Low Level Laser Therapy for the Treatment of Tendinopathy With Emphasis on the Achilles Tendon

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Thesis submitted for Doctor of Philosophy (PhD)

2010
Abstract

Low level laser therapy (LLLT) has emerged as a potential treatment option for tendinopathy. Like other electrotherapy modalities, LLLT is a dose dependant modality, thus studies are required to refine dosage guidelines, and to determine effectiveness. Despite evidence from laboratory studies supporting the beneficial effects of LLLT, it still remains on the fringes of mainstream medicine; in particular, positive results obtained in the laboratory have not been consistently reproduced in the clinical setting. The review of the literature undertaken for this thesis highlighted a number of shortcomings in research to date on LLLT: this includes poor methodology, poor reporting of parameters, and varying application techniques. Tendinopathy has become the scourge of the musculoskeletal practitioner because of the nature of the pathogenesis of the condition. Existing literature indicates that tendinopathy is the result of a failure of one of two processes: the healing response, or the normal turnover/remodeling response; however, the definitive solution to the problem remains an enigma. One intervention that is popular, especially for the Achilles tendon (tendo calcaneus) and patellar tendons, is heavy load eccentric exercises. Utilizing methodologies from the top two tiers of the hierarchy of evidence, the thesis investigated the clinical effectiveness of LLLT as an adjunct to an eccentric exercise protocol to treat Achilles tendinopathy. A systematic review with meta-analysis of the literature reporting the use of LLLT to treat tendinopathy was conducted. Twelve studies provided evidence to support the relationship between positive outcomes and current dosage recommendations. Subsequently, a pilot study was conducted using the recommended dose (i.e. 810nm, 100mW applied to six points on the tendon for 30s, for a total of 3J per point and 18J per session) to assess the feasibility of a larger, adequately powered controlled trial. Although the results of the pilot study were not statistically significant, the active treatment group did demonstrate superior change scores for both pain, and function compared to placebo group. Responding to criticism of the parameters used in the pilot study, power density was altered from 2.375W/cm² to 100mW/cm² for the main randomised controlled trial (RCT). Although participants in the main trial showed improvements in function scores at 3 months, which were maintained for a further 9 months, there was no difference in change scores between active and placebo groups at any of the follow-up points. These findings provide additional evidence for the effectiveness of heavy load eccentric exercises, but suggest that LLLT treatment, used as an adjunct and at the parameters indicated, provided no additional benefit for participants in the treatment group. This thesis adds to the evidence surrounding the use of laser therapy to treat tendinopathy. The need to refine current guidelines concerning description of parameters and dose has been highlighted by the findings of the pilot and main RCTs. Another important issue raised, relates to exercise adherence and clinical effectiveness of the prescribed dose of eccentric exercise. Finally, the complexity of accurately measuring the effectiveness of physiotherapeutic interventions in the clinical setting has also been highlighted, and presents challenges for the profession in the future.
Acknowledgements

Without the support of a number of individuals and organisations, the completion of this thesis would not have been possible. Their help and assistance is gratefully acknowledged.

I would like to give a special thanks to Professor G.David. Baxter for supplying the initial impetus that got me started, the ongoing support and supervision during the process, and for all the extra skills and knowledge that I have acquired due to his facilitation and mentorship.

I am grateful to my supervisors and advisors: Professor Suzanne McDonough and Drs Deirdre Hurley-Osing, Joanne Munn, Jeffrey Basford, and J. Haxby Abbott, for all their hard work, patience, and advice.

My colleagues at the School of Physiotherapy must also share in this achievement, as without their taking on the extra load to provide me with time to work on the thesis, I would not now be at this stage.

Finally, the biggest thank you and expression of my gratitude goes to Irene, Emma and Simon, who are my inspiration.
Outputs from Work Conducted During the Thesis

Publications:


Conference Presentations:

• Laser Therapy in the Treatment of Achilles Tendinopathy: A Randomized Controlled Trial.
  *Laser Florence 2009.*

• The Dose That Works: low Level Laser Treatment of Tendinopathy.
  *Laser Florence 2009.*

• The Use of Low Level Laser Therapy in Musculoskeletal Physiotherapy in New Zealand.
  IPTA Congress 2009 Laser Tokyo. (Awarded best presentation)

• Low Level Lasers in Treating Tendinopathy: A systematic Review with Meta-analysis.
  *IPTA Congress 2008 NZLaser*. *Laser Therapy 2008 17(1); 14.*

• Laser Therapy in the Treatment of Achilles Tendinopathy: a Pilot Study.
  *Proceedings of the Southern Physiotherapy Symposium 2007*

• Laser Therapy in the Treatment of Achilles Tendinopathy: a Pilot Study.
  *Laser Florence 2007*. (Conference abstracts published in *Lasers in Medical Science* 2008 23(1); 93.). (Awarded best presentation)
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<th>Description</th>
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<tbody>
<tr>
<td>ACC</td>
<td>Accident Compensation Corporation</td>
</tr>
<tr>
<td>ADAM</td>
<td>a Disintegrin &amp; Metalloproteinase</td>
</tr>
<tr>
<td>ADAMTS</td>
<td>a Disintegrin &amp; Metalloproteinase with Thrombospondin Motifs</td>
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<tr>
<td>AGREE</td>
<td>Appraisal of Guidelines Research Evaluation</td>
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<tr>
<td>AMSTAR</td>
<td>Assessment of Multiple Systematic Reviews</td>
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<tr>
<td>ANCOVA</td>
<td>Analysis of Variance (considering co-variants)</td>
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<tr>
<td>ANS</td>
<td>Autonomic Nervous System</td>
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<td>AT</td>
<td>Achilles tendon</td>
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<tr>
<td>ATP</td>
<td>Adenosine Triphosphate</td>
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<tr>
<td>CCT</td>
<td>Controlled Clinical Trial</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>CO₂</td>
<td>Carbon Dioxide</td>
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<td>Con</td>
<td>Concentric</td>
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<td>CTGF</td>
<td>Connective Tissue growth Factor</td>
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<tr>
<td>DASH</td>
<td>Disabilities of the Arm, Shoulder and Hand Questionnaire</td>
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<tr>
<td>DB</td>
<td>David Baxter</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>DH</td>
<td>Deirdre Hurley-Osing</td>
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<tr>
<td>EBM</td>
<td>Evidence Based Medicine</td>
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<tr>
<td>Ecc</td>
<td>Eccentric</td>
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<tr>
<td>ECM</td>
<td>Extracellular Matrix</td>
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<tr>
<td>ESWT</td>
<td>Extracorporeal Shock Wave Therapy</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration (USA)</td>
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<tr>
<td>GaAlAs</td>
<td>Gallium-Aluminium-Arsenide</td>
</tr>
<tr>
<td>GaAs</td>
<td>Gallium-Arsenide</td>
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<tr>
<td>GTN</td>
<td>Glyceryl-Trinitrate</td>
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<tr>
<td>He-Ne</td>
<td>Helium-Neon</td>
</tr>
<tr>
<td>InGaAlP</td>
<td>Indium-Gallium-Aluminium-Phosphate</td>
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<tr>
<td>IGF-I</td>
<td>Insulin like Growth Factor</td>
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<tr>
<td>INIT</td>
<td>Initial</td>
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<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention to Treat</td>
</tr>
<tr>
<td>J</td>
<td>Joule</td>
</tr>
<tr>
<td>JB</td>
<td>Jeffrey Basford</td>
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</table>
JM: Joanne Munn

Kg: Kilogram

LASER: Light Amplification by Stimulated Emission of Radiation

LED: Light Emitting Diode

LOCF: Last Observation Carried Forward

LLLT: Low Level Laser Therapy

mJ: milliJoules

mm: millimetres

mRNA: messenger Ribonucleic Acid

mW: milliWatts

MCAR: Missing Completely at Random

MCID: Minimal Clinical Important Difference

MHz: MegaHertz

MMP: Matrix Metalloproteinase

MRC: Medical Research Council (UK)

MRI: Magnetic Resonance Imaging

nm: nanometers
<table>
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<th>Acronym</th>
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<tr>
<td>NASA:</td>
<td>National Aeronautics and Space Administration</td>
</tr>
<tr>
<td>NdYAG:</td>
<td>Neodymium-Yttrium-Aluminium-Garnet</td>
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<tr>
<td>Nm:</td>
<td>Newton meter</td>
</tr>
<tr>
<td>NO:</td>
<td>Nitric Oxide</td>
</tr>
<tr>
<td>NOS:</td>
<td>Nitric Oxide Synthases</td>
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<tr>
<td>NPRS:</td>
<td>Numeric Pain Rating Scale</td>
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<tr>
<td>NSAID:</td>
<td>Non-steroidal Anti-inflammatory Drug</td>
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<td>OA:</td>
<td>Osteoarthritis</td>
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<tr>
<td>PRISMA:</td>
<td>Preferred Reporting Items for Systematic Reviews and Meta-Analyses</td>
</tr>
<tr>
<td>QUORUM:</td>
<td>Quality of Reporting of Meta-Analyses</td>
</tr>
<tr>
<td>RA:</td>
<td>Rheumatoid Arthritis</td>
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<tr>
<td>RCT:</td>
<td>Randomised Controlled Trial</td>
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<tr>
<td>REDOX:</td>
<td>Reduction-Oxidation Reaction</td>
</tr>
<tr>
<td>RNS:</td>
<td>Reactive Nitrogen Species</td>
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<tr>
<td>ROC:</td>
<td>Receiver Operating Characteristic</td>
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<tr>
<td>ROM:</td>
<td>Range of Motion</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
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</tr>
<tr>
<td>ROS</td>
<td>Reactive Oxygen Species</td>
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<tr>
<td>RR</td>
<td>Relative Risk</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SM</td>
<td>Suzanne McDonough</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
</tr>
<tr>
<td>ST</td>
<td>Steve Tumilty</td>
</tr>
<tr>
<td>TGF-β-I</td>
<td>Transforming Growth Factor β-I</td>
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<tr>
<td>TIMPS</td>
<td>Tissue Inhibitors of Metalloproteinases</td>
</tr>
<tr>
<td>µm</td>
<td>micrometers</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
</tr>
<tr>
<td>VISA-A</td>
<td>Victoria Institute of Sport Assessment – Achilles</td>
</tr>
<tr>
<td>W</td>
<td>Watts</td>
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<tr>
<td>WALT</td>
<td>World Association of Laser Therapy</td>
</tr>
<tr>
<td>WMA</td>
<td>World Medical Association</td>
</tr>
<tr>
<td>WMD</td>
<td>Weighted Mean Difference</td>
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1 Introduction

“There are two kinds of light; the glow that illuminates, and the glare that obscures”

James Thurber

The intention of this PhD is to provide a glow that illuminates the topic of low level laser therapy for the treatment of tendinopathy, and adds to the body of knowledge surrounding the subject. Low level laser devices used in physiotherapy generally fall into the Class 3B category (based on relative risk), wavelengths are commonly in the range of 600nm-950nm, output power is typically less than 500mW and these are essentially athermic devices (Bazin et al., 2006).

