Rates of fructose malabsorption in gout cases and non-gout controls in Christchurch, New Zealand

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Rates of fructose malabsorption in gout cases and non-gout controls in Christchurch, New Zealand

Caitlin Batt
Abstract

**Background:** Gout is a common form of inflammatory arthritis caused by the precipitation of monosodium urate crystals in the joints. The prevalence of gout in New Zealand is 9.62% in Māori men and 5.12% in European men. Hyperuricaemia is a risk factor for gout and has been associated with fructose, a sugar found in fruit and sweeteners. Fructose malabsorption has a prevalence of 34% in healthy individuals. The aim of this case-control study is to observe whether there is an association between fructose malabsorption and gout.

**Method:** Cases (n=65) were those with clinically diagnosed gout. Controls (n=65) were age and gender matched from the general population. Fructose malabsorption was measured in cases and controls using a breath test that measures gas products of the metabolism of fructose by bacteria in the gastrointestinal tract.

**Results:** The rate of fructose malabsorption in cases was 49.2% and in controls was 53.8%. The odds of malabsorbing fructose in those with gout compared to those without was 0.82 (95%CI 0.41-1.67).

**Conclusion:** There is no significant difference in rates of fructose malabsorption between gout cases and controls. Future studies are required to determine whether the effect of fructose load on serum urate is different between malabsorbers and absorbers in gout cases and those without gout. In future practice dietary advice for gout could be individualised based on absorption status, improving compliance.
Preface

This work was undertaken in the Department of Medicine, University of Otago, Christchurch during 2013. It was submitted in fulfilment of the criteria of a Bachelor of Medical Sciences (Honours) degree.

Ethical for the field work in Chapter Two was granted by the Southern Health and Disability Ethics Committee on 18th September 2012 (12/STH/11).

I undertook this thesis to broaden my own understanding of how to conduct a research project and write a scientific thesis in preparation for my career. I thoroughly enjoyed the experience.

Some changes in protocol were made while completing this work. The original proposal for this thesis called for recruitment of 100 gout cases and 100 non-gout controls. Due to time constraints this was not possible and a total of 130 individuals were recruited to the study.

Our initial plan to recruit non-gout controls was to ask gout cases to bring along a friend of a similar age, gender and ethnicity to do the study. Unfortunately this did not yield enough controls and so the recruitment strategy was widened further (Chapter Two).

I would like to thank my supervisors Professor Lisa Stamp and Associate Professor Richard Gearry for their guidance and support throughout this work. I would also like to thank Associate Professor Chris Frampton for his input into the statistics undertaken for this thesis, Digestive Health Services, Christchurch, the Department of Rheumatology, Immunology and Allergy, Christchurch Hospital, and the staff of the Nicholls research centre at the University of Otago, Christchurch.
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</thead>
<tbody>
<tr>
<td>AMP</td>
<td>Adenosine monophosphate</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>ARIC</td>
<td>Atherosclerosis risk in communities</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
</tr>
<tr>
<td>GWAS</td>
<td>Genome wide association scan</td>
</tr>
<tr>
<td>g</td>
<td>Grams</td>
</tr>
<tr>
<td>g/kg BW/hr</td>
<td>Grams per kilogram body weight per hour</td>
</tr>
<tr>
<td>&gt;</td>
<td>Greater than</td>
</tr>
<tr>
<td>HFCS</td>
<td>High fructose corn syrup</td>
</tr>
<tr>
<td>IBD</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>IMP</td>
<td>Inosine monophosphate</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>IBS</td>
<td>Irritable bowel syndrome</td>
</tr>
<tr>
<td>kg</td>
<td>Kilograms</td>
</tr>
<tr>
<td>&lt;</td>
<td>Less than</td>
</tr>
<tr>
<td>MSU</td>
<td>Monosodium urate</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
</tr>
<tr>
<td>NZ</td>
<td>New Zealand</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>Non steroidal anti-inflammatories</td>
</tr>
<tr>
<td>NA</td>
<td>Not available</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SU</td>
<td>Serum urate</td>
</tr>
<tr>
<td>SE</td>
<td>Standard error</td>
</tr>
<tr>
<td>SSB</td>
<td>Sugar sweetened beverages</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
</tbody>
</table>
Chapter One

1.1 Introduction

Gout is a common form of inflammatory arthritis. Its prevalence is high in New Zealand (NZ) (1). Gout has a large impact on peoples’ lives in terms of their quality of life, mobility, ability to work and to spend time with their families (2, 3). The association between gout and sugar was first noticed by Osler in the 18th Century (4). It is proposed that fructose increases serum urate (SU) levels via the dephosphorylation of adenosine triphosphate (ATP) molecules (5). Dietary intervention is common in gout management with patients asked to avoid many foods including alcohol and seafood (6). Recently it has been suggested that gout patients avoid fructose in their diets to lessen their risk of gout attacks (7, 8).

Malabsorption of fructose is common in the population with 34% of healthy volunteers found to malabsorb a fructose load of 35 grams (9). Fructose malabsorption has primarily been considered in the context of dietary treatment for irritable bowel syndrome (9). It has not yet been examined in the context of gout.

The aim of this study was to determine the incidence of fructose malabsorption in gout patients compared to healthy controls without gout. This could provide information as to why some people are more susceptible to gout than others. Ultimately this research is the starting point for individualizing dietary treatment for gout, which may increase compliance with dietary advice and improve control of gout.

1.2 Gout

1.2.1 Definition

Gout is caused by precipitation of monosodium urate (MSU) crystals in the joints. It causes excruciatingly painful and debilitating attacks of joint pain (10). Gout, in the form of inflammation of the first metatarsophalangeal (MTP) joint of the big toe (podagra), was first
identified in 2640BC by the Egyptians. It has historically been associated with wealth and overindulgence of wine, meat and other rich foods (11). More recently gout has been perceived as an embarrassing and shameful disease that should be hidden and endured (12).

During an attack of gout the affected joints become acutely painful, swollen, hot and red with a limited range of movement (13). Attacks have a sudden onset, often between 12-24 hours (10). Pain can be so severe that sufferers are unable to weight bear and have to rely on others to care for them (12). Attacks commonly involve the first MTP joint but can also occur in other joints, for example in the hands, knees and ankles. Attacks can be mono- or polyarticular (11). Attacks can last a week or more if untreated and there may be gaps between attacks of weeks, months or years during which the patient will suffer no symptoms (10).

As the disease progresses attacks become more frequent or constant, are more difficult to control and can lead to joint damage. In chronic, poorly controlled gout, subcutaneous deposits of MSU crystals known as tophi may form (10, 11). This late stage of gout is far more debilitating and can have a large impact on the patient’s quality of life, including decreased ability to work and increased risk of hospitalisation (12).

While the diagnosis of gout can be made clinically, definitive diagnosis is made by the detection of negatively birefringent, needle-shaped MSU crystals in synovial fluid or tophus (10, 11).

1.2.2 Pathogenesis

Hyperuricaemia (SU>0.42mmol/L) is integral to the development of gout. SU is produced when purines (adenine and guanine) are metabolized (Figure 1) (14). Fructose is also metabolized to uric acid.
Accumulation of SU occurs in humans as we lack the uricase enzyme that breaks uric acid down to the more water soluble allantoin. The loss of this enzyme may be because uric acid has antioxidant properties, so higher levels gave an evolutionary advantage (15, 16).

Hyperuricaemia results from either an over-production or under-excretion of urate. Over-production of urate may be due to dietary influences, high cell turnover or rare genetic causes. Under-excretion of urate may be due to use of diuretics or kidney disease (10, 17). 90% of hyperuricaemia is caused by renal urate under-excretion (11).
1.2.3 Prevalence

Gout is common in New Zealand (18, 19). In 2009 the overall prevalence of gout was 2.69% (18). A more recent NZ study reported the overall prevalence as 4.67% (19).

Gout is more common in males than females with a prevalence of 5.98% in NZ males and 1.76% in NZ females (18). Gout prevalence increases in women after menopause when the uricosuric effect of oestrogen is lost (20). 85% of female gout is found in post-menopausal women (13).

The prevalence of gout differs between ethnic groups in NZ, with higher rates in Māori and Pacific Islanders. The prevalence in Maori men is 9.62% and in Pacific Island men is 12.32%, compared to 5.12% in Caucasian (18). The prevalence of gout in elderly (>65 year old) Maori and Pacific Island men has been reported to be as high as 38% and 30% respectively (19).

The prevalence of gout in NZ is higher than in many other parts of the world. The prevalence of gout in England 2001-2007 was reported to be 0.46% (21). However, the gout prevalence in the United States of America (USA) of 3.9% is similar to prevalence in the NZ population (22).

The prevalence of gout in NZ and around the world has been increasing due to the aging population and use of medications that increase SU, amongst other factors. An increase from 4.5%-10.4% to 13.9% in Maori men and from 0.7-2.0% to 5.8% in European men was observed between 1958-1984 and 1997 (1). The prevalence of gout in the USA increased by 1.2% between 1988-1994 and 2007-2008 (22).

With a global increase in gout prevalence there is an increasing burden on healthcare systems. Hospital admissions in NZ where gout was the primary cause for admission increased by 61% between 1999-2000 and 2008-2009, an increase of 5.5% per year (23).
1.2.4 Modifiable Risk Factors for Gout

There are a number of modifiable risk factors for gout (Table 1). Below only those factors directly relevant to this thesis will be discussed.

**Table 1**: Modifiable risk factors for gout (3,6,11)

<table>
<thead>
<tr>
<th>Modifiable risk factors for gout</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hyperuricaemia</td>
</tr>
<tr>
<td>• Increased dietary purine intake</td>
</tr>
<tr>
<td>• Alcohol intake</td>
</tr>
<tr>
<td>• Obesity</td>
</tr>
<tr>
<td>• Low socioeconomic status</td>
</tr>
<tr>
<td>• Medications (e.g. diuretics, low dose aspirin)</td>
</tr>
<tr>
<td>• Organ transplantation</td>
</tr>
</tbody>
</table>

1.2.4.1 Hyperuricaemia

The leading modifiable risk factor for gout is hyperuricaemia (SU >0.42mmol/l in men and >0.36mmol/L in women) (11). Like gout, the prevalence of hyperuricaemia is higher in in Maori men than European men (27% vs. 9.4% respectively) (1).

Approximately 5% of those with hyperuricaemia go on to develop gout (24). Hyperuricaemia without disease is called asymptomatic hyperuricaemia and may precede gout (11, 13). It is not known why some hyperuricaemic individuals do not go on to develop gout.

Serum urate has also been associated with a number of other conditions including chronic kidney disease, obesity, hypertension, diabetes, nephrolithiasis, stroke, myocardial infarction and heart failure (11, 22, 25).
1.2.4.2 Diet

Purine Intake

An association between increasing dietary purine intake and increased serum urate levels has been reported (3, 26). In a study of 14,809 participants a higher mean SU concentration was found in participants with the highest intake of meat (>1.53 servings/day) compared to the lowest (<0.59 servings/day) (p(trend) <0.001) (Table 2) (3). This study also found that an increase in SU concentration in those with the highest seafood intake (>0.30 servings/day) compared to the lowest (<0.03 servings/day) (p(trend) = 0.005) (3). Another large study found no association between SU concentration and seafood intake (26).

An association between meat and seafood intake and risk of gout has also been observed (Table 2) (27).

No association between total protein intake and a higher SU concentration was observed leading to the conclusion that the associations demonstrated in table 2 were due to the purine content of the foods rather than the protein content (3). No association was found between serum urate or gout and purine rich vegetables (3, 26). On this basis, current recommendations for gout patients include limiting purine rich foods, such as red meat and seafood, to help control gout attacks (6, 11).

Table 2: Mean difference in SU concentration and multivariate relative risk of gout in those consuming large amounts of meat and seafood, compared to those with low intake (3, 6).

<table>
<thead>
<tr>
<th></th>
<th>Highest meat intake (compared to lowest)</th>
<th>Highest seafood intake (compared to lowest)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SU difference, mmol/L (95% CI*)</td>
<td>0.0095 (0.0036-0.016)</td>
<td>0.03 (0.020-0.036)</td>
</tr>
<tr>
<td>P</td>
<td>0.005</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariate Relative Risk (RR) of gout (95% CI*)</td>
<td>1.51 (1.17-1.95)</td>
<td>1.41 (1.07-1.86)</td>
</tr>
<tr>
<td>P(trend)</td>
<td>0.02</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*95% confidence interval
Alcohol intake and gout have long been known to be associated. Specific beverages have more of an effect on SU than others. A recent study of 14,809 people found an association between total alcohol intake and SU concentration. The mean difference in SU in those consuming ≥1 serving of beer per day compared to those consuming 0 was 0.025mmol/L (95% confidence interval (95%CI) 0.19-0.36, p<0.001), and for those consuming ≥1 serving of liquor compared to those consuming 0 was 0.015mmol/L (95% CI 0.08-0.27, p<0.001). There was no association between consumption of wine and SU (28).

These findings are consistent with the association found between different alcoholic beverages and risk of gout. A cohort study involving 47,150 men found that the risk of gout increased by 17% per 10g increase in alcohol consumption per day (RR = 1.17 (95% CI 1.11-1.22)). Beer conferred the highest risk, with an intermediate risk increase from liquor consumption and no association between wine consumption and risk of gout (29).

It is currently recommended that gout sufferers limit alcohol intake to a moderate level of less than 1 standard drink per day for women, and 1-2 standard drinks per day for men (6).

1.2.4.3 Body Mass Index

A study using data from the National Health and Nutrition Examination Survey (NHANES) from 1988-1994, 2007-2008 and 2009-2010 examined the association between body mass index (BMI) and gout (30). In the 2007-2010 group data from 11,589 participants revealed an increased prevalence of gout at each category of BMI (Table 3). When the association between gout and BMI was adjusted by serum urate the relationship remained statistically significant although attenuated (30). This is consistent with data from another study where weight gain over time was associated with an increased risk of gout (31).
1.2.4.4 Other diseases and drugs

A decrease in the renal urate excretion also causes an increase in SU. This can be caused by renal disease or by the use of medications such as diuretics (11, 20). The multivariate relative risk of gout in those taking a diuretic compared to those not taking a diuretic was 1.77 (95% CI 1.42-2.00). This association was adjusted for diagnosis of hypertension. In the same study chronic renal failure was found to be strongly associated with gout risk (RR=3.61, 95%CI 1.60-8.14) (31).

Low dose aspirin and medications used in organ transplant, such as cyclosporine, have also been associated with increased SU levels and increased gout risk (20).

