r=0.35, f=3.1, p=0.09) predicted BMI at that time point (Table 4-14). However, fasting leptin concentrations at day 6 predicted both the minimum BMI at one to two years (n=25, r=0.44, f(1,23)=5.5, p=0.03) and the BMI at the final follow up assessment (n=25, r=0.5, f(1,23)=7.7, p=0.01), accounting for 16% and 22% of the total variation respectively (Figure 4-11). Examination of residuals supported the validity of this model. Cook’s distance was <1 in all cases, the leverage statistic was 0.04 (expected 0.08), and DFBeta for the constant and each independent variable was <1. 5% of cases had studentised residuals > ±1.96 but <2.58. Standardised residuals were all within ±2. The regression equations were:

\[
\text{Ln(x) Minimum BMI (kg/m}^2\text{)} = 2.32 + (0.12 \times \text{Ln(x) fasting leptin (pg/ml) on day 6})
\]

\[
\text{Ln(x) BMI (kg/m}^2\text{)} \text{ at final assessment} = 2.01 + (0.16 \times \text{Ln(x) fasting leptin (pg/ml) on day 6})
\]

These models remained significant when adjusting for baseline BMI. Fasting leptin at baseline (r=0.004, f<0.01, p=0.99) and day 6 (r=0.23, f=1.3, p=0.3) did not predict the subsequent change in BMI over the study period. Furthermore, the change in leptin from baseline to day 6 did not clearly predict either the minimum BMI (r=0.35, f=3.0, p=0.1) or final BMI (r=0.4, f=3.8, p=0.06), and did not predict the change in BMI from baseline to minimum (r=0.08, f=0.2, p=0.7), minimum to final follow up (r=0.2, f=0.9, p=0.4), or over the entire study period (r=0.24, f=1.3, p=0.3).

Table 4-14 Univariate regression analyses outcomes for fasting leptin on day 6 against BMI at baseline and follow up. Outcomes are following logarithmic transformation of both leptin and BMI data.
Figure 4-11  Regression variable plots to show a) day 6 fasting leptin against the minimum BMI at one to two years, and b) day 6 fasting leptin against the BMI at final follow up
4.2.4.8.2 Ghrelin

Fasting ghrelin at each time point, or the change in fasting ghrelin between time points did not predict BMI outcome or change in this study. Fasting ghrelin at baseline (n=25, r=0.01, f=0.01, p=0.98) and final follow up (n=25, r=0.04, f=0.32, p=0.9) did not predict BMI at that time point. Furthermore, fasting ghrelin concentrations at day 6 did not predict either the minimum BMI at one to two years (n=25, r=0.1, f=0.2, p=0.7) or the BMI at the final follow up assessment (n=25, r=0.03, f=0.2, p=0.9). Fasting ghrelin at baseline (n=25, r=0.1, f=0.4, p=0.5) and day 6 (n=25, r=0.1, f=4.3, p=0.5) did not predict the subsequent change in BMI over the study period. Furthermore, the change in ghrelin from baseline to day 6 did not predict either the minimum BMI (n=25, r=0.05, f=0.04, p=0.9) or final BMI (n=25, r=0.05, f=0.6, p=0.8), and did not predict the change in BMI from baseline to minimum (n=25, r=0.2, f=0.9, p=0.3), minimum to final follow up (n=25, r=0.2, f=0.9, p=0.4), or over the entire study period (n=25, r=0.3, f=1.7, p=0.2).

4.2.4.8.3 PYY

Fasting PYY at baseline (n=10, r=0.1, f=0.1, p=0.8) did not predict baseline BMI (kg/m$^2$). However, fasting PYY at final follow up predicted the BMI at that assessment (n=19, r=0.5, f=4.6, p=0.046) and accounted for 17% of the total variation observed (Table 4-15 and Figure 4-12). Examination of residuals supported the validity of the model. Cook’s distance was <1 in all cases, the leverage statistic was 0.05 (expected 0.11), and DFBeta for the constant and each independent variable was <1. 5% of cases had studentised residuals > ±1.96 but <2.58. Standardised residuals were all within ±2. The regression equation was:

\[
\text{Ln(x) BMI (kg/m}^2\text{) at final assessment} = 5.35 + (-0.37 \times \text{Ln(x) fasting PYY (pg/ml) on day 6})
\]

Fasting PYY concentrations at day 6 did not predict the minimum BMI at one to two years (n=9, r=0.1, f=0.1, p=0.8) or the BMI at the final follow up assessment (n=9, r=0.05, f=0.03, p=0.9). Furthermore, fasting PYY at baseline (n=10, r=0.3, f=0.8, p=0.4) and day 6 (n=10, r=0.2, f=0.4, p=0.6) did not predict the subsequent change in BMI over the study period.
The change in PYY from baseline to day 6 predicted both the minimum BMI at one to two years (n=9, \( r=0.68, f=6.1, p=0.04 \)) and the BMI at the >5 year assessment (n=9, \( r=0.8, f=10.1, p=0.01 \)), and accounted for 40% and 53% of the total variation at each time point (Table 4-15 and Figure 4-13). Furthermore, the change in PYY from baseline to day 6 predicted subsequent change in BMI across the entire study period (n=9, \( r=0.74, f=8.7, p=0.02 \)) and accounted for 49% of the total variation.

Table 4-15  Univariate regression analyses outcomes for fasting PYY (absolute concentrations and change) against BMI and change in BMI (dependent variables)

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>BMI (kg/m²)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>Final follow up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td>Independent variable</td>
<td>P value</td>
<td>Constant</td>
<td>Independent variable</td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td>PYY (pg/ml) *</td>
<td>4.0</td>
<td>-0.04</td>
<td>0.8</td>
<td>5.3</td>
<td>-0.4</td>
<td>0.046</td>
<td></td>
</tr>
<tr>
<td>Change in fasting PYY (pg/ml) from baseline to day 6</td>
<td>BMI (kg/m²)</td>
<td>One to two year minimum BMI</td>
<td>Final follow up</td>
<td>Constant</td>
<td>Independent variable</td>
<td>P value</td>
<td>Constant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Constant</td>
<td>-0.9</td>
<td>0.042</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.53</td>
<td>-1.27</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Baseline to minimum</td>
<td>Baseline to final follow up</td>
<td></td>
<td>Constant</td>
<td>0.36</td>
<td>0.4</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.26</td>
<td>0.73</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* paired with baseline or follow up BMI
Examination of residuals supported the validity of these models. Cook’s distance was <1 in all cases, the leverage statistic was 0.11 (expected 0.22), and DFBeta for the constant and each independent variable was <1. The standardised and studentised residuals all had values of less than ±2. The regression equations were:

\[
\text{Ln(x) minimum BMI (kg/m}^2) = 3.42 + (-0.9 \times \text{change in Ln(x) fasting PYY (pg/ml) from baseline to day 6})
\]

\[
\text{Ln(x) minimum BMI (kg/m}^2) = 3.53 + (-1.27 \times \text{change in Ln(x) fasting PYY (pg/ml) from baseline to day 6})
\]

\[
\text{Change in Ln(x) BMI (kg/m}^2) \text{ from baseline to final follow up} = 0.26 + (0.73 \times \text{change in Ln(x) fasting PYY (pg/ml) from baseline to day 6})
\]
Figure 4-13  Regression variable plot to show Ln(x) PYY (pg/ml) on day 6 against a) Ln(x) minimum BMI (kg/m²), b) Ln(x) BMI (kg/m²) at final follow up, and c) change in Ln(x) BMI (kg/m²) from baseline to final follow up

a) 

b) 

c)
4.2.4.8.4 Amylin

Fasting amylin at each time point, or the change in fasting amylin between time points did not predict BMI outcome or change in this study. Neither fasting amylin at baseline \((r=0.04, \ f=0.4, \ p=0.8)\) or final follow up \((r=0.1, \ f=0.3, \ p=0.6)\) predicted BMI at that time point. Furthermore, fasting amylin concentrations at day 6 did not predict either minimum BMI at one to two years \((r<0.01, \ f<0.01, \ p=0.96)\) or the BMI at the final follow up assessment \((r=0.04, \ f=0.04, \ p=0.9)\). Fasting amylin at baseline \((r=0.3, \ f=2.7, \ p=0.1)\) and day 6 \((r=0.28, \ f=2.0, \ p=0.2)\) did not predict the subsequent change in BMI over the study period. Furthermore, the change in amylin from baseline to day 6 did not predict either the minimum BMI \((r=0.17, \ f=0.7, \ p=0.4)\) or final BMI \((r=0.18, \ f=0.81, \ p=0.4)\), and did not predict the change in BMI from baseline to minimum \((r=0.07, \ f=0.1, \ p=0.7)\), minimum to final follow up \((r=0.1, \ f=0.2, \ p=0.7)\), or over the entire study period \((r<0.01, \ f<0.01, \ p=0.99)\).
4.2.5 Discussion

RYGB results in significant weight loss in most who undergo the procedure, which is associated with improvements in glucose homeostasis (chapters 1.3.2 and 1.3.3). Furthermore, these effects appear to be durable in the majority of people (chapter 3.1). In contrast, whilst caloric restriction by any method will result in weight loss if energy intake is decreased below energy expenditure, non-surgical methods are associated with a high rate of weight regain. Therefore, whilst the underlying mechanism may be similar (primarily caloric restriction), there appears to be additional factors subsequent to surgical rather than non-surgical methods that result in these different long term outcomes.

Alterations in the function of hormones that play a role in energy homeostasis must be considered as possible contenders to explain or partially explain this difference. As discussed in chapter 1.1.2.3 (page 11), a large number of hormones secreted by the adipocyte or throughout the gastrointestinal tract are integral in the regulation of appetite and satiety, and matching energy intake to requirements. Furthermore, bariatric surgery is known to effect the secretion and function of these hormones (chapter 1.4.2 (pages 99-104)). This study was therefore designed to initially explore whether alterations in adipocyte or gastrointestinal hormones induced by bariatric surgery, may underlie the significantly greater maintenance of weight loss after surgery when compared to other methods of caloric restriction.

4.2.5.1 Leptin

Fasting leptin concentrations fell after RYGB, with an increased reduction by day 6 appearing to predict a lower BMI at early and late follow up. However, surprisingly, fasting leptin concentrations did not predict concurrent BMI at any time point in this study.

Leptin circulates in proportion to the number of adipocytes. As BMI is also strongly associated with adipocyte volume, leptin concentrations are closely related to BMI. However, concentrations fall rapidly at the onset of severe caloric restriction, prior to any change in adiposity, and help to initiate the physiological response to starvation. Thus, the significant decrease in leptin concentrations by day 6 after RYGB in this study is a predictable response to reduced energy intake. Furthermore, this early reduction is consistent with most but not all published studies of RYGB. Whilst a number of published studies have reported on the leptin trajectory after surgery, it is
perhaps not appropriate to conduct such an analysis here, as it is impossible to conclude how much of this early reduction, resulting in leptin concentrations comparable to those seen at >5 years of follow up, can be attributed simply to the acute response to starvation. However, the fasting leptin concentration at day 6 positively predicted the BMI at both the 1-2 years and >5 years follow up, such that a greater fasting leptin at day 6 was associated with a higher BMI at each follow up assessment. In contrast, the change in leptin concentrations from baseline to day 6 did not predict weight outcomes.

This data therefore suggests that the reduction in leptin concentrations by day 6 predicts weight outcomes thereafter. However, there are clear concerns with this conclusion. Firstly, the absence of any association between BMI and serum leptin concentrations at baseline in this study is in contrast to the published literature, and raises concerns as to the validity of other conclusions. It is possible this lack of association relates simply to the small sample size; certainly the relationship between fasting leptin concentration and BMI at the >5 year assessment approached statistical significance (p=0.09), but the magnitude of this relationship (r=0.35) was far less than observed in other studies.940,941,942 Furthermore, the reduction in fasting leptin concentrations with starvation is considered an adaptive mechanism that partially initiates the response to sudden reduced energy availability. Assuming this to remain the case in this context, the apparent greater weight loss with lower leptin levels would be somewhat paradoxical. Furthermore, whilst it is tempting to suggest that a greater reduction in leptin concentrations early after surgery may indicate that the intervention has resulted in greater reductions in caloric availability, in reality the energy intake of each person is closely regulated up until day 6 after surgery, and therefore any possible differences in procedure effectiveness (e.g. pouch size, tract transit time) would not be expected to be evident as yet. However, as discussed above, this apparent relationship between fasting leptin at day 6 and future BMI may simply reflect the well established relationship between fasting leptin and BMI in humans, despite this not being observed at baseline in this study.

Nonetheless, if the fasting leptin concentration at day 6 was truly predictive of subsequent weight loss, we should expect the change in leptin concentrations from baseline to day 6 to also positively predict subsequent weight loss, as baseline values, albeit not in this study, should associate with BMI at that point. Whilst not observed in this study, the prediction of final BMI by the change in leptin concentrations by day 6 did approach statistical significance, however, with a p value of 0.06. Further study is therefore justified to test whether any such relationship exists.
4.2.5.2 Ghrelin

Ghrelin concentrations had fallen significantly at the >5 year assessment when compared with baseline. However, the absolute ghrelin concentration or change in ghrelin concentrations between time points did not predict weight outcomes.

Ghrelin is an appetite initiating hormone that therefore circulates at the highest concentrations when fasting. Obesity is associated with reduced ghrelin levels, although the normal suppressive effect of food on ghrelin secretion is blunted. As discussed in chapter 1.1.2.3.1, circulating ghrelin exists in acylated and des-acylated isoforms, with acylated ghrelin accounting for approximately 10% of total ghrelin concentrations. As only active (acylated) ghrelin was measured in this study, the circulating concentrations at baseline appear similar to those in other studies reporting active or total ghrelin concentrations immediately prior to bariatric surgery.