Although the use of light to treat ailments is not new and has been practiced in various forms for centuries, laser (Light Amplification by Stimulated Emission of radiation) devices have only been available and utilized in the clinical setting since the 1960s; while they have gained in popularity for clinical applications, their use as part of low level laser therapy still remains on the fringes of mainstream medicine. Indeed, clearance to treat musculoskeletal conditions with low level laser therapy (with the premarket notification/510 (K)) by the American Food and Drug Administration (FDA) was only granted as late as 2002 (FDA, 2002). To gain full FDA “approval” sufficient randomised controlled trials (RCTs) must be conducted to satisfy the FDA of a given laser’s effectiveness and safety in the clinical setting.

Tendinopathy has become the scourge of the musculoskeletal practitioner because of the multifactorial nature of the pathogenesis of the condition (Kannus et al., 2002; Paavola et al., 2002; Soma & Mandelbaum, 1994). It is generally accepted that
tendinopathy is the result of a failure of one of two processes: the healing response, or the normal turnover/remodeling response, but the definitive solution to the problem remains an enigma.

This work described in the thesis explored the use of low level laser therapy (LLLT) to treat tendinopathy. The early chapters (Chapters 1-3) provide a narrative review of the relevant literature; these define the problem, provide the context, and set the aims of the thesis. Using an evidence based approach, Chapter 4 reports on the results of a systematic review and meta-analysis to assess current evidence for the use of this modality to treat tendinopathy. Based upon the information from the systematic review, first a pilot study was conducted (Chapter 5) to test a protocol and provide data for power calculations, and then a larger, adequately powered RCT (Chapter 6) was carried out. Finally, Chapter 7 discusses the main points of the thesis, puts this work in perspective with regards to current literature, and suggests ways forward for future work in this area.

1.1 Low Level Laser Therapy

The use of light for therapeutic purposes, i.e. using sunlight or heliotherapy as it was known, has been practiced for thousands of years. Ancient civilisations worshiped the sun as they recognised the energy provided by it, and the power of light to stimulate and maintain life. In ancient Greek and Roman cultures sunbathing was considered a healthy means of preventative medicine: Herodotus recognised the importance of sunlight in bone growth as early as the 6th century BC (Cory, 1904). However, sun worship was considered heresy to the early Christians and the rise of Christianity led to the demise of any mainstream practice of heliotherapy, and there is no reference to it in
the literature until the 18\textsuperscript{th} century (Licht, 1983). By that time, sun baths were prescribed for a number of conditions including scurvy, rickets, rheumatoid arthritis and depression (Cauvin, 1815; Ebermaier, 1799).

Finsen pioneered the use of ultraviolet (UV) light to treat dermal tuberculosis and developed a carbon arc lamp incorporating lenses and filters to treat Lupus Vulgaris (Finsen, 1901). During the first half of the 20\textsuperscript{th} century, the use of varying wavelengths of light, especially UV, to treat such conditions as nephritis, rheumatoid arthritis, haemophilia and herpes zoster (Krusen, 1933) gained in popularity.

The first clinical applications of laser appeared in the 1960s after Maiman, using a ruby crystal, produced the first pulse of laser radiation of a fixed wavelength in the visible red spectrum, 694nm (Maiman, 1960). Apart from applications of the new technology in other fields of medicine and surgery, in the latter half of the sixties Prof. E. Mester of Hungary, one of the pioneers of LLLT, performed the first of many studies exploring the effects of low intensity laser at the cellular level and on wound healing (Mester & Jaszsagi Nagy, 1973; Mester, Korenyi Both, & Spiry, 1973; Mester et al., 1968; Mester, Spiry, Szende, & Tota, 1971). Based upon initial results showing stimulatory effects of such irradiation, the term laser biostimulation came into being.

Cellular studies have shown that after irradiation with laser light at parameters relevant to LLLT, specific components of the mitochondrial respiratory chain absorb certain wavelengths more readily, and this primary reaction leads to secondary reactions involving intracellular signaling leading to the beneficial effects that promote healing (Breitbart, Levinshal, Cohen, Friedmann, & Lubart, 1996; Chen et al., 2009; Gavish, Perez, & Gertz, 2006; Gavish, Perez, Reissman, & Gertz, 2008; Grossman, Schneid, Reuveni,
Halevy, & Lubart, 1998; Hou et al., 2008; Karu, Pyatibrat, & Kalendo, 1995; Karu & Kolyakov, 2005; Karu, Pyatibrat, & Afanasyeva, 2005; Kreisler, Christoffers, Willershausen, & D'Hoedt, 2003; Stein, Benayahu, Maltz, & Oron, 2005; Vinck, Cagnie, Cornelissen, Declercq, & Cambier, 2003; Young, Bolton, Dyson, Harvey, & Diamantopoulos, 1989). Deeper penetration into the tissues is achievable with longer wavelengths i.e. beyond the wavelengths initially used, thus enabling the clinician to target deeper structures (Karu, 1989). Laboratory experiments using animals have provided further evidence of specific effects such as increases in collagen synthesis, angiogenesis and cell proliferation, along with decreased pain and inflammation (Al-Watban, Zhang, Andres, & Al-Anize, 2009; Bjordal, Lopes-Martins, & Iversen, 2006; Enwemeka et al., 2004; Oliveira et al., 2009; Reddy, Stehno-Bittel, & Enwemeka, 1998; Ribeiro et al., 2009; Salate et al., 2005). Importantly, these experiments have also generated information concerning the most efficacious dosage window (i.e. 3-5J/cm²).

Unfortunately, clinical trials on human subjects have not always demonstrated the expected benefits from the application of LLLT, as the positive results from laboratory studies have not been consistently carried over into trials; indeed, the outcomes from clinical trials are mixed, resulting in limited evidence and few recommendations for the use of LLLT from systematic reviews (Bjordal et al., 2007; Chow & Barnsley, 2005; Coombes, Bisset, & Vicenzino, 2009; Green, Buchbinder, & Hetrick, 2003; Jamtvedt et al., 2008; McLauchlan & Handoll, 2001; Smidt et al., 2003; Stasinopoulos & Johnson, 2005; Yousefi-Nooraie et al., 2008). Such recommendations have also been confounded by a lack of correct reporting of parameters and methods of applications in published papers; this has been a particular problem in the past and varies among studies, leading to
controversy over such issues as the actual dose delivered to the target tissue. The
effective dosage window for many conditions remains very broad despite guidelines that
have been published from a number of sources (Bjordal, Couppe, Chow, Tuner, &
Ljunggren, 2003; Bjordal, Couppe, & Ljunggren, 2001; WALT, 2005); the optimum dose
for most conditions has yet to be found. Low level laser therapy, like many other forms
of electrotherapy, remains a dose dependant modality, and many more studies are
required to adequately refine dosage guidelines and establish effectiveness.

1.2 Tendinopathy

The pathogenesis of tendinopathy is not yet fully understood, but a combination
of extrinsic and intrinsic factors as a cause of chronic Achilles tendon disorders is
common (Kannus et al., 2002; Paavola et al., 2002; Soma & Mandelbaum, 1994).
Tendinopathy is generally considered a process of degeneration rather than an
inflammatory problem (Khan, Cook, Bonar, Harcourt, & Astrom, 1999; Spacca, Necozione,
& Cacchio, 2005). Two interactive hypotheses have been put forward to try to explain
the failure of the tendon to repair or remodel itself: the biomechanical hypothesis
(Wang, Losifidis, & Fu, 2006), and the recently revived biochemical hypothesis
(Danielson, 2009); these hypotheses are not mutually exclusive.

1.2.1 The Biomechanical Hypothesis

The biomechanical hypothesis is primarily concerned with matrix abnormality
resulting from trauma, overuse, or immobilisation/underuse. This changes the
viscoelastic properties of the tendon (stress/strain, hysteresis), and alters the
biomechanical efficiency of the tendon to store and release energy, or resist
deformation, and thus overwhelms the ability of the cells to repair/remodel structural
damage (Jozsa & Kannus, 1997). The difference between the energy stored and released (i.e. the area enclosed by the hysteresis loop), is given off as heat (Reimersma & Schamhardt, 1985); this is important as temperatures above 42.5°C are known to cause cell death in vitro (Hall, 1988). Fibroblasts in vitro, subjected to 45°C for 10 minutes exhibited a mortality rate of 9% ± 4% (Birch, Wilson, & Goodship, 1997). Apart from apoptosis, excessive heat has also been shown to increase the level of pro-inflammatory cytokines (Hosaka et al., 2006), thus exacerbating the problem. Thus, the biomechanical hypothesis could be simply defined as failure of the tendon structure to cope with the loads put upon it due to changes in the viscoelastic properties of the tendon as a result of matrix abnormalities, the consequences of which are excessive heat and potentially cell apoptosis.

1.2.2 The Biochemical Hypothesis

The most important part of the biochemical hypothesis is the putative local production of signal substances such as acetylcholine (ACh), substance P and catecholamines in human tendon cells (Andersson, Danielson, Alfredson, & Forsgren, 2008; Danielson, 2009; Danielson, Alfredson, & Forsgren, 2006b; Danielson, Andersson, Alfredson, & Forsgren, 2007c). These signal substances are thought to affect pain signaling and regulation of vascularity and tissue changes. Other biochemical changes influence the interaction between glycoproteins, proteoglycans, and collagen, which determines the morphology and structure of the tendon. Tenocytes produce the components of the extracellular matrix as well as the enzymes that degrade them. The fine balance between synthesis and degradation (remodeling) is mediated by matrix metalloproteinase (MMP), a disintegrin and metalloproteinase (ADAM), and a disintegrin
and metalloproteinase with thrombospondin motifs (ADAMTS) (Corps, Curry, Buttle, Hazleman, & Riley, 2004). Low proteoglycan and ADAMTS levels, with associated higher levels of versican and aggrecan, have been implicated in tendinopathy (Smith et al., 2008; Tom et al., 2009). Repeated loading elicits responses at the cellular level that are thought to adapt the tendon structure to this increased load (Curwin, Vailas, & Wood, 1988; Langberg et al., 2007; Langberg, Rosendal, & Kjaer, 2001; Michna & Hartmann, 1989). However, there are no data on the potential relevance of magnitude, rate or frequency of loading to suggest how much is beneficial or detrimental: i.e. the presence of a potential ‘dosage-response’ relationship is unknown. To summarise the biochemical hypothesis: tenocytes reacting to mechanical loading produce signal substances, proteins and enzymes that may have effects on pain signaling, tissue maintenance/repair processes, and vascular regulation; however, whether the increase in these substances are causative or a by-product of the degenerative pathology has yet to be determined.

1.3 Treatment of Tendinopathy

A multitude of treatment options are available to reduce symptoms and to attempt to control or enhance the tendon healing response. These modalities, (which include various electrotherapy modalities, eccentric exercise; a variety of injection techniques; and application of glyceryl trinitrate patches [GTN]), have been found to provide mixed or uneven benefit across patient populations (Andres & Murrel, 2008; Green et al., 2003; McLauchlan & Handoll, 2001), and the optimal treatment regime has yet to be established. Over the last ten years or so, eccentric exercises have emerged as the exercise treatment of choice for tendinopathy, despite the lack of high quality research evidence (Meyer, Tumilty, & Baxter, 2009; Woodley, Newsham-West, & Baxter,
Although the exact mechanism behind the effects of eccentric exercise remains unknown, it is thought to influence elements relevant to both the biomechanical and biochemical hypotheses as it results in increased collagen synthesis and improved viscoelastic properties (Kubo, Kanehisa, & Fukunaga, 2002; Langberg et al., 2007; Mafi, Lorentzon, & Alfredson, 2001; Miller et al., 2005).