### 1.2.4 Non-modifiable Risk Factors for Gout

#### 1.2.4.1 Genetics

Genome wide association scans (GWAS) have identified genes involved in coding for renal urate transporters that have a role in the control of serum urate level hyperuricaemia and/or
gout (17, 32-37). A review of these genes is beyond the scope of this thesis and the studies are summarised in Table 4.

**Table 4**: Summary of evidence for associations between genes and hyperuricaemia and gout. Adapted from table in Merriman et al (17)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Phenotype</th>
<th>Association with risk variant</th>
<th>Function</th>
<th>Population</th>
<th>Gender</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SLC2A9/GLUT9</strong></td>
<td>Hyperuricaemia</td>
<td>Increases risk</td>
<td>Codes for the GLUT9 renal transporter in the kidney</td>
<td>Caucasian, Pacific Island, NZ Maori</td>
<td>Greater effect in women than men.</td>
<td>(32-34, 36, 110)</td>
</tr>
<tr>
<td></td>
<td>Gout</td>
<td>Increases risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ABCG2</strong></td>
<td>Hyperuricaemia</td>
<td>Increases risk</td>
<td>ATP binding cassette family in the kidney</td>
<td>Pacific Island, Caucasian</td>
<td>Greater effect in men than women</td>
<td>(32-34, 37)</td>
</tr>
<tr>
<td></td>
<td>Gout</td>
<td>Increases risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SLC17A3/NPT4</strong></td>
<td>Hyperuricaemia</td>
<td>Increases risk</td>
<td>NPT4 Sodium potassium transporter in the kidney</td>
<td>Caucasian</td>
<td></td>
<td>(33)</td>
</tr>
<tr>
<td></td>
<td>Gout</td>
<td>Increases risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SLC17A1/NPT1</strong></td>
<td>Serum urate</td>
<td>NA</td>
<td>NPT1</td>
<td>Caucasian</td>
<td></td>
<td>(32)</td>
</tr>
<tr>
<td></td>
<td>Gout</td>
<td>Increases risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GCKR</strong></td>
<td>Serum urate</td>
<td>NA</td>
<td>Glucokinase regulator protein</td>
<td>Caucasian</td>
<td></td>
<td>(32, 35)</td>
</tr>
<tr>
<td><strong>LRRC16A</strong></td>
<td>Serum urate</td>
<td>NA</td>
<td>Encodes CARMIL, a protein in the kidney</td>
<td>Caucasian</td>
<td></td>
<td>(32)</td>
</tr>
<tr>
<td><strong>SLC22A12/URAT1</strong></td>
<td>Serum urate</td>
<td>NA</td>
<td>Organic anion transporter (OAT)</td>
<td>Caucasian</td>
<td></td>
<td>(32)</td>
</tr>
<tr>
<td></td>
<td>Hyperuricaemia</td>
<td>Increases risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SLC22A11/OAT1</strong></td>
<td>Serum urate</td>
<td>NA</td>
<td>OAT</td>
<td>Caucasian</td>
<td></td>
<td>(32, 35)</td>
</tr>
<tr>
<td><strong>SLC16A9</strong></td>
<td>Serum urate</td>
<td>NA</td>
<td>Monocarboxylic acid transporter 9</td>
<td>Caucasian</td>
<td></td>
<td>(32, 35)</td>
</tr>
<tr>
<td><strong>PDZK1</strong></td>
<td>Serum urate</td>
<td>NA</td>
<td>Scaffolding protein that interacts with OAT4</td>
<td>Caucasian</td>
<td></td>
<td>(32, 35)</td>
</tr>
</tbody>
</table>
1.2.5 Management

The treatment of gout has two aims; firstly to treat the acute gouty attacks, and secondly to reduce the number of attacks long term and to decrease complications by sustained reduction in SU (38, 39). Some medications are used only during acute attacks, while changes to diet and weight can be used alongside regular urate lowering medications for long term management (39).

1.2.5.1 Medications

The treatment of acute attacks aims to decrease joint pain and inflammation. Non-steroidal anti-inflammatory drugs (NSAIDs), colchicine and corticosteroids can be used with the choice of agent dictated by the patients co-morbidities and con-comitant medications (38). Treatment is best initiated at the first sign of an attack and can decrease the length of attacks (11).

Long-term therapy aims to prevent attacks and reduce complications by lowering SU (11, 38). Allopurinol is the first line urate lowering agent. It is a xanthine oxidase inhibitor that is taken once daily. Drugs that increase the renal excretion of urate can also be used e.g. benzobromarone. The goal of treatment is sustained reduction in SU to less than 0.36mmol/L (39).

1.2.5.2 Lifestyle

The lifestyle changes that are recommended for gout patients are weight loss and dietary changes.

Weight loss

Weight loss has been shown to decrease the number and severity of gout attacks. In one study, 13 men with confirmed gout were put on a 16 week diet to encourage weight loss, but not decrease purine intake. At the end of the study period the average weight loss was 7.7
kilograms (kg) (range 0-21kg). SU had decreased by 0.10mmol/L (range 0.03-0.16mmol/L, p<0.001) and the number of gout attacks per month decreased by 1.5 (range 0-2.5, p<0.002). Thus weight loss improved gout control in this small study (40).

A lower risk of developing gout following weight loss has also been observed. Men who lost 4.5kg have a 39% lower risk of gout compared to those who maintain their weight. An increased risk of gout was associated with weight gain (31).

Weight loss is, therefore, effective in both the management and the primary prevention of gout (6).

**Diet**

Gout has traditionally been associated with rich foods and over consumption. Many dietary recommendations are made for people with gout. In a study from Shulten et al ninety seven per cent of rheumatologists considered diet in the management of their gout patients, and 84% of gout patients had received dietary advice regarding gout management (41).

Dietary guidelines for gout patients commonly include avoidance or limiting of red meats, shellfish and alcohol. High fructose foods, for example sugar-sweetened beverages, are now being included as the association between fructose and gout becomes clearer (6, 7, 42). It has been reported that diets allowing more protein intake but lower calorie intake have significant effects on weight loss and lowering SU. A focus on diets encouraging weight loss rather than lowering purine intake may be more successful in decreasing gout attacks (40).

Dairy products and coffee have been found to decrease the risk of both hyperuricaemia and gout (3, 27, 43-45). One study showed a multivariate relative risk of gout for those consuming >1.67 servings/ day of low fat dairy compared to those consuming <0.2 servings per day was 0.58 (0.45-0.76; P(trend) <0.001) (3). Increased dairy consumption is protective for gout and gout sufferers are thus advised to consume low fat dairy products regularly (6, 7).
The risk of gout in men drinking 4-5 cups of coffee per day is 40% lower than those who do not drink coffee (RR = 0.60 (CI 0.41-0.87); P(trend) <0.0001) (45). The authors of this study proposed that this may have been due to the antioxidant effects of coffee. Tea, which has a lower antioxidant capacity, did not appear to decrease SU or gout risk (43-45). Gout sufferers are, therefore, encouraged to continue drinking coffee (6, 7).

Figure 2 outlines the dietary changes recommended to gout patients as part of the management of the disease.

Figure 2: Dietary impact on the risk of gout and their implications within a healthy eating guideline pyramid adapted from (6).
1.2.6.3 Adherence

Adherence with both dietary advice and urate lowering therapy (ULT) is a significant issue in the management of gout. Martini et al reported that despite 85% of participants knowing that gout was associated with foods and beverages, only 51% made an effort to avoid trigger foods in their diet. In the same study 21% of patients did not take their medications as prescribed as they did not want to take them long term, or did not know when they were supposed to take them (2).

Dietary changes alone may not have a significant impact on SU, but may have additional benefits for health such as weight loss in obese patients (38). Dietary modification and weight loss are hard to achieve and to sustain. The current one-diet fits all approach does not take into account individual variation in absorption or metabolism of key dietary factors that may influence SU and gout. It would seem likely that patients may be more compliant with an individualized approach to dietary management, based on identification of individual triggers or absorption/metabolism of key dietary factors such as fructose, which will be explored in this thesis. This is supported by evidence that a multi-dimensional approach to management including education, individualized lifestyle advice and appropriate ULT reduces serum urate to <0.36mmol/L in 92% of gout sufferers over a 12 month period (46).
1.3 Fructose

1.3.1 Structure

The fructose molecule is a 6-carbon structure that is found in multiple forms in the diet. On its own the fructose molecule is a monosaccharide sugar. The fructose molecule also makes up half of the disaccharide molecule sucrose, more commonly known as table sugar. Sucrose is made up of one molecule of glucose and one molecule of fructose. Fructose can be found in the diet as oligosaccharides and polysaccharides (fructans, fructo-oligosaccharides and inulins), where multiple fructose molecules are bound to each other (Figure 3) (47).

![Figure 3: Structure of the fructose molecule alone and as part of sucrose and inulin (fructans). The inulin molecule has a repeating fructose unit that is labelled n. From Gibson et al (47).](image_url)
1.3.2 Sources of fructose

In New Zealand, fructose is found naturally in fruit and vegetables, and added as sucrose to beverages and other food products (47, 48). Fructose is found naturally in honey, with about 2.9 grams (g) fructose per teaspoon (7g) of honey (49). Apples, grapes and pears are also high in fructose with 12.6g, 12.4g and 11.8g fructose per medium piece respectively, compared to watermelon or oranges which have lower fructose levels, 6.0 or 6.1g respectively (49). Fructose is also added to sweeten foods such as bread, sweets, cereals, sauces and condiments (50, 51).

High Fructose Corn Syrup (HFCS) is a sweetener that was introduced into the food industry in the late 1960s. HFCS contains molecules of fructose and glucose, with fructose making up 42% or 55% fructose depending on the HFCS producer (52, 53). HFCS has benefits over sucrose including taste (53). Fructose has been found to be up to 1.8 times sweeter than sucrose (54). It is increasingly being used, particularly in the USA, to sweeten foods such as non-diet beverages, fruit juice, cakes, jams and pies. Products containing HFCS are not used widely in NZ currently.

HFCS is commonly used in the beverage industry. Soft drinks sweetened with HFCS contain around 23.8g per 350ml serving compared to 21.8g fructose in sucrose sweetened beverages (49). Fructose content is, therefore, high in drinks sweetened with either sweetener. Fruit juices also contain fructose (10.5g/240ml serving orange juice, 15.8g/240ml serving apple juice) (49).

1.3.3 Fructose Intake

1.3.3.1 New Zealand

In NZ adults, the median daily intake of fructose is 21.6g for males and 18.3g for females (51). 29% of fructose intake is from fruit (e.g. apples and pears), with 23% being from
beverages particularly fruit juices with apple and pear bases and non-diet soft drinks (18% non-alcoholic beverages, 5% alcoholic beverages) (Figure 4) (51).

Fructose intake is lower overall in older age groups who also consume more of their fructose intake from natural sources, such as fruit. Those in the younger age groups consume more of their fructose intake from sweetened beverages. The highest fructose intake is in Pacific Island males in the 15-18 year age range, followed by NZ European males in the 19-30 year age range (51).

1.3.3.2 United States of America

Fructose intake in the USA is as high as 54.7g per day (50), over twice that found in a NZ population (51). This is the equivalent of 10.2% of daily energy intake in an American adult (50). 30% of fructose intake in a North American population comes from beverages, an industry where HFCS is often used as a sweetener and 18% is from fruit (50) (Figure 4).

Figure 4: Sources of dietary intake of fructose in New Zealand (right) and American (left) adults. Adapted using data from 2008/2009 New Zealand Adult Nutrition Survey (NZ) (51) and Vos et al (USA) (50).

*Ready-to-eat (RTE)
1.3.3.3 Increasing consumption

The consumption of sucrose, and therefore fructose, has been increasing across the world since the 1800’s (55). The consumption of fructose in the USA increased by 30% between 1970 and 2000, coinciding with the introduction and continuing use of HFCS (56). In NZ the use of added sugars is also on the increase. Thornley et al reported that between 1980 and 2005 there was a 25% increase in the consumption of added sugars (48). This is concerning as the evidence for added sugars as part of the pathogenesis of multiple medical conditions is increasing (48, 55).

1.3.4 Absorption of fructose

1.3.4.1 Mechanism

Fructose is absorbed in the mid to distal small intestine. It is transported across the intestine wall into the portal circulation by GLUT5 and GLUT2 (Figure 5) (5, 57).

GLUT5 is the main fructose transporter in the intestinal lumen with intestinal fructose absorption decreased by 75% in GLUT5 knockout mice (58). GLUT5 is found primarily on the apical membrane and transports fructose across the brush border. It has also been found at the basolateral membrane (57).

GLUT2 is found on the basolateral membrane of intestinal epithelial cells. GLUT2 transports both glucose and fructose into the blood (57). GLUT2 may also have a role in apical transport where there is a high fructose load, although thus far this has only been found in animal models (57, 59).
The expression of the GLUT2 and GLUT5 transporters is influenced by exposure to fructose and glucose. Fructose up-regulates expression of both receptors, while GLUT2 expression is also up-regulated by glucose (47, 57). When fructose is absorbed with glucose, as in many food stuffs, fructose absorption is enhanced (60).

Following absorption, fructose is transported from the intestine via the portal vein to the liver where it is taken up into hepatocytes by the GLUT2 transporter. Because most ingested fructose is metabolised by the liver, fructose concentration in the circulation following ingestion is low (54, 61).
1.3.4.2 Malabsorption of fructose

Fructose absorption is saturable and the ability of the human intestine to absorb fructose depends on the fructose dose given (62). Individuals lie on a spectrum, with a range of abilities to absorb fructose present (57). Gibson et al defines fructose malabsorption as “any situation in which free fructose is available to fermentative metabolism by luminal bacteria before it can be absorbed across the small intestine mucosa” (47). This fermentative metabolism results in the production of hydrogen or methane, which can be detected in the breath and thus used as a measure of fructose malabsorption (60, 62). Fructose malabsorption is defined by a hydrogen or methane reading above a certain point at a certain time period after a fructose load. The specific cut off points vary by study (9, 47, 62).

Symptoms
Fructose malabsorption can lead to symptoms in some individuals, particularly those with irritable bowel syndrome (IBS) where there often visceral afferent hypersensitivity leading to a “sensitive” gut. The unabsorbed fructose passes through the small intestine and into the large intestine where it is fermented by microflora. This fructose leads to an increased osmotic load, drawing water into the small intestine. These changes lead to an increased delivery of water to the colon and production of gas, causing flatulence, abdominal pain and diarrhoea (47, 62). Symptoms tend to be more pronounced with higher fructose doses and less where fructose and glucose are combined due to co-transport of these molecules (62-64).

Prevalence
Fructose absorptive capacity depends on the dose of fructose used, therefore, the dose used when testing determines the prevalence of fructose malabsorption found in a given population (Table 5) (9, 47, 62, 63, 65, 66).