Studies reporting the effect of RYGB on circulating ghrelin concentrations have produced contrasting results with both no change, and reduced concentrations reported. In this study, acylated ghrelin concentrations had not changed at 6 days but were significantly lower at the >5 year follow up assessment. It is possible that this apparent discordancy relates to both the timing of post operative assessments, and the reporting of total versus acylated ghrelin. As in our study, the only two other studies reporting changes in acylated ghrelin levels demonstrated a reduction after RYGB, with the earliest time point at which the hormone was measured being 6 weeks after surgery. To my knowledge, this is the first study to report acylated ghrelin concentrations within 6 weeks of surgery and it is therefore not possible to compare the day 6 result against published data. With the exception of one study, no other study reported significant changes in total ghrelin concentrations within 12 months of surgery. It should be noted that, whilst Korner et al reported a trend to reducing total ghrelin concentrations prior to this time, the concentrations were not statistically different from baseline within the 12 month post-operative period. It is therefore possible, that reductions in total ghrelin are not evident for some time after RYGB, which is perhaps counterintuitive to the concept that the reduced ghrelin concentrations relate directly to gastric anatomical changes at surgery as clearly seen after SG. If this were the case, the apparent reduction in acylated ghrelin may be compensated by an increase in circulating des-acylated ghrelin, as demonstrated in some studies, and accounting for the early stable total ghrelin concentrations.

Irrespective of whether absolute ghrelin concentrations were altered by RYGB, the change in ghrelin concentrations between time points over the study period did not predict weight outcomes in this
This study therefore supports the conclusions drawn from ghrelin knockout mice models that ghrelin plays little role in weight loss after RYGB.528

4.2.5.3 Amylin

Fasting amylin concentrations were significantly lower at day six in comparison to baseline, and remained lower at the >5 year follow up. However, fasting amylin concentrations did not predict either the BMI at any time point, or the change in weight over the study period.

As discussed in chapter 1.1.2.3.3 (page 14), amylin is secreted by pancreatic beta cells in response to a carbohydrate load; therefore, amylin secretion changes alongside changes in insulin concentrations.117,119 Fasting amylin concentrations increase with weight gain, with a greater post prandial rise in the context of obesity associated with insulin resistance.120 Increased post prandial amylin concentrations appear to reduce food intake during a meal, decrease gastric motility and emptying, and inhibit glucagon secretion.117,119,125 Furthermore, amylin appears to augment leptin and PYY signalling, thereby increasing satiation.945,946

Fewer studies have reported changes in amylin concentrations after bariatric surgery than changes in other hormone concentrations.947 Whilst some studies have shown no change in fasting amylin concentrations after RYGB,634,651,948 others have shown reduced fasting concentrations and reduced post-prandial area under the curves in humans.665,949 One study reported no change in fasting amylin concentrations at 15 days, but a significant reduction when assessed at 12 months.717 In contrast, a study using a rat model reported no change in fasting amylin concentrations and a marked increase in post prandial elevations.550 This discrepancy does not appear to relate to the timing of assessment as a reduction in fasting amylin concentrations was evident at 6 days in this study and one month in two others,665,949 but was not evident within 1 month in other studies.634,651,717,948 Furthermore, it appears unlikely that this discordancy can be attributed to the glycaemic status of patients at baseline. As amylin is secreted by the beta cell alongside insulin, amylin concentrations are expected to fall in parallel with progressive beta cell failure observed in longstanding type 2 diabetes.120 Thus, if a change in fasting amylin was induced bariatric surgery, this may be less apparent in those with longstanding type 2 diabetes where hyperinsulinaemia is less likely to be present at baseline. However, two of the studies reporting no early change in fasting amylin concentrations included only obese participants with normal glucose tolerance at baseline,634,948 whilst the mean pre-surgical duration of type 2 diabetes was
relatively short (approximately 5-8 years) in participants in the two studies that enrolled participants with established dysglycaemia.\textsuperscript{651,717}

Irrespective of the above literature, amylin does not appear to play a significant role in weight loss following RYGB, consistent with the finding in this study that fasting amylin did not predict weight outcomes. Whilst this study and a few others have reported reduced fasting amylin concentrations, this is likely simply to relate to reduced beta cell output with weight loss associated improved insulin sensitivity. Furthermore, given amylin’s apparent satiating effect in humans, reduced concentrations induced by surgery would not be favourable to weight loss or weight loss maintenance.

4.2.5.4 PYY

Fasting PYY concentrations were similar at baseline, day six, and at the >5 year follow up assessment. However, fasting PYY concentrations at the >5 year follow up assessment predicted BMI at that time point, such that the BMI decreased with an increasing fasting PYY concentration. Perhaps in contrast to this finding, the change in PYY concentrations between baseline and day 6 predicted the BMI at 1-2 and >5 years of follow up, and the change in BMI over the study period, such that a greater reduction in PYY concentrations from baseline to day 6 predicted a lower BMI at each subsequent time point and a greater reduction in BMI over the study period.

PYY is an anorexigenic hormone produced widely throughout the lower digestive tract in response to a meal (see chapter 1.1.2.3.2 (page 13)).\textsuperscript{110} PYY concentrations are elevated 30-60 minutes after the commencement of a meal, with satiating effect evident through studies reporting a clear reduction in food intake when PYY is infused throughout a meal.\textsuperscript{115} Obesity is associated with both a reduced fasting PYY concentration and a blunted response to meal ingestion.\textsuperscript{116} It is therefore possible that the relationship between fasting PYY and BMI at the >5 year assessment reflects simply the established negative relationship between PYY and weight in non-surgical populations.

The literature reveals discordant results with respect to the effect of RYGB on fasting PYY concentrations with some studies demonstrating a clear reduction,\textsuperscript{610,617} others reporting a clear increase,\textsuperscript{619,657,667} and other studies including our study reporting no change in fasting PYY concentrations.\textsuperscript{660,665} However, there was a trend to reducing PYY concentrations from baseline through to the >5 year assessment in our study, with the mean fasting PYY concentration at >5 years
being 25% lower than the mean fasting PYY at baseline. Whilst 19 samples were available at the >5 year follow up assessment, only nine of these participants had comparable samples at baseline. Both of the other listed studies that reported no change in fasting PYY concentrations after RYGB were also limited by small sample sizes of six and eleven participants.\textsuperscript{660,665} Indeed, one of these studies reported a fasting PYY at 12 months that was 21% lower than baseline values, although this was not statistically significant.\textsuperscript{665} It is therefore quite possible that the failure to demonstrate any change in circulating fasting PYY concentrations in our study and others is a limitation of the sample size, although it should be acknowledged that the sample size in all listed studies was relatively small.

All studies reporting the PYY response to a meal reported a significantly increased area under the curve after RYGB.\textsuperscript{610,617,619,657,658,659,660,663,665} Furthermore, the increase in post prandial PYY concentrations by day six predicted subsequent weight loss by 52 weeks after surgery in one study,\textsuperscript{658} and poor and good weight loss after RYGB could be discriminated by the PYY response to a meal at 2 years after surgery.\textsuperscript{659} In contrast, no correlation between PYY concentrations in the fasting or fed state and weight loss at 52 weeks was observed in one study.\textsuperscript{659} In our study, fasting PYY concentrations at the >5 year follow up assessment predicted BMI at that time point, a finding supported by one other study after both RYGB and BPD, albeit in the context of an increase in PYY concentrations.\textsuperscript{667} Neither study listed above that observed a relationship between post meal PYY responses and weight loss after RYGB reported fasting PYY concentrations, and therefore did not consider whether this relationship was persistent for fasting samples. As noted above, it should also be acknowledged that increasing BMI is associated with decreasing fasting PYY concentrations in non-surgical populations, although the PYY response to a meal is also blunted in this group and may be restored by RYGB. To further support a significant role of PYY in longer term weight outcomes after RYGB, le Roux and colleagues recruited 13 participants who had undergone RYGB and inhibited PYY secretion with octreotide treatment.\textsuperscript{659} A significant increase in food intake was evident in comparison to when saline was instead infused, and this was associated with a clear reduction in satiety scores during an observed meal.

The perhaps counterintuitive finding that a greater reduction in fasting PYY early after surgery predicts greater longer term weight loss should be interpreted with caution given the small sample size of nine participants. However, as the majority of interest in the physiological role of PYY thus far has been in the fed state. Whilst this study found no statistical difference between PYY concentrations at baseline and >5 years after RYGB, there was a trend to a reduction. If a fall in fasting PYY concentrations truly is observed after RYGB, this possible relationship should be re-examined, and the function of PYY in the fasting state should be re-explored.
4.2.5.5 Comparison with hormonal responses to non-surgical weight loss

This study and others have therefore demonstrated that severe caloric restriction through RYGB results in a reduction in the concentrations of leptin, ghrelin, CCK, and amylin, whilst the changes in fasting PYY concentrations are less clear. It is of interest to consider hormonal responses to non-surgical caloric restriction, and whether any differences may explain the more durable nature of surgically induced weight loss.

Leptin, PYY, cholecystokinin, and amylin concentrations fall in response to non-surgical caloric restriction, whilst circulating concentrations of ghrelin and GIP increase. Furthermore, this response appears to persist for many months or years after the initial period of weight loss. In combination with decreases in total, resting, and physical energy expenditure, these adaptive responses to caloric restriction favour weight regain.

Therefore, the apparent difference between the gut peptide responses to surgical and non-surgical caloric restriction include opposite changes in fasting and post-prandial ghrelin, CCK, and PYY concentrations. Whilst the increased ghrelin and reduced CCK and PYY observed after non-surgical weight loss favour weight regain, the decreased ghrelin and increased post-prandial CCK and PYY observed after RYGB favour weight loss maintenance. This study supports that reductions in fasting ghrelin and PYY concentrations are observed after RYGB.

4.2.5.6 Study limitations

As noted above, the sample size in this study was small given the retrospective nature of the study and the limited number of suitable participants. However, data from this study will be used to adequately power future studies in this field.

Because of the retrospective nature of this study we were unable to assess all hormones of interest in weight loss outcomes following bariatric surgery. Ideally the incretin hormones, GLP-1 and GIP, would be assessed and certainly show promise as additional components in the mechanism of improved glucose homeostasis following surgery (chapter 1.4.4.3). However, the incretin hormones have a short half-life in plasma as a result of rapid deactivation by dipeptidyl peptidase (DPP) enzymes; analysis of incretin concentrations therefore requires that a DPP inhibitor is added to the sample at collection.
which did not occur at baseline or day 6 in this study. Further work planned given the outcomes of this study will be prospective in nature and will thus allow the inclusion of additional hormones of interest.

Furthermore, we were unable to assess the response of each of these hormones to meal ingestion, as appropriate studies were not conducted at the historical time points. This is clearly of importance when considering the function of PYY and ghrelin and will be included in future studies.
4.2.6 Conclusion

Non-surgical weight loss results in decreased circulating concentrations of leptin, PYY, CCK, and amylin, with increased concentrations of ghrelin. This study supports other data demonstrating reduced fasting concentrations of leptin, amylin, and ghrelin following RYGB surgery, with no clear changes in fasting PYY observed. Furthermore, weight outcomes were predicted by the early change in PYY following surgery, although this finding requires further study given the small study sample. The adaptive gut hormone response to surgical caloric restriction differs from that observed after non-surgical caloric restriction in that favourable effects on ghrelin, PYY, and CCK, all promoting weight loss maintenance, are observed after surgery but not after non-surgical interventions. Further research is required to clarify the mechanisms by which these hormonal changes occur, and whether differences in weight outcomes after RYGB may relate to differing effects on gut peptide physiology. Furthermore, as the early favourable metabolic consequences of RYGB appear to be mostly reproducible through matched non-surgical caloric restriction, further research to clarify whether the additional longer term effects can be mimicked through pharmaceutical manipulation of these gut peptides would be of significant interest.
Chapter Five: Summary

5.1. Summary

5.2. Proposed further research
 Chapter 5: Summary

5.1 Summary

The body of work presented in this thesis was conceived and initiated in 2012. At that time, whilst bariatric surgery was in widespread use for the management of obesity and to a lesser extent type 2 diabetes, high quality evidence to support this intervention was lacking. Since then a number of high quality randomised controlled trials have been undertaken and published that support the effectiveness of bariatric surgery in this clinical context. Consequently, a number of national and international organisations now advocate the use of bariatric surgery in obese patients with type 2 diabetes, and furthermore, suggest that it may be provided at an earlier stage than previously considered.405,961

The undertaking of a study designed to report the longer term outcomes after bariatric surgery is therefore timely, as, in light of these recent policy changes, a greater number of patients will undoubtedly undergo surgery, and many will be young enough to reasonably expect several decades of post-surgery life expectancy. In the long term follow up study (chapter 3.1, pages 134-242) I have shown that RYGB surgery is an effective treatment for obesity and type 2 diabetes and furthermore, that it is durable over a 10 year follow up period. Specifically, this study demonstrated a mean weight loss of 29.6% (38.5kg) and that weight regain over the study period was not associated with the duration of follow up. No patient with normal glucose tolerance prior to surgery progressed to type 2 diabetes at follow up, whilst 86% of those with pre-operative dysglycaemia (prediabetes or type 2 diabetes) had either normal glucose tolerance or significantly improved glucose tolerance (partial remission by criteria) at follow up. 28% of participants with pre-operative type 2 diabetes remained with type 2 diabetes at follow up, a figure that compares favourably to reported outcomes in other similar studies (chapter 3.2, page 243). Significant improvements in blood pressure and lipid levels were observed, along with a reduction in the frequency of depression, gout, and sleep apnoea following surgery. No clear effects on cardiovascular endpoints was observed, but this study was not designed to adequately explore this. Contrary to popular opinion, vitamin B12 deficiency was not clearly more common after surgery than expected in this population based on baseline features, whilst copper deficiency was not observed. Zinc deficiency does however appear to be common (49% of participants); further research will be required to explore the best method with which to prevent morbidity as a result of this after surgery. Equally as important as the above findings, quality of life was improved in this population to matched non-surgical controls, and almost all participants were positive about their decision to have undergone surgery.
This study therefore supports the contemporary view that RYGB is a highly effective treatment for established obesity and type 2 diabetes when compared against existing non-surgical strategies, and furthermore that bariatric surgery should considered at an earlier stage in appropriate patients. In chapter 3.2, however, I have highlighted one of the methodological issues that pervades throughout the literature in this field, which collectively still hamper efforts to definitively place bariatric surgery in the treatment paradigm for obesity associated with type 2 diabetes. A number of definitions for the diagnosis of states of glucose tolerance both before and after bariatric surgery are employed, and frequently are different enough to render comparative analysis of studies reporting outcomes after bariatric surgery meaningless. This study supports the widespread enforcement of one standardised set of definitions in this context, with those proposed by the American Diabetes Association seemingly the most reasonable.