Reviews of the effectiveness of treatment modalities for different tendinopathies are generally not supportive of the use of low level laser therapy (Ejnisman et al., 2004; Green et al., 2003; Maher, 2006; McLauchlan & Handoll, 2001; Stasinopoulos & Johnson, 2005). However, as already stated, laser is a dose dependant modality and when reviews are restricted to studies using recommended wavelength and doses, positive recommendations have been made: e.g. as in a review of the use of low level laser for lateral epicondylitis (Bjordal et al., 2008). However, such reviews are few in number, and more work is needed in this area to build a body of evidence around the use of LLLT for different anatomical sites of tendinopathy. As stated above, there is evidence from laboratory studies that explain the observed clinical effects, such as decreased inflammation, increased angiogenesis, increased fibroblast activity, leading in turn to increased collagen production and on to increased tensile strength, and decreased pain (Bjordal et al., 2006; Oliveira et al., 2009; Reddy et al., 1998; Ribeiro et al., 2009; Salate et al., 2005).

Despite the myriad of treatment options available there is not one modality or one therapeutic approach that stands out as the definitive management solution for this condition. The combination of eccentric exercise and low level laser therapy, because of the previously discussed evidence of their effects, may be beneficial in treating
tendinopathy. These two modalities in combination should enhance the healing response and recondition the tendon to enable the patient to return to previous levels of activity.

1.4 Evidence Based Medicine

In today’s health care climate, it is important to use the best available evidence to support clinical practice. Funders of health care, whoever they may be, are looking for ways to maximize the benefit of every health care dollar. An attempt to achieve more efficiency in the system saw the emergence of Evidence Based Medicine (EBM) in the early 1990s (Guyatt et al., 1992). EBM put more emphasis on the examination of evidence from clinical research for clinical decision making, rather than that of intuition, clinical experience, and patho-physiological rationale. However, EBM is not without its opponents, because of the failure of EBM proponents to produce evidence of its superiority over traditional clinical decision making (Feinstein & Horwitz, 1997; Tonelli, 2006); indeed it is argued that the use of EBM is largely based upon expert opinion, the lowest grade of evidence (Figure 1-1). Such studies which might be able to evaluate the impact of EBM are highly unlikely (Guyatt et al., 1992), with researchers citing ethical and practical obstacles that would prevent such trials (Straus & McAlister, 2000).

One of the most widely accepted definitions of EBM is "the explicit, judicious, and conscientious use of current best evidence from health care research in decisions about the care of individuals and populations" (Sackett, Straus, Richardson, Rosenberg, & Haynes, 2000). As part of this, formal rules have been established to evaluate relevant literature, and a hierarchy of evidence has been proposed (Figure 1-1) which includes the systematic review with meta-analysis as the highest level of evidence. Various methods
of grading the evidence from systematic reviews has also emerged (e.g. Clark, Burkett, & Stanko-Lopp, 2009; Harbour & Miller, 2001; van Tulder, Furlan, Bombardier, & Bouter, 2003), along with ways to evaluate the methodological quality of individual trials (for review see: Olivo et al., 2008). Organisations such as the Cochrane Collaboration, the US Preventative Services Task Force, the UK National Institute for Clinical Excellence, and the Scottish Intercollegiate Guideline Network have developed and evolved with the overarching purpose of reviewing the literature to formulate guidelines or make recommendations.
Figure 1-1: Level of Evidence Pyramid.
(Library of the Health Sciences, 2010)

The Physiotherapy Evidence Database, PEDro scale was developed specifically for use in physiotherapy as a means of rating the quality of published RCTs (PEDro, 2007; Sherrington, Herbert, Maher, & Moseley, 2000): the scale includes important quality criteria such as concealed allocation, intention to treat analysis, the use of objective outcome measures, and adequate follow up. The PEDro scale is considered to be one of the most reliable and valid measures for the purpose of assessing the quality of physiotherapy RCTs (Maher, Sherrington, Herbert, Moseley, & Elkins, 2003; Olivo et al., 2008).
Bearing in mind the ongoing debate over EBM, it must be acknowledged that the evidence from research is just one component of the information gathered together to make clinical decisions. Therefore there will always be a need for research based evidence to inform practice. Where possible, research should be conducted at the highest level in the hierarchical pyramid in Figure 1-1, and to this end, this body of work set out to use methodologies from the top two tiers of the pyramid.

1.5 The Problem

A healthy functioning tendon relies on a complicated interaction between biomechanical load and biochemical stimulation of a process designed to constantly remodel and adjust the structure of the tendon, and therefore maintain the viscoelastic properties to enable the tendon to cope with the mechanical loads placed upon it.

Pathogenesis of tendinopathy is multifactorial, and despite the myriad of treatment options available there is no single modality or treatment approach that stands out as the definitive solution, based upon current evidence. Logic suggests that some form of reconditioning to enable the tendon to withstand the loads put upon it (and therefore resist negative changes in viscoelastic properties, such as changes in stress/strain, hysteresis, and Young’s modulus) must be included in any rehabilitation process; heavy load eccentric exercises, as opposed to alternate forms of exercise, have the best supporting evidence for their inclusion in any such regime.

For low level laser therapy, positive evidence from cellular and animal studies suggests that beneficial effects should be forthcoming in the clinical treatment of tendinopathy. However, research shows that in the clinical setting, the success expected from the results of lab based studies has not always been realised. More work is needed
to establish the evidence for the use of low level laser therapy, and to define the optimum treatment application and parameters.

1.6 Aims of the Thesis

The overall aim of the thesis was to investigate the clinical effectiveness of Low level laser therapy (LLLT) for the treatment of tendinopathy.

Two main objectives were set:

1. Assess if LLLT is effective for the treatment of tendinopathy.

2. Determine the relevance of irradiation parameters to outcome, and the validity of current dosage recommendations for the treatment of tendinopathy.

A systematic review with meta-analysis was the first methodology employed to answer these questions. Further, an adequately powered randomised controlled trial (RCT) was carried out to test the effectiveness of dosage recommendations identified in the literature in the treatment of Achilles tendinopathy.
2 Low Level Laser Therapy

Further to Chapter one, this chapter provides a broad overview of the topic of low level laser therapy and places it in the context of this thesis. It starts with the underlying theory of stimulated emission of radiation published by Einstein in 1917, and progresses through the development of laser devices and their application in the medical field. The unique characteristics of laser light, and the relevance of these characteristics to clinical practice are presented, along with a description of the different laser parameters, and the importance of these in treatment. Work in the laboratory on cell cultures and animals has been important in providing evidence on the interaction of laser irradiation with the cell that underpin the production of clinical effects that benefit the whole organism. The focus then shifts to evidence from clinical trials and systematic reviews involving low level laser therapy to present a case for the investigation of the use of this modality to treat tendinopathy.

2.1 Historical Perspective

This has been well covered in previous accounts (Baxter, 1991b, 1994; Tuner & Hode, 2007c) and is described briefly below.

The use of light to treat ailments, as described in the previous chapter, is not a new phenomenon and predates the earliest written records. Rather, the technological advancements underlying the method of producing the therapeutic light is what has marked the advancement in this field (e.g. the development of artificial sources of ultraviolet radiation, which then allowed the treatment of dermal tuberculosis). This
equally applies to the development of laser photobiomodulation in the late 1960s and early 1970s.

While Einstein had published “Zur Quantum Theori der Strahlung” in which he explained his theory on how to produce stimulated emission of photons as early as 1917, it was over 40 years before Maiman, using a ruby crystal, produced laser radiation (Light Amplification by Stimulated Emission of Radiation) of a fixed wavelength in the visible red spectrum, 694nm (Maiman, 1960). Over the next few years, laser technology advanced rapidly and saw the production of a range of lasers using different media to produce different wavelengths, including the Helium-Neon (He-Ne) laser (632.8nm) which was developed in 1961. These new systems rapidly found applications in medicine and surgery; some common examples of clinical laser applications are presented in Table 2-1.

In parallel with early investigations of potential clinical applications for high power systems in ophthalmology and surgery, in the latter half of the sixties Professor Endre Mester of Hungary, regarded as one of the pioneers of clinical applications of low level laser therapy, performed many of the early studies which explored the effects of laser at the cellular level and on wound healing (Mester et al., 1973; Mester et al., 1968; Mester et al., 1971). As a result of this early pioneering work, the term “laser biostimulation” came into being to describe the typically stimulatory effects of these devices upon cellular processes; however, this term has subsequently been modified to “laser biomodulation” to better reflect the potential to induce either stimulatory or inhibitory effects through irradiation with these lasers (Azevedo, De Paula Eduardo, Moreira, De Paula Eduardo, & Marques, 2006; Carnevalli, Soares, Zangaro, Pinheiro, &

<table>
<thead>
<tr>
<th>Laser Medium</th>
<th>Wavelength (nm)</th>
<th>Colour</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excimer</td>
<td>198-308</td>
<td>Ultraviolet</td>
<td>Dermatology; Ophthalmology</td>
</tr>
<tr>
<td>Argon</td>
<td>350-514</td>
<td>Blue</td>
<td>Dermatology; Ophthalmology; Photodynamic Therapy (PDT)</td>
</tr>
<tr>
<td>Krypton</td>
<td>568-647</td>
<td>Yellow</td>
<td>Ophthalmology</td>
</tr>
<tr>
<td>Copper</td>
<td>510-578</td>
<td>Blue-Green</td>
<td>Dermatology; Ophthalmology</td>
</tr>
<tr>
<td>Rhodamine</td>
<td>560-650</td>
<td>Yellow</td>
<td>Dermatology; Photodynamic Therapy (PDT)</td>
</tr>
<tr>
<td>Helium-Neon (HeNe)</td>
<td>633</td>
<td>Red</td>
<td>Biomodulation</td>
</tr>
<tr>
<td>Ruby</td>
<td>694</td>
<td>Red</td>
<td>Tattoo &amp; Hair Removal</td>
</tr>
<tr>
<td>Indium Gallium Aluminium Phosphate (InGaAlP)</td>
<td>630-700</td>
<td>Red</td>
<td>Biomodulation</td>
</tr>
<tr>
<td>Gallium Aluminium Arsenide (GaAlAs)</td>
<td>780-870</td>
<td>Infra-red</td>
<td>Biomodulation</td>
</tr>
<tr>
<td>Gallium Arsenide (GaAs)</td>
<td>904</td>
<td>Infra-red</td>
<td>Biomodulation</td>
</tr>
<tr>
<td>Neodymium-Yttrium-Aluminium-Garnet (NdYAG)</td>
<td>900-1,350</td>
<td>Infra-red</td>
<td>Ophthalmology; Oncology; Coagulation of Tumours</td>
</tr>
<tr>
<td>Carbon Dioxide (CO2)</td>
<td>10,600</td>
<td>Infra-red</td>
<td>Surgery; Dermatology</td>
</tr>
</tbody>
</table>

Adapted from Baxter, 1994; Tuner & Hode, 2007c

The medical use of laser devices for therapeutic applications expanded rapidly in Eastern European countries, however, probably due to the lack of English language publications, such application of these devices didn’t gain popularity in the West until the 1980s (Baxter, 1994). The 1980s also saw significant advances in semiconductor technology, which in turn led to the clinical use of diode-based laser systems in laser therapy. While these systems were relatively inexpensive, smaller and more portable, they also had large angles of divergence and rather broad wavebands. Technological
advances continued through the 1990s, including contributions by scientists at NASA (Whelan, Houle, & Whelan, 2000; Whelan et al., 2001), who developed powerful, quasimonochromatic light emitting diodes (LEDs) to enable production of therapeutic laser devices across a wide spectrum of wavelengths. Although LEDs have broader wavebands and cannot produce true monochromatic light, studies have shown that these are just as effective as the more expensive laser media (Corazza, Jorge, Kurachi, & Bagnato, 2007; Klebanov et al., 2005; Klebanov, Shuraeva, Chichuk, Osipov, & Vladimirov, 2006; Vinck et al., 2005; Vinck et al., 2003), and thus have aided the growth in clinical use of “laser” devices.