Some of these studies also observed the effect on fructose absorption when a combined fructose and glucose load was given. In the study by Densupsoontorn et al a fructose dose of
25 g with a glucose dose of 25 g led to no malabsorption, compared to a rate of 14% when 25 g fructose was given alone (67). Kim et al reported that breath hydrogen was higher among those who consumed only fructose, compared to a combination of fructose and glucose, and that gastrointestinal symptoms were higher amongst those who consumed fructose alone (64).

Table 5: A summary of results of studies from 2000 onwards assessing frequency of fructose malabsorption amongst healthy adults.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n = (% male)</td>
<td>17 (0%)</td>
<td>71 (28%)</td>
<td>20 (50%)</td>
<td>77 (48%)</td>
<td>15 (30%)</td>
<td>32 (53%)</td>
</tr>
<tr>
<td>% malabsorbers at fructose dose:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 grams</td>
<td>-</td>
<td>-</td>
<td>0%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>25 grams</td>
<td>-</td>
<td>-</td>
<td>10%</td>
<td>14%</td>
<td>53%</td>
<td>19%</td>
</tr>
<tr>
<td>35 grams</td>
<td>-</td>
<td>34%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>50 grams</td>
<td>53%</td>
<td>-</td>
<td>80%</td>
<td>-</td>
<td>73%</td>
<td>81%</td>
</tr>
</tbody>
</table>

Fructose malabsorption is more common in those with gastrointestinal disorders such as irritable bowel syndrome (IBS) or inflammatory bowel disease (IBD) (49). A significantly higher frequency of fructose malabsorption in those with Crohn’s disease compared to healthy volunteers has been observed (61% Crohn’s disease vs. 34% controls, p<0.03) (9). It has been reported that in 91% of those with IBS and a positive breath test, IBS symptoms are reproduced by the 25 g fructose load (68).
Aetiology

There is no consensus as to what causes an individual to have a lower capacity for the absorption of fructose. No difference in the GLUT5 gene between those with isolated fructose malabsorption and healthy controls has been observed (69). Other potential causes of fructose malabsorption include changes in the up-regulation of intestinal transporters by luminal sugars, and differences in microflora causing unabsorbed fructose to be handled differently (57, 69).

1.4 Fructose and serum urate

1.4.1 Mechanisms

Fructose is metabolised in the liver by fructokinase leading to adenosine triphosphate (ATP) depletion and production of a glyceraldehyde-3-phosphate molecule that becomes substrate for the pathways of glycolysis, gluconeogenesis, glycogenesis, lipogenesis and fatty acid esterification (5, 54, 61, 70) (Figure 6). Increased uric acid production occurs as the metabolism of fructose results in depletion of ATP, which reduces feedback inhibition of uric acid production, and increased adenine monophosphate (AMP) production, which is a substrate for uric acid metabolism. Fructose metabolism differs from the metabolism of glucose in that it is not regulated by insulin. Glucose metabolism also replenishes the ATP molecules used in the process so there is no accumulation of ADP, AMP, inosine monophosphate (IMP) and eventually uric acid as in the metabolism of fructose (5).
1.4.2 Intravenous Fructose and Serum Urate

The effect of fructose on SU was initially studied where fructose was used intravenously for calorie and fluid replacement (71). The results of these early studies showed no effect or a variable increase in SU (Table 6) (72-76). Budillon et al observed a mean percentage increase in SU of 28% from baseline (mean absolute SU increase 0.08mmol/l) following a fructose infusion in 10 healthy controls (77). A second study observed a similar mean percentage increase in SU (30%) but a larger absolute increase (0.11mmol/L) following fructose infusion in 8 healthy male controls (78). Two studies found no significant change in SU with a fructose dose of 0.5 g per kilogram body weight per hour (g/kg BW/hr) (79, 80). The observed lack of effect on SU may relate to the speed of fructose load delivery with

Figure 6: Pathways for the metabolism of fructose in the liver including phosphorylation of fructose and the subsequent production of ADP to uric acid (5,54,61,70).
those studies with a prolonged infusion time showing no effect and those with a short infusion time showing an increased in SU (Table 6).

**Table 6:** Studies assessing SU in response to one off intravenous fructose load in healthy adult controls. Fructose dose measure in grams per kilogram body weight (g/kg BW).

<table>
<thead>
<tr>
<th>Study</th>
<th>n (% male)</th>
<th>Fructose dose concentration</th>
<th>Infusion time (min)</th>
<th>Significant increase in SU</th>
<th>Peak SU (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamamoto (1997) (72)</td>
<td>7 (100%)</td>
<td>1g/kg BW (10%)</td>
<td>60</td>
<td>Increased</td>
<td>-</td>
</tr>
<tr>
<td>Loguercio (1996) (73)</td>
<td>10 (90%)</td>
<td>0.5g/kg BW (40%)</td>
<td>10</td>
<td>Increased (not statistically significant)</td>
<td>-</td>
</tr>
<tr>
<td>Budillon (1992) (77)</td>
<td>10 (60%)</td>
<td>0.5g/kg BW (40%)</td>
<td>-</td>
<td>Increased</td>
<td>~30</td>
</tr>
<tr>
<td>Maso (1983) (74)</td>
<td>30 (73%)</td>
<td>0.3g/kg BW</td>
<td>3</td>
<td>Increased</td>
<td>~30</td>
</tr>
<tr>
<td>Fiaschi (1977) (75)</td>
<td>8 (63%)</td>
<td>0.3g/kg BW</td>
<td>~10</td>
<td>Increased</td>
<td>~15</td>
</tr>
<tr>
<td>Brodan (1975) (76)</td>
<td>7</td>
<td>12g (20%)</td>
<td>3</td>
<td>Increased</td>
<td>~10</td>
</tr>
<tr>
<td>Narins (1974) (78)</td>
<td>8 (100%)</td>
<td>24g (20%)</td>
<td>6</td>
<td>Increased</td>
<td>~10</td>
</tr>
<tr>
<td>Curreri (1970) (71)</td>
<td>10 (100%)</td>
<td>100g (10%)</td>
<td>120-300</td>
<td>No change</td>
<td>-</td>
</tr>
<tr>
<td>Sahebjami (1971) (80)</td>
<td>10 (100%)</td>
<td>0.5g/kg BW/hr (10%)</td>
<td>60</td>
<td>No change</td>
<td>-</td>
</tr>
<tr>
<td>Heuckenkamp (1971) (70)</td>
<td>30 (100%)</td>
<td>0.5g/kg BW/hr (10%)</td>
<td>360</td>
<td>No change</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1g/kg BW/hr (10%)</td>
<td></td>
<td>Increased (not statistically significant)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.5g/kg BW/hr (10%)</td>
<td></td>
<td>Increased</td>
<td>90 minutes</td>
</tr>
</tbody>
</table>
1.4.3 Oral Fructose and Serum Urate

In real life, fructose is acquired through dietary intake (49) and it is therefore important in the context of gout to assess the effect of oral fructose on SU. Studies exploring this relationship were published as far back as the 1970s and consistently reveal an increase in SU (81-84) (Table 7).

**Table 7:** Summarised results of trials assessing SU and urate excretion in response to one off oral fructose loads in healthy adult controls. Some studies used different ratios of fructose to glucose (F:G).

<table>
<thead>
<tr>
<th>Study</th>
<th>n (% male)</th>
<th>Study Design</th>
<th>Fructose form</th>
<th>Comparison</th>
<th>Fructose Dose/F:G</th>
<th>Plasma SU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bidwell (2010)</td>
<td>10 (100%)</td>
<td>RCT</td>
<td>Liquid</td>
<td>100g glucose</td>
<td>55g:45g</td>
<td>Increased (not statistically significant)</td>
</tr>
<tr>
<td>Akhavan (2007)</td>
<td>19 (100%)</td>
<td>CO</td>
<td>Liquid</td>
<td>Water</td>
<td>300kcal in 300 ml</td>
<td></td>
</tr>
<tr>
<td>Lotito (2004)</td>
<td>6 (50%)</td>
<td>CO</td>
<td>Liquid or apples</td>
<td>Bagels</td>
<td>0.83g/kg BW</td>
<td>Increased</td>
</tr>
<tr>
<td>Buemann (2000)</td>
<td>8 (100%)</td>
<td>CO</td>
<td>Liquid</td>
<td>Water</td>
<td>30g</td>
<td>Increased</td>
</tr>
<tr>
<td>Douglas (1982)</td>
<td>12</td>
<td>CO</td>
<td>Liquid</td>
<td>-</td>
<td>50g</td>
<td>Increased</td>
</tr>
<tr>
<td>MacDonald (1978)</td>
<td>9 (100%)</td>
<td>CO</td>
<td>Liquid</td>
<td>Glucose, sucrose, sorbitol</td>
<td>0.25g/kg BW</td>
<td>Increased</td>
</tr>
</tbody>
</table>

|                |            |              |               |                   | 0.5g/kg BW        | Increased                 |
|                |            |              |               |                   | 0.75g/kg BW       | Increased                 |
|                |            |              |               |                   | 1.0g/kg BW        | Increased                 |
A fructose load of 0.5kg/kg BW (35g in a 70kg person) resulted a mean increase in SU of 0.03mmol/L at 30 minutes (85). Further studies found significant increases in the area under the curve (AUC) of SU following fructose ingestion, compared to water (86, 87).

The current evidence demonstrates an effect of fructose dose on the effect on SU. In a study of 19 males who received 6 oral solutions with differing concentrations of fructose to glucose in a crossover trial design, no increase in SU was found when a water control or the lowest proportion of fructose (fructose 20: glucose 80) were given. The largest increase in SU was observed following consumption of the solution with the highest proportion of fructose (fructose 80:glucose 20) (Figure 7) (87).

![Figure 7](image)

Figure 7: Change in SU from baseline plotted against time for solutions containing different ratios of fructose to glucose. G20:F80 (●), G35:F65 (□), G50:50 (▲), sucrose (*), G80:20 (○), Water (◇). Means at the same time-point with different letters were significantly different (p<0.05). Adapted From (86).

However not all studies have observed this dose response effect. MacDonald et al reported a significant increase in SU following administration of varying strength fructose solutions, but no significant difference between the increase in SU in those given the largest fructose load compared to those given the smallest (85).

In addition to these short term interventional studies, dietary studies examining the effect on SU of fructose as a percentage of the normal daily dietary caloric intake (isocaloric) or as an
additional daily intake of fructose above the normal dietary caloric intake (hypercaloric) have been undertaken (88).

A 2012 meta-analysis assessed the effect of fructose intake on SU in 18 isocaloric and 3 hypercaloric controlled dietary trials (88). A mean increase in SU of 0.03mmol/L (CI 0.015-0.046mmol/L) was observed in the hypercaloric trials, while there was no significant increase in SU in the isocaloric trials. These results, and the evidence from specific fructose loading studies trials (Table 8), raises the question as to whether the observed association between fructose and SU is in fact due to increased calories associated with increased fructose intake (89).
Table 8: Summarised results of trials assessing SU in response to dietary oral fructose in healthy adult controls

<table>
<thead>
<tr>
<th>Study</th>
<th>n= (% male)</th>
<th>Study design</th>
<th>Study Length</th>
<th>Form</th>
<th>Comparison</th>
<th>Fructose dose (grams/day)</th>
<th>% Daily intake</th>
<th>Plasma SU compared to control</th>
<th>Isocaloric (I)/ Hypercaloric (H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silbernagel (2011) (91)</td>
<td>20 (60%)</td>
<td>RCT</td>
<td>4 wk</td>
<td>L</td>
<td>Glucose</td>
<td>150</td>
<td>+ 35%</td>
<td>No change</td>
<td>H</td>
</tr>
<tr>
<td>Ngo Sock (2010) (89)</td>
<td>11 (100%)</td>
<td>CO</td>
<td>1 wk</td>
<td>L</td>
<td>Diet</td>
<td>~213</td>
<td>+ 35%</td>
<td>Increased</td>
<td>H</td>
</tr>
<tr>
<td>Perez-Pozo (2010) (100)</td>
<td>36 (100%)</td>
<td>RCT</td>
<td>2 wk</td>
<td>L</td>
<td>Allopurinol</td>
<td>200</td>
<td>-</td>
<td>Increased</td>
<td>H</td>
</tr>
<tr>
<td>Le (2009) (90)</td>
<td>8 (100%)</td>
<td>CO</td>
<td>1 wk</td>
<td>L</td>
<td>Diet</td>
<td>~213</td>
<td>+ 35%</td>
<td>Increased</td>
<td>H</td>
</tr>
<tr>
<td>Reiser (1989) (93)</td>
<td>10 (100%)</td>
<td>CO</td>
<td>5 wk</td>
<td>M</td>
<td>Starch</td>
<td>167</td>
<td>20%</td>
<td>Increased</td>
<td>I</td>
</tr>
<tr>
<td>Hallfrisch (1986) (92)</td>
<td>12 (100%)</td>
<td>CO</td>
<td>5 wk</td>
<td>S</td>
<td>Starch</td>
<td>50</td>
<td>7.50%</td>
<td>Increased</td>
<td>I</td>
</tr>
<tr>
<td>Crapo (1984) (103)</td>
<td>11 (64%)</td>
<td>CO</td>
<td>2 wk</td>
<td>M</td>
<td>Sucrose</td>
<td>63-99</td>
<td>24%</td>
<td>No change</td>
<td>I</td>
</tr>
<tr>
<td>Huttunen (1976) (98)</td>
<td>68; 35 fructose</td>
<td>RCT</td>
<td>2 yr</td>
<td>M</td>
<td>Sucrose</td>
<td>69.1</td>
<td>-</td>
<td>No change</td>
<td>I</td>
</tr>
<tr>
<td>Emmerson (99)(1974)</td>
<td>3 (100%)</td>
<td>CO</td>
<td>12 d</td>
<td>L</td>
<td>Diet, Glucose</td>
<td>270</td>
<td>-</td>
<td>Increased</td>
<td>I</td>
</tr>
</tbody>
</table>

Mixed M; Solid S; Liquid L. Crossover CO; Randomised control trial RCT
Three recent hypercaloric trials observed a significant increase in SU when fructose was added to the diet (88-91). Two of these studies reported that SU increased significantly when glucose was added to the diet (89, 91). Other studies have reported that the association with SU is specific to fructose, and unrelated to any additional calories, by substituting fructose for equivalent amounts of starch and other sugars in the diet (92, 93). In a study by Hallfrisch et al, 12 men consumed diets where 0% fructose, 7.5% fructose or 15% fructose were substituted for an equivalent amount of starch over a 5 week period. The SU response to a sucrose load of 2g/kg BW was measured before and after the different diets. Consuming fructose everyday made the participants more susceptible to the effect of a fructose load on SU, with men consuming the largest amount of fructose measured to have the greatest rise in SU (92). Further to this Akhavan et al observed greater increases in SU when participants were given solutions containing increasingly larger amounts of fructose and smaller amounts of glucose, as would be expected if it was specifically fructose responsible for the rise in SU (87).