However, as effective as bariatric surgery is, it does not address the root of the problem which is a rapid increase in the prevalence of obesity in most societies. As discussed in chapter 1.1.1 (page 2), obesity and type 2 diabetes are now reaching epidemic proportions with no convincing evidence to suggest that this increase in prevalence is slowing. The major focus of research in the field of obesity and type 2 diabetes should therefore be in preventing these conditions developing in the first place. Bariatric surgery provides an intriguing insight into the pathophysiology of both of these conditions. In chapter 4 I have reported outcomes from two studies designed to further explore the mechanisms by which bariatric surgery is effective. Whilst studies of this nature may help to optimise outcomes following bariatric surgery, they may also provide important insights into these two conditions that will guide preventative interventions. Of particular relevance here is the clear difference between longer term weight outcomes in those people who initially lose weight by surgical or non-surgical means. Whilst weight regain is observed in the majority of those who lose a significant proportion of body weight through non-surgical caloric restriction, it does not occur in the majority of those who achieve weight through surgical means. Our present understanding of the mechanisms underlying bariatric surgery does not sufficiently explain this discordancy. In chapter 4 I have reported outcomes from two small studies that exploring these mechanisms in further detail. Firstly, I have shown that, whilst hormonal changes induced acutely as part of a stress response to RYGB surgery normalise rapidly, inflammation is likely to persist, and does therefore need consideration when performing studies to explore the mechanism by which bariatric surgery induced early dramatic improvements in glucose homeostasis. Secondly, I have performed an initial study exploring whether differences in the circulating concentrations of gut peptides in the fasting state may underlie differences in weight outcomes after RYGB. As discussed below, this research question will be developed further in the coming years.
I intend to continue the lines of research established in this thesis over the coming years. Of primary interest will be further work exploring the mechanisms underlying sustained weight loss maintenance or conversely weight regain following bariatric surgery, and comparing these mechanisms to those that drive weight regain commonly after dietary interventions. I believe there is further work to be done to fully describe the role of alterations in gut peptide physiology in this context. In particular, work presented in this thesis and elsewhere supports a favourable role of PYY, ghrelin, and leptin along with GLP-1, GIP, and CCK. I plan to study in further detail the physiology of these peptides following bariatric surgery in those who have achieved differing weight outcomes, and complement this with work to explore the contribution any differences may make to the overall picture. Furthermore, our research group has an interest in energy expenditure, and have recently developed techniques to study this in greater detail. I plan to further quantify any changes in energy expenditure that bariatric surgery may induce, above and beyond those predicted by weight loss. From a clinical perspective, I am to further contribute to the longer term literature around sleeve gastrectomy which is now performed in greater numbers in my institution. As discussed in chapter 1, the evidence underlying the mechanisms and outcomes after sleeve gastrectomy is less established than for LAGB or gastric bypass. It is plausible that sleeve gastrectomy may become the preferred bariatric surgery in obese patients with type 2 diabetes, due to lower costs and reduced complication rates when compared with RYGB. Clearly therefore, longer term outcomes and clinical aspects of surgery follow up require further clarification.

In conclusion, the work presented in this thesis supports that RYGB is an effective and durable treatment for obesity and type 2 diabetes, and is not associated with a high long term risk of complications. RYGB, and other forms of bariatric surgery with an equally compelling evidence, should be employed more frequently in the management of established obesity and type 2 diabetes. Further research into the mechanisms underlying this therapeutic effect is required both to optimise outcomes following surgery, and, perhaps more importantly, to fully clarify the pathophysiology of these two increasingly prevalent disorders.
i. Appendix A

Appendix i-1 Ethics approval letter

29 June 2012

Dr Jeremy Krebs
Diabetes, Endocrine and Research Centre
Capital and Coast DHB
PO Box
Wellington

Dear Dr Krebs

Re: Ethics ref: MEC/11/04/040 (please quote in all correspondence)
Study title: Long term follow up on metabolic characteristics and nutritional aspects following gastric bypass surgery compared with a non-surgical group
Investigators: Dr Jeremy Krebs, Dr John Wilson, Ms Amber Parry Strong, Professor Jim Mann, Professor Richard Stubb, Associate Professor Mark Weatherall
Site: Capital Coast District Health Board

This study was given ethical approval by the Multi-region Ethics Committee on 19 June 2012.

Approved Documents

- NAF
- Signed Part 4 for Jeremy Krebs, Wellington Hospital
- Signed Form A
- part 5: Use of Human Tissue
- Signed locality Assessment for Wellington Hospital
- Information Sheet Version 2, dated 21 July 2011
- Consent Form Version 2, dated 21 July 2011
- Interview Version 3, dated 14 March 2012
- Three Day Diet Record
- Letters of Invitation
- Invitation Version 3 dated 5 May 2012
- Letter from RAG-M

Noted comments to researcher:

- That the investigator undertake telephone follow up to the recruitment letter to maximise participation; and
RESEARCH ADVISORY GROUP MAORI (RAG-M)

6 May 2011

Dr Jeremy Krebs
Level 5
Grace Neil Block
Wellington Hospital

Tena koe Dr Krebs

RAG-M 2011/129 - Letter of Endorsement

On behalf of the Research Advisory Group Māori I write in relation to your study titled Long term follow up on metabolic characteristics and nutritional aspects following gastric bypass surgery compared with a non surgical group.

You have supplied a RAG-M coversheet, an ethics application to the Multi-Region Ethics Committee, patient information sheet, interview questionnaire and consent forms.

Our reading of your proposal characterises the research as:

- A case control study, with cases defined as having had Roux-en-Y Gastric Bypass (RYGB) surgery compared with a group not undergoing Bypass surgery.
- Participants will be recruited from the Wakefield Obesity Clinic database (~800 cases, 150 controls) of these about 5% are expected to be Māori.
- Eligible patients will be invited by letter to participate and once consented they will undergo an interview, physical assessment and blood & urine tests.

We note that:
- you are seeking approval from the Multi Region Ethics Committee;
• you will advise the Research Committee of the CCDHB of the conduct of this research.

Recommendations/concerns

Given that this topic is of high significance to Māori we highly recommend and encourage that there be active recruitment of Māori participants. We would expect that:

• you would ensure that any Māori who participate are well informed and supported, including their whanau as appropriate;
• you would recognise any cultural expectations and seek to meet these expectations responsively;
• you treat any blood and tissue samples taken consistently with the CCDHB policy on human samples which is endorsed by this Committee.
• as the disposal of blood and specimens may be an issue for Māori participants you are advised this should be carefully discussed at the consent stage and written consent obtained.

We note there is no evidence of Māori consultation either in the design of this project, or plans for any formal ongoing involvement of Māori advisors/researchers. Given the significance of this issue we would strongly recommend, you seek Māori advice prior to the commencement of the study and again prior to the dissemination of the study results.

Whānau Care Services WCS: We also note you have not obtained a support agreement with Whanau Care Services. You will be aware that WCS operate within the Wellington Regional Hospital. WCS have a responsibility to both patients of the hospital and staff. Given that this research may operate within the hospital campus, or involve CCDHB staff, we would expect that you:

a) advise WCS of the operation of this research project
b) negotiate with WCS the nature of their support,
and c) notify us of the arrangements which are in place. Please email wcs@ccdhb.org.nz

We would be interested in receiving a copy of the final report of your study (March 2015. We would also like a report sent to us detailing the total number of Māori patients recruited to this study.

On confirmation that the expectations specified above are understood and accepted by you we will be happy to endorse your research proposal. Please confirm these details with the RAG-M secretary, Ms Vanessa Mill by email to ragm@ccdhb.org.nz.

We thank you for consulting RAG-M and wish you well in your study.

Naaku noa na,

Jack Rikihana

Chair RAG-M
May 21st 2011

To Jack Rikihana, Chair RAG-M

Re: RAG-M 2011/129

In response to your recommendations and concerns

The participants for this study are defined by those who have either had gastric bypass surgery or were referred and seen for consideration of gastric bypass surgery by Prof Stubbs. We will be actively recruiting those Māori participants who are within these parameters to take part in this follow up study as we too feel that this project has high significance to Māori.

We will ensure that any Māori who participate are well informed and supported including their whanau as appropriate. We have the support of Whanau Care Services at CCDHB (letter attached). We encourage all participants to have their support networks and whanau present for any discussions, interviews or assessments if requested.

We would seek to recognize and meet any cultural expectations. All our research nurses have had training in cultural responsibility and interacting with in the context of Maoritanga and the principles of the Treaty of Waitangi.

We treat any blood or tissue samples taken consistent with the CCDHB policy on human samples. All samples will be processed within commercial laboratories that all have robust policies regarding blood and tissue sampling handling, storage and disposal

All Māori will have the opportunity as part of the consent process to discuss the disposal of blood and specimens. Again all samples will be sent to accredited commercial laboratories who all have robust specimen disposal policies

Maori consultation and support has been obtained for various projects performed at Wakefield Obesity Clinic and for collaborative projects between Wakefield Obesity Clinic and the Wellington hospital Diabetes centre. Consultation has taken place in the past with Te Kaunihera Kaumatua in respect of the Wakefield Diabetes research programme, which resulted in their support for the programme being given. They have not been involved in the conception and design of individual studies.

Your endorsement of our project is appreciated

Dr Jeremy Krebs
Principal Investigator
Appendix i-4  Letter of invite to those who had undergone bariatric surgery

Richard S Stubbs
Visc, FRACS, FRACSS
GI & Hepatobiliary Surgeon

1 May 2014

Dear xxxxxxx

Some years ago you had a gastric bypass performed by me at Wakefield Hospital. We are very interested to know how you are, and to document the results of the surgery up to 20 years later. For this reason I and a number of colleagues in the diabetes department at Wellington Hospital are conducting a study on those of my patients operated between 1990 and 2007, looking particularly at the long term metabolic and nutritional outcomes after gastric bypass surgery. Once completed, this will be the most comprehensive and long term study of its kind in the World and the results are likely to be very important in guiding the way in which surgery is offered to individuals in the future. I hope you will agree to take part and help shape the future management of severe obesity in others, both in New Zealand and elsewhere.

Please read the enclosed information sheet regarding the study and indicate your willingness or otherwise to participate with your reply in the enclosed postage paid envelope.

With best wishes

Yours sincerely

Professor Richard S Stubbs
Appendix i-5  Letter of invite to those who had not undergone bariatric surgery

Richard S Stubbs
MB, FACS, FERACS
GI & Hepatobiliary Surgeon

Date

Dear

I am writing to invite you to take part in a study being performed by me and a number of colleagues in the diabetes department at Wellington Hospital. The study is looking at the long term metabolic and nutritional status of individuals who have or have not undergone surgery for severe obesity. Some years ago you consulted me about the possibility of having gastric bypass surgery, but did not proceed. Providing you have not had surgery somewhere else since that time, we would be interested in having you participate in this study, so we may make a comparison with a large group who did undergo the surgery with me. Once completed, this will be the most comprehensive and long term study of its kind in the World and the results may be very important in guiding the way in which severely obese individuals are managed in the future. I hope you will agree to take part and help shape the future management of severe obesity in others, both in New Zealand and elsewhere.

Please read the enclosed information sheet regarding the study and kindly reply in the enclosed postage paid envelope.

Yours sincerely

Professor Richard S Stubbs

Diabetes Research
Diabetes, Endocrine and Research
Level 5, Grace Neil Building, Private Bag 7902, Wellington South (Tel: 04 8062458)
Information sheet

Long term follow up on metabolic characteristics and nutritional aspects following gastric bypass surgery compared with a non surgical group.

Principal Investigator-
Dr Jeremy Krebs, Clinical leader, Endocrine, Diabetes and Research Centre, Wellington Hospital, Wellington.

Co-Investigators
Dr John Wilson, Research Fellow, Endocrine, Diabetes and Research Centre, Wellington Hospital, Wellington;
Dr Amber Parry-Strong, Dietician, Endocrine, Diabetes and Research Centre, Wellington Hospital, Wellington;
Dr Richard Carroll, Research Fellow, Endocrine, Diabetes and Research Centre, Wellington Hospital, Wellington;
Professor Richard Stubbs, Wakefield Clinic, Wakefield Hospital Wellington;
Professor Mark Weatherall, Statistician, University of Otago, Wellington;
Professor Jim Mann, University of Otago, Dunedin.

You are invited to take part in the above study. Your participation is entirely voluntary (your choice). You do not have to take part in this study, and if you choose not to take part this will not affect any future care or treatment. If you do agree to take part in the study, you are free to withdraw from the study at any time, without having to give a reason, and this will in no way affect your future or continuing health care.
About the study

You have been selected either because you have had a gastric bypass at Wakefield Hospital between 1990 and 2007 or you have had a referral made to Mr Richard Stubbs at Wakefield Hospital, Wellington or its affiliates in Christchurch for consideration of gastric bypass surgery.

The aims of the study are to look at the long term follow up of subjects with obesity that have had or not had gastric bypass surgery. The principal factors we will be looking at are metabolic and cardiovascular risk factors such as weight, blood pressure, glucose control or diabetes, lipids (fat and cholesterol) and nutritional aspects such as dietary intake, nutritional supplementation and micronutrient deficiency. We wish to compare the surgical group to the non surgical group.

There is increasing interest in New Zealand regarding the use of gastric bypass (a type of bariatric surgery) in regards to the management of obesity and other related co morbidities. Most bariatric surgery in New Zealand has been done in the private sector with only small numbers being done in the public system. The Associate Minister of Health, Tariana Turia, has recently announced increased funding for bariatric surgery over the next 2-4 years. Already it is known that bariatric surgery is the only long term effective method for weight loss in obese subjects. In the USA over 400,000 bariatric surgery operations are being done currently every year.

There is a wealth of information on bariatric surgery and its effects on improvements in blood pressure, diabetes, lipids, and weight over the short term of 1-2 years. Long term data is however lacking.

Two major studies show decreased mortality at 10 years post surgery but they largely used data from operations not routinely performed today. Follow up data from the largest of these studies also suggests type 2 diabetes is resolved in 80% of subjects at 2 years but only in about 30% at 10 years.