Today lasers are commonly used in surgery, dermatology, dentistry, and in the case of laser therapy systems, in the treatment of wound healing, musculoskeletal diseases and injuries, and for pain relief (Alster & Zaulyanov-Scanlon, 2007; Baxter, Bleakley, & McDonough, 2008; Bjordal et al., 2003; Bjordal et al., 2001; Butani, Dudelzak, & Goldberg, 2009; Chow, Heller, & Barnsley, 2006; Hoggan, Cameron, & Maddern, 2009; Lomke, 2009; Naspro et al., 2009; Santana-Blank, Rodraeguez-Santana, & Santana-Rodraeguez, 2005; Wu & Wong, 2008). Other published studies on low level laser therapy have investigated the effects on neural tissue regeneration (Rochkind, 2006; Takzare et al., 2007; Wu et al., 2009) and for stimulation of the immune system (Lim et al., 2008; Samoilova et al., 2004; Samoilova, Zhevago, Menshutina, & Grigorieva, 2008; Schumm, 2008; Zhevago & Samoilova, 2006; Zhevago, Samoilova, & Obolenskaya, 2004). Claimed indications for these devices continue to grow: indeed, based upon the instruction manuals that come with many of the devices on the market today, the range of applications would appear to be endless. This has positive and negative implications
with regards to clinical acceptance, as anything that is promoted as a panacea tends to be looked upon with some degree of scepticism when not supported by robust evidence.

### 2.2 Characteristics of Laser Light

The characteristics of laser light that make it unique are: monochromaticity, divergence/collimation, coherence, and polarisation (Nussbaum, Baxter, & Lilge, 2003a). Lasers produce light that is clustered in a very narrow band around a single wavelength and thus its photons have the same energy; there is an inverse relationship between wavelength and photon energy, and thus shorter wavelengths produce photons with higher energy than longer wavelengths. The light beam produced by a laser is also highly collimated, meaning that there is little divergence or angle of spread, which translates into the maintainance of a small spot size with high power density over relatively large distances. The average divergence of a diode-based laser system is in the region of 3-10 degrees (Diamantopoulos, 1988). Coherence describes the relationship of the electromagnetic waves to one another in time and in space, and for coherent light the photons can be considered to be “in step”. Polarisation, which is characteristic of some systems, occurs when electromagnetic waves are orientated in one plane only.

The clinical relevance of coherence and polarisation is not clear and has been a matter of ongoing debate among scientists. Smith has argued that once light enters the skin, refraction and scattering occur, and thus polarisation and coherence become irrelevant (Smith, 2005); in contrast, Hode has proposed that coherence is not lost but only reduced, and that when directly compared, coherent light produces superior biological and clinical results to non-coherent light (Hode, 2005). However, this superiority has not been demonstrated in vitro and is only relevant to bulk tissue as
highlighted by Karu in “Ten Lectures on Basic Science of Laser Phototherapy” Pp25-30 (Karu, 2007). For the clinician, the decision to be made is whether to use a laser or LED device, based upon the available evidence. Research has demonstrated that both laser and LED are effective, albeit to differing degrees, in producing biological and clinical effects at the cellular level, in animal studies, and in human studies (Corazza et al., 2007; Klebanov et al., 2005; Klebanov et al., 2006; Plavskii & Barulin, 2008; Vinck et al., 2005; Vinck et al., 2003; Whelan et al., 2001). Thus it would appear that both types of devices may be effectively used clinically; however, both are dose dependant in their clinical effectiveness, and for most applications the most efficacious dose has yet to be found.

### 2.3 Laser Parameters

The basic premise underpinning laser biomodulation is the Grotthus-Draper Law, which, put simply, states that without absorption there is no reaction. This is important as the main factor determining light absorption in biological tissues is not output power but wavelength. Due to such wavelength-specificity of absorption at the biomolecular and cellular levels, wavelength governs the depth of penetration (Figure 2-1) (Breitbart et al., 1996; Karu, Tiphlova, Esenaliev, & Letokhov, 1994; Lubart, Friedmann, Sinyakov, Cohen, & Breitbart, 1997; Schindl, Merwald, Schindl, Kaun, & Wojta, 2003; Young et al., 1989). Extensive work by Karu’s group and others has resulted in the discovery of action spectra (or active regions), within the range of wavelengths most commonly used in phototherapy (600-904nm), which estimate the efficiency with which electromagnetic radiation produces a photochemical reaction plotted as a function of the wavelength of the radiation (see Figure 2-1) (Karu & Kolyakov, 2005). Different biomolecules absorb certain wavelengths more readily than others (Figure 2-2); for instance peak absorption
occurs for water molecules (which are present throughout biological tissues) at wavelengths below 200nm and above 1200nm. Haemoglobin, depending on whether it is in its oxygenated or de-oxygenated state, shows peak absorption at wavelengths of 577nm and 420nm, or 560nm respectively, and melanin, another important chromophore, exhibits peak absorption around 300nm.

Based upon this, it is easy to appreciate the context of Calderhead’s assertion that “wavelength is thus probably the single most important consideration in phototherapy” (Calderhead, 2007). He comes to this standpoint because of two main criteria: wavelength specificity of the target chromophore, the biological structure that absorbs the light energy from the laser, and the depth of the target chromophore, as the amount of energy penetrating to deeper layers, and therefore being available for absorption, is wavelength dependant (Figure 2-1). However, as a qualifier to this, Calderhead recognises that the energy reaching the target tissue must have a high enough intensity (in terms of photons) to induce the desired reaction.
Figure 2-1: Depth of Penetration of Different Wavelengths through Human Skin.
Adapted from Karu, 1989.
(The amount of energy expressed as a percentage of that at the surface that reaches the indicated depths.)
It has been commonly shown in cellular and lab based studies, as well as in clinical trials, that irradiance (power density) and radiant exposure (energy density; see text box) are also important factors in determining the biological effects underpinning the clinical effectiveness of laser radiation (Bolton, Young, & Dyson, 1991; Hashimoto, Kemmotsu, Otsuka, Numazawa, & Ohta, 1997; Karu & Kolyakov, 2005; Karu, Pyatibrat, & Ryabykh, 1997); published guidelines for the clinician reflect this in recommending treatment...
dosages (Bjordal et al., 2003; Bjordal et al., 2001; WALT, 2005). Reporting energy density implicates the “time” parameter, which is important as it determines how much of the circulating blood is exposed to LLLT, with the consequent activation of the immune system and modulation of systemic effects (Rodrigo et al., 2009; Schindl, Heinze, Schindl, Pernerstorfer-Schoen, & Schindl, 2002).

<table>
<thead>
<tr>
<th>These parameters can be calculated using the following equations;</th>
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| \[
\text{Power Density } \left( \frac{\text{mW}}{\text{cm}^2} \right) = \frac{\text{Output Power } (\text{mW})}{\text{Irradiated area } (\text{cm}^2)}
\] |

Adding time to the equation then gives energy density;

| Energy Density \left( \frac{\text{J}}{\text{cm}^2} \right) = \frac{\text{Output Power } (\text{W}) \times \text{time } (\text{s})}{\text{Irradiated area } (\text{cm}^2)} |

However, specification of laser parameters relating to power and dose can be contentious. Calculation (and reporting) of such parameters continue to cause heated debate among laser scientists and researchers (Chow, 2001; Enwemeka, 2009; Tuner & Hode, 1998): for example power density can be calculated using the output power of the probe and the area of the spot size, or the output power of the probe averaged across an assumed 1 cm² of tissue. There is also debate on the measurement and calculation of spot sizes (Carroll, 2009; Nussbaum et al., 2003a; Tuner & Hode, 2007c). Nussbaum et al
(2003) have proposed “that if the diameter of the laser beam is equal to or less than one penetration depth of the radiation, that is approximately less than 1mm, the effect will be as for a point source, and one should no longer try to define irradiance or radiant exposure, but rather the power (W) or total energy (J) of the treatment” (Nussbaum et al., 2003a). This is an important issue and further discussion around this issue is presented in a subsequent chapter.

Pulsing of the laser beam can be achieved either electrically, switching it “on and off”; or mechanically, by interrupting the light with a mechanical shutter or chopper; there are also inherently pulsed systems. When using pulsed lasers two factors need to be taken into consideration: the peak power and the average power. The average power can be calculated by multiplying the peak power by the duty cycle which is expressed as a percentage of time the light is on, i.e. a 10mW probe with a 50% duty cycle has an average power of 5mW but a peak power of 10mW. Depending on the technology used to pulse the laser, the average power may vary with the pulse frequency: it can rise as frequency increases, or can remain constant regardless of the frequency (fixed duty cycle). This is important for two reasons: average power is important for calculating dose (using the energy density equation above), while peak power is critical for delivery of a sufficient photon density into target tissue at deeper layers in the irradiated tissue.