There have been a number of large observational studies using data from trials such as the Atherosclerosis Risk in Communities study (ARIC) and NHANES supporting the relationship between diet and SU (25, 94-96).

These studies have used 24 hour diet recalls and food frequency questionnaires to ascertain total fructose intake by calculating the amount of fructose in given foods (95, 96), and to assess markers of fructose intake, such as sugar-sweetened beverage intake (94).

Total fructose intake and SU have been found to be variably associated with each other. In the 4,994 individuals from the NHANES 2001-2002 cohort there was a statistically significant increase in mean SU in those consuming the highest amounts of fructose compared to those consuming the lowest (95). However, other studies examining the
association between total fructose intake and SU found no significant association (26, 94, 96).

Sugar-sweetened beverage intake is often used as a marker of fructose intake. An association between sugar-sweetened beverage intake and SU was observed in data from the NHANES 1944-1994 study. The adjusted odds ratio for hyperuricaemia (SU >0.42mmol/L in males and >0.34mmol/L in females) in those drinking ≥ 4 sugar-sweetened soft drinks per day compared to those drinking no sugar-sweetened soft drinks was 1.82 ( (P(trend)=0.003). An association was also found between orange juice, a source of natural fructose, and increased SU. However, no association was found with diet soft drinks leading to the conclusion that sugar sweeteners were causing the increase in SU (94). Further studies have also found an association between sugar-sweetened beverage intake and SU. No association has been found between SU and fruit juice (26, 95, 97).

1.4.4 Limitations in the current research

The current research concerning the relationship between SU and fructose has a number of limitations. These include the small number of participants in each study and variable parameters around the doses and form of fructose given.

Many of the interventional studies involved only a small number of participants. The largest sample size of all the dietary intervention studies was 68 people over two years (98). The number of participants in the other studies ranged from 3 to 36 making the results difficult to interpret (99, 100). The small numbers used in the studies so far may account for some of the inconsistent results, and make it difficult to generalise these results to the wider population. Studies to date have predominantly been undertaken in male participants. It is unclear if there is a difference in the metabolism of fructose to SU between males and females. However, a gender difference in this process could account in part for the higher prevalence of hyperuricaemia in men (1).
Observational studies use larger numbers of men and women, but there is some inconsistency in their ability to measure fructose intake. Some studies have used markers of fructose intake, such as sugar-sweetened beverages (94, 95). Sun et al took the data from a 24 hour diet recall, then used a sugar intake estimation system to calculate the fructose contents in the diets (96). They also do not measure the direct effect of fructose loads on SU but rather the association between a larger fructose intake in the diet and an overall higher SU (25, 26, 94-96).

The amount of fructose given varied between interventional studies and appears to be important with regards to effects on SU (76, 87). Evidence for an association between SU and fructose has been compelling when larger fructose doses have been used (89-91, 99, 100). A recent review article has stated that there is only evidence for an association between fructose and SU at doses above average daily fructose intakes in the general population, making the relevance of the association questionable in real life (50, 51, 101). However, both interventional and observational studies using doses within the range of current daily intakes have found an association between SU and fructose intake (25, 50, 51, 92, 94, 95).

Many of the observational studies have used sugar-sweetened beverages as a measure of fructose intake (25, 94, 95). According to American data, sugar-sweetened beverages are the greatest source of fructose in the United States of America (50). Criticism of this research has highlighted that sugar-sweetened beverages also contain large amounts of glucose and contribute excess calories to the diet (102). They may also be a marker of an unhealthy diet. However, the associations observed remained significant following adjustment for multiple other dietary factors including total calorie intake (94). It is, therefore, less likely that the observed association was purely due to the calories from sugar-sweetened soft drinks. Furthermore, glucose has not been found to have the same effect as fructose on SU when given in interventional studies (87).
Fructose is found in various forms in the diet and there is currently only limited research as to whether each has a different effect on SU (47). The majority of interventional studies have used fructose solutions. It has been found that drinks sweetened with both HFCS and sucrose, two common forms of sweetener, cause significant increases in SU (90). A similar effect on SU has also been observed using apples or a fructose solution with similar amounts of fructose (83). Polymers of fructose, such as fructans, are not absorbed and so do not affect serum urate (47).

The comparison sugar used may also affect the results of interventional studies. Studies that have used sucrose as the comparison sugar have found no significant increase in SU following fructose ingestion compared to the sucrose group (98, 103). These studies are difficult to assess as sucrose is a disaccharide made up of one molecule of fructose and one molecule of glucose (47). The findings may be due to the intake of fructose in the comparison group and the effect of the additional glucose on fructose absorption. Suitable comparison groups are those that do not affect the production of SU such as starch or glucose.

1.5 Fructose and gout

Many studies have assessed the relationship between fructose and SU, but evidence for an association between fructose and gout is limited.

In the 1800s Osler identified a link between sugars, sweet fruits and gout (4). It is now hypothesised that increasing access to sugars, and particularly fructose, may have been partly responsible for the high prevalence of gout in 17th century England. Sugar was originally available only to the rich in England and as it became cheaper and more easily accessible the prevalence of gout rose (104). This parallel increase in fructose consumption and gout has continued into the 21st century (1).
1.5.1 Evidence for link between fructose and gout

Interestingly only a small number of interventional studies have compared the effect of fructose in gout patients to that in a healthy population. One small study (n=17) found that the increase in SU following an oral fructose load was greater in those with gout, and their offspring, than in the those without gout (81). Two studies assessed the effect of IV fructose on gout sufferers. One study administered fructose to four gout patients and one control and found that SU increased by 22% (range 16%-28%) in all patients (105). A further study also found a significant increase in SU following IV fructose infusion in 4 gout patients (106). These studies all involved no or very few control subjects making it is difficult to assess whether the response to fructose was greater in those with gout. This small body of literature suggests that gout patients are as, or possibly more, susceptible to the effects of fructose on uric acid than healthy controls.

A number of observational studies have found association between higher fructose intake and higher incidence of gout. Using data from the 46,393 men surveyed in the Health professionals follow up study, an association between fructose intake, intake of sugar-sweetened beverages and an increased risk of gout was identified. The multivariate relative risk of gout in those in the highest fructose intake group (>6.6% of total energy) compared to those in the lowest (<3.5%) was 1.81 (CI 1.38-2.38, p<0.001). The risk of gout in those drinking ≥ 2 servings of sugar-sweetened beverages per day, compared to those drinking ≤ 1 per month was 1.85 ( CI 1.08-3.16, P(trend) <0.002) (107). In a cohort study of 78,906 women the relative risk of developing gout if drinking ≥2 servings of sugar-sweetened beverages per day, compared to those drinking <1/month was 2.39 (CI 1.34-4.26, P(trend) <0.001) (108). Both the association found in men and women showed evidence of a dose response with increasing gout risk as consumption of sugar-sweetened beverages increased (107, 108).
A recent study in a New Zealand population of 1,634 gout cases and non-gout controls has found an association between a sugar-sweetened beverage (SSB) intake of 4-4.99 servings/day and risk of gout (Table 9) (109).

**Table 9:** Adjusted odds ratios of risk of gout in those consuming 4-4.99 sugar-sweetened beverages (SSB)/day compared to those drinking none by ethnic group in a NZ population. Data from Batt et al (109)

<table>
<thead>
<tr>
<th>Ethnicity group</th>
<th>NZ European Caucasian</th>
<th>NZ Māori</th>
<th>NZ Pacific Islander</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted* OR for 4-4.99 SSB servings per day (95% CI)</td>
<td>6.89 (1.05 to 45.44)</td>
<td>5.19 (1.48 to 18.17)</td>
<td>2.84 (1.04 to 7.77)</td>
</tr>
<tr>
<td>P Value</td>
<td>0.045</td>
<td>0.010</td>
<td>0.043</td>
</tr>
</tbody>
</table>

*Adjusted by age, sex, BMI, alcohol (continuous variable), fruit intake (continuous variable), kidney disease, high blood pressure

**1.5.2 Fructose restriction in management of gout**

While it has been suggested that dietary fructose should be avoided or minimized in patients with gout (6, 7), there are no interventional studies that have examined the long-term effects of such dietary modification on gout. Only one randomised control trial in healthy volunteers has examined the effect of fructose restriction on SU. Participants were randomised to either a moderate fructose (50-70 g fructose) or a low fructose diet (10-20 grams fructose). SU decreased in both groups from baseline and there was no significant difference in the degree of reduction between the groups (p 0.9) (110).
1.5.3 Genetic links between fructose and gout

Those with gout may be more susceptible to an increase in SU following a fructose load (81, 105, 106). This may be due to genetic differences between gout patients and the general population.

The main gene studied in relation to this association is SLC2A9, which encodes a renal urate transporter which also transports fructose (36, 111). SLC2A9 is associated with gout risk in NZ European, NZ Māori and Pacific Island populations (36).

Recent evidence from New Zealand has also suggested a gene environment interaction between SLC2A9 and fructose, in the context of gout pathogenesis. The form of the SLC2A9 gene that has been found to protect against gout in previous studies (36), was associated with greater increases in gout risk and SU per increase in sugar-sweetened beverage intake (109).

1.6 Conclusions

Gout is a condition that is painful and debilitating (2). The prevalence of gout is high in New Zealand and is continuing to increase (1, 18). The consumption of fructose has increased in parallel with the increase in gout prevalence (48, 104).

Recent evidence has supported an association between fructose intake and serum urate. Fructose has been found to increase serum urate in both oral and intravenous forms. Consumption of foods that contain large amounts of fructose, for example sugar-sweetened beverages, have been found to be associated with an increased risk of gout (26, 107).

Approximately 34% of a healthy population malabsorb fructose using a test dose of 35g (9). However no studies assessing oral fructose and serum urate have measured whether or not participants were absorbing fructose, and so failed to assess what effect this may have had on the association with SU.
The current study aims to assess the rates of fructose malabsorption in gout cases and non-gout controls. Those malabsorbing fructose may be less susceptible to a rise in serum urate following a fructose dose, and therefore less likely to develop gout as a result of fructose consumption. We hypothesise that there will be a lower rate of fructose malabsorption in gout cases than in non-gout controls.
Chapter Two – Methods

We undertook a case control study to determine the rate of fructose malabsorption in an unselected population of gout cases and age and sex-matched non-gout controls. Ethical approval was obtained from the Southern Health and Disability Ethics Committee on 18\textsuperscript{th} September 2012 (12/STH/11). Written informed consent was obtained from all patients. The study was registered with the Australian New Zealand Clinical Trial Registry (ANZCTR) is 12612000879864.

2.1 Recruitment

2.1.1 Cases

Cases were patients, 18 years or older, with gout as defined by the American Rheumatism Association (ARA) Preliminary classification criteria for gout (Table 10)(112). All participants had to be willing and able to give written consent.

Cases were recruited from databases of gout patients in Christchurch Hospital who had been enrolled in previous gout studies, through the Christchurch Hospital Outpatient department, the Nicholls Research Centre, University of Otago, Christchurch, and through public advertisements.
These ARA criteria define gout if the patient fulfils either A,B or C of the following criteria:

A. The presence of characteristic urate crystals in the joint fluid

B. A tophus proved to contain urate crystals by chemical means or polarised light microscopy

C. The presence of 6 of the following 12 clinical laboratory, and x-ray phenomena
   1. Maximum inflammation developed within one day
   2. More than one attack of acute arthritis
   3. Attack of monoarthritis
   4. Redness observed over the affected joint(s)
   5. First metatarsopharyngeal joint painful or swollen
   6. Unilateral first metatarsopharyngeal joint attack
   7. Unilateral attack involving tarsal joint
   8. Suspected tophus
   9. Hyperuricaemia
   10. Asymmetric swelling with a joint
   11. Subcortical cysts without erosions
   12. Negative culture of joint fluid for microorganisms during attack of joint inflammation

2.1.2 Controls

For each gout case a single control without gout was recruited. Controls were matched for gender, age ± 10 years, and where possible, diuretic use and ethnicity.

Controls were recruited from a variety of sources including public advertising, Christchurch hospital medical staff, the Nicholl’s Research Centre and referral from clinicians involved in the study (appendix 8.1). Healthy volunteers who had previously enrolled in the Genetics Profiles of Healthy Volunteers for the Study of Heart Disease (Upper South A Ethics Committee Approval No 01/05/062) and had indicated that they would be willing to take part in future studies were also contacted.
2.1.4 Exclusion

Cases and controls were excluded if they met any of the following criteria:

1. Known inflammatory bowel disease or irritable bowel syndrome as a high rate of fructose malabsorption is associated with these diagnoses (47).
2. Receiving antibiotic therapy as antibiotics can affect the breath test.
3. Presence of chronic infection or other severe concomitant medical illness or psychiatric disease.
4. Patients with active, concomitant malignancies as the treatments for malignancies, such as chemotherapy, increase cell turnover and, therefore, the purine load so may predispose certain individuals to gout.
5. Unable to provide written informed consent.

2.1.4 Study Procedures

Recruitment commenced in November of 2012.

Cases and controls were pre-screened. Medical records were reviewed for any obvious exclusion criteria. If none were found, contact was made.

Cases and controls were sent a letter (appendix 8.2) inviting them to participate in the study along with the information sheet (appendix 8.3). The participants were then contacted by phone, where possible within 2 weeks. During this phone call participants were screened for the inclusion and exclusion criteria. If the gout cases had previously been enrolled in other studies that used the ARA criteria for gout, they were assumed to have met the inclusion criteria. If cases had not previously been enrolled in a gout study they were asked for clinical information regarding their gout, and their online hospital patient records were reviewed for laboratory and radiology results to ensure they fulfilled the ARA criteria.
If the participant was suitable and consented, an appointment time was made and the information about the fructose breath test was sent out (appendix 8.4).

Potential controls and cases who responded to advertisements were contacted by phone initially. During this phone call they were given information about the study. If they were interested in participating they were screened for the inclusion and exclusion criteria. Suitable participants were sent the information sheets. They were then contacted to make an appointment time.

2.2 Testing

2.2.1 Hydrogen breath testing

The hydrogen breath test is a standard protocol for testing for fructose malabsorption. The equipment and protocol used in this study are from Digestive Health Services, Christchurch. The equipment used for the hydrogen readings was the gastrolyzer (Bedfont® Scientific Ltd., Kent, England) (Figure 8). This equipment is commercially available. It was used according to the manufacturer’s instructions and is maintained regularly. This is a hand held machine that

![Figure 8: The Bedfont® Gastrolyzer (left), and the Gastrolyzer in use (right) used to test breath hydrogen](image-url)
requires the patient to hold their breath for 15 seconds before exhaling into a mouthpiece (Figure 8). It is easy to operate and each breath test takes approximately 20 seconds to complete.