Nutritional data at longer term follow up is also lacking. This is also important as the gastric bypass operation is a malabsorptive procedure (i.e. it inhibits the absorption of some nutrients). Some micronutrients are stored in the body and it may be years before that deficiency manifests itself.
For this study we wish to assess the long term effect of gastric bypass surgery versus not having a gastric bypass (or other form of bariatric surgery eg banding, sleeve, gastroplasty).

What will happen during the study

To do this we require one interview where we ask some demographic details, perform a Quality of Life assessment, obtain a medical history, medication history and a basic examination. You do not have to answer all the questions, and you may stop the interview at any time. These will be performed at the Endocrine, Diabetes and Research Centre at Wellington Hospital, Wellington (or other approved sites as per your location). This should take about 2 hours. You will also be asked to perform some fasting blood tests and some urine tests at your local laboratory and to complete a 4 day food diary at home. We plan to run this study over a period of 3 years for the data collection. The results of these will be collated and direct comparisons made between the 2 study groups.

Benefits, Risks and Safety

The major benefit of this study is to further our knowledge on the long term aspects of gastric bypass surgery of which data greater than 5 years is lacking. Direct benefits to participants are mainly assessment of nutritional and metabolic status. Your GP will be informed of your participation and results of the investigations will be forwarded onto your GP for any action.

There is little risk to taking part in the study. We require some of your time and the inconvenience of a blood and urine test. Any adverse outcome should be covered by ACC compensation provisions.

This study is a non-therapeutic study. There will be no additional treatments or medications given.

There will be no direct cost to you for taking part in the study. We expect to be able to cover parking but there is no payment for taking part in the study.

If you require additional information on the trial you can contact Dr Jeremy Krebs or Dr Richard Carroll at the Endocrine, Diabetes and Research Centre, Wellington Hospital, Wellington. Phone (04) 806 2458 or email diabetesresearch@ccdhb.org.nz.
If required an interpreter can be provided.
If you have any queries regarding your rights as a participant in this study, you may wish to contact an independent health and disability advocate:
Free phone: 0800 555 050
Free fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

Compensation

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation, and Compensation Act 2001. ACC cover is not automatic, and your case will need to be assessed by ACC according to the provisions of the Injury Prevention, Rehabilitation, and Compensation Act 2001. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors, such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses, and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators.

If you have any questions about ACC, contact your nearest ACC office or the investigator.

You are also advised to check whether participation in this study would affect any indemnity cover you have or are considering, such as medical insurance, life insurance and superannuation.

Confidentiality

All details will be kept in a confidential way as per Capital and Coast DHB policy. All subjects will be given a unique identifying code and only this will be used as a marker for analysis. No material that could personally identify you will be used in any reports on this study will be used in any of the final reports.

We expect publication of results in international journals and presentations at national or international conferences. Participants are able to get copies of reports and presentations if they wish. There will be a delay between data collection and publication of results.
This study has received ethical approval from the Multi-region Ethics Committee, which reviews national and multi regional studies. The ethics reference number is MEC/11/04/040.

Please fill out the attached acceptance form and post back in the enclosed envelope.

Please feel free to contact the researchers if you have any questions about this study on (04) 806 2458.

Signed THE INVESTIGATORS

Dr Jeremy Krebs
Dr John Wilson
Dr Amber Parry-Strong
Dr Richard Carroll
Professor Richard Stubbs
Professor Mark Weatherall
Professor Jim Mann
Consent Form

**Long term follow up on metabolic characteristics and nutritional aspects following gastric bypass surgery compared with a non surgical group.**

Principal investigator-
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Professor Mark Weatherall, Statistician, University of Otago, Wellington;
Professor Jim Mann, University of Otago, Dunedin

**Request for interpreter (to be included on all consent forms)**

<table>
<thead>
<tr>
<th>Language</th>
<th>Request for interpreter</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>English</td>
<td>I wish to have an interpreter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaf</td>
<td>I wish to have a NZ sign language interpreter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Māori</td>
<td>E hiaha ana ahau ki tetahi kaiwhaka Māori/kaiwhaka pakeha korero</td>
<td>Ae</td>
<td>Kao</td>
</tr>
<tr>
<td>Cook Island Māori</td>
<td>Ka inangaro au i tetai tangata uri reo</td>
<td>Ae</td>
<td>Kar</td>
</tr>
<tr>
<td>Fijian</td>
<td>Au gadreva me dua e vakadewa vosa vei au</td>
<td>Io</td>
<td>Sega</td>
</tr>
<tr>
<td>Niuean</td>
<td>Fia manako au ke faka aoga e taha tagata fakahokohoko kupu</td>
<td>E</td>
<td>Nakai</td>
</tr>
<tr>
<td>Sāmoan</td>
<td>Ou te mana’o ia i ai se fa’amatala upu</td>
<td>Ioe</td>
<td>Leai</td>
</tr>
<tr>
<td>Tokelaun</td>
<td>Ko au e fofoi ki he tino ke fakaliliu te gagana Peletania ki na gagana o na motu o te Pahefika</td>
<td>Ioe</td>
<td>Leai</td>
</tr>
<tr>
<td>Tongan</td>
<td>Oku ou fiema’u ha fakatunulea</td>
<td>Io</td>
<td>Ikai</td>
</tr>
<tr>
<td>Statement</td>
<td>Y</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------------------</td>
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<td>---</td>
<td></td>
</tr>
<tr>
<td>I have read and I understand the information sheet dated 24/06/13 for volunteers taking part in the study designed to assess long term follow results of gastric bypass surgery. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.</td>
<td>Y</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>I have had the opportunity to use whānau support or a friend to help me ask questions and understand the study.</td>
<td>Y</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>I understand that taking part in this study is voluntary (my choice), and that I may withdraw from the study at any time, and this will in no way affect my future health care or continuing healthcare.</td>
<td>Y</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>I have had this project explained to me by ____________________</td>
<td>Y</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>I understand that my participation in this study is confidential and that no material that could identify me will be used in any reports on this study.</td>
<td>Y</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>I understand the compensation provisions for this study.</td>
<td>Y</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>I have had time to consider whether to take part in the study.</td>
<td>Y</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>I know who to contact if I have any questions about the study in general.</td>
<td>Y</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>I agree to an approved auditor appointed by either the ethics committee or the regulatory authority or their approved representative and approved by the Multi-region ethics committee reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.</td>
<td>Y</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>I consent to the researchers storing a specimen of my blood (or other tissue) for its later use as a part of this study or other research</td>
<td>Y</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>I wish to receive a copy of the results. Participants should be advised that a significant delay may occur between data collection and publication of the results.</td>
<td>Y</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>I agree to my GP or other current provider being informed of my participation in this study/the results of my participation in this study.</td>
<td>Y</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>I consent to my GP being contacted for additional details regarding my medical history</td>
<td>Y</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>I consent to us contacting additional laboratories and hospitals for results and medical details</td>
<td>Y</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>I consent to sending samples overseas if required. (this will require additional approval by ethics committee)</td>
<td>Y</td>
<td>N</td>
<td></td>
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<tr>
<td>---</td>
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<td></td>
</tr>
<tr>
<td>I consent to the use of any previous stored blood for additional investigation</td>
<td>Y</td>
<td>N</td>
<td></td>
</tr>
</tbody>
</table>

5. I ___________________________ hereby consent to take part in this study.

<table>
<thead>
<tr>
<th>Date:</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Signature:</td>
<td></td>
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</tbody>
</table>

Project explained by: 

<table>
<thead>
<tr>
<th>Project role:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature:</td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**

1. A copy of the consent form is to be retained by each participant and (in the case of patients) a copy is to be placed in the medical file.
Appendix i-7  Interview datasheet

Gastric Bypass Follow Up Study

Section 1

CODE NUMBER __ __ __ __ __ __

Date: __/___/____

Name: ________________________________

NHI: ________________________________

DOB: ________________________________

Gender: Male □ Female □

Address: ________________________________

____________________________________

____________________________________

Ph Home: ______________

Ph Mobile: ______________

Email: ......................................................@......................................................

GP Name: ________________________________

GP Address: ________________________________

____________________________________

____________________________________

GP Phone: ______________
QOL Questionnaire □

4 Day Food Diary □

Can we contact you about other gastric bypass studies?  Yes □  No □

**Bariatric Surgery**

1. Bypass Group

   *If subject has not undergone bypass surgery proceed to Q3*

   1.1. When was your operation? (DD/MON/YYYY)

   __ __ / __ __ __ / __ __ __ __

2. Have you had subsequent bariatric surgery (e.g. Banding, revision bypass, gastroplasty, gastric sleeve)?

   YES / NO

   *If subject has undergone proceed to question 4*

3. Non Bypass Group

   3.1. Have you ever had Bariatric Surgery (e.g. Banding, gastric bypass, gastroplasty, gastric sleeve)?

   YES / NO

4. Are you satisfied with your current weight?

   1                     2                     3                     4                     5
   Very Unsatisfied    Unsatisfied     Indifferent      Satisfied      Very Satisfied
Ethnicity

5. Which of the following ethnic groups do you belong to?

- New Zealand European □
- Niuean □
- Maori □
- Chinese □
- Samoan □
- Indian □
- Cook Island Maori □
- Other ____________
- Tongan □

Please fill in the following boxes for each of your grandparents. If you do not know their origin please indicate this with a question mark. Tick as many circles as you need within each box.

Paternal Grandfather

Tick as many circles as you need to show which Ethnic group(s) you belong to:

- NZ Maori
- NZ European or Pakeha
- Other European
- Samoan
- Cook Island Maori
- Tongan
- Niuean
- Chinese
- Indian
- Other

Which of these Groups?
- English
- Dutch
- Australian
- Scottish
- Irish
- Other

Please print your ethnic groups (Such as Fijian, Korean)

Paternal Grandmother

Tick as many circles as you need to show which Ethnic group(s) you belong to:

- NZ Maori
- NZ European or Pakeha
- Other European
- Samoan
- Cook Island Maori
- Tongan
- Niuean
- Chinese
- Indian
- Other

Which of these Groups?
- English
- Dutch
- Australian
- Scottish
- Irish
- Other

Please print your ethnic groups (Such as Fijian, Korean)

Maternal Grandfather

Tick as many circles as you need to show which Ethnic group(s) you belong to:

- NZ Maori
- NZ European or Pakeha
- Other European
- Samoan
- Cook Island Maori
- Tongan
- Niuean
- Chinese
- Indian
- Other

Which of these Groups?
- English
- Dutch
- Australian
- Scottish
- Irish
- Other

Please print your ethnic groups (Such as Fijian, Korean)

Maternal Grandmother

Tick as many circles as you need to show which Ethnic group(s) you belong to:

- NZ Maori
- NZ European or Pakeha
- Other European
- Samoan
- Cook Island Maori
- Tongan
- Niuean
- Chinese
- Indian
- Other

Which of these Groups?
- English
- Dutch
- Australian
- Scottish
- Irish
- Other

Please print your ethnic groups (Such as Fijian, Korean)

6. If applicable, who are your iwi? ________________________________
Social / diet / exercise information

7. Smoker? Yes □ No □ Ex-smoker □

7.1 If Yes/Ex, How many pack years? ________________

One pack year is 20 cigarettes per day for 1 year. (i.e. 10 cigarettes/day for 20 years would be 10 pack/years)

8. Alcohol Yes □ No □ Ex □

8.1 If yes, how much alcohol did you drink in the last 7 days (units)?

   a. Beer
   b. Wine
   c. Spirits
   d. Other

8.2 Is this an average intake for you? If no, how many standard drinks would you usually consume per week?

   Standard drinks____________________

9. Are you currently working? Yes □ No □

9.1 If Yes, How many hours per week? _________

9.2 At this time are you: (Please tick all that apply)

   □ In paid employment?
   □ Self-employed?
   □ Working full time?
   □ Working part time?
   □ In physical/manual employment?
   □ In non-physical employment?
   □ Retired?
   □ A home-maker?
   □ A student?
   □ Unemployed?
   □ Not working because of ill health/disability?
Appendix

☐ Other _________________________________

10. How many years of education have you completed?

   2  3  4  5  6  7  8  9  10  11 (5th form)  12  13 (7th form)  14  15  16  17  18  19  20

   Please circle the number of years at school, college, university etc

11. Exercise habits (tick one)

   ☐ Sedentary
   ☐ Moderate (minor strenuous exercise at least 4hrs/wk e.g. walking/cycling)
   ☐ Regular strenuous exercise (at least 3hrs/wk e.g. sports)
   ☐ Regular hard physical training (e.g. for competition)

12. How many sugar-sweetened drinks (including fruit juice), but not including diet drinks, do you normally drink per day?