2.4 **Mechanisms of Action: Cellular Studies**

The challenge for therapeutic laser scientists/researchers is that the product central to the treatment (laser) is competing with the pharmaceutical industry with regards to the effects obtained from the intervention. Whereas the pharmaceutical industry follow a strict sequence of staging (Figure 2-3) to bring a drug to market, laser
therapy has evolved along a different path, with laboratory studies at the in vitro and in vivo levels being conducted simultaneously with clinical trials on humans, resulting in a perceived weakness in evidence (Lucas, Criens-Poublon, Cockrell, & de Haan, 2002) and delays in being granted FDA approval in the United States of America (FDA, 2002). While Lucas et al., 2002), in their review of 36 studies on the use of low level laser therapy for wound healing concluded that the evidence from cell studies and animal experiments was inconclusive, therefore failing to justify trials on human subjects; Peplow, Chung, & Baxter, 2009) in a more recent review of 47 studies published between 2003 and 2008 came to the opposite conclusion: that results from the included studies consistently showed the benefit of laser therapy to biomodulate wound healing, and thus further research on human subjects was justified. Regardless of the route taken, to justify conducting clinical trials on human subjects, there needs to be a critical level of evidence from in vitro and animal studies to suggest that there are potential beneficial effects at the clinical level. Determining the mechanisms of action at the cellular level, and how these effects might potentially be realised to benefit the living multicellular organism, is an important part of the research process, and also leads to acceptance of any treatment modality.
Cellular research has provided information on the basic mechanisms of laser-tissue interactions, and a theoretical basis for clinical practice; evidence of a range of cellular effects have been demonstrated using a variety of cell types (fibroblasts; lymphocytes; osteoblasts; stem cells; smooth muscle cells) and in vitro (Chen et al., 2009;
Gavish et al., 2006; Huang, Chen, Sharma, Wu, & Hamblin, 2010; Kreisler et al., 2003; Peplow et al., 2009; Stadler et al., 2000; Stein et al., 2005; Tuby, Maltz, & Oron, 2007; Vinck et al., 2003). However, the results of such studies in the laboratory cannot be taken as definitive evidence of clinical effectiveness, as extrapolation of the findings into clinical use cannot be taken for granted. What is known, is that these effects are the result of primary reactions involving absorption of specific wavelengths of light by components of the mitochondrial respiratory chain such as cytochromes, cytochrome oxidase, and flavin dehydrogenases; these result in changes in REDOX status of cytoplasm and mitochondria, which in turn leads to increased levels of ATP (Karu, 2007). In her book (Figure 7.9), Karu proposes five possible hypotheses for these primary reactions from work done in her laboratory over several decades (Karu, 2007);

1. REDOX properties alteration hypothesis (Karu, 1988).

2. Nitric Oxide (NO) hypothesis (Karu et al., 2005).


5. Transient local heating hypothesis (Karu, Tiphlova, Matveyets, Yartsev, & Letokhov, 1991).

Karu goes on to emphasise some key points from her work: any one of these hypotheses occurring in isolation is unrealistic and more probably, all are occurring simultaneously; rather the mechanism which is decisive for the given situation under investigation, is the question remaining. Another key point Karu makes, is the
importance of the changes in the REDOX properties of the cytochrome c oxidase molecule and/or the release of NO (hypothesis 2). A local increase in availability of NO is thought to be beneficial to the healing process (Murrell, 2007; Xia, Szomor, Wang, & Murrell, 2006), and this form of intervention through the use of Glyceryl trinitrate (GTN) patches for the treatment of tendinopathy is becoming more popular, evidenced by a number of publications on the topic in recent years (Kane, Ismail, & Calder, 2008; Paoloni, Appleyard, Nelson, & Murrell, 2003, 2004, 2005). Thus it would appear that increases in NO at the site of the tendon lesion may well be one of the mechanisms behind the beneficial effects of laser therapy reported in the literature.

These primary reactions stimulate a cascade of secondary reactions at cellular level involving intracellular signaling and leading to stimulation of cytokine reactions, and NO production (Gavish et al., 2006; Gavish et al., 2008); release of growth factors (Hou et al., 2008; Junior, Vieira, De Andrade, & Aarestrup, 2009; Saygun et al., 2008); up-regulation of ATP (Gao & Xing, 2009; Hawkins & Abrahamse, 2006; Karu et al., 1995; Oron, Illic, De Taboada, & Streeter, 2007; Silveira et al., 2009), and increased metabolism, changes in REDOX signaling, increased reactive oxygen species (ROS) and therefore cell proliferation (Fillipin et al., 2005; Gao & Xing, 2009; Grossman et al., 1998; Hawkins & Abrahamse, 2006; Karu, 1999). Many of these secondary reactions have the potential to modulate the processes involved in tendinopathy, which are discussed in Chapter 3, and enhance the inflammation, proliferation, and remodeling phases of the healing tendon.

Animal studies can bridge the gap from cell to whole organism, but once again extrapolation into clinical practice is tenuous. However, evidence from animal studies can provide justification to proceed to human experiments. The dosage and treatment
parameters that show effect on a cell in the bottom of a laboratory well, or on the hind limb of a mouse irradiated with a laser that is relatively so large that it illuminates the whole limb, cannot ultimately compensate for clinical trials involving human subjects to establish effectiveness. Some of the effects reported from animal studies are increased healing of both normal and abnormal wounds, increased collagen synthesis, pain attenuation, angiogenesis, and decreased inflammation (Al-Watban et al., 2009; Bjordal et al., 2006; Enwemeka et al., 2004; Oliveira et al., 2009; Reddy et al., 1998; Ribeiro et al., 2009; Salate et al., 2005).

2.5 Laboratory Studies of Tendinopathy

Given the mechanisms of action derived from the experiments described in the previous section, further laboratory investigations have taken place specifically to assess the efficacy of low level laser therapy for the treatment of tendinopathies.

Generally, rabbits, mice and rats are used to study the healing process of tendons and ligaments, which are experimentally injured under controlled conditions; the majority of studies use surgical procedures to inflict the wounds (Carrinho et al., 2006; Casalechi et al., 2008; Demir, Menku, Kirnap, Calis, & Ikizceli, 2004; Elwakil, 2007; Ng & Fung, 2008; Reddy et al., 1998) but some have dropped weights onto stretched tendons to induce blunt trauma (Fillipin et al., 2005; Oliveira et al., 2009; Salate et al., 2005). With the exception of Ng et al (2008), all of the above studies began treatment on day one, and in some cases, within a few hours of injury. However, Ng and colleagues designed a study on rats that more closely resembled a clinical scenario and waited until day 5 following injury before beginning treatment (this represents the case that often patients don’t present until the sub-acute or even chronic phase of their injuries). Ng’s group also
combined exercise with laser treatment (660nm) and measured the effects of three
different doses of both of these treatment modalities in a Latin Square design, resulting
in nine different combinations of treatment (laser at 4J/cm$^2$, 1J/cm$^2$, 0J/cm$^2$; running for
30 min, 15 min, 0 min). Treatment as per group allocation was given on every second
day, and the final analysis of the tendon repair was completed at day 22 post injury. Their
findings showed superior results of the biomechanical testing of the tendons in the group
that received 4J/cm$^2$ combined with 30 minutes of running.

One study investigated treatment with laser (904nm; 1J/cm$^2$), ultrasound (1MHz;
0.5W/cm$^2$; 5 minutes), and a combination of both modalities (Demir et al., 2004). Rats
used in the study had surgically induced injuries to both Achilles tendons, and after nine
daily sessions of treatments they were sacrificed 3 weeks post injury. The authors
reported that both modalities showed significant differences pre to post treatment in the
biochemistry and biomechanical properties of the tendons, but there was no significant
difference between groups, and no added benefit from the combination treatment. The
significance of these findings are hard to interpret, as the contralateral limb was used as
controls on each animal; any systemic effects of the laser treatment (Rodrigo et al., 2009;
Weber, Fussganger-May, & Wolf, 2007), which may have diluted the effect (Tuner &
Hode, 1998; Tuner & Hode, 2007a) as assessed on the treated side, were not considered
in the authors’ discussion or conclusion.

All of the above mentioned studies undertook final analysis of the tendons at
between 7 and 22 days post-injury; the positive effects of laser treatment were increased
biomechanical properties, enhanced biochemical processes, increased
production/presence of collagen fibres and better orientation of the fibres, and increased
angiogenesis, overall resulting in a superior repair process (Carrinho et al., 2006; Casalechi et al., 2008; Demir et al., 2004; Elwakil, 2007; Fillipin et al., 2005; Ng & Fung, 2008; Oliveira et al., 2009; Reddy et al., 1998; Salate et al., 2005).

Interestingly, none of the animal studies continued for more than 3 weeks, yet it is widely accepted that tendons are slow to heal and have a remodeling phase of more than 100 days (Khan & Maffulli, 1998); this is particularly interesting, as it raises the question if treatment had continued for longer, maybe even better results might emerge? Possible evidence supporting this theory is presented in Chapter 5, Figures 5-2 and 5-3 where the group treated with laser, compared to the control group, continued to improve for both pain and function even beyond the phase of laser application.

Data from these animal studies have provided evidence of effectiveness with regards to certain mechanisms of the repair process, and also some guidance on potentially effective types of treatment applications, protocols and dosages for the clinical setting. The next logical step is to use such findings to design clinical trials on humans in an attempt to replicate these results clinically and to define an optimum dose.

2.6 Clinical Trials

In parallel to these cellular and animal studies at the in vitro and in vivo level, other researchers have undertaken clinical trials on humans to assess the clinical effectiveness of laser therapy. Some of the musculoskeletal applications studied have included treatment of osteoarthritis (OA), rheumatoid arthritis (RA), neck and back pain, and various tendinopathies (see current reviews section below) (Bjordal et al., 2007; Brosseau et al., 2005; Chow et al., 2006; Coombes et al., 2009; Djavid et al., 2007; Goats,
Hunter, Flett, & Stirling, 1996; Gur et al., 2003; Jamtvedt et al., 2008; Stergioulas, Stergioula, Aarskog, Lopes-Martins, & Bjordal, 2008; Yousefi-Nooraie et al., 2008).

The putative effectiveness of low level laser therapy for the treatment of a range of tendinopathies has been studied many times over the last several decades. Reported clinical effects have generally matched those from the laboratory-based experiments (Bjordal et al., 2006; England, Farrell, Coppock, Struthers, & Bacon, 1989; Haker & Lundeberg, 1991a; Konstantinovic, Antonic, & Brdareski, 1997; Lam & Cheing, 2007; Melegati et al., 1994; Saunders, 1995, 2003; Sharma, Thukral, Kumar, & Bhargava, 2002; Stergioulas, 2007; Stergioulas et al., 2008; Vasseljen, Hoeg, Kjeldstad, Johnsson, & Larsen, 1992). However, it is important to stress that not all findings are positive (Basford, Sheffield, & Cieslak, 2000; Costantino, Pogliacomi, & Vaienti, 2005; Darre et al., 1994; Haker & Lundeberg, 1991b; Hernandez Herrero et al., 2006; Krasheninnikoff et al., 1994; Muller, Gross, Grosse, Rochet, & Sengler, 1993; Oken, Kahraman, Ayhan, Canpolat, & Yorgancioglu, 2008; Papadopoulos, Smith, Cawley, & Mani, 1996; Siebert, Seichert, Siebert, & Wirth, 1987; Tumilty et al., 2008; Vasseljen, 1992; Vecchio et al., 1993). A more detailed analysis of the current evidence from clinical trials exploring the use of LLLT in the treatment of tendinopathies is reported in Chapter 4.

Poor methodology, poor reporting of parameters, and varying application techniques were criticisms leveled at both positive and negative studies. There are many manufacturers of laser devices, all with their own preferred delivery systems, and often it is not possible to choose, or even report, many of the important parameters discussed above. This heterogeneity in systems and in application makes it very difficult to replicate results or to pool data from multiple studies. Although in vitro and animal
studies have provided evidence that LLLT should potentially work in the clinical setting to treat tendinopathies, the problems associated with dosage and treatment protocols have led to a lack of a systematic informed approach to the clinical research, and thus contributed to mixed results.

As stated above, the important effects associated with laser irradiation which might underpin the treatment of tendinopathy are decreased inflammation, increased angiogenesis, increased fibroblast activity leading to increased collagen production and on to increased tensile strength, and decreased pain. Often during clinical trials involving humans it is not possible to measure these effects directly, as is the case with animal studies, and thus indirect measurement (which are in their own right important clinical outcome measures), using functional questionnaires or pain rating scales are used. This highlights the benefit of lab-based studies to explain the mechanisms behind positive results, but also adds an element of speculation to clinical trials as the specific effect has not been measured. A lack of high quality evidence of clinical effectiveness means that still more work needs to be done to define the optimum treatment parameters and protocols.