Samples for methane testing were taken using a bag and mouthpiece system (Figure 9). The samples were then drawn into sealed plastic syringes and, if required, were tested within 12 hours of being taken. The equipment used for the methane readings was the Quintron Microlyser DP (QuinTron Instrument Company, Inc., Milwaukee, WI, USA) which measures both hydrogen and methane using solid state sensors. The methane testing was performed by an experienced Scientific Officer.

![Figure 9: The bag and mouthpiece system used to collect methane samples](image-url)
Fructose malabsorption is diagnosed by testing for breath hydrogen which is produced when an oral fructose load is not absorbed in the small intestine (Figure 10) (60, 62). The hydrogen is measured in parts per million (ppm) in the breath. A positive test is exhibited by a significant rise in breath hydrogen (two consecutive readings >10ppm above baseline or one reading >20ppm above baseline).

![Diagram of fructose absorption and malabsorption](image)

**Figure 10:** Oral fructose is ingested and is either absorbed or passes through to the colon where it produces hydrogen or methane that are absorbed into the bloodstream and can be detected by breath testing (60,62).

The day prior to testing participants were asked to follow a low fermentable diet (Table 11). This diet avoids foods that are fermented in the bowel and can, therefore, cause the production of hydrogen and methane that could interfere with the results of this test.
Participants were fasted from 10pm the night prior to testing and were asked to only drink small amounts of water.

Participants were also asked to avoid taking vitamins, minerals, laxatives, anti-laxatives, yakult® and fish oil capsules on the day of and the day prior to testing. They were asked not to smoke the morning of their test, not to use mouthwash, and to avoid perfume or aftershave as all of these may interfere with accurate hydrogen readings.

When participants arrived for testing they were consented for the study and any questions were answered. They were then asked to perform a baseline hydrogen breath test using the Bedfont gastrolyser. A baseline breath sample was also collected for methane measurement in case the patient was not a hydrogen producer. Participants then consumed a solution of 35g of pure

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**Table 11:** Information about a low fermentable diet given to patients before the breath test and to be followed for 24 hours prior to the test. Similar to the diet used in diagnostic absorption testing in Christchurch.

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**On the day before the test please only have food and drinks from the list below**

**Drinks:** Water (unflavoured, non-fizzy), coffee (but not coffee substitutes), tea, lactose free milk, rice milk

Alcohol maximum 250mls wine, 60mls spirits or 200ml beer

**Cereal, crackers and breads: please do not eat in excess quantities:** Corn flakes, rice bubbles, corn thinks, plain rice crackers

**Grains: please do not eat in excess quantities:** Any type of rice, corn, maize, buckwheat, amaranath, quinoa, millet

**Meat etc:** Eggs, plain fresh or tinned fish, plain meat such as beef, lamb, venison, pork, chicken, ham

**Fruit and veges:** Mandarin, green kiwi fruit, strawberries, orange, rockmelon (only 1 palm full of fruit per 2 hours)

Sweet corn, green beans, potato (peeled), pumpkin, carrot, courgette, tomato, lettuce, spinach, silverbeet

**Extras:** White or brown sugar, barley sugars, boysenberry, raspberry or strawberry jam, marmalade, vegemite, jelly, oil margarine, butter, peanut butter, nuts, seeds

Many packaged or canned foods have sauces, spices, onion flavouring, artificial sweeteners, soy products etc which you cannot have
fructose dissolved in water. The hydrogen breath test was then repeated every 15 minutes. If there was no significant increase in hydrogen then methane was measured again at the 2 and 3 hour timepoints. If there was a significant rise in hydrogen no further breath samples for methane measurement were required, and their first sample was discarded.

A positive reading, signalling fructose malabsorption, was defined as two consecutive readings 10ppm above the baseline reading, or one reading 20ppm above the baseline. If a patient had a positive reading the testing was discontinued. If no rise had been seen in the breath test results by 3 hours then testing was discontinued.

2.2.2 Questionnaire

During the study visit the participants were asked to complete a detailed questionnaire (appendix 8.5) which included information about clinical parameters, previous medical history, employment and education, diet, medications, quality of life and bowel symptoms. The questionnaire for cases included extra information about their gout, including dietary triggers.

Demographic details including data on age, gender weight, height, waist circumference (centimetres) and blood pressure (milligrams of mercury (mmHg)) were measured by the study coordinator at the time of the visit. Height and weight were used to calculate the body mass index (BMI) using the equation weight in kilograms divided by height in metres squared (BMI = kg/m$^2$). The ethnicity data was collected as per the standard New Zealand Census Ethnicity question (Figure 11).
The date and result of the most recent SU (mmol/L) and serum creatinine (umol/L) were accessed from the patients online records. Estimated creatinine clearance was calculated using the Cockcroft-Gault formula \( (eCrCl = ((140 - \text{age}) \times \text{weight} \times \text{constant}) / \text{serum creatinine}; \text{constant} = 1.04 \text{ women, 1.23 men}) \).

Information on co-existing medical conditions including kidneys problems, heart problems, type 2 diabetes mellitus, hypertension, hyperlipidaemia and hypercholesterolaemia was collected. A list of current medications, doses, frequencies and side effects were also collected.

To assess fructose intake participants were asked how many sugar-sweetened beverages, including fruit juice, but not including diet drinks they normally drunk per day on a scale of 0 to more than 5. They were also asked how many pieces of fresh fruit they usually ate per day on a scale of 0 to 5 or more. Participants were asked how many times they had eaten seafood in the past week and how much alcohol, split by wine, beer, spirits and other, they had consumed in the past week.

Figure 11: New Zealand Census Ethnicity question.
The HAQ-II Questionnaire (HAQ-II) (appendix 8.5) was used to assess the ability of participants to function in day to day life (113). The irritable bowel syndrome module of the Rome III Diagnostic Questionnaire for the Adult Functional GI disorders was used to assess symptoms associated with irritable bowel syndrome (questions 41, 43, 45, 46, 47, 48, 49, 50, 53, 61) and red flag symptoms for more serious underlying pathology (questions 82, 83, 85, 87, 88) (appendix 8.5) (114).

Cases were asked for additional information about their gout, including about current gout attacks and number of attacks in the past month and year, past x-rays of affected joints, age at first attack and family history of gout. Information was also collected on about past or present treatment with allopurinol, steroids, anti-inflammatories, probenecid, colchicine or any other medication for their gout and any associated side effects.

2.3 Follow up

Patients who were seen to malabsorb fructose and had evidence of IBS on the Rome III questionnaire were given dietary advice on the day of the visit. This included avoiding foods high in fructose, particularly fruits and sweetened beverages, and self monitoring of bowel symptoms in relation to these dietary changes.

Patients who gave positive answers to the red flag questions on the bowel symptom questionnaire were advised to see their GP. A letter was also written to the GP with the permission of the participant.

2.5 Analysis

All data were entered from paper collection forms into an online database. A random sample of approximately 10% of the collected records were checked against the paper forms for data input accuracy.
2.5.1 Power Calculation

As the rate of fructose malabsorption had been found to be 34% in an Australian population (9), we calculated the sample size required to show a 1/3 reduction in this rate in gout patients. Using McNemar’s Chi-square test it was found that a sample size of 100 pairs will have sufficient power (>80%) to show this difference as statistically significant (two tailed $\alpha = 0.05$).

2.5.2 Statistics

The statistical analysis was undertaken using the SPSS software package (115). Statistical significance was determined with a two tailed p value of < 0.05.

The relationship between variables in the case and control groups were investigated using paired t tests and McNemar’s Chi square tests to take into account the matching of cases and controls. The odds ratio for the relationship between gout and absorption status was calculated taking into account the paired samples.

Total fructose intake was calculated by adding the intake of SSB to the intake of fruit to give a total intake measured in servings per day.

The relationships between clinical and demographic features and absorbption status in the case and control groups, were tested using the non-parametric Mann-Whitney U test.

Wilcoxon signed ranks test was used to compare fruit, sugar-sweetened beverage (SSB) and total fructose intake with gout status (cases vs controls). The frequency of bowel symptoms was compared between absorbers and malabsorbers within case and control groups using Chi square tests.

GraphPad PRISM software was used to draw graphs (116).
3.1 Recruitment

276 gout patients were identified from the search strategies described in Chapter 2, section 2.1. The electronic medical records were reviewed and 68 patients were excluded (64 medically unfit, 4 no current address). Of the remaining 208 who were sent information about the study 106 were contacted. Of these 26 declined, 4 were excluded and 7 did not arrive (DNA) for their appointment. 65 were enrolled into the study and all of these participants were included in the analysis (Figure 12).

![Flow diagram of numbers of cases in recruitment process](image-url)
196 potential controls were pre-screened using their medical records. 19 of these were considered medically unsuitable and information was sent to 177 people. Of these 105 could be contacted by phone for screening. 33 people declined, 1 was excluded and 5 did not arrive for their appointments. 66 were enrolled in the study and underwent testing. One female control was tested but not used in the analysis as her matched case cancelled the appointment and another case was unable to be found within the recruitment period (Figure 13).

Figure 13: Flow diagram of numbers of controls through recruitment process
One matched case-control pair were identical twin brothers. One of the gout cases was the father of one of the recruited controls. No other cases or controls were related.

### 3.2 Demographics

Demographic details for cases and controls are summarised in Table 12.

Cases and controls were well matched for ethnicity, diuretic use and gender. We also matched the cases and controls for age ± 10 years. A small difference in age between the two cohorts was observed, with the mean age of cases being 63.4 years while the mean age of controls was 62.0 years (P = 0.047).

**Table 12**: Summary of demographic data for cases and controls.

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>65</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Age, mean, years (range)</td>
<td>63.4 (30-86)</td>
<td>62.0 (30-82)</td>
<td>0.047</td>
</tr>
<tr>
<td>Gender, (% male)</td>
<td>92.3%</td>
<td>92.3%</td>
<td></td>
</tr>
<tr>
<td>Diuretic use (%)</td>
<td>26.2%</td>
<td>18.5%</td>
<td>0.180</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td>0.112</td>
</tr>
<tr>
<td>European</td>
<td>51 (78.5%)</td>
<td>58 (89.2%)</td>
<td></td>
</tr>
<tr>
<td>NZ Maori</td>
<td>9 (13.8%)</td>
<td>4 (6.2%)</td>
<td></td>
</tr>
<tr>
<td>Pacific Island</td>
<td>3 (4.6%)</td>
<td>1 (1.5%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (3.1%)</td>
<td>2 (3.1%)</td>
<td></td>
</tr>
<tr>
<td>BMI, mean (range)</td>
<td>28.5 (18.9-38.9)</td>
<td>27.3 (19.9-37.7)</td>
<td>0.080</td>
</tr>
<tr>
<td>Height, mean, cm, (range)</td>
<td>176.0 (154.4-195.0)</td>
<td>177.7 (153.6-204.5)</td>
<td>0.170</td>
</tr>
<tr>
<td>Systolic BP, mean, mmHg, (range)</td>
<td>131 (90-160)</td>
<td>131 (96-170)</td>
<td>0.838</td>
</tr>
</tbody>
</table>

Unless otherwise stated all results were calculated using the full data set (Cases = 65, controls = 65).
The serum urate and creatinine concentration results were collected retrospectively from medical records. These data were incomplete in the control group. 26 controls had a serum urate result available, and 55 controls had a serum creatinine available. These data were complete for cases. For those controls that did have data (n= 26), and their matched cases there was no significant difference between the serum urate concentration results (SU mean + SD cases 0.37+0.12 mmol/L, vs. controls 0.38+0.11 mmol/L, p = 0.796. There was a significant difference between the serum creatinine concentration results between cases (n=65) and controls (n=55) (mean + SD cases 98.6+20.4 umol/Lversus controls 89.7+15.3 umol/L, p=0.008). However, there was no significant difference in calculated creatinine clearance between the cases and controls.

3.2.1 Comorbidities

As expected, significantly more cases had kidney disease, high blood pressure and high cholesterol compared to controls (Table 12).

Table 13: Summary of comorbidity data for gout cases and non-gout controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney disease (%)</td>
<td>10 (15.4%)</td>
<td>1 (1.5%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Renal calculi (%)</td>
<td>2 (3.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure (%)</td>
<td>5 (7.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (%)</td>
<td>3 (4.6%)</td>
<td>1 (1.5%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>35 (53.8%)</td>
<td>18 (27.7%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Type 2 Diabetes Mellitus (%)</td>
<td>11 (16.9%)</td>
<td>6 (9.2%)</td>
<td>0.302</td>
</tr>
<tr>
<td>Hypercholesterolaemia (%)</td>
<td>26 (40.0%)</td>
<td>16 (24.6%)</td>
<td>0.041</td>
</tr>
<tr>
<td>Heart disease (%)</td>
<td>25 (28.5%)</td>
<td>19 (29.2%)</td>
<td>0.238</td>
</tr>
<tr>
<td>Ischaemic Heart Disease (%)</td>
<td>14 (21.5%)</td>
<td>9 (13.8%)</td>
<td></td>
</tr>
<tr>
<td>Atrial Fibrillation (%)</td>
<td>3 (4.6%)</td>
<td>4 (4.6%)</td>
<td></td>
</tr>
<tr>
<td>Heart Failure (%)</td>
<td>6 (9.2%)</td>
<td>5 (7.7%)</td>
<td></td>
</tr>
<tr>
<td>Other (%)</td>
<td>2 (3.1%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Apart from those medications specific for gout (Table 15 – section 3.2.2) there were no significant differences in the types of medications being taken by the cases compared to the controls (Table 14).