   Can or large glass: (Please circle the number that applies)

   0  1  2  3  4  5  more than 5

13. How many pieces of whole fresh fruit do you usually eat per day: (please circle the number that applies)

   0  1  2  3  4  5  more than 5

14. How many times do you normally eat seafood in a week? _____________

15. Approximately at what age do you recall developing problems with weight? ___________
Medical information

15. Hypertension
   Yes □ No □

<table>
<thead>
<tr>
<th>Year of diagnosis</th>
<th>Year of commencing treatment</th>
<th>Ongoing treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>YES / NO</td>
</tr>
</tbody>
</table>

16. High Cholesterol
   Yes □ No □

<table>
<thead>
<tr>
<th>Year of diagnosis</th>
<th>Year of commencing treatment</th>
<th>Ongoing treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>YES / NO</td>
</tr>
</tbody>
</table>

17. Heart problems
   a. Angina?
      Yes □ No □
   b. Heart failure?
      Yes □ No □
   c. Pacemaker/stent/bypass?
      Yes □ No □
   d. Heart attack?
      Yes □ No □
   e. Stroke?
      Yes □ No □

A positive answer at least one of 17a – 17d constitutes a positive cardiac history for the purposes of bariatric follow up study

18. Do you have/have previously had gout?
   Yes □ No □

19. Associated medical problems

<table>
<thead>
<tr>
<th>Condition</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep apnoea</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td></td>
</tr>
<tr>
<td>Gallbladder surgery</td>
<td></td>
</tr>
<tr>
<td>Osteoporotic fracture</td>
<td></td>
</tr>
<tr>
<td>Fatty liver disease</td>
<td></td>
</tr>
</tbody>
</table>

0 = Never, 1 = Before surgery, resolved,
2 = Before surgery, not resolved, 3 = After surgery only
Medications

20. Please list all current medications and dose

21. Please list all relevant over the counter medications, Herbal or complementary medications

22. How often do you take Multivitamins?

1 2 3 4 5
Every Day 3-4/week 1-2/week Not regular Never

23. Do you receive Vitamin B12 injections? Yes □ No □
Current symptoms

24. Do you suffer from symptoms of low blood sugar?    Yes □  No □

If yes, please describe time of day, characteristics, use of diabetes medications, treatment strategies

25. Do you suffer from dumping syndrome?    Yes □  No □

If yes, please describe time of day, characteristics, other investigations treatment strategies

26. How would you describe your enjoyment of food?

<table>
<thead>
<tr>
<th>Before the operation</th>
<th>Since the operation</th>
</tr>
</thead>
</table>

1 = Always enjoy my food, 2 = Occasionally don’t enjoy my food, 3 = Always do not enjoy my food

27. Have you developed any of the following negative symptoms since surgery?
   a. Frequent vomiting    Yes □  No □
   b. Indigestion    Yes □  No □
   c. Change in bowel habit    Yes □  No □

28. Do you feel any benefits you have received from the surgery outweigh negative symptoms?
    Yes □  No □  Not applicable □
Diabetes information

29. Do you have diabetes?  Yes □  No □

<table>
<thead>
<tr>
<th>Year of diagnosis</th>
<th>Year of commencing treatment</th>
<th>Ongoing treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>YES / NO</td>
</tr>
</tbody>
</table>

Confirm type 2 diabetes if positive answer to above

If yes, have you ever used insulin?  Yes □  No □

<table>
<thead>
<tr>
<th>Year of commencement</th>
<th>Ongoing treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES / NO</td>
</tr>
</tbody>
</table>

30. Diabetes related medical problems

<table>
<thead>
<tr>
<th>Condition</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy</td>
<td></td>
</tr>
<tr>
<td>Neuropathy</td>
<td></td>
</tr>
<tr>
<td>Nephropathy</td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
</tr>
</tbody>
</table>

0 = Never, 1 = Before surgery, resolved, 2 = Before surgery, not resolved, 3 = After surgery only

31. Diabetes medications

<table>
<thead>
<tr>
<th>Name</th>
<th>Year commenced</th>
<th>BMI at time</th>
<th>HbA1c at time</th>
<th>Therapy compliance score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Therapy compliance score: Always taken=1; missed once per week =2; missed more than once per week=3
2. Age at first gout attack _____________ Years

3. Number of gout attacks in the past year ________________

4. Is there tophus as evidenced by clinical examination?
   Yes □ No □

5. Has the participant ever had diuretic treatment?
   Yes □ No □
   If so, did this induce gout? YES/NO

6. What treatment has the participant had for gout in the past?
   Allopurinol YES / NO
   Steroid YES / NO
   Anti-inflammatory YES / NO
   Probenecid YES / NO
   Colchicine YES / NO
   Other YES / NO

7. Were there any side effects from these treatments? (specify drug)
   ______________________________________________________

8. Do certain foods/drink trigger your gout? YES / NO
   If so, please list them:
   ______________________________________________________

9. Does seafood trigger your gout? YES / NO

10. Does alcohol trigger your gout? YES / NO

11. Urate (at diagnosis) (Date: ___/____/____) _____________ mmol/L
Exam

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>__ __ __</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>__ __ __</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>__ __ __</td>
</tr>
<tr>
<td>Hip (cm)</td>
<td>__ __ __</td>
</tr>
</tbody>
</table>
| Pulse (beats/minute) on 3 occasions | __ __ __  
|                  |         |
|                  |         |
| BP (3 occasions) | __ __ __/ __ __ __ |
|                  | __ __ __/ __ __ __ |
|                  | __ __ __/ __ __ __ |
| O2 Saturations (%) | __ __ % |
| Neck Circumference (cm) | __ __ __ |
| Travel voucher received | ____________________ |


**Impact of Weight on Quality of Life Questionnaire—Lite Version (IWQOL-Lite)**

Please answer the following statements by circling the number that best applies to you in the past week. Be as open as possible. There are no right or wrong answers.

<table>
<thead>
<tr>
<th>Physical Function</th>
<th>ALWAYS TRUE</th>
<th>USUALLY TRUE</th>
<th>SOMETIMES TRUE</th>
<th>RARELY TRUE</th>
<th>NEVER TRUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Because of my weight I have trouble picking up objects.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2. Because of my weight I have trouble tying my shoes.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3. Because of my weight I have difficulty getting up from chairs.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>4. Because of my weight I have trouble using stairs.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>5. Because of my weight I have difficulty putting on or taking off my clothing.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>6. Because of my weight I have trouble with mobility.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>7. Because of my weight I have trouble crossing my legs.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>8. I feel short of breath with only mild exertion.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>9. I am troubled by painful or stiff joints.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>10. My ankles and lower legs are swollen at the end of the day.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>11. I am worried about my health.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Self-esteem</th>
<th>ALWAYS TRUE</th>
<th>USUALLY TRUE</th>
<th>SOMETIMES TRUE</th>
<th>RARELY TRUE</th>
<th>NEVER TRUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Because of my weight I am self-conscious.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2. Because of my weight my self-esteem is not what it could be.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3. Because of my weight I feel unsure of myself.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>4. Because of my weight I don’t like myself.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>5. Because of my weight I am afraid of being rejected.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>6. Because of my weight I avoid looking in mirrors or seeing myself in photographs.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>7. Because of my weight I am embarrassed to be seen in public places.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
### Sexual Life

<table>
<thead>
<tr>
<th></th>
<th>ALWAYS TRUE</th>
<th>USUALLY TRUE</th>
<th>SOMETIMES TRUE</th>
<th>RARELY TRUE</th>
<th>NEVER TRUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Because of my weight I do not enjoy sexual activity.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2. Because of my weight I have little or no sexual desire</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3. Because of my weight I have difficulty with sexual performance</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>4. Because of my weight I avoid sexual encounters whenever possible</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

### Public Distress

<table>
<thead>
<tr>
<th></th>
<th>ALWAYS TRUE</th>
<th>USUALLY TRUE</th>
<th>SOMETIMES TRUE</th>
<th>RARELY TRUE</th>
<th>NEVER TRUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Because of my weight I experience ridicule, teasing, or unwanted attention.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2. Because of my weight I worry about fitting into seats in public places (e.g., theaters, restaurants, cars, or airplanes).</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3. Because of my weight I worry about fitting through aisles or turnstiles.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>4. Because of my weight I worry about finding chairs that are strong enough to hold my weight.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>5. Because of my weight I experience discrimination by others.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

### Work (Note: For homemakers and retirees, answer with respect to your daily activities.)

<table>
<thead>
<tr>
<th></th>
<th>ALWAYS TRUE</th>
<th>USUALLY TRUE</th>
<th>SOMETIMES TRUE</th>
<th>RARELY TRUE</th>
<th>NEVER TRUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Because of my weight I have trouble getting things accomplished or meeting my responsibilities.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2. Because of my weight I am less productive than I could be.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3. Because of my weight I don’t receive appropriate raises, promotions or recognition at work.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>4. Because of my weight I am afraid to go on job interviews.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
IWQOL-Lite Scoring

Raw scores for each scale are computed for each of the five scales only if a minimum of 50% of the items for that scale are answered, and for the total score only if 75% of the answers for all items are completed. (The required number of minimum responses is: Physical Function=6 of 11; Self-Esteem =4 of 7; Sexual Life=2 of 4; Public Distress=3 of 5; Work=2 of 4; Total=24 of 31.) In computing raw scores, we use a pro-rated system for handling missing data. To calculate the raw score for any scale or total score, the procedures are as follows:

1. Determine if the minimum number of items are answered for that scale. The required number of minimum responses is: Physical Function=6 of 11; Self-Esteem =4 of 7; Sexual Life=2 of 4; Public Distress=3 of 5; Work=2 of 4; Total=24 of 31.

Example 1: If an individual answered 5 of 11 Physical Function questions, the Physical Function score would be considered missing and coded as 999.

Example 2: If an individual answered 26 items on the entire scale, a valid score would be calculated for the IWQOL-Lite total.

2. Take the average of the valid items for that scale. Compute the average for the valid responses to items for that scale where 1=“Never True” and 5=“Always True”. The average must be a number between 1 and 5. For example, if the respondent answered “3” on every item of the Physical Function scale, the mean would be 3.

Example 3: An individual answered the 11 Physical Function questions as follows (9 indicates missing question): 2, 3, 2, 4, 9, 2, 2, 3, 1, 9, 3, 5. The individual answered 9 of 11 questions, with an average of 3.0 (27/9).

Example 4: An individual answered the 5 Public Distress questions as follows: 3, 1, 3, 4, 3. The individual answered 5 of 5 questions with an average of 2.8 (14/5).

3. Multiply that average by the total number of items for that scale. The total number of items on IWQOL-Lite scales are as follows: Physical Function=11, Self-Esteem=7, Sexual Life=4, Public Distress=5, Work=4, Total=31. Round to the nearest whole integer. For example, if the mean of the Physical Function scale is 3.0, then you would multiply 3.0 x 11 = 33.

Example 5: From the Physical Function answers in Example 3, multiply the average (3.0) times the number of total questions in the Physical Function scale (11) and round to the nearest whole integer: 3 x 11 = 33 (no need to round). This is the Physical Function Raw Score.
### ii. Appendix B

Table ii-1  Baseline characteristics of study participants based on bariatric procedure

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Mean (SD)</th>
<th>95% CI</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transected RYGB (N=99)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at operation (years)</td>
<td>48.1 (10.9)</td>
<td>46.0 to 50.3</td>
<td>23.5</td>
<td>68.5</td>
</tr>
<tr>
<td>Age at follow up (years)</td>
<td>55.9 (11.2)</td>
<td>53.7 to 58.1</td>
<td>30.1</td>
<td>77.4</td>
</tr>
<tr>
<td>Duration of follow up (years)</td>
<td>7.8 (2.5)</td>
<td>7.3 to 8.2</td>
<td>5.1</td>
<td>14.0</td>
</tr>
<tr>
<td>Pre-operative weight (kg)</td>
<td>129.4 (26.7)</td>
<td>124.1 to 134.7</td>
<td>83.0</td>
<td>202.0</td>
</tr>
<tr>
<td>Pre-operative BMI (kg/m2)</td>
<td>46.4 (8.6)</td>
<td>44.6 to 48.1</td>
<td>33.0</td>
<td>73.6</td>
</tr>
<tr>
<td><strong>Silastic ring RYGB (N=13)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at operation (years)</td>
<td>47.0 (9.0)</td>
<td>41.6 to 52.4</td>
<td>23.4</td>
<td>60.2</td>
</tr>
<tr>
<td>Age at follow up (years)</td>
<td>65.4 (9.9)</td>
<td>59.4 to 71.4</td>
<td>40.5</td>
<td>78.1</td>
</tr>
<tr>
<td>Duration of follow up (years)</td>
<td>18.4 (2.9)</td>
<td>16.7 to 20.1</td>
<td>14.6</td>
<td>22.9</td>
</tr>
<tr>
<td>Pre-operative weight (kg)</td>
<td>126.1 (32.5)</td>
<td>106.4 to 145.7</td>
<td>89.0</td>
<td>192.0</td>
</tr>
<tr>
<td>Pre-operative BMI (kg/m2)</td>
<td>47.3 (10.6)</td>
<td>40.9 to 53.7</td>
<td>34.8</td>
<td>74.9</td>
</tr>
<tr>
<td><strong>Vertical banded gastroplasty (N=1)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at operation (years)</td>
<td>33.1 (N/A)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Age at follow up (years)</td>
<td>57.3 (N/A)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Duration of follow up (years)</td>
<td>24.2 (N/A)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Pre-operative weight (kg)</td>
<td>124.0 (N/A)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Pre-operative BMI (kg/m2)</td>
<td>44.5 (N/A)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Gastric bypass (N=5)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at operation (years)</td>
<td>37.5 (5.0)</td>
<td>31.3 to 43.7</td>
<td>30.9</td>
<td>42.6</td>
</tr>
<tr>
<td>Age at follow up (years)</td>
<td>66.5 (6.15)</td>
<td>58.9 to 74.2</td>
<td>59.5</td>
<td>72.5</td>
</tr>
<tr>
<td>Duration of follow up (years)</td>
<td>29.0 (1.8)</td>
<td>26.8 to 31.3</td>
<td>25.9</td>
<td>30.6</td>
</tr>
<tr>
<td>Pre-operative weight (kg)</td>
<td>125.3 (18.2)</td>
<td>102.7 to 147.9</td>
<td>104.0</td>
<td>144.0</td>
</tr>
<tr>
<td>Pre-operative BMI (kg/m2)</td>
<td>50.0 (5.1)</td>
<td>41.9 to 58.0</td>
<td>43.3</td>
<td>54.5</td>
</tr>
<tr>
<td><strong>Revision (N=2)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at operation (years)</td>
<td>41.6 (N/A)</td>
<td>N/A</td>
<td>38.6</td>
<td>44.5</td>
</tr>
<tr>
<td>Age at follow up (years)</td>
<td>64.2 (N/A)</td>
<td>N/A</td>
<td>23.5</td>
<td>68.5</td>
</tr>
<tr>
<td>Duration of follow up (years)</td>
<td>22.7 (N/A)</td>
<td>N/A</td>
<td>22.2</td>
<td>23.1</td>
</tr>
<tr>
<td>Pre-operative weight (kg)</td>
<td>99.0 (N/A)</td>
<td>N/A</td>
<td>68.0</td>
<td>130.0</td>
</tr>
<tr>
<td>Pre-operative BMI (kg/m2)</td>
<td>37.6 (N/A)</td>
<td>N/A</td>
<td>26.3</td>
<td>48.9</td>
</tr>
</tbody>
</table>
Table ii-2  Smoking status, alcohol use, and employment history at follow up by type of bariatric procedure