2.7 Optimum Dose?

Low level laser therapy is a dose dependent modality and as discussed above, has many parameters that can influence outcomes. From the animal studies exploring the effects of LLLT on tendons (Carrinho et al., 2006; Casalechi et al., 2008; Demir et al., 2004; Elwakil, 2007; Fillipin et al., 2005; Ng & Fung, 2008; Oliveira et al., 2009; Reddy et al., 1998; Salate et al., 2005) it can be deduced that positive outcomes such as increased biomechanical properties, increased biochemical changes, increased collagen and
orientation of the fibers, and increased angiogenesis are typically achieved using a dose
of between 3-5J/cm².

The World Association of Laser Therapy (WALT) has published (clinical) dosage
guidelines for tendinopathies which range from 1.5-4.0J/cm² for wavelengths in the
range of 780-820nm (WALT, 2005). In the past few years work has been carried out to
establish such guidelines from an evidence based standpoint (Bjordal et al., 2001)
resulting in slightly different results. Evidently, more refinement of the guidelines is
required, as the optimum dosage windows for many conditions are quite broad. With
the expansion of the body of work investigating the relevance of parameters, the
accuracy of such recommendations should also increase.

2.8 Clinical Effectiveness: Current Reviews

There have been many reviews of the clinical effectiveness of laser therapy, some
of which have specifically assessed laser therapy to treat certain conditions (Bjordal et al.,
2003; Bjordal et al., 2001; Chow & Barnsley, 2005; Enwemeka et al., 2004; Stasinopoulos
& Johnson, 2005; Yousefi-Nooraie et al., 2008), while others have been more focused on
a particular pathology, and LLLT has emerged as one of a number of possible treatment
options (Bjordal et al., 2007; Coombes et al., 2009; Green et al., 2003; Jamtvedt et al.,
2008; McLauchlan & Handoll, 2001; Smidt et al., 2003). Others, particularly from Bjordal
and colleagues, have concentrated on answering specific questions related to laser
therapy, i.e. what is the most efficacious dose (Bjordal et al., 2003; Bjordal et al., 2001)?
However, the evidence derived from multiple reviews has not always been consistent,
and thus result are mixed, with approximately a 50/50 split of the above reviews
between positive findings in favour of LLLT treatment, or conclusions based on
insufficient evidence, or reports of no effect from LLLT. When evaluating evidence from such works, it is important to bear in mind that reviews are not flawless; even systematic reviews with meta-analyses, which have become the gold standard in recent times, are not without sources of bias (Bjordal, Bogen, Lopes-Martins, & Klovning, 2005) or weakness in review protocols (Herbert & Bø, 2005). Often pooling of data is performed and results reported in cases when clinical heterogeneity and statistical heterogeneity invalidates any such pooling of data. It is also not unknown for the authors of such reviews to base conclusions or recommendations on inadequate numbers of studies: e.g. McLauchlan, two studies (McLauchlan & Handoll, 2001); Green & Buchbinder, one study for each condition analysed (Green et al., 2003). It is therefore important to assess the question the review is trying to answer, along with inclusion/exclusion criteria of the chosen studies, to assess the validity of the review. Another weakness of systematic review and meta-analysis is publication bias: small studies or negative studies may not reach publication or are published in obscure journals that are difficult to access, leading to an over optimistic view of the effects.

A number of authors have criticised systematic review methodology and identified weaknesses (Bjordal et al., 2005; Chou, 2008; Herbert & Bø, 2005). Even though the QUOROM statement (now updated to PRISMA) (Moher et al., 1999; PRISMA, 2009) has been produced in an attempt to standardise protocols for such reviews, there is often a variation in quality of the published works. One group of critics (Bjordal et al., 2005) pointed out a number of biases in a Cochrane review of LLLT for osteoarthritis, and through the use of sensitivity analyses with the same data produced very different results and conclusions. A best evidence synthesis can give a different result to effect size
calculations or pooling of data. Other authors (Herbert & Bǿ, 2005) suggest that the actual intervention in each trial should be described and evaluated to improve the quality of a review. Chou recommends that conclusions of systematic reviews should not be taken at face value and provides a list of factors to consider that help distinguish a high quality piece of work (Chou, 2008). As for every piece of information (e.g. from randomised controlled trials) that is used to underpin evidence based practice, a systematic review should be critically analysed in terms of methodology, results and conclusions.

2.9 Summary

Lasers have been utilized for therapeutic applications in the clinical setting since the 1960s and although they have gained in popularity, due in part to the development of the semiconductor technology which made manufacture less expensive and led to subsequent increases in availability, low level laser therapy still remains on the fringes of mainstream medicine.

There is evidence that specific components of the mitochondrial respiratory chain absorb certain wavelengths more readily, and that this primary reaction leads to secondary reactions involving intracellular signaling resulting in the beneficial effects that promote healing. Longer wavelengths penetrate deeper into tissue and enable the clinician to target deeper structures. However, absorption (which limits penetration) is fundamental to these effects. Laboratory experiments using animals have provided evidence of specific effects such as increases in collagen, angiogenesis and cell proliferation; along with decreased pain and inflammation. These experiments have also provided evidence of a potential dosage window (3-5J/cm²).
Unfortunately such generally positive results from laboratory studies have not easily translated into clinical effectiveness in humans, and the results from clinical trials are mixed. Adequate reporting of parameters and methods of applications has been a problem in the past and varies among studies, leading to controversy over the actual dose delivered to the target tissue. Guidelines have been published from a number of sources, but the effective dosage window for many conditions remains very broad and the optimum dose has yet to be found. Low level laser therapy, like many other forms of electrotherapy, remains a dose dependant modality and many more studies are required to refine dosage guidelines.

Nevertheless, there is enough evidence as to the effects at cellular level and organism level which benefit the healing and repair process of tendons, as well as a number of clinical trials that show LLLT is dose dependant and effective when the correct application is used. Given this evidence, this thesis will investigate the clinical effectiveness of current dosage recommendations through the use of methodologies from the top tiers of the hierarchy of evidence pyramid, that is randomised controlled trials and systematic review with meta-analysis, on the treatment of Achilles tendinopathy, a condition on which there have been relatively few studies (see Chapter 4).
3  Tendinopathy: with Emphasis on the Treatment of the Achilles tendon

3.1 Overview of Chapter

This chapter provides an overview of tendons and the aetiology of tendinopathy. Rather than being a comprehensive, narrative review of the literature regarding tendinopathy, the aim is to cover the relevant literature with regards to setting the scene in the context of this thesis. For this, the structure of the tendon, the pathology of tendinopathy, a description of the healing and remodeling processes, and finally some of the treatment approaches are presented and discussed. To conclude, a model of tendinopathy is proposed and justification presented for the treatment options chosen for this thesis.

3.2 Introduction

3.2.1 Tendon Structure

Tendons are tough fibrous structures that attach muscle to bone; their function is to store and release energy, and transfer the force produced by the muscle to produce movement. Healthy tendons are mostly composed of parallel arrays of collagen fibers, arranged in parallel along lines of tension, and cross-links between fibres influence the tensile strength of the tendon. Seventy to eighty percent of the dry weight of the tendon, which makes up about 30% of the total mass in water, is collagen type I (O'Brien, 1992), which is well suited to resisting tensile but not shear forces. Other components are elastin, proteoglycans, and a small amount of inorganic substances such as copper, manganese, and calcium. In tendons, the fibrils then assemble further to form
fascicles, and groups of fascicles are bounded by the epitendon and peritendon to form the tendon organ (Figure 3-1).

![Diagram of Tendon Structure](www.pponline.co.uk/encyc/img/266cfig2.png)

Figure 3-1: The Hierarchical Organization of Tendon Structure.
Adapted from [www.pponline.co.uk/encyc/img/266cfig2.png](www.pponline.co.uk/encyc/img/266cfig2.png)

The tenocyte is the main cellular component of tendon and produces the fibres, ground substance, and proteins that are required for the continuous turnover of extracellular components that maintain the mechanical properties of the tendon. The ground substance, found between the collagen fibers, and consisting of glycosaminoglycans,
proteoglycans and glycoproteins, also influences the mechanical properties of the tendon by contributing to its viscoelasticity (O'Brien, 1992).

3.3 Tendinopathy

In recent times, the term “tendinopathy” has become used as a general clinical descriptor to indicate pain in the region of the tendon, without any indication of the underlying cause (Maffuli, Kahn, & Puddu, 1998); in contrast, the previously popular term, “tendonitis” implies that inflammation is present, while “tendinosis” suggests degeneration of the tendon. Tendinopathy represents a relatively common work and sport related injury (Satyendra & Byl, 2006; Sayana & Maffulli, 2007), but is not solely associated with traumatic events, as sedentary individuals can also develop this pathology (Sayana & Maffulli, 2007). The prevalence of tendinopathies are apparently increasing (Suchak, Bostick, Reid, Blitz, & Jomha, 2005): for example in New Zealand the incidence of Achilles tendon ruptures (usually regarded as the final sequelae of Achilles tendinopathy) more than doubled between the years 1998 to 2003, from 4.7/100,000 to 10.3/100,000, a phenomenon that follows international trends (Tumilty, 2007). Patella tendinopathy accounted for 20% of all knee injuries reported over a 6 month period at a sports injury clinic (Kannus, Aho, Jarvinen, & Niittymaki, 1987), while tennis elbow affects approximately 1%-2% of the population (Gabel, 1999). Other common sites of tendinopathy are golfer’s elbow at the medial side of the elbow, and the rotator cuff tendons in the shoulder.

Pathogenesis of tendinopathy is considered multifactorial, and is not yet fully understood; e.g. a combination of extrinsic and intrinsic factors as a cause of chronic Achilles tendon disorders is common (Kannus et al., 1987; Paavola et al., 2002; Soma &
Mandelbaum, 1994). It has been observed in mainly retrospective studies that age, anatomical variations, and strength deficit are associated with the development of Achilles tendinopathy (Almekinders & Temple, 1998; Hirschmüller, Baur, Müller, & Mayer, 2005; Kannus, 1997; Soma & Mandelbaum, 1994).

The putative problem within the tendon which leads to tendinopathy is failure of one of two processes: the normal healing response, or the normal turnover/remodeling response, resulting in degeneration of the tendon structure. Such failures can be explained, at least in part, by the interaction of the biochemical hypothesis (Danielson, 2009) and the biomechanical hypothesis (Wang et al., 2006) (see below). Apart from any structural damage to the tendon, tenocytes reacting to mechanical loading produce signal substances, proteins, and enzymes, that may have effects on pain signaling, tissue maintenance/repair processes, and vascular regulation, but whether the increase in these substances are causative or a by-product of the degenerative pathology has yet to be determined.

Degeneration is a broad term and does little to indicate which entity is abnormal; furthermore, there is evidence that degeneration is not always symptomatic. Magnetic resonance Imaging and ultrasound show only moderate correlation to clinical signs and symptoms (Kayser, Mahlfeld, & Heyde, 2005; Khan et al., 2003). Cook et al (1998), compared patellar tendon sonographic findings in asymptomatic elite athletes with controls. Abnormalities were found in 22% of the athletes and only 4% of the controls; hypoechoic regions were present in 14% of the athletes who had never had knee pain (Cook et al., 1998). Such abnormal findings in asymptomatic tendons have been reported in other studies (Bleakney, Tallon, Wong, Lim, & Maffulli, 2002; Cook, Khan, Kiss,
Coleman, & Griffiths, 2001), and in a study of 14-18 year old basketball players, findings of ultrasonographic tendon abnormality were three times as common as clinical symptoms (Cook, Khan, Kiss, & Griffiths, 2000a). This is an interesting phenomenon and may in part explain the processes underlying tendon rupture: tendons with signs of degeneration may be asymptomatic, but studies have shown that ruptured tendons are significantly more degenerated than tendinopathic tendons (Maffulli, Barrass, & Ewen, 2000; Tallon, Maffulli, & Ewen, 2001); perhaps this subclinical tendinosis predisposes rupture?