Table 14: Summary of medications being taken by cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>P value *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antihypertensives</strong></td>
<td>33 (50.8%)</td>
<td>28 (43.1%)</td>
<td>0.405</td>
</tr>
<tr>
<td>(excluding diuretics) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids (%)</td>
<td>10 (5.4%)</td>
<td>4 (6.2%)</td>
<td>0.180</td>
</tr>
<tr>
<td>NSAIDs (%)</td>
<td>10 (5.4%)</td>
<td>6 (9.2%)</td>
<td>0.454</td>
</tr>
<tr>
<td><strong>Antiplatelet</strong></td>
<td>24 (36.9%)</td>
<td>18 (27.7%)</td>
<td>0.327</td>
</tr>
<tr>
<td>(including aspirin and clopidogrel) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypoglycaemics</strong></td>
<td>8 (12.3%)</td>
<td>5 (7.7%)</td>
<td>0.549</td>
</tr>
<tr>
<td>(including metformin, sulphonylureas and insulin) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins (%)</td>
<td>24 (36.9%)</td>
<td>18 (27.7%)</td>
<td>0.327</td>
</tr>
<tr>
<td>Warfarin/Dabigatran (%)</td>
<td>10 (15.4%)</td>
<td>7 (10.8%)</td>
<td>0.629</td>
</tr>
<tr>
<td>Laxatives (%)</td>
<td>0 (0%)</td>
<td>2 (3.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Antidiarrhoeals</strong></td>
<td>1 (1.5%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamins/minerals (%)</td>
<td>11 (16.9%)</td>
<td>8 (12.3%)</td>
<td>0.648</td>
</tr>
<tr>
<td>Probiotics (%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
3.2.2 Clinical characteristics of gout cases

The majority of the gout patients (86.2%) were taking allopurinol (Table 16). Those that were not were managing their gout using dietary and lifestyle modification. Only a small number of gout patients were having a gout flare at the time of the visit, although 70.8% of the patients had suffered a flare in the past year.

Table 15: Summary of gout specifics characteristics in gout cases.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol (%)</td>
<td>56 (86.2%)</td>
</tr>
<tr>
<td>NSAIDs (%)</td>
<td>10 (15.4%)</td>
</tr>
<tr>
<td>Colchicine (%)</td>
<td>8 (12.3%)</td>
</tr>
<tr>
<td>Prednisone (%)</td>
<td>8 (12.3%)</td>
</tr>
</tbody>
</table>

**Gout flare history**

| Age at first flare, mean (range) | 41.3 (15-84) |
| Flare at time of study visit     | 10 (15.4%)   |
| Number of patients experiencing a flare in past month (y/n), n(%) | 20 (30.8%)   |
| Number of patients experiencing a flare in past year (y/n), n (%) | 46 (70.8%)   |
| Family history of gout           | 32 (49.2%)   |
3.3 Primary Analysis

The rate of fructose malabsorption in cases and controls was not significantly different (p = 0.720) (Table 16).

The odds ratio for this association was 0.82 (95%CI 0.41-1.67).

**Table 16:** Rates of malabsorption in cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Case</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorbers</td>
<td>33 (50.8%)</td>
<td>30 (46.2%)</td>
</tr>
<tr>
<td>Malabsorbers</td>
<td>32 (49.2%)</td>
<td>35 (53.8%)</td>
</tr>
</tbody>
</table>

3.4 Clinical Characteristics of fructose absorbers and malabsorbers

There were no significant differences in clinical characteristics of the fructose absorbers and malabsorbers within the case and control groups with the exception of age (table 18). Within the control group the absorbers were significantly younger than the malabsorbers (p=0.003) When a difference in age by absorption status was measured in the full cohort, irrespective of case/control status, a significant difference was found again (mean absorbers vs malabsorbers p=0.040).

Two participants (1.5%) produced methane exclusively rather than hydrogen in the entire cohort. Both were controls. One was an absorber and the other a malabsorber.
<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Non-gout Controls</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absorber</td>
<td>Malabsorber</td>
<td>P</td>
</tr>
<tr>
<td>N</td>
<td>33</td>
<td>32</td>
<td>0.844</td>
</tr>
<tr>
<td>Age, mean, years (range)</td>
<td>63.7 (40-85)</td>
<td>63.0 (30-86)</td>
<td>66.5 (44.0-82.0)</td>
</tr>
<tr>
<td>Gender, (% male)</td>
<td>30 (90.9%)</td>
<td>30 (93.8%)</td>
<td>0.670</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>27 (81.8)</td>
<td>24 (75%)</td>
<td>25 (83.3%)</td>
</tr>
<tr>
<td>NZ Maori</td>
<td>4 (12.1)</td>
<td>5 (15.6%)</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>Pacific Island</td>
<td>2 (6.1)</td>
<td>1 (3.1%)</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (6.3%)</td>
<td>2 (6.7%)</td>
<td></td>
</tr>
<tr>
<td>Methane producer, n (%)</td>
<td>0</td>
<td>0</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>BMI, mean (range)</td>
<td>28.8 (21.8-38.9)</td>
<td>28.2 (18.9-36.9)</td>
<td>27.1 (21.6-34.4)</td>
</tr>
<tr>
<td>Systolic BP, mean, mmHg, (range)</td>
<td>130 (90-160)</td>
<td>131.3 (90.0-152.0)</td>
<td>129 (102-170)</td>
</tr>
</tbody>
</table>

**Table 17:** Demographics of absorbers and malabsorbers within case and control groups
3.5 Discussion

In this case control study we found similar rates of fructose malabsorption of 49.2% in patients with gout compared to 53.8% in controls without gout.

It is, therefore, unlikely that fructose malabsorption plays a role in the susceptibility of some individuals to gout. To the best of our knowledge this is the first study that has examined fructose malabsorption in individuals with gout.

The rates found in this study were higher in both groups than that found in previous studies. Only one previous study used a fructose dose of 35 grams to measure fructose malabsorption. Given the increase in the rate of fructose malabsorption with increasing dose we are only able to compare our rate to this study (62). This study found a rate of malabsorption of 34% in healthy volunteers (9). There is no obvious reason why the rates were found to be so much higher in the current study. The protocol for breath testing was almost identical for both studies, with the only significant difference being that Barrett et al excluded non-hydrogen producers of which we only had two. It is unlikely that this would have affected the final results.

Another possibility is that the higher rates in NZ are due to differences in the populations studied, including age and country of origin of participants. Our study was made up of 92.3% men with an average age of 63.4 years in cases and 62.0 years in controls. In comparison previous studies observing rates of fructose malabsorption have included a higher percentage of women, and younger populations (9, 62, 63, 65-67). In the study by Barrett et al the sample size of 71 was 72% men with a median age of 34 years (9).

Two previous studies had not shown a difference in the prevalence of fructose malabsorption between males and females (9, 62). However, one study of Thai individuals found only its female participants malabsorbed fructose (67). Therefore it appears unlikely that the difference in rates is due genders in the population.
Only one recent study has investigated the relationship between age and fructose malabsorption and reported a trend towards higher rates of fructose malabsorption with increasing age (9). Our data are consistent with this study with the fructose malabsorbers being significantly older than the absorbers. This relationship between fructose malabsorption and age, and the mechanism of this requires further investigation. Given the increased rate of malabsorption with age, the difference in age between study populations may account for the difference in rates of malabsorption reported.

Ethnic differences between the populations may also account for the differences in rates. Barrett et al examined a Caucasian population from Australia (9). Our study involved a mix of ethnicities (Table 12) but with a predominance of European individuals. There are no published New Zealand data from healthy controls to compare with our results. There may, therefore, be genetic or environmental reasons that could account for higher rates of fructose malabsorption in this New Zealand population.

The sample size may have influenced the results of this study. The original power calculations for this study called for a sample size of 100 in each group, but due to time constraints only the results for 65 cases and 65 controls are reported in this thesis. However based on our results it is unlikely that recruitment of further cases and controls would have changed the result. The difference in the rates of malabsorption between cases and controls was not as large as predicted when the original power calculations were done.

The results of this study are important in our understanding of the pathogenesis of gout. We hypothesised that those with gout would have lower rates of malabsorption than those without meaning more fructose would be absorbed, and therefore be available for metabolism to uric acid. This could contribute to hyperuricaemia and potentially gout. As there was no difference in rates of fructose absorption between the cases and controls in our study it is unlikely that this is so.
However, the results give evidence that a large proportion of gout patients are malabsorbing fructose. Current guidelines advise gout patients to avoid high fructose corn syrup sweetened beverages and limit fruit juice, table sugar and sweetened foods, irrespective of absorption status (42). However, in those malabsorbing fructose there may be no effect on SU and, therefore, no benefit in decreasing fructose consumption. The next stage in this research is to investigate whether absorption status modifies the relationship between fructose ingestion and increasing serum urate.

Furthermore, as fructose malabsorption can lead to abdominal symptoms some malabsorbers may be modifying their diet to include less fructose to prevent these symptoms. This is investigated in the next chapter.
Chapter Four – Diet and symptom analysis in fructose absorbers and malabsorbers

Malabsorption of fructose frequently results in abdominal symptoms such as flatulence, abdominal pain and diarrhoea (47, 62). It is possible that patients avoid foods high in fructose to minimise such symptoms. This may occur even in the event that patients have not been formally identified as being fructose malabsorbers. It is also possible that patients with gout avoid fructose rich foods if they precipitate gout.

In this chapter we investigate whether there is a difference in reported abdominal symptoms and dietary fructose intake between absorbers and non-absorbers and between cases and controls. Participants were asked for their average intake of fruit and sugar-sweetened beverages (SSB) in servings per day (appendix 8.5). Participants were also asked a series of questions concerning gastrointestinal symptoms, including whether they had experienced abdominal discomfort or pain in the past six months (appendix 8.5).

4.1 Diet

4.1.1 Sugar-Sweetened Beverages

The frequency of sugar-sweetened beverage (SSB) intake in malabsorbers and absorbers by case and control are shown in Figure 14. The majority of participants (64.6%) reported drinking no SSB per day. Very few people (3%) reported drinking more than two SSB/day. However, these differences were not significant (case p value = 0.545, control p value = 0.348).

There was also no significant difference in the intake of SSB between cases and controls (p = 0.465).
4.1.2 Fruit

Most participants (53.8%) consumed 1-2 pieces of fresh fruit per day, with a small number (3.8%) eating more than 5 pieces. The type of fruits consumed were not recorded.

There was no significant difference in fruit intake between cases and controls (p = 0.893) (figure 15). When this relationship was assessed in the absorbers and malabsorbers within the case and control groups, no significant association was found. In the case group the p value was 0.565. In the control group the p value was 0.328.
4.1.3 Total fructose intake

The total fructose intake was calculated by adding together the individual fruit and SSB intakes. The results are shown as servings of fructose per day (Figure 16). Overall, there was no significant difference in total fructose intake between cases and controls (p = 0.706). However, fewer controls consumed more than 5 servings of fructose per compared to cases (controls 4.6% vs. cases 12.3%).

There was no significant difference in total fructose intake between the absorbers and malabsorbers within the case and control groups (controls p=0.083, cases p=0.759).
Figure 16: Intake of total fructose (servings/day) in absorbers and malabsorbers within the case and control groups. Total fructose was calculated by adding together intakes of fruit and SSB to give total servings/day.
4.2 Abdominal symptoms

The frequency of abdominal pain or discomfort in the past 6 months in cases and controls, and malabsorbers and absorbers is displayed in Table 18.

There was no significant difference in abdominal symptoms between absorbers and malabsorbers within the case and control groups.

Table 18: Number of participants suffering abdominal pain in the past 6 months

<table>
<thead>
<tr>
<th>Abdominal pain in the past 6 months, n (%)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorbers</td>
<td>12 (36.4%)</td>
<td>6 (20.7%)</td>
</tr>
<tr>
<td>Malabsorbers</td>
<td>12 (37.5%)</td>
<td>13 (37.1%)</td>
</tr>
</tbody>
</table>

4.4 Discussion

We found no significant difference in the fructose intake of absorbers and malabsorbers within the case and control groups or between gout cases and non-gout controls. There was also no difference in abdominal symptoms between the two groups.

Our data trended towards a greater SSB consumption in cases with some cases consuming up to four servings per day, while no controls consuming greater than two SSB/day. However, there was no significant difference in SSB intake between the gout cases and non-gout controls. This is inconsistent with previous studies that have found a higher consumption of sugar-sweetened beverages in gout cases compared to non-gout controls (107, 109).
Consistent with previous studies we found no difference in fruit intake between gout cases and non-gout controls (109). We also found no significant difference in total fructose intake, however there was a non-significant trend towards higher consumption in gout cases compared to non-gout controls.

The fruit and SSB intake data are only markers of fructose intake. Total fructose intake was calculated by adding these two together. Although these are two of the main forms in which New Zealanders consume fructose, it is probable that data on some other forms in which fructose is found in the diet were not collected and this may change the associations found (51).

There was no significant difference in diet between malabsorbers and absorbers. We had hypothesised that malabsorbers may be modifying their diet due to abdominal symptoms induced by fructose consumption. This, however, does not seem to be the case with similar consumption of SSB, fruit and total fructose within each group. This may be due to there being no significant difference in abdominal symptoms between absorbers and malabsorbers within the case and control groups.

If malabsorbers absorb less fructose and, therefore, do not have the same serum urate response to an oral fructose load, we could individualise dietary treatment of gout so that only those who absorb fructose would be advised to avoid it. This, however, would have been unnecessary if those malabsorbing fructose were already consuming less of the sugar due to abdominal symptoms. However this does not seem to be the case, and so individualising dietary treatment may still be able to improve compliance to management and outcomes for gout patients.
Chapter Five - Urate study protocol

5.1 Introduction

The current research has observed that there is no significant difference between the rate of fructose malabsorption between those with gout and those without gout (p= 0.720). 49.2% of individuals with gout were found to be fructose malabsorbers. Fructose malabsorption may influence the SU response to an oral fructose load. If fructose is incompletely absorbed there will be less available for metabolism to urate in the liver. To date the relationship between fructose absorption status and SU change following a fructose load has not been assessed. Current dietary guidelines for patients with gout recommend limiting fructose intake (6, 7, 42). However, if fructose malabsorbers have a lower serum urate response such a dietary change may not provide significant clinical benefit and alternative dietary strategies may be more appropriate.

We hypothesise that fructose will have more of an effect on serum urate in those who absorb fructose compared to those who malabsorb fructose. Previous studies that tested the effect of fructose on serum urate have not tested for absorption status but, considering the high rate of fructose malabsorption, it is likely that samples tested were a mix of fructose absorbers and malabsorbers. Due to this, the mean increase in serum urate observed in fructose absorbers may be higher than recorded in previous studies, while there may be no difference or a smaller mean increase in serum urate in fructose malabsorbers.

The aim of this chapter is to design a study to ascertain whether there is a difference in urate measurements pre and post a 35g oral fructose load in known fructose absorbers and malabsorbers.
We propose a case control study that will be an extension of the research already completed for this thesis. However two important questions need to be answered to ensure the study design is appropriate and will address the aim:

1. Time course: We need to determine the time course for SU response following an oral fructose load: This will help us define the time course over which we will measure SU.

2. Magnitude of effect on SU: In order to calculate the sample size required to give sufficient power to detect a difference in SU response between fructose absorbers and malabsorbers we need to determine what the likely increase in SU following a fructose load.

In this chapter I will address these issues and outline the proposed study design.

5.2 Methods

The literature was reviewed to address the two key issues, namely time course of change in SU and the magnitude of change in SU after a fructose load. A medline search was undertaken using the key words “fructose”, “serum urate” and “hyperuricaemia”.