<table>
<thead>
<tr>
<th>Status</th>
<th>Transected RYGB (N=99)</th>
<th>Silastic ring RYGB (N=13)</th>
<th>Other (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N/120 (%)</td>
<td>Mean (SD)</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>56 (57)</td>
<td>Pack years</td>
<td></td>
</tr>
<tr>
<td>Ex</td>
<td>36 (36)</td>
<td>20.8 (26.1)</td>
<td>11.2 to 30.3</td>
</tr>
<tr>
<td>Current</td>
<td>7 (7)</td>
<td>17.3 (9.1)</td>
<td>7.8 to 26.9</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>32 (32)</td>
<td>Units per week</td>
<td></td>
</tr>
<tr>
<td>Ex</td>
<td>33 (33)</td>
<td>9.2 (12.8)</td>
<td>4.6 to 13.8</td>
</tr>
<tr>
<td>Current</td>
<td>34 (34)</td>
<td>7.2 (8.0)</td>
<td>4.2 to 10.2</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed at follow up</td>
<td>67 (67)</td>
<td>36.0 (17.4)</td>
<td>31.8 to 40.0</td>
</tr>
<tr>
<td>Silastic ring RYGB (N=13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>10 (77)</td>
<td>Pack years</td>
<td></td>
</tr>
<tr>
<td>Ex</td>
<td>2 (15)</td>
<td>7.5 (N/A)</td>
<td>N/A</td>
</tr>
<tr>
<td>Current</td>
<td>1 (8)</td>
<td>40.0</td>
<td>N/A</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>6 (46)</td>
<td>Units per week</td>
<td></td>
</tr>
<tr>
<td>Ex</td>
<td>5 (38)</td>
<td>11.4 (10.4)</td>
<td>-1.5 to 24.3</td>
</tr>
<tr>
<td>Current</td>
<td>2 (15)</td>
<td>17.0 (18.4)</td>
<td>-148 to 182</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed at follow up</td>
<td>9 (69)</td>
<td>38.9 (17.6)</td>
<td>25.3 to 52.4</td>
</tr>
<tr>
<td>Other (n=8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>3 (37)</td>
<td>Pack years</td>
<td></td>
</tr>
<tr>
<td>Ex</td>
<td>5 (63)</td>
<td>31.2 (22.1)</td>
<td>3.7 to 59.7</td>
</tr>
<tr>
<td>Current</td>
<td>0 (0)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>4 (50)</td>
<td>Units per week</td>
<td></td>
</tr>
<tr>
<td>Ex</td>
<td>2 (25)</td>
<td>22.0 (28.3)</td>
<td>-232 to 276</td>
</tr>
<tr>
<td>Current</td>
<td>2 (25)</td>
<td>6.5 (4.9)</td>
<td>-38.0 to 51</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed at follow up</td>
<td>4 (50)</td>
<td>48.8 (8.5)</td>
<td>35.2 to 62.3</td>
</tr>
</tbody>
</table>
Figure ii-1  Frequency histograms showing (left hand column) a) weight (kg) and b) BMI (kg/m$^2$) at baseline. Histograms of transformed (ln(x)) data are shown in the right hand column.

Table ii-3  Shapiro-Wilk test of normality results for non-transformed and logarithmic transformed weight at (kg), and BMI (kg/m$^2$) at baseline. The null hypothesis is accepted (i.e. data is not clearly not normally distributed) if $p>0.05$. 

<table>
<thead>
<tr>
<th></th>
<th>Non-transformed</th>
<th>Logarithmic transformed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statistic</td>
<td>P value</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.96</td>
<td>0.02</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>0.94</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Figure ii-2  Frequency histograms showing (left hand column) a) weight (kg) and b) BMI (kg/m²) at follow up. Histograms of transformed (ln(x)) data are shown in the right hand column.

Table ii-4  Shapiro-Wilk test of normality results for non-transformed and logarithmic transformed weight (kg) and BMI (kg/m²) at follow up. The null hypothesis is accepted (i.e. data is not clearly not normally distributed) if p>0.05.

<table>
<thead>
<tr>
<th></th>
<th>Non-transformed</th>
<th>Logarithmic transformed</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=118</td>
<td>Statistic</td>
<td>P value</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.96</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.96</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Figure ii-3  Frequency histograms to show distribution of a) change in weight, b) change in BMI, and c) body weight loss % for all participants (left column) and those who had undergone tRYGB (right column, n=98)

a) Frequency histograms for change in weight (kg) showing mean, standard deviation, and sample size.

b) Frequency histograms for change in BMI (kg/m²) showing mean, standard deviation, and sample size.

c) Frequency histograms for body weight loss % showing mean, standard deviation, and sample size.
Table ii-5  Baseline and follow up characteristics of participants stratified by obesity classification at baseline. Paired T tests results are shown.

<table>
<thead>
<tr>
<th>N=118</th>
<th>Baseline</th>
<th>Follow up</th>
<th>Paired T test for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>IQR</td>
<td>Min/Max</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class 1 obesity (n=8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.2 (9.4)</td>
<td>17.7</td>
<td>38.6/65.4</td>
</tr>
<tr>
<td>Duration of follow up (years)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>95.5 (12.6)</td>
<td>21.3</td>
<td>83.0/83.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>34.1 (0.7)</td>
<td>1.3</td>
<td>33.0/34.8</td>
</tr>
<tr>
<td>Body weight loss (%)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Class 2 obesity (n=18)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.3 (8.1)</td>
<td>7.5</td>
<td>25.1/65.2</td>
</tr>
<tr>
<td>Duration of follow up (years)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>100.9 (7.3)</td>
<td>10.2</td>
<td>91.0/119.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>37.8 (1.1)</td>
<td>1.6</td>
<td>35.7/39.6</td>
</tr>
<tr>
<td>Body weight loss (%)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow up</td>
<td>Paired T test for equality of means</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------------</td>
<td>--------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)  IQR Min/Max</td>
<td>Mean (SD)  IQR Min/Max</td>
<td>Estimated difference  95% CI  P value</td>
</tr>
<tr>
<td><strong>Class 3 obesity (n=56)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.0 (11.0)  18.5 23.5/68.1</td>
<td>57.1 (11.8)  16.5 30.1/78.1</td>
<td>10.1  8.5 to 11.8  &lt;0.001</td>
</tr>
<tr>
<td>Duration of follow up (years)</td>
<td>N/A  N/A N/A</td>
<td>10.1 (6.3)  7.1 5.1/29.5</td>
<td>N/A  N/A N/A</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>124.7 (14.8)  20.5 100.9/162.0</td>
<td>87.2 (15.4)  24.3 61.3/123.2</td>
<td>37.4  33.9 to 40.9  &lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>44.5 (2.88)  4.8 40.0/49.9</td>
<td>31.2 (4.8)  4.9 22.0/47.4</td>
<td>13.3  12.1 to 14.6  &lt;0.001</td>
</tr>
<tr>
<td>Body weight loss (%)</td>
<td>N/A  N/A N/A</td>
<td>29.9 (9.8)  10.8 3.0/50.4</td>
<td>N/A  N/A N/A</td>
</tr>
<tr>
<td><strong>Class 4 obesity (n=36)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>45.7 (11.2)  15.0 23.4/68.5</td>
<td>55.6 (11.5)  18.0 32.6/74.4</td>
<td>9.9  7.8 to 11.9  &lt;0.001</td>
</tr>
<tr>
<td>Duration of follow up (years)</td>
<td>N/A  N/A N/A</td>
<td>9.9 (6.1)  4.7 5.5/30.6</td>
<td>N/A  N/A N/A</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>156.7 (22.6)  34.0 117.0/202.0</td>
<td>108.0 (22.4)  30.4 69.0/171.0</td>
<td>48.7  41.6 to 55.9  &lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>57.0 (6.5)  6.4 50.0/74.9</td>
<td>39.2 (6.8)  9.7 24.5/51.5</td>
<td>17.8  15.1 to 20.4  &lt;0.001</td>
</tr>
<tr>
<td>Body weight loss (%)</td>
<td>N/A  N/A N/A</td>
<td>30.8 (12.1)  17.3 2.4/65.8</td>
<td>N/A  N/A N/A</td>
</tr>
</tbody>
</table>
Table ii-6  Univariate regression analyses outcomes for baseline variables (independent) against change in BMI over study period (dependent variable)

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Coefficients</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Constant</td>
<td>p value</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>11.80</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>13.89</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>-1.03</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>-6.23</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Diabetes status</td>
<td>12.2</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>12.2</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>11.5</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Fasting insulin (pmol/L)</td>
<td>12.8</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>11.0</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>21.3</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>15.5</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>17.3</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>15.9</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>10.7</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>7.73</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>11.5</td>
<td>0.55</td>
<td></td>
</tr>
</tbody>
</table>
Table ii-7  Descriptive data for all participants, stratified by duration of follow up (years)

<table>
<thead>
<tr>
<th></th>
<th>n=118</th>
<th>Duration of follow up</th>
<th></th>
<th></th>
<th>Independent T test for equality of means</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;10.0 years (n=81)</td>
<td>≥10 years (n=37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (SD)</td>
<td>IQR</td>
<td>Min/Max</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Age at operation (years)</td>
<td>48.1</td>
<td>11.2</td>
<td>17.7</td>
<td>23.5/68.5</td>
<td>46.3</td>
</tr>
<tr>
<td>Age at follow up (years)</td>
<td>54.9</td>
<td>11.3</td>
<td>17.6</td>
<td>30.1/77.4</td>
<td>63.6</td>
</tr>
<tr>
<td>Duration of follow up  (years)</td>
<td>6.9</td>
<td>1.4</td>
<td>2.3</td>
<td>5.1/9.9</td>
<td>17.3</td>
</tr>
<tr>
<td>Weight at baseline (kg)</td>
<td>132.1</td>
<td>25.9</td>
<td>39.5</td>
<td>83.0/202.0</td>
<td>121.6</td>
</tr>
<tr>
<td>Weight at follow up (kg)</td>
<td>91.3</td>
<td>22.4</td>
<td>33.2</td>
<td>49.4/171.0</td>
<td>88.1</td>
</tr>
<tr>
<td>Weight loss (kg)</td>
<td>40.8</td>
<td>16.9</td>
<td>22.0</td>
<td>3.4/93.1</td>
<td>33.6</td>
</tr>
<tr>
<td>BMI at baseline (kg/m²)</td>
<td>47.3</td>
<td>8.8</td>
<td>12.2</td>
<td>33.0/73.6</td>
<td>45.2</td>
</tr>
<tr>
<td>BMI at follow up (kg/m²)</td>
<td>32.6</td>
<td>7.4</td>
<td>9.5</td>
<td>19.6/51.5</td>
<td>32.9</td>
</tr>
<tr>
<td>Change in BMI (kg/m²)</td>
<td>14.7</td>
<td>6.3</td>
<td>7.1</td>
<td>1.3/36.6</td>
<td>12.3</td>
</tr>
<tr>
<td>Body weight loss (%)</td>
<td>30.7</td>
<td>10.8</td>
<td>13.0</td>
<td>2.4/56.8</td>
<td>26.8</td>
</tr>
</tbody>
</table>
Figure ii-4  Frequency histograms to show distributions of a) fasting glucose, b) HbA1c, c) fasting insulin, and d) HOMA-IR at baseline (left column) and follow up (right column).

a)

![Frequency histogram for fasting glucose at baseline and follow up](image)

- Mean = 6.16
- Std. Dev. = 2.076
- N = 315

b)

![Frequency histogram for HbA1c at baseline and follow up](image)

- Mean = 7.11
- Std. Dev. = 1.602
- N = 42

- Mean = 10.07
- Std. Dev. = 3.265
- N = 219

c)

![Frequency histogram for fasting insulin at baseline and follow up](image)

- Mean = 139.2
- Std. Dev. = 85.333
- N = 94

- Mean = 41.54
- Std. Dev. = 22.838
- N = 100
Table ii-8  Shapiro-Wilk test of normality results for diabetes variables at baseline and follow up.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=118</td>
<td></td>
</tr>
<tr>
<td>Statistic</td>
<td>P value</td>
<td>Statistic</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>0.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>0.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting insulin (pmol/L)</td>
<td>0.92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.96</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

---

d)
Figure ii-5  Frequency histograms to show distributions of a) Ln(x) fasting glucose, b) Ln(x) HbA1c, c) Ln(x) fasting insulin, and d) Ln(x) HOMA-IR at baseline (left column) and follow up (right column).
Figure ii-6  Frequency histograms to show the distribution of the change in a) fasting glucose (mmol/L) b) HbA1c (mmol/mol), c) fasting insulin (pmol/L) and d) HOMA-IR from baseline to follow up (left column) and following logarithmic transformation (right column)
Figure ii-7  Frequency histograms to show distributions of a) systolic blood pressure at baseline (left column) and follow up (right column), and b) diastolic blood pressure at baseline (left column) and follow up (right column)

Table ii-9  Shapiro-Wilk test of normality results for systolic and diastolic blood pressure at baseline and follow up.