3.4 Factors Influencing Tendon Healing/Re-modeling.

As indicated above, there are primarily two hypotheses proposed to explain the processes underlying tendon repair and remodeling. These are explained below, along with other factors that may influence the process.

3.4.1 Biomechanical Changes

This hypothesis is primarily to do with collagen separation and changes in the viscoelastic properties of tendon (stress/strain, hysteresis, Young’s modulus) (Figure 3-2 & 3-3). This matrix abnormality due to trauma, overuse, or immobilisation/underuse may be considered to be the primary event, altering the biomechanical efficiency of the tendon to store and release energy, and overwhelming the ability of the cells to repair/remodel structural damage (Jozsa & Kannus, 1997).
Figure 3-2: Viscoelastic Properties of Tendon (stress-strain curve).
(The tendon functions safely in the green area; failure begins at approx 8-10% strain; Peterson & Renstrom, 1986)

The effects of changes in viscoelastic properties are illustrated by the findings of a variety of different studies. Immobilisation, stress shielding, or underuse, are all detrimental to the biomechanical properties of tendon (Yamamoto et al., 1993; Yasuda, Kinoshita, Abe, & Shibayama, 2000) and can lead to cell apoptosis (Kawabata et al., 2009). Re-stressing can reverse these changes (Maeda et al., 2009). For example Kubo et al (2002) measured the viscoelastic properties of the Achilles tendon before and after resistance and stretching training programmes (n=8). Each subject performed resistance training for the tendon on one side, and resistance plus stretching on the contralateral side. Results showed that both sides exhibited an increased stiffness in the tendon (i.e. the slope of the stress/strain curve became steeper). However, a decrease in hysteresis was only seen on the side that completed stretching exercises: in this case, the load and
unload curves came closer together (Kubo et al., 2002). This is an important finding, as the area enclosed by the hysteresis loop represents the energy stored by the tendon and not recovered on unloading; this is in the order of 5-10% and is released as heat (Reimersma & Schamhardt, 1985), which results in heating of the tendon. This may have potential implications for apoptosis within the tendon, as temperatures above 42.5°C are known to cause cell death in vitro (Hall, 1988), and a further study (Birch et al., 1997), which subjected tendon fibroblasts to a temperature of 45°C in vitro, found that after 10 minutes the cell mortality rate was 9% ± 4%. This excessive level of heat has also been shown to increase the level of pro-inflammatory cytokines (Hosaka et al., 2006) (see further below). It therefore follows that decreasing hysteresis has the potential to decrease heating of the tendon, and thus in turn the risk of apoptosis and release of pro-inflammatory cytokines.

Figure 3-3: Viscoelastic Properties of Tendon (Hysteresis).
A series of studies in the UK explored the effect of heat on the equine superficial digital flexor tendon, a tendon that functions very much like the human Achilles tendon. Wilson & Goodship (1994) recorded tendon core temperatures of 43-45°C after horses galloped for 5 minutes. Using these results the authors developed a mathematical model and extrapolated their findings to the human Achilles tendon, estimating that the central core of the tendon would reach temperatures 6°C higher than the periphery of the limb during extended periods of stress (Wilson & Goodship, 1994).

3.4.2 Mechanotransduction

What follows is a description of mechanotransduction, a process of repeated loading that is thought to elicit responses at the cellular level that may adapt the extracellular matrix to this increased load. Tenocytes produce the components of the extracellular matrix as well as the enzymes that degrade them. Production of collagen and proteoglycans as well as changes in protein and enzyme production by the tenocytes when not kept in balance, may contribute to the changes seen in tendinopathic tendons.

The interaction between glycoproteins, proteoglycans, and collagen determines the morphology and structure of the tendon. Exercise results in an increased rate of collagen turnover (synthesis and degradation), which has been well studied in animals (Curwin et al., 1988; Michna, 1984; Michna & Hartmann, 1989) and in humans (Langberg et al., 2007; Langberg et al., 2001). However, there are no data on the potential relevance of magnitude, rate or frequency of loading to suggest how much is beneficial or detrimental: i.e. the presence of a potential “dosage-response” relationship is unknown.
Findings from a recent animal model study (Smith et al., 2008) highlighted the importance of proteoglycans, of which there are many (for review see Rees, Dent, & Caterson, 2009) to normal tendon structure. Smith and colleagues (2008) used the infraspinatus tendon of sheep to evaluate chemical changes in four differently stressed zones of the tendon. Strain induced tendon abnormalities were accompanied with low proteoglycan expression, decreased ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs), and increased levels of aggrecan. These findings suggest that aggrecan is critical in the development of tendinopathy. Other authors have investigated changes in the extracellular matrix of tendinopathic human patellar tendons and compared these with the matrix of normal tendons. This group noted an increased deposition of versican and aggrecan in the pathological tendons, and concluded that the typical changes seen in tendinopathy were due to the metabolic turnover of (rather than changes in the expression of) these macromolecules (Tom et al., 2009).

3.4.3 Inflammation

It is generally accepted that tendinopathy is a problem of degeneration rather than inflammation, given the lack of evidence of the presence of inflammatory markers in the tendon (Alfredson, Forsgren, Thorsen, & Lorentzon, 2001; Alfredson, Ljung, Thorsen, & Lorentzon, 2000; Alfredson, Thorsen, & Lorentzon, 1999). However, these studies are based upon relatively low numbers, and measurements taken at rest. In contrast, other authors have found increased levels of inflammatory markers in Achilles tendons immediately after exercise (Bjordal et al., 2006), and such findings are supported by similar increases in such markers after cyclic loading of human tendon fibroblasts (Li et al., 2004; Wang et al., 2003). While this phenomenon may well be the normal response
to cyclic loading, over production of prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) and leukotreine B\textsubscript{4} (LTB\textsubscript{4}) could potentially contribute to the onset of tendinopathy.

3.4.4 Metalloproteinase

The normal state of the tendon is a fine balance between synthesis and degradation of the extracellular matrix; this re-modeling is mostly mediated by enzymes of the metalloproteinase family, matrix metalloproteinase (MMP), a disintegrin and metalloproteinase (ADAM), and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS). There are 23 MMPs, 30 ADAMs and 19 ADAMTS and these are involved in tendon degradation/turnover and signaling activities. The action of these metalloproteinases is inhibited by tissue inhibitors of metalloproteinases (TIMPS) and the local balance of these proteins is very important in the maintenance of the tendon extracellular matrix (Ireland et al., 2001; Jones et al., 2006; Kjaer et al., 2009; Pasternak & Aspenberg, 2009). Normal production of MMPs is low, and is stimulated by cytokines such as interleukin-1, interleukin-4, interleukin-6, and interleukin-10; tumour necrosis factor-α; growth factors; extracellular MMP inducer; and intracellular signaling pathways, as well as intercellular signaling (Corps et al., 2004; Gabison, Hoang-Xuan, Mauviel, & Menashi, 2005; Hidalgo & Eckhardt, 2001; Kossakowska et al., 1999; Meller, Li, & Tseng, 2000).

Apart from their role in tendinopathy, MMPs are also implicated in diseases where the body attacks itself (autoimmune disorders), or where tissue is degraded, such as osteoarthritis and rheumatoid arthritis (Bramono, Richmond, Weitzel, Kaplan, & Altman, 2004). MMPs are also thought to play a role in cancer, and thus MMP inhibitors have been used in the treatment of such conditions. However, simply blocking all MMPs
may cause as many problems as it cures. This is well illustrated by the side effects of broad spectrum MMP inhibitors when used to restrict tumor metastases: in such cases the inhibitors disrupt connective tissue homeostasis, and as a result tendinopathy has been reported in shoulders, hands, and knees (Drummond et al., 1999; Hutchinson, Tierney, Parsons, & Davis, 1998; Wojtowicz-Praga et al., 1998). This eloquently highlights the role MMPs play in tendinopathy.

The presence of pro-inflammatory cytokines after cyclic loading of the tendon has been discussed above; these inflammatory markers are also known to be one of the stimuli that increase production of MMPs (Pasternak & Aspenberg, 2009). MMPs react to this particular stimulus by processing anti-inflammatory cytokines and chemokines, and thus help to reduce inflammation (Gueders et al., 2005; Owen, Hu, Lopez-Otin, & Shapiro, 2004).

3.4.5 Biochemical Changes

Using microdialysis techniques, researchers in Sweden discovered high levels of glutamate in tendinopathic tendons compared to normal tendons (Alfredson et al., 2001; Alfredson et al., 2000; Alfredson et al., 1999). They postulated that elevated glutamate levels may mediate the pain response. The same group carried out a further study to compare glutamate levels before and after a 12 week programme of eccentric exercise (Alfredson & Lorentzon, 2003); there was no difference seen in glutamate levels even though there was a significant drop in mean pain scores (69-17 on 100mm VAS). Therefore they concluded that glutamate does not play a role in pain generation from Achilles tendons in tendinopathy.
Reactive oxygen species (ROS) and reactive nitrogen species (RNS) generated both within the vicinity of the tendon and also from the tenocytes themselves, have been implicated in tendinopathy (Longo, Olivia, Denaro, & Maffulli, 2008), possibly as a response to hyperthermia. Muscles can reach temperatures of 47°C and exhibit increased ROS production (Clanton, Zuo, & Klawitter, 1999); while core tendon temperatures of racehorses have been shown to reach 45°C in vivo following exercise (Wilson & Goodship, 1994). Therefore repetitive exercise induces ROS production from the mitochondrial respiratory chain, and excessive levels may become toxic causing apoptosis. This process is mediated by the intracellular antioxidant/pro-oxidant redox mechanism (Morel & Barouki, 1999). In contrast nitric oxide, synthesized by a family of enzymes named the nitric oxide synthases (NOS), is thought to enhance tendon healing (Murrell, 2007). NOS is expressed by fibroblasts after tendon injury, and is not present in normal tendons; it is important in collagen synthesis and is a major determinant of the volume of tissue synthesized (Xia et al., 2006).

In response to mechanical loading, tenocytes produce growth factors that stimulate collagen synthesis (Olesen et al., 2007), in particular the expression of collagen types I & III which seem to depend on transforming growth factor-β-I (TGF-β-I) (Kim, Akaike, Sasagaw, Atomi, & Kurosawa, 2002; Nakatani et al., 2002; Yang, Crawford, & Wang, 2004). Recent animal studies (Heinemeier et al., 2007a; Heinemeier et al., 2007b) investigated mRNA expression of the growth factors insulin-like growth factor (IGF-I), connective tissue growth factor (CTGF), and TGF-β-I, as well as collagen types I and III synthesis, in response to exercise. TGF-β-I and IGF-I levels were found to be increased in the rat Achilles tendon but not CTGF; findings also suggested that the type of exercise
(concentric, eccentric) made no difference to this stress response. Collagen types I and III synthesis followed this increase in growth factors, and supports the role of TGF-β-I and IGF-I as mediators of this response. The importance of these growth factors is further supported by animal studies, where IGF-I was demonstrated to enhance healing in tendons and ligaments (Kurtz, Loebig, Anderson, DeMeo, & Campbell, 1999; Provenzano et al., 2007).