The current literature on SU response to fructose load was reviewed, looking for the time to peak SU after a fructose load and the time for SU to return to baseline concentrations. We focussed on studies that used a similar fructose dose to that used previously in this thesis, i.e. 35 grams.

5.3 Results

Fifteen studies were identified as assessing the relationship between oral fructose and serum urate response. Of these six used one off fructose doses, with the remaining nine being dietary trials. Only two studies used fructose test doses of between 20-50grams and reported a peak time and return of SU to baseline (Table 19).
From the above studies it is apparent that SU following a 35g fructose load peaks at around the 30-60 minute post dose, is decreasing towards normal by 90 minutes and has almost completely returned to baseline by 240 minutes. For this reason it would be appropriate to test SU at baseline and 15, 30, 60, 90, 120, 180 and 240 minutes following the fructose load.

### 5.3.2 Power Calculations

To calculate the sample size needed to have sufficient power to find a change in serum urate information on the rate of fructose malabsorption and the expected change in SU is required.

MacDonald et al tested 9 healthy men using oral fructose doses of varying amounts. At a dose of 0.5g/kg body weight (35g in a 70 kg man) a peak increase of 0.03mmol/L (standard deviation 0.06mmol/L) was seen at 15-60 minutes (Figure 17) (85). There was no information on absorption status for the participants in this study so we can assume that the sample population included both fructose absorbers and malabsorbers. Therefore, if our hypothesis is correct, we would expect an increase of greater than 0.03mmol/L in our fructose absorbers, and less in our fructose malabsorbers. We therefore need a sufficient sample size to detect this change.

From the research described in this thesis, the rate of fructose malabsorption in gout cases and non-gout controls is ~50%.

<table>
<thead>
<tr>
<th>N (% male)</th>
<th>Fructose dose</th>
<th>Peak in SU</th>
<th>Return to baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buemann (2000) (86)</td>
<td>8 (100%)</td>
<td>30 g</td>
<td>50 minutes</td>
</tr>
<tr>
<td>MacDonald (1978) (85)</td>
<td>9 (100%)</td>
<td>0.5 g /kg BW (~35g in a 70kg person)</td>
<td>15-30 minutes</td>
</tr>
</tbody>
</table>

Table 19: Characteristics of studies that observed the effect of a fructose load between 20-50 grams on SU
On this basis with a total sample size of 70 participants (Cases n=35, controls n=35) we will have sufficient power (>80%) to detect a difference in the change of 0.04mmol/L or more. As statistically significantly (2 tailed alpha = 0.05). Additionally the study will have sufficient power to detect a differential effect of malabsorption between gout cases and non-gout controls of approximately 0.06mmol/L.

5.4 Study Protocol

5.4.1 Participants

Further to the 130 cases and controls tested for this thesis, 35 cases and 35 controls will be recruited to give a total of 100 participants in each group.

Cases will be recruited through the Christchurch Rheumatology service and databases from previous rheumatology studies. Controls will be recruited through advertisements and word of mouth.

Cases and controls will be matched on age, gender, ethnicity and diuretic use. The inclusion and exclusion criteria will be as in the previous study.
5.4.2 Testing

Testing will be completed during one visit. During this visit the participants will be tested for fructose malabsorption, and serial blood samples will be taken to assess the effect of fructose on serum urate. They will also be asked to fill out a questionnaire (appendix 8.5) and have clinical parameters such as height, weight and blood pressure assessed.

The testing for malabsorption will be completed according to the protocol used in the previous study in this thesis (Chapter 2).

Serum urate will be tested at baseline and 15, 30, 60, 90, 120, 180 and 240 minutes following the oral fructose load. A blood sample to test renal function (creatinine) will be collected at baseline.

![Figure 18: Timecourse for study showing time points for SU blood tests and hydrogen breath tests](image)

Figure 18: Timecourse for study showing time points for SU blood tests and hydrogen breath tests
5.4.3 Analysis

The primary outcome will be the time to peak of serum urate. Secondary outcomes will include the area under the curve for change in serum urate in malabsorbers compared to absorbers and in cases compared to controls.

5.5 Conclusion

This study is expected to identify the impact of absorption status on the relationship between fructose and serum urate.

Individuals with gout are currently advised to avoid fructose containing foods in their diet as they increase serum urate (6, 7, 42). If those that malabsorb fructose do not experience the associated increase in serum urate as absorbers there may be little benefit in them avoiding fructose rich foods.

Individualisation of advice may lead to better compliance and ultimately better outcomes for gout sufferers. For those that malabsorb fructose it may mean that they are not having to avoid a food group that has no effect on their gout. This is particularly important as some high fructose foods are fruits, which have other health benefits beyond their negative effects on serum urate and so should not be unnecessarily avoided.
Chapter Six - Discussion

The hypothesis of this case control study was that the rate of fructose malabsorption would be lower in cases with gout compared to healthy controls. Those that absorb fructose would have the sugar available for metabolism to serum urate, making them more susceptible to hyperuricaemia which is a risk factor for gout. We found no difference in the rates of fructose malabsorption between gout cases and non–gout controls.

However, we observed that the rate of fructose malabsorption in our cases and controls was higher than what we had expected from our literature review (9). As the rate of fructose malabsorption is dose dependent only one study could be compared to ours (63). The study presented in this thesis is the only study, to our knowledge, that has measured the rate of fructose malabsorption in a New Zealand population and there may be genetic or environmental reasons for this higher rate.

The higher rate in our study may also be due to a difference in age between our study population and those of previous studies. Our study population was older than in previous research (mean age in controls 62 years, mean age in Barrett et all 34 years). We also found that the fructose malabsorbers in our study were significantly older than fructose absorbers. A trend towards this association has been found in previous studies (9). We could find no evidence for why this occurs and this, therefore, opens an interesting avenue for future research.

This research may be the basis for improving non-pharmaceutical management of gout. If there is no rise in serum urate following a fructose load in fructose malabsorbers, then there is no benefit for gout patients who are also fructose malabsorbers in reducing dietary fructose intake, as is recommended by current guidelines (42).
To be able to do this we must know whether absorption status changes the way fructose affects serum urate. We hypothesise that those who malabsorb fructose will have a smaller serum urate response to an oral fructose load than those who absorb fructose normally. We have designed a protocol to test for this association (Chapter 5). If this is so then there may be less benefit in avoiding fructose for gout patients who are malabsorbers compared to those who are absorbers.

This research may be the basis for improving non-pharmaceutical management of gout. Gout patients could be tested for absorption status and this result could be used to individualise lifestyle advice. The breath hydrogen testing is simple and non-invasive and could be done in an outpatient setting. It is time intensive, taking about 3 hours, but participants are able to work or read in between the breath tests and the visits would only need to be once off. Individualising lifestyle advice may lead to better compliance by patients.
References


102. White JS. Fructose as a significant cause of gout is unfounded and premature. QJM. 2012;105(8):809-10.


115. IBM Corporation. SPSS Statistics for Mac. 21.0.0.0 ed. Chicago2012.

116. GraphPad Software. GraphPad Prism version 5.00 for Windows. La Jolla California, USA: GraphPad Software Inc; 2013.
HEALTHY VOLUNTEERS WANTED FOR RESEARCH

The University of Otago, Christchurch is currently conducting a study of patients with gout. We are looking for some healthy volunteers without gout.

To be part of the study you need to be:

- Male
- Between 45 and 85 years old
- Not have gout
- Not have irritable bowel syndrome or inflammatory bowel disease
- Not be on antibiotics currently

The study is one visit that takes about 3 hours.

This study has ethical approval.

If you are interested in being part of this research, please contact us to get more information:

Caitlin Batt, BMedSci(Hons) Student, 03 364 0640 ext 86107 or caitlin.batt@cdhb.health.nz
Dear ____________,

We are currently conducting a study examining fructose absorption in patients with gout. We are inviting people with gout to take part in the study. Your name has been given to us as someone who may be interested in participating in the study.

I have included the information sheet about this study. This explains in more detail why we are doing the study and what it involves. Our study coordinator, Caitlin Batt, will be in touch with you in the next few weeks to see if you have any further questions about the study and to ask if you are willing to participate. If you are willing to be involved they will make a time to see you.

If you have any questions regarding this please do not hesitate to contact Caitlin Batt our study coordinator (xx-xxxx ext: xxxx or xxxxxxxxxx@student.otago.ac.nz) or one of the rheumatologists involved (xxx- xxx).

Yours sincerely

L. Stamp

Lisa Stamp
INFORMATION SHEET

Investigators

Assoc Prof Lisa Stamp, Rheumatologist, Christchurch Hospital
Assoc Prof Richard Gearry, Gastroenterologist, Christchurch Hospital
Ms Caitlin Batt, BMedSci student

You are invited to participate in a study of fructose malabsorption in gout. Gout is a major problem in New Zealand. High levels of uric acid in the blood are the cause of gout. Fructose is a sugar that is found in many fruits and honey. It has been shown that fructose can increase blood uric acid levels and thus contribute to gout. We currently recommend that people with gout reduce their intake of fructose to help improve their gout.

About 20% of people do not absorb fructose in the gut. This can lead to abdominal symptoms. For people who do not absorb fructose, reducing fructose intake is not likely to be so important in controlling their gout. The aim of this study is to find out if people with gout are more likely to absorb fructose than people without gout.

Study Procedure

If you agree to participate in this study one of the investigators will see you. You will be asked to fill out a questionnaire about your gout (e.g. how old you were when you had your first attack, how many attacks you have had in the last year and other medical problems) and some questions about your bowel habits.

You will have a test to see how well you absorb fructose. This test requires you to avoid some foods for 24 hours before the test. You will be given some fructose to drink and then you will need to breath into a special bag every 15 minutes for 2-3 hours.

We will also ask you to see if a friend who does not have gout would like to be involved as well. Your friend would need to be the same sex as you and roughly the same age.

Your participation is entirely voluntary and you may withdraw from the study at any stage without this affecting your treatment.

Nature and Duration of the Study

IF you agree to participate in this study you will need to be seen once to complete the questionnaires and have the breath test

Some Common Questions

Will my GP be told I am in the study? Your GP will be advised that you are participating in this study.

What will happen at the end of the study? You will continue your treatment as prescribed by your doctor. If we find that you malabsorb fructose and you have some bowel symptoms we will give you some diet advice that may help.

Where can I get more information about the study? If at any time you have any concerns or questions about this study, do not hesitate to contact any of the study investigators or the study coordinator.

If I need an interpreter, can one be provided? We will endeavor to provide you with an interpreter if you need one.

Are there any risks to me by being in the study? You may feel symptoms of abdominal discomfort, flatulence, diarrhea after the breath test.
Confidentiality

No material which could personally identify you will be used in any reports on this study. Your study records will be stored in a locked cabinet in the Department of Medicine/Rheumatology and stored for a maximum of 20 years.

Results

Overall results of the study will be available from the investigators several months after the study has been completed.

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. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention Rehabilitation and Compensation Act. 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.

Rights

If you have any queries or concerns regarding your rights as a participant in this research study you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act.

Telephone (NZ wide): 0800 555 050.

Free Fax (NZ wide): 0800 2787 7678 (0800 2 SUPPORT).

Email (NZ wide): advocacy@hdc.org.nz

Statement of Approval

This study has received ethical approval from the Health and Disability Ethics Committee.

If at any time you Further Information

have concerns or questions about this study, do not hesitate to contact any of the study investigators.

Assoc Prof Lisa Stamp Phone xx-xxx-xxxxx

Ms Caitlin Batt Phone xx-xxx-xxxx ext: xxxxx
8.4 Fructose breath test information

Information about Your Fructose Breath Test

Please read this information carefully

Your name:
Your appointment date for the breath tests is:

Where do I go for the tests and how do I contact the study coordinators?

Your test takes place at the Nicholls Clinical Research Unit on the ground floor of the Christchurch Medical School building. To find the centre go to the main reception of Christchurch Public Hospital. Go to the corridor on the right of the reception and the first door on the right is the reception area to the research centre.

If you need help finding the research centre please go to the main hospital reception and ask them to call the research centre on 88127.

How do I prepare for the tests?

For the breath tests to be valid, it is important that you follow these instructions concerning medications, supplements and diet prior to each test.

1. Please take no antibiotics or probiotics (eg acidophilus or bifidobacteria powders or capsules) for 2 weeks before your test.

2. Follow the diet on the back of this information sheet for 24 hours before the test.

3. Fast from 10pm the night before the test

Do I continue my normal medications?

If taking antibiotics you need to wait 2 weeks between finishing them and having the test. Take all your usual medications. If you are diabetic, do not take your morning dose of diabetes medication. Continue with your medications as normal after the test.

Unless absolutely necessary we prefer you not to take vitamins, minerals, laxatives, anti-laxatives, yakult and fish oil capsules on the day before and the day of your test.

What do I eat prior to the test?

On the day before the test please only have food and drinks from the list below

Drinks: Water (unflavoured, non-fizzy), coffee (but not coffee substitutes), tea, lactose free milk, rice milk
Alcohol maximum 250mls wine, 60mls spirits or 200ml beer
Cereal, crackers and breads: please do not eat in excess quantities. Corn flakes, rice bubbles, corn thinks, plain rice crackers.

Grains: please do not eat in excess quantities. Any type of rice, corn, maize, buckwheat, amaranath, quinoa, millett.

Meat etc: Eggs, plain fresh or tinned fish, plain meat such as beef, lamb, venison, pork, chicken, ham.

Fruit and veges: Mandarin, green kiwi fruit, strawberries, orange, rockmelon (only 1 palm full of fruit per 2 hours). Sweet corn, green beans, potato (peeled), pumpkin, carrot, courgette, tomato, lettuce, spinach, silverbeet.

Extras: White or brown sugar, barley sugars, boysenberry, raspberry or strawberry jam, marmalade, vegemite, jelly, oil margarine, butter, peanut butter, nuts, seeds.

Many packaged or canned foods have sauces, spices, onion flavouring, artificial sweeteners, soy products etc which you cannot have.

If the food or drink is not on the list please do not eat it the day before your test.

Fast from 10pm on the night before your test.
After 10pm the night before your test:
You can drink small amounts of water.
Do not smoke on the morning of your test.
Clean your teeth and rinse your mouth well with water.
Do not use mouthwash.
Do not use perfume or aftershave, deodorant is ok.

Please bring with you to the test: Some food to eat after the test, a list of your medications and their doses.

During the test: You will be called into a clinic room and breath into a machine or a bag every 15 minutes for 2-3 hours. Feel free to bring reading material, laptop computers etc to use throughout the morning. Occasionally people experience symptoms of abdominal discomfort, flatulence, diarrhoea during these tests. A doctor is available in the unlikely event that medical attention is necessary.