<table>
<thead>
<tr>
<th></th>
<th>N=118</th>
<th>Baseline</th>
<th></th>
<th>Follow up</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statistic</td>
<td>P value</td>
<td>Statistic</td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.98</td>
<td>0.09</td>
<td>0.96</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.97</td>
<td>0.05</td>
<td>0.99</td>
<td>0.60</td>
<td></td>
</tr>
</tbody>
</table>
Figure ii-8  Frequency histograms to show the distribution of the change in a) systolic blood pressure (mmHg), b) diastolic blood pressure (mmHg), and c) mean arterial blood pressure (mmHg) from baseline to follow up
Table ii-10 Univariate regression analyses outcomes for baseline variables (independent) against change in systolic, diastolic, and mean arterial blood pressure at the follow up assessment (dependent variables)

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Systolic blood pressure</th>
<th>Diastolic blood pressure</th>
<th>Mean arterial blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficients</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td>Independent variable</td>
<td>P value</td>
</tr>
<tr>
<td>Blood pressure status</td>
<td>-3.7</td>
<td>-9.0</td>
<td>0.1</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>48.4</td>
<td>-0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>29.4</td>
<td>-0.5</td>
<td>0.003</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>45.7</td>
<td>-0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of BP medications</td>
<td>-12.5</td>
<td>1.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Duration of HTN (years)</td>
<td>-10.3</td>
<td>0.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Duration of treated HTN (years)</td>
<td>-6.8</td>
<td>-0.06</td>
<td>0.9</td>
</tr>
<tr>
<td>BMI at baseline(kg/m²)</td>
<td>-9.9</td>
<td>-0.03</td>
<td>0.9</td>
</tr>
<tr>
<td>BMI at follow up (kg/m²)</td>
<td>-16.3</td>
<td>0.15</td>
<td>0.6</td>
</tr>
<tr>
<td>BMI (kg/m²) change</td>
<td>-7.5</td>
<td>-0.28</td>
<td>0.4</td>
</tr>
<tr>
<td>Duration of follow up (years)</td>
<td>-13.6</td>
<td>0.26</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Figure ii-9  Frequency histograms to show distributions of a) total cholesterol, b) HDL, c) LDL, d) Triglycerides at baseline (left column) and follow up (right column)
Table ii-11  Shapiro-Wilk test of normality results for total cholesterol, HDL, LDL, and triglyceride concentrations at baseline and follow up. The null hypothesis is accepted (i.e. data is not clearly not normally distributed) if p>0.05.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>P value</th>
<th>Follow up</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>0.99</td>
<td>0.40</td>
<td>0.99</td>
<td>0.36</td>
</tr>
<tr>
<td>HDL</td>
<td>0.95</td>
<td>0.001</td>
<td>0.98</td>
<td>0.05</td>
</tr>
<tr>
<td>LDL</td>
<td>0.98</td>
<td>0.29</td>
<td>0.99</td>
<td>0.34</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.77</td>
<td>&lt;0.001</td>
<td>0.91</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Figure ii-10  Frequency histograms to show logarithmic transformed distributions of a) HDL, and b) Triglycerides at baseline (left column) and follow up (right column)
Table ii-12  Shapiro-Wilk test of normality results for logarithmic transformed HDL and triglyceride concentrations at baseline and follow up. The null hypothesis is accepted (i.e. data is not clearly not normally distributed) if p≥0.05.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th></th>
<th>Follow up</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statistic</td>
<td>P value</td>
<td>Statistic</td>
<td>P value</td>
</tr>
<tr>
<td>Ln(X) HDL</td>
<td>0.99</td>
<td>0.63</td>
<td>0.98</td>
<td>0.22</td>
</tr>
<tr>
<td>Ln(X) Triglycerides</td>
<td>0.97</td>
<td>0.05</td>
<td>0.99</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Figure ii-11  Frequency histograms to show the distribution of the change in a) total cholesterol (mmol/L), b) HDL (mmol/L), c) LDL (mmol/L), and d) triglycerides (mmol/L) from baseline to follow up.
Table ii-13  Estimated differences for lipid concentrations at baseline and follow up in participants not using a cholesterol lowering medication at either time point

<table>
<thead>
<tr>
<th></th>
<th>Baseline mean (SD)</th>
<th>Follow up mean (SD)</th>
<th>Paired T test for Estimated difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated difference</td>
<td>95% CI</td>
<td>P value</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.48 (0.94)</td>
<td>5.39 (0.84)</td>
<td>-0.09</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.37 (0.35)</td>
<td>1.97 (0.53)</td>
<td>0.36</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>3.37 (0.83)</td>
<td>2.93 (0.75)</td>
<td>-0.44</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.60 (0.62)</td>
<td>1.06 (0.33)</td>
<td>-0.39</td>
</tr>
</tbody>
</table>

* following logarithmic transformation for HDL and Triglyceride data
Table ii-14  Univariate regression analyses outcomes for baseline variables (independent) against the change in LDL, HDL, and triglyceride concentrations from baseline to the follow up assessment (dependent variables)

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Change in LDL</th>
<th>Change in HDL</th>
<th>Change in Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficients</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td>Independent variable</td>
<td>P value</td>
</tr>
<tr>
<td>LDL at baseline (mmol/L)</td>
<td>-1.89</td>
<td>0.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL at baseline (mmol/L)</td>
<td>-0.09</td>
<td>0.39</td>
<td>0.21</td>
</tr>
<tr>
<td>Triglycerides at baseline (mmol/L)</td>
<td>0.66</td>
<td>-0.1</td>
<td>0.23</td>
</tr>
<tr>
<td>BMI at baseline</td>
<td>0.22</td>
<td>0.005</td>
<td>0.73</td>
</tr>
<tr>
<td>BMI at follow up</td>
<td>0.79</td>
<td>-0.01</td>
<td>0.49</td>
</tr>
<tr>
<td>Change in BMI (kg/m²)</td>
<td>0.07</td>
<td>0.03</td>
<td>0.17</td>
</tr>
<tr>
<td>% Body weight loss</td>
<td>-0.1</td>
<td>0.02</td>
<td>0.1</td>
</tr>
<tr>
<td>Duration of follow up (years)</td>
<td>-0.43</td>
<td>0.11</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Table ii-15  Descriptive lipid data for participants at baseline and follow up, stratified by duration of dyslipidaemia prior to surgery. Results of an independent T test are shown.

<table>
<thead>
<tr>
<th>n=29</th>
<th>&lt; 5 years duration of dyslipidaemia (n=15)</th>
<th>≥ 5 years duration of dyslipidaemia (n=14)</th>
<th>Independent T test for Estimated difference *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>Age at baseline (years)</td>
<td>50.9 (10.3)</td>
<td>45.2 to 56.6</td>
<td>52.7 (7.7)</td>
</tr>
<tr>
<td>Age at follow up (years)</td>
<td>58.6 (10.7)</td>
<td>52.7 to 64.5</td>
<td>60.2 (8.3)</td>
</tr>
<tr>
<td>Duration of follow up (years)</td>
<td>7.6 (1.9)</td>
<td>6.6 to 8.7</td>
<td>7.6 (3.1)</td>
</tr>
<tr>
<td>BMI at baseline (kg/m²)</td>
<td>45.7 (8.3)</td>
<td>41.1 to 50.3</td>
<td>44.1 (11.3)</td>
</tr>
<tr>
<td>BMI at follow up (kg/m²)</td>
<td>32.7 (5.8)</td>
<td>29.5 to 35.9</td>
<td>30.1 (5.6)</td>
</tr>
<tr>
<td>Body weight loss (%)</td>
<td>28.0 (9.1)</td>
<td>22.9 to 33.0</td>
<td>29.8 (12.6)</td>
</tr>
<tr>
<td>Number of lipid lowering medications at baseline</td>
<td>0.3 (0.5)</td>
<td>0.01 to 0.5</td>
<td>0.7 (0.5)</td>
</tr>
<tr>
<td>Number of lipid lowering medications at follow up</td>
<td>0.1 (0.4)</td>
<td>0 to 0.3</td>
<td>0.4 (0.5)</td>
</tr>
</tbody>
</table>

* Logarithmic transformed data used to calculate independent T test values for BMI
Figure ii-12  Frequency histogram to show the distribution of vitamin B12 concentrations in all participants at follow up

Figure ii-13  Histogram to show the distribution of a) zinc concentrations, and b) logarithmic transformed zinc concentrations in all participants at follow up
Figure ii-14  Frequency histogram to show the distribution of copper concentrations in all participants at follow up

Mean = 103.51
Std. Dev. = 18.00
N = 108
Table ii-16  IWQOL-lite answers provided by participants to each question

<table>
<thead>
<tr>
<th>Physical function (n=118)</th>
<th>Chosen answer %</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Because of my weight I have trouble picking up objects</td>
<td>64</td>
<td>21</td>
</tr>
<tr>
<td>Because of my weight I have trouble tying my shoes</td>
<td>75</td>
<td>11</td>
</tr>
<tr>
<td>Because of my weight I have difficulty getting up from chairs</td>
<td>69</td>
<td>17</td>
</tr>
<tr>
<td>Because of my weight I have trouble using stairs</td>
<td>63</td>
<td>14</td>
</tr>
<tr>
<td>Because of my weight I have difficulty putting on or taking off my clothing</td>
<td>83</td>
<td>10</td>
</tr>
<tr>
<td>Because of my weight I have trouble with mobility</td>
<td>66</td>
<td>14</td>
</tr>
<tr>
<td>Because of my weight I have trouble crossing my legs</td>
<td>72</td>
<td>9</td>
</tr>
<tr>
<td>I feel short of breath with only mild exertion</td>
<td>54</td>
<td>16</td>
</tr>
<tr>
<td>I am troubled by painful or stiff joints</td>
<td>36</td>
<td>14</td>
</tr>
<tr>
<td>My ankles and lower legs are swollen at the end of the day</td>
<td>53</td>
<td>21</td>
</tr>
<tr>
<td>I am worried about my health</td>
<td>2</td>
<td>28</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Self-esteem (n=118)</th>
<th>Chosen answer %</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Because of my weight I am self-conscious</td>
<td>35</td>
<td>22</td>
</tr>
<tr>
<td>Because of my weight my self-esteem is not what it could be</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>Because of my weight I feel unsure of myself</td>
<td>48</td>
<td>25</td>
</tr>
<tr>
<td>Because of my weight I don’t like myself</td>
<td>54</td>
<td>17</td>
</tr>
<tr>
<td>Because of my weight I am afraid of being rejected</td>
<td>57</td>
<td>14</td>
</tr>
<tr>
<td>Because of my weight I avoid looking in mirrors or seeing myself in photographs</td>
<td>53</td>
<td>17</td>
</tr>
<tr>
<td>Because of my weight I am embarrassed to be seen in public places</td>
<td>68</td>
<td>14</td>
</tr>
<tr>
<td>Sexual life (n=118)</td>
<td>Chosen answer %</td>
<td>1</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------------</td>
<td>---</td>
</tr>
<tr>
<td>Because of my weight I do not enjoy sexual activity</td>
<td>53</td>
<td>20</td>
</tr>
<tr>
<td>Because of my weight I have little or no sexual desire</td>
<td>52</td>
<td>21</td>
</tr>
<tr>
<td>Because of my weight I have difficulty with sexual performance</td>
<td>55</td>
<td>21</td>
</tr>
<tr>
<td>Because of my weight I avoid sexual encounters whenever possible</td>
<td>59</td>
<td>18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Public distress (n=118)</th>
<th>Chosen answer %</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>N/A</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Because of my weight I experience ridicule, teasing, or unwanted attention</td>
<td>64</td>
<td>19</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>8</td>
<td>1.4 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Because of my weight I worry about fitting into seats in public places (e.g. theaters, restaurants, cars, or airplanes)</td>
<td>63</td>
<td>15</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td>8</td>
<td>1.6 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Because of my weight I worry about fitting through aisles or turnstiles</td>
<td>67</td>
<td>16</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>8</td>
<td>1.4 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Because of my weight I worry about finding chairs that are strong enough to hold my weight</td>
<td>66</td>
<td>15</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>9</td>
<td>1.5 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Because of my weight I experience discrimination by others</td>
<td>64</td>
<td>14</td>
<td>11</td>
<td>0</td>
<td>3</td>
<td>9</td>
<td>1.5 (1.0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Work (n=118)</th>
<th>Chosen answer %</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>N/A</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Because of my weight I have trouble getting things accomplished or meeting my responsibilities</td>
<td>70</td>
<td>14</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>9</td>
<td>1.3 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Because of my weight I am less productive than I could be</td>
<td>65</td>
<td>13</td>
<td>10</td>
<td>2</td>
<td>1</td>
<td>9</td>
<td>1.5 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Because of my weight I don’t receive appropriate raises, promotions or recognition at work</td>
<td>77</td>
<td>8</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>1.2 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Because of my weight I am afraid to go on job interviews</td>
<td>76</td>
<td>4</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>11</td>
<td>1.3 (0.7)</td>
<td></td>
</tr>
</tbody>
</table>
Table ii-17  IWQOL-lite scores for participants stratified by BMI. Reference data from a separate cohort are reported.