After your test: You may feel symptoms of abdominal discomfort, flatulence, diarrhoea after the test. You will be able to drive and work after your test.

If you have any questions or cannot make your appointment time please contact our study coordinator Caitlin Batt (Phone xx xxx xxxx ext xxxxx or email xxxxxx@student.otago.ac.nz).

8.5.1 Case questionnaire
8.5 Cases Questionnaire

**FRUCTOSE AND GOUT - CASES**

**Inclusion Criteria**

Patient fulfils the diagnostic criteria of gout which are as follows  

Clinical diagnosis of gout requires either A, B, or C to be met (please circle all those that apply)

A. The presence of characteristic urate crystals in the joint fluid
B. A tophus proved to contain urate crystals by chemical means or polarised light microscopy
C. The presence of 6 of the following 12 clinical laboratory, and x-ray phenomena
   1. Maximum inflammation developed within one day
   2. More than one attack of acute arthritis
   3. Attack of monoarthritis
   4. Redness observed over the affected joint(s)
   5. First metatarsophalangeal joint painful or swollen
   6. Unilateral first metatarsophalangeal joint attack
   7. Unilateral attack involving tarsal joint
   8.Suspected tophus
   9. Hyperuricaemia
   10. Asymmetric swelling within a joint
   11. Subcortical cysts without erosions
   12. Negative culture of joint fluid for microorganisms during attack of joint inflammation

**Exclusion Criteria**

1. Known inflammatory bowel disease or irritable bowel syndrome
2. Receiving diuretic or antibiotic therapy
3. Presence of chronic infection or other severe concomitant medical illness or psychiatric disease.
4. Patients with active, concomitant malignancies.

**CONSENT OBTAINED**  

YES / NO
Cases Questionnaire

1. Age _____________ years
2. Male / female
3. Weight _____________ kg
4. Height _____________ cm
5. BMI _____________ kg/m²
6. Waist circumference __________ cm (measured at belly-button)
7. Blood pressure _______________
8. Most recent urate (Date: ___/___/_____) ____________ mmol/l
9. Most recent creatinine (Date: ___/___/_____) ____________ mmol/l
10. Does participant currently have acute gout? YES / NO
    a. Have past X-rays been taken of affected joints? YES / NO
    b. If YES, consistent with gout? YES / NO
Cases Questionnaire

1. How old were you when you had your first attack of gout? ____________________
2. How many attacks of gout have you had in the last year? ____________________
3. How many of those attacks have been in the last month? ____________________
4. Does anyone else in your family have gout? YES / NO
   a. If yes whom? ______________________________________________________
5. What treatment have you had for your gout in the past?
   i. Allopurinol YES / NO
   ii. Steroid YES / NO
   iii. Anti-inflammatory YES / NO
   iv. Probenecid YES / NO
   v. Colchicine YES / NO
   vi. Other YES / NO
6. Have you had any side effects from these medications?
   i. If YES: what? ______________________________________________________
7. Do you have any of the following medical conditions:
   a. Kidney problems YES / NO If YES: what? ____________________________
   b. Type 2 Diabetes YES / NO If YES: how is it treated? __________________
   c. High blood pressure YES / NO If YES: treated? YES / NO
   d. High cholesterol or lipids YES / NO If YES: treated? YES / NO
   e. Heart problems YES / NO If YES: what? ____________________________
   f. Any other health conditions__________________________________________
8. At this time are you: (Please circle all that apply)
   a. Are you in paid employment / self employed?
   b. Are you working full time / part time?
   c. Are you in physical/manual or non-physical employment?
d. Are you retired?

e. Are you a home maker full time or student?

f. Are you unemployed?

g. Are you not working because of ill health/disability?

h. Other ______________________________________

9. What is your current occupation?

________________________________________________

10. If you are not working what was your past occupation?

________________________________________

11. Have you had any time off work in the last month because of your gout? YES / NO

i. If YES, how many days?

____________________

12. How many years of education have you completed? Please circle the number of years at school, college, university etc

13. 4 5 6 7 8 9 10 11 (5th form) 12 13 (7th form) 14 15 16 17 18 19 20

14. 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)

i. 0 1 2 3 4 5 more than 5

15. How many pieces of fresh fruit do you usually eat per day: (please circle the number that applies)

i. 0 1 2 3 4 5 more than 5

16. How many times did you eat seafood in the past week? ______________

17. Does seafood trigger your gout? YES / NO

18. How much alcohol did you drink in the last week?
Cases Questionnaire

a. Beer
b. Wine
c. Spirits
d. Other

19. Does alcohol trigger your gout? YES / NO

11. Are there any other foods / drinks that trigger your gout?
_______________________________
Cases Questionnaire

**Current medications:**
Please include all drugs, pills, medicines bought with or without prescription.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Frequency</th>
<th>Any side effects?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Allopurinol</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**Ethnicity:**
This questionnaire includes information not available from blood tests or any source other than you. Please try to answer each question even if you do not think it is related to you at this time. There are no right or wrong answers. Thank you.

Which ethnic group do you belong to?
*Mark the space or spaces which apply to you.

- NZ European
- Māori
- Samoan
- Cook Island Maori
- Tongan
- Niuean
- Chinese

Ko tēhea momo tāngata e whai pānga atu ana koe?
*Tohua te katoa o raro nei e hāngai ana ki a koe.*

- Pākehā
- Māori
- Hāmoa
- Māori Kuki Airani
- Tonga
- Niue
- Hainamana
Cases Questionnaire

**HAQ-II questionnaire**

We are interested in learning how your gout affects your ability to function in daily life.

Place an x in the box which best describes your usual abilities over the past week.

<table>
<thead>
<tr>
<th>Are you able to:</th>
<th>Without any difficulty</th>
<th>With some difficulty</th>
<th>With much difficulty</th>
<th>Unable</th>
</tr>
</thead>
<tbody>
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<td>Reach and get down a 2 kilo object (such as a bag of sugar) from just above your head?</td>
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<td>Do outside work (such as yard work)?</td>
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<tr>
<td>Move heavy objects?</td>
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</tbody>
</table>

*HAQ-II Score _______________

On a scale of 0 to 10, with 0 being no pain at all and 10 being the worst pain you could imagine, what would your level of pain be today? 

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
### IBS Module

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the last three months, how often have you discomfort or pain anywhere in your abdomen?</td>
<td>0: Never, 1: Less than one day a month, 2: One day a month, 3: Two or three days a month, 4: One day a week, 5: More than one day a week, 6: Everyday, <strong>Skip remaining questions</strong></td>
</tr>
<tr>
<td>For women: Did this discomfort or pain occur only during your menstrual bleeding and not at other times?</td>
<td>0: No, 1: Yes, 2: Does not apply</td>
</tr>
<tr>
<td>Have you had this discomfort or pain 6 months or longer?</td>
<td>0: No, 1: Yes</td>
</tr>
<tr>
<td>How often did this discomfort or pain get better or stop after you had a bowel movement?</td>
<td>0: Never or rarely, 1: Sometimes, 2: Often, 3: Most of the time, 4: Always</td>
</tr>
<tr>
<td>When this discomfort or pain started, did you have more frequent bowel movements?</td>
<td>0: Never or rarely, 1: Sometimes, 2: Often, 3: Most of the time, 4: Always</td>
</tr>
<tr>
<td>When this discomfort or pain started, did you have less frequent bowel movements?</td>
<td>0: Never or rarely, 1: Sometimes, 2: Often, 3: Most of the time, 4: Always</td>
</tr>
<tr>
<td>When this discomfort or pain started, were your bowel movements looser?</td>
<td>0: Never or rarely, 1: Sometimes, 2: Often, 3: Most of the time, 4: Always</td>
</tr>
<tr>
<td>When this discomfort or pain started, how often did you have harder stools (bowel movement)?</td>
<td>0: Never or rarely, 1: Sometimes, 2: Often, 3: Most of the time</td>
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<tr>
<td>Question</td>
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<tr>
<td>In the last three months how often did you have hard or lumpy stools?</td>
<td>0</td>
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<tr>
<td>In the last three months how often did you have loose, mushy or watery stools?</td>
<td>0</td>
</tr>
<tr>
<td>In the last three months, how often have you noticed blood in your stools?</td>
<td>0</td>
</tr>
<tr>
<td>In the last 3 months how often have you noticed black stools?</td>
<td>0</td>
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<tr>
<td>Have you been told by your doctor that you are anaemic (a low blood count or iron)? If female, not due to your periods</td>
<td>0</td>
</tr>
<tr>
<td>In the last 3 months have you unintentionally lost more than 10 pounds (4.5kg)?</td>
<td>0</td>
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<tr>
<td>If you are over 50, have you had a recent major change in bowel movements (change in frequency or consistency)?</td>
<td>0</td>
</tr>
</tbody>
</table>

**Gout Genetics Study**

Previously enrolled

Declined

Agreed

If agreed:  Consent signed

Documentation completed, copied, and sent to Dunedin

Blood and urine samples sent to Dunedin

Date ________________
FRUCTOSE AND GOUT - CONTROLS

Inclusion criteria

Exclusion Criteria
5. Known inflammatory bowel disease or irritable bowel syndrome
6. Receiving diuretic or antibiotic therapy
7. Presence of chronic infection or other severe concomitant medical illness or psychiatric disease.
8. Patients with active, concomitant malignancies.
9. Known gout

CONSENT OBTAINED       YES / NO

12. Age _______________ years
13. Male / female
14. Weight ____________kg
15. Height ____________cm
16. BMI ________________kg/m^2
17. Waist circumference __________ cm (measured at belly-button)
18. Blood pressure _________________
19. Most recent urate (Date: __/___/____) _____________mmol/l
20. Most recent creatinine (Date: __/___/____) _____________mmol/l
Control questionnaire

22. Do you have any of the following medical conditions:
   a. Kidney problems   YES / NO   If YES: what? ______________________________
   b. Type 2 Diabetes   YES / NO   If YES: how is it treated? ______________________
   c. High blood pressure    YES / NO   If YES: treated?    YES / NO
   d. High cholesterol or lipids    YES / NO   If YES: treated?    YES / NO
   e. Heart problems    YES / NO   If YES: what? ____________________________
   f. Any other health conditions____________________________________________________________

20. At this time are you: (Please circle all that apply)
   a. Are you in paid employment / self employed?
   b. Are you working full time / part time?
   c. Are you in physical/manual or non-physical employment?
   d. Are you retired?
   e. Are you a home maker full time or student?
   f. Are you unemployed?
   g. Are you not working because of ill health/disability?
   h. Other ________________________________

21. What is your current occupation? ________________________________________________

22. If you are not working what was your past occupation? ____________________________

23. How many years of education have you completed? Please circle the number of years at school, college, university etc

   4  5  6  7  8  9  10  11 (5th form)  12  13 (7th form)  14  15  16  17  18  19  20

24. 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)

   i. 0  1  2  3  4  5  more than 5

25. How many pieces of fresh fruit do you usually eat per day: (please circle the number that applies)

   i. 0  1  2  3  4  5  more than 5
Control Questionnaire

26. How many times did you eat seafood in the past week? __________

27. How much alcohol did you drink in the last week?
   a. Beer
   b. Wine
   c. Spirits
   d. Other

Current medications:
Please include all drugs, pills, medicines bought with or without prescription.

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Control Questionnaire

**Ethnicity:**
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Control Questionnaire

**HAQ-II questionnaire**

Place an x in the box which best describes your usual abilities over the past week.

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</table>

**HAQ-II Score** __________

On a scale of 0 to 10 with 0 being no pain at all and 10 being the worst pain you could imagine, what would your level of pain be today?

[0 1 2 3 4 5 6 7 8 9 10]
<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
<th>Answer Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the last three months, how often have you discomfort or pain anywhere in your abdomen?</td>
<td>0: Never 1: Less than one day a month 2: One day a month 3: Two or three days a month 4: One day a week 5: More than one day a week 6: Everyday</td>
<td>Skip remaining questions</td>
</tr>
<tr>
<td>For women: Did this discomfort or pain occur only during your menstrual bleeding and not at other times?</td>
<td>0: No 1: Yes 2: Does not apply</td>
<td></td>
</tr>
<tr>
<td>Have you had this discomfort or pain 6 months or longer?</td>
<td>0: No 1: Yes</td>
<td></td>
</tr>
<tr>
<td>How often did this discomfort or pain get better or stop after you had a bowel movement?</td>
<td>0: Never or rarely 1: Sometimes 2: Often 3: Most of the time 4: Always</td>
<td></td>
</tr>
<tr>
<td>When this discomfort or pain started, did you have more frequent bowel movements?</td>
<td>0: Never or rarely 1: Sometimes 2: Often 3: Most of the time 4: Always</td>
<td></td>
</tr>
<tr>
<td>When this discomfort or pain started, did you have less frequent bowel movements?</td>
<td>0: Never or rarely 1: Sometimes 2: Often 3: Most of the time 4: Always</td>
<td></td>
</tr>
<tr>
<td>When this discomfort or pain started, were your bowel movements looser?</td>
<td>0: Never or rarely 1: Sometimes 2: Often 3: Most of the time 4: Always</td>
<td></td>
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<tr>
<td>When this discomfort or pain started, how often did you have harder stools (bowel movement)?</td>
<td>0: Never or rarely 1: Sometimes 2: Often 3: Most of the time 4: Always</td>
<td></td>
</tr>
<tr>
<td>In the last three months how often did you have hard or lumpy stools?</td>
<td>0: Never or rarely 1: Sometimes 2: Often 3: Most of the time 4: Always</td>
<td>0: Never or rarely 1: About 25% of the time 2: About 50% of the time 3: About 75% of the time 4: Always, 100% of the time</td>
</tr>
<tr>
<td>Question</td>
<td>Options</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
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</tr>
</tbody>
</table>
| In the last three months how often did you have loose, mushy or watery stools? | 0: Never or rarely  
1: Sometimes  
2: Often  
3: Most of the time  
4: Always          |
| In the last three months, how often have you noticed blood in your stools? | 0: Never or rarely  
1: Sometimes  
2: Often  
3: Most of the time  
4: Always          |
| In the last 3 months how often have you noticed black stools?          | 0: Never or rarely  
1: Sometimes  
2: Often  
3: Most of the time  
4: Always          |
| Have you been told by your doctor that you are anaemic (a low blood count or iron)? If female, not due to your periods | 0: No  
1: Yes          |
| In the last 3 months have you unintentionally lost more than 10 pounds (4.5kg)? | 0: No  
1: Yes          |
| If you are over 50, have you had a recent major change in bowel movements (change in frequency or consistency)? | 0: No  
1: Yes  
2: Does not apply |