<table>
<thead>
<tr>
<th>IWQOL-lite domain</th>
<th>BMI (kg/m²)</th>
<th>Bariatric follow up study (n=119)</th>
<th>IWQOL-lite reference data (n=11,640)</th>
<th>Unpaired T test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean</td>
<td>SD</td>
<td>n</td>
</tr>
<tr>
<td>Physical function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18.0 to 24.9</td>
<td>14</td>
<td>90.4</td>
<td>12.9</td>
</tr>
<tr>
<td></td>
<td>25.0 to 29.9</td>
<td>31</td>
<td>90.2</td>
<td>8.9</td>
</tr>
<tr>
<td></td>
<td>30.0 to 34.9</td>
<td>35</td>
<td>82.5</td>
<td>18.0</td>
</tr>
<tr>
<td></td>
<td>35.0 to 39.9</td>
<td>15</td>
<td>79.5</td>
<td>13.8</td>
</tr>
<tr>
<td></td>
<td>&gt;40.0</td>
<td>19</td>
<td>65.6</td>
<td>20.1</td>
</tr>
<tr>
<td>Self esteem</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18.0 to 24.9</td>
<td>14</td>
<td>91.3</td>
<td>20.6</td>
</tr>
<tr>
<td></td>
<td>25.0 to 29.9</td>
<td>31</td>
<td>91.8</td>
<td>11.0</td>
</tr>
<tr>
<td></td>
<td>30.0 to 34.9</td>
<td>36</td>
<td>77.2</td>
<td>26.7</td>
</tr>
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<td></td>
<td>35.0 to 39.9</td>
<td>14</td>
<td>65.6</td>
<td>20.6</td>
</tr>
<tr>
<td></td>
<td>&gt;40.0</td>
<td>18</td>
<td>49.6</td>
<td>24.0</td>
</tr>
<tr>
<td>Sexual life</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18.0 to 24.9</td>
<td>14</td>
<td>91.7</td>
<td>14.6</td>
</tr>
<tr>
<td></td>
<td>25.0 to 29.9</td>
<td>29</td>
<td>94.2</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td>30.0 to 34.9</td>
<td>30</td>
<td>82.1</td>
<td>20.8</td>
</tr>
<tr>
<td></td>
<td>35.0 to 39.9</td>
<td>13</td>
<td>84.6</td>
<td>27.3</td>
</tr>
<tr>
<td></td>
<td>&gt;40.0</td>
<td>15</td>
<td>71.3</td>
<td>30.6</td>
</tr>
<tr>
<td>IWQOL-lite domain</td>
<td>BMI (kg/m²)</td>
<td>Bariatric follow up study (n=119)</td>
<td>IWQOL-lite reference data (n=11,640)</td>
<td>Unpaired T test</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------</td>
<td>-----------------------------------</td>
<td>-------------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Public distress</td>
<td>18.0 to 24.9</td>
<td>14</td>
<td>95.0</td>
<td>10.9</td>
</tr>
<tr>
<td></td>
<td>25.0 to 29.9</td>
<td>31</td>
<td>99.7</td>
<td>1.2</td>
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<tr>
<td></td>
<td>30.0 to 34.9</td>
<td>32</td>
<td>88.6</td>
<td>18.5</td>
</tr>
<tr>
<td></td>
<td>35.0 to 39.9</td>
<td>14</td>
<td>80.0</td>
<td>19.1</td>
</tr>
<tr>
<td></td>
<td>&gt;40.0</td>
<td>17</td>
<td>63.8</td>
<td>25.5</td>
</tr>
<tr>
<td>Work</td>
<td>18.0 to 24.9</td>
<td>14</td>
<td>97.8</td>
<td>8.4</td>
</tr>
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<td>25.0 to 29.9</td>
<td>31</td>
<td>99.0</td>
<td>3.3</td>
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<td>30.0 to 34.9</td>
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<td>92.3</td>
<td>13.2</td>
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<tr>
<td></td>
<td>35.0 to 39.9</td>
<td>14</td>
<td>86.6</td>
<td>16.6</td>
</tr>
<tr>
<td></td>
<td>&gt;40.0</td>
<td>16</td>
<td>82.0</td>
<td>16.9</td>
</tr>
<tr>
<td>Total</td>
<td>18.0 to 24.9</td>
<td>14</td>
<td>92.5</td>
<td>12.8</td>
</tr>
<tr>
<td></td>
<td>25.0 to 29.9</td>
<td>29</td>
<td>93.8</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>30.0 to 34.9</td>
<td>27</td>
<td>84.1</td>
<td>16.8</td>
</tr>
<tr>
<td></td>
<td>35.0 to 39.9</td>
<td>14</td>
<td>75.5</td>
<td>12.3</td>
</tr>
<tr>
<td></td>
<td>&gt;40.0</td>
<td>14</td>
<td>64.3</td>
<td>18.8</td>
</tr>
</tbody>
</table>
Figure ii-15 Bivariate correlation using Pearson’s correlation coefficient for a) physical function, b) self-esteem, c) sexual function, d) public distress, e) work, and f) total % scores against BMI (kg/m$^2$) at follow up.
Table ii-18  Baseline characteristics of the recruited participants (n=118) and non-recruited persons (n=1114). Results of an independent T test are shown

<table>
<thead>
<tr>
<th></th>
<th>Recruited population (n=118)</th>
<th>Non-recruited population (n=1114)</th>
<th>Independent T test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Mean (SD)</td>
<td>IQR</td>
</tr>
<tr>
<td>Age (years)</td>
<td>118 (100)</td>
<td>47.5 (10.5)</td>
<td>14.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>118 (100)</td>
<td>128.8 (26.8)</td>
<td>36.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>118 (100)</td>
<td>46.6 (8.6)</td>
<td>11.8</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>105 (89)</td>
<td>6.16 (2.08)</td>
<td>1.75</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>92 (78)</td>
<td>47.1 (14.7)</td>
<td>16.0</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>99 (84)</td>
<td>141.9 (20.7)</td>
<td>30.0</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>98 (83)</td>
<td>81.9 (12.1)</td>
<td>13.5</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mmHg)</td>
<td>98 (83)</td>
<td>101.9 (13.9)</td>
<td>15.3</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>92 (78)</td>
<td>5.40 (0.99)</td>
<td>1.42</td>
</tr>
</tbody>
</table>
Table ii-19  One and two year follow up data for recruited participants (n=118) and non-recruited persons (n=684). Results of an independent T test are shown

<table>
<thead>
<tr>
<th></th>
<th>Recruited population (n=118)</th>
<th>Non-recruited population (n=684)</th>
<th>Independent T test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Mean (SD)</td>
<td>IQR</td>
</tr>
<tr>
<td><strong>One year data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>92 (78)</td>
<td>84.2 (20.3)</td>
<td>26.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>92 (78)</td>
<td>29.7 (6.3)</td>
<td>5.8</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>88 (75)</td>
<td>4.87 (0.85)</td>
<td>0.65</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>88 (75)</td>
<td>35.8 (5.6)</td>
<td>7.0</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>92 (78)</td>
<td>119.1 (17.3)</td>
<td>20.0</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>92 (78)</td>
<td>72.1 (11.6)</td>
<td>15.0</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mmHg)</td>
<td>92 (78)</td>
<td>87.8 (12.5)</td>
<td>16.0</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>92 (78)</td>
<td>4.8 (0.8)</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>Recruited population (n=118)</td>
<td>Non-recruited population (n=684)</td>
<td>Independent T test</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------------------------</td>
<td>----------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td>Mean (SD)</td>
<td>IQR</td>
</tr>
<tr>
<td><strong>Two year data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>92 (78)</td>
<td>83.1 (20.6)</td>
<td>28.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>92 (78)</td>
<td>29.4 (6.3)</td>
<td>6.7</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>92 (78)</td>
<td>4.88 (0.73)</td>
<td>0.5</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>89 (75)</td>
<td>37.0 (7.0)</td>
<td>7.0</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>92 (78)</td>
<td>121.1 (16.0)</td>
<td>22.0</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>92 (78)</td>
<td>73.5 (11.7)</td>
<td>10.0</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mmHg)</td>
<td>92 (78)</td>
<td>89.3 (11.7)</td>
<td>12.0</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>92 (78)</td>
<td>4.8 (0.9)</td>
<td>1.1</td>
</tr>
</tbody>
</table>
iii. **Appendix C**

Figure iii-1 Frequency histograms showing the distribution of a) fasting glucose (mmol/L), b) HbA1c (mmol/mol), c) insulin (pmol/L), and d) HOMA-IR, at baseline (left column) and follow up (right column)
Table iii-1  Shapiro-Wilk test of normality results for glycaemic markers at baseline and follow up.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statistic</td>
<td>P value</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>0.78</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.83</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>0.93</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.97</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Figure iii-2  Frequency histograms showing the distribution of a) fasting glucose (mmol/L), b) HbA1c (mmol/mol), c) insulin (pmol/L), and d) HOMA-IR, at baseline (left column) and follow up (right column) after logarithmic transformation.
iv. Appendix D

Health and disability research

These screening questions will help determine whether HDEC review is required for your study. They are based on the rules contained in section three of the Standard Operating Procedures for Health and Disability Ethics Committees. Don’t hesitate to contact us if you’d like help answering these questions, or any others in the HDEC form.

A. Health and disability research

Does your study aim to improve health outcomes, or outcomes for disabled people?

☐ Yes
☐ No

Human reproductive research

B. Will your study involve the creation or use of a human gamete, a human embryo or a hybrid embryo?

☐ Yes
☐ No

Type of study

C. Is your study:

☐ an intervention study?

In intervention studies, the investigator controls and studies the preventive, diagnostic or therapeutic intervention(s) provided to participants for the purpose of adding to knowledge of the health effects of the intervention(s). Many intervention studies are clinical trials.  

☐ an observational study?

In observational studies the researcher has no control over study variables, and merely observes outcomes.

Main criteria

D. Will your study involve human participants recruited in their capacity as:

- consumers of health or disability support services, or
- relatives and/or caregivers of consumers of health or disability support services, or
- volunteers in clinical trials (including bioequivalence and bioavailability studies)?

☐ Yes
☐ No

E. Does your study involve the use, collection or storage of human tissue (as defined by section 7 of the Human Tissue Act 2008)?

Examples of human tissue include:

Page 1
NZ Forms (c) 2012 Version 1.0 (2012)
• all or any part of a body
• whole human organs or parts of them
• human stem cells or other human cells
• human blood
• human bone marrow
• human hair, nails, and skin
• human mucus, sputum, or urine.

☐ Yes
☐ No

F. You don’t need HDEC approval to use human tissue for research if:

• informed consent to this use has already been obtained, and the research team won’t be able to identify the individual(s) concerned
or
• the tissue can be used without HDEC review under statute (see section 20(f) of the Human Tissue Act 2008 and Right 7(10)(c) of the Code of Health and Disability Services Consumer Rights 1996).

Does one of these exceptions to the need to obtain HDEC approval apply to your study?

☐ Yes
☐ No

G. Will your study involve the use or disclosure of health information (as defined by section 4(1) of the Health Information Privacy Code 1992)?

Health information is about identifiable individuals. It includes:

• information about the health of an individual, including his or her medical history
• information about any disabilities that individual has, or has had
• information about any health services or disability services that are being provided, or have been provided, to that individual
• information in connection with the donation of any body part or any bodily substance of that individual
• information derived from the testing or examination of any body part, or any bodily substance of that individual
• information about the individual which is collected before or in the course of, and incidental to, the provision of any health service or disability service to that individual.

☐ Yes
☐ No

H. You don’t need HDEC approval to use health information for research if:

• informed consent to this use has already been obtained
or
• the health information won’t be disclosed to researchers in a form that would allow them to identify the individual(s) concerned, or to match the information with other datasets through a non-encrypted identifier (eg. an NHI number).

Does one of these exceptions to the need to obtain HDEC approval apply to your study?

☐ Yes
☐ No
Exemptions

I. Exemption for low risk medical devices

Does your study involve evaluating a low-risk (class I) medical device?

Low-risk (class I) medical devices are defined from page 77 of the Australian Therapeutic Goods Administration's Australian Regulatory Guidelines for Medical Devices:

☐ yes  
☐ no

II. Exemption for audits and related activities

i. Is your observational study an audit or related activity?

The term "audit and related activity" is defined in the Ethical Guidelines for Observational Studies.

☐ yes  
☐ no

K. Exemption for minimal risk observational studies

Does your study involve more than minimal risk?

A study involves more than minimal risk if the probability and magnitude of possible harms resulting from participation in the study is greater than those encountered in everyday life.

A study always involves more than minimal risk if it involves one or more of the following:

- one or more participants who will not have given informed consent to participate
- one or more participants are vulnerable
- standard treatment being withheld from one or more participants
- the storage, preservation or use of human tissue without consent
- the discloser of health information without authorisation.

☐ yes  
☐ no


III. Please briefly explain your answer above.

[≤ 1200 characters]

INCLUSIONS

Ma. Guthrie cards

Will your study involve the use of human tissue samples (known as Guthrie cards) obtained as part of New Zealand’s Newborn Metabolic Screening Programme?
The Newborn Metabolic Screening Program Policy Framework contains further information on the use of Guthrie cards for research.

- yes
- no

**Mb. HRC-funded research**

Is your study funded by the Health Research Council of New Zealand (HRC), and unable to be reviewed by an approved institutional ethics committee?

- yes
- no

**Mo. Tissue banks**

Does your application involve the establishment or maintenance of a tissue bank?

*A tissue bank is a collection of human tissue samples stored for potential use in research beyond the life of a specific research project.*

- yes
- no

---

**HDEC REVIEW**

According to your answers above, your study does not require HDEC review.

- If you'd like a formal letter to confirm this, please complete and submit an application. The application form may also help you to think through the ethical issues that might be involved in your study.
- If your study involves a DHB, you must contact the DHB's research office before you begin.
- If your study involves a university or polytechnic, you must contact its institutional ethics committee before you begin.
Appendix E

Figure v-1  Frequency histograms to show distributions of a) BMI at baseline, b) minimum BMI, c) BMI at final follow up before (left column) and after logarithmic transformation (right column)

a)

b)

c)
Figure v-2  Frequency histograms to show the distribution of a) change in BMI from baseline to minimum BMI, b) change in BMI from baseline to final follow up assessment, and c) change in BMI from minimum BMI to final follow up assessment.
Figure v-3 Frequency histograms to show distributions of a) fasting glucose at baseline, b) fasting glucose at follow up, c) HbA1c at baseline, d) HbA1c at follow up, e) fasting insulin at baseline, f) fasting insulin at follow up, g) HOMA-IR at baseline, and h) HOMA-IR at follow up before (left column) and after logarithmic transformation (right column)
Table v-1  Mean (Standard deviations) and 95% confidence intervals for ln(x) leptin (pmol/L), ln(x) ghrelin (pmol/L), ln(x) PYY (pmol/L), and ln(x) amylin (pmol/L) measured on the day before gastric bypass surgery, on day six following surgery, and at follow up greater than five years following surgery.
Figure v-4  Frequency histograms showing (left hand column) fasting concentrations of Leptin (pg/dl) before surgery, on day six following surgery, and at greater than five years. Histograms of transformed (ln(x)) data are shown in the right hand column.
Appendix

Figure v-5  Frequency histograms showing (left hand column) fasting concentrations of Ghrelin (pg/ml) before surgery, on day six following surgery, and at greater than five years. Histograms of transformed (ln(x)) data are shown in the right hand column.

- Baseline Ghrelin (pg/ml):
  - Mean = 20.64
  - Std. Dev. = 4.83
  - N = 25

- Day 6 Ghrelin (pg/ml):
  - Mean = 21.24
  - Std. Dev. = 4.91
  - N = 25

- Greater than 5 Years Ghrelin (pg/ml):
  - Mean = 18.54
  - Std. Dev. = 3.06
  - N = 25

- Baseline Ln(x) Ghrelin (pg/ml):
  - Mean = 3.00
  - Std. Dev. = 0.21
  - N = 25

- Day 6 Ln(x) Ghrelin (pg/ml):
  - Mean = 3.03
  - Std. Dev. = 0.21
  - N = 25

- Greater than 5 Years Ln(x) Ghrelin (pg/ml):
  - Mean = 2.91
  - Std. Dev. = 0.15
  - N = 25
Figure v-6 Frequency histograms showing (left hand column) fasting concentrations of PYY (pg/ml) before surgery, on day six following surgery, and at greater than five years. Histograms of transformed (ln(x)) data are shown in the right hand column.
Figure v-7 Frequency histograms showing (left hand column) fasting concentrations of amylin (pg/ml) before surgery, on day six following surgery, and at greater than five years. Histograms of transformed (ln(x)) data are shown in the right hand column.


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