### 3.4.6 Autonomic Nervous System

Due to the role of the autonomic system (ANS) in the regulation of blood vessels, and the angiogenesis observed in tendinopathy, a relatively new hypothesis has emerged implicating indirect involvement of the ANS in maintaining the chronic condition. A number of studies explored this possible involvement in the patellar and Achilles tendons (Bjur, Danielson, Alfredson, & Forsgren, 2008a, 2008b; Danielson, Alfredson, & Forsgren, 2006a; Danielson et al., 2006b; Danielson, Alfredson, & Forsgren, 2007a, 2007b; Danielson et al., 2007c; Danielson, Andersson, Alfredson, & Forsgren, 2008). These studies suggest that both sensory and sympathetic nerves exist in the walls of blood vessels entering the tendon through paratendinous tissue, and adrenergic receptors were found in the walls of the blood vessels as well as in the tenocytes themselves. Evidence emerged that tenocytes may respond to sympathetic transmitters and local production of catecholamines result, suggesting that both a nerve related and a local cholinergic system was in place. This adrenergic stimulation may induce or help maintain the degenerative changes seen in tendinopathy due to the autocrine and paracrine effects of these substances.
3.5 Treatment Options

Many factors contribute to the pathogenesis of tendinopathy, which is recognised as being multifactorial (Riley, 2004; Sharma & Maffulli, 2005); there is a plethora of treatment modalities available to reduce symptoms, and to attempt to control or enhance the tendon healing response. These modalities (which include various electrotherapy modalities, eccentric exercise; a variety of injection techniques and application of glyceryl trinitrate patches [GTN]), provide mixed or uneven benefit across patient populations (Andres & Murrel, 2008; Green et al., 2003; McLauchlan & Handoll, 2001) and the optimal treatment regime has yet to be found. These various treatment approaches are considered further below.

3.5.1 Eccentric Exercise

As the tendon is essentially a mechanical load bearing structure, it would appear that some form of reconditioning should be included in any rehabilitation process in order to prepare the tendon to withstand the loads put upon it, and therefore resist negative changes in viscoelastic properties, and to provide greater resistance to trauma. This approach is supported by findings that after an eccentric exercise regime, increased collagen synthesis occurs in injured tendons only and not healthy tendons. This increased synthesis correlated with a decrease in pain, suggesting a mismatch between the strength of the tendon and the loads placed upon it (Langberg et al., 2007).

Over the last ten years or so, eccentric exercises have emerged as the exercise treatment of choice for the treatment of tendinopathy despite a lack of high quality research evidence of effectiveness. Due to heterogeneity of studies, poor compliance data, and modifications to the original protocol in some studies, it is difficult to
recommend any particular regime of eccentric exercise (Meyer et al., 2009; Woodley et al., 2007).

Eccentric exercises have previously shown superior results to concentric exercises for Achilles patients (Mafi et al., 2001), but the exact mechanism behind this remains unknown. As discussed above, too much strain, resulting in abnormal stretching of the tenocytes, can affect gene expression, influencing mechanotransduction and subsequently collagen turnover. However, some level of production of proteoglycans, growth factors, inflammatory cytokines, and ROS as a response to exercise is normal; thus it would appear that finding the appropriate amount of strain and achieving the correct balance of collagen and ECM turnover is the challenge.

Exercise is known to induce elevated collagen synthesis in the patellar tendon in the region of 1-3% and the rate remains elevated for 2-3 days after exercise (Miller et al., 2005). To date there is no evidence to suggest a relationship between the magnitude of the exercise and the rate of collagen synthesis, and no indication of a minimum level of stimulation to switch on this effect. Single bouts of loading, as well as frequent exercise sessions in different studies have each resulted in elevated collagen synthesis (Langberg et al., 2007; Langberg et al., 2001; Miller et al., 2005), which is an important finding given the current popularity of eccentric exercise regimes that advocate twice daily sessions seven days per week as the optimal approach.

Another recent study brings into question the amount of loading required to rehabilitate tendinopathy in the Achilles tendon (Rees, Lichtwark, Wolman, & Wilson, 2008). Seven healthy volunteers performed concentric and eccentric exercises and the investigators used a combination of motion analysis, force plate data, and real time
ultrasound to determine tendon force and length changes. Results showed there was no
difference in peak force or tendon length changes when comparing concentric and
eccentric exercises, but there were high frequency oscillations in tendon force found
during eccentric exercise. These authors concluded that such oscillations might be the
key to the success of the eccentric exercise regime. However, it is not entirely clear to
what degree healthy tendons behave differently to pathological tendons, and thus the
generalisability of these findings to tendinopathies is not possible. Beyond this, data
displaying tendon force and length for both concentric and eccentric exercise for two
participants, provided by the authors, showed that although there was no difference in
tendon length changes between the two different forms of exercise, during the eccentric
exercise the tendons were longer (under more strain). Given this, it may be possible that
change in tendon length was not the important factor but rather that the loading
occurred in a different part of the range of the movement (equating to more strain, i.e.
further up the linear portion of the stress/strain curve in Figure 3-2), and thus subjecting
the tenocytes to a sufficient amount of strain to induce gene expression.

One theory that may go some way to explaining the superior results reported for
eccentric exercise in the treatment of tendinopathies is that stretching exercises,
performed in weight bearing as in the study by Kubo et al (Kubo et al., 2002) reduced
hysteresis and therefore the heating effect of exercise. As indicated above, excessive
heat is known to cause apoptosis (Birch et al., 1997), increased levels of inflammatory
cytokines (Hosaka et al., 2006), and increased production of ROS (Longo et al., 2008).
Eccentric exercise also provides a controlled stretch under load, therefore stiffening the
tendon and giving it a heightened resistance to deformation through a larger range of movement, as may be hypothesized from the findings of Rees et al., 2008).

3.5.2 Low Level Laser Therapy

The use of low level laser therapy for the treatment of a range of tendinopathies has been studied extensively over the last two decades. Specifically for the Achilles tendon, there have been four randomised controlled trials that have delivered mixed results (Bjordal et al., 2006; Darre et al., 1994; Meier & Kerkour, 1988; Stergioulas et al., 2008). The two most recent studies used current guidelines for dosage, and robust methodologies, and produced positive results (Bjordal et al., 2006; Stergioulas et al., 2008); in contrast, the earlier two studies were weaker methodologically (refer to Table 4-3 methodological quality scores using the PEDRO scale, and appendix III for a description of the PEDro scale) and found no benefit from the use of laser therapy (Darre et al., 1994; Meier & Kerkour, 1988). Reviews of effectiveness of treatment modalities for different tendinopathies are on the whole not supportive of the use of low level laser therapy, and give weak or negative recommendations (Ejnisman et al., 2004; Green et al., 2003; Maher, 2006; McLauchlan & Handoll, 2001; Stasinopoulos & Johnson, 2005). However, one recent review of the use of low level laser for lateral epicondylitis did recommend this modality when optimal wavelength and doses were utilized (Bjordal et al., 2008).

From cellular studies exploring the biological effects of laser radiation there is evidence that specific components of the mitochondrial respiratory chain absorb certain wavelengths more readily, and this primary reaction leads to secondary reactions involving intracellular signaling leading to observed clinical effects such as promotion of
tissue repair and healing. These biological effects include: changes in membrane permeability, stimulation of cytokine reactions, release of growth factors, up-regulation of ATP, NO and REDOX signaling, and therefore increased metabolism and cell proliferation (Gavish et al., 2008; Grossman et al., 1998; Hou et al., 2008; Karu et al., 1995). Arising from these effects at the cellular or subcellular level, important effects of laser therapy in the treatment of tendinopathy are decreased inflammation, increased angiogenesis, and increased fibroblast activity, leading in turn to increased collagen production and on to increased tensile strength, and decreased pain (Bjordal et al., 2006; Oliveira et al., 2009; Reddy et al., 1998; Ribeiro et al., 2009; Salate et al., 2005).

3.5.3 Corticosteroids and Non-steroidal Anti-inflammatory Medication

Non-steroidal anti-inflammatory (NSAID) medication is commonly used to treat tendinopathy even though presence of an inflammatory component to this condition is contentious. A comprehensive review (Almekinders & Temple, 1998) found only nine studies that were placebo controlled and of these, five demonstrated an analgesic effect and four found no benefit from the use of NSAIDs. Follow-up periods in these studies ranged from 7 to 28 days therefore providing evidence for short term pain relief only. A more recent review supports the conclusions of this earlier work (Andres & Murrel, 2008), and also recommends short term use mainly for pain relief. There is no evidence that NSAIDs contribute to tendon healing or changes in clinical symptoms; in fact because of their anti-inflammatory action these could potentially be detrimental to tendon remodeling (Ferry, Dahners, Afshari, & Weinhold, 2007; Marsolais, Cote, & Frenette, 2003).
Corticosteroids are also used in tendinopathy for their potent anti-inflammatory action, but once again the evidence for their efficacy is weak, and it would appear that these provide only limited short term benefit. Five from eight studies in one review, failed to show a clear difference when compared with placebo at follow-ups ranging from 2-12 weeks (Almekinders & Temple, 1998). A more recent review looked at the efficacy for corticosteroids to treat rotator cuff problems and also found little or no evidence to support their use (Koester, Dunn, Kuhn, & Spindler, 2007). Beyond this, there have also been reports of Achilles tendon ruptures after corticosteroid injection (Kleinman & Gross, 1983), so their use is not without risk.

3.5.4 Sclerotherapy

Neovascularisation into tendinopathic tendons and the accompanying nerve fibers have been implicated with the pain experienced by patients (Cook, Malliaras, De Luca, Ptasznik, & Morris, 2005). Injection of sclerosants such as polidocanol into the blood vessel results in sclerosis of the new vessel and eradication of the pain generating nerve fibers. Promising results have been shown with this approach in the Achilles, patellar and rotator cuff tendons (Alfredson, Harstad, Haugen, & Ohberg, 2006; Alfredson & Ohberg, 2005a, 2005b); another study on Achilles tendons that completed a 2 year follow-up, reported 38 out of 42 participants were satisfied and had considerably less pain than before treatment (Lind, Ohberg, & Alfredson, 2006). Two studies assessed the effect of polidocanol for lateral epicondylalgia: while a case series showed positive results (Zeisig, Ohberg, & Alfredson, 2006), a subsequent randomised controlled trial showed no difference between groups (Zeisig, Fahlstrom, Ohberg, & Alfredson, 2008). However, this latter result is perhaps not surprising: it is not known whether
sclerotherapy has any effect on the histopathology of the healing tendon, and it has been shown that in the long term there is no correlation between decreased pain and vascularity in the patellar tendon (Hoksrud, Ohberg, Alfredson, & Bahr, 2008).

### 3.5.5 Injection Therapies

Various injection therapies have shown some early promise with positive results reported from small pilot studies or case series. However, methodological limitations weaken the evidence provided by these studies, and overall the evidence is mixed. For instance, platelet rich plasma injections have been reported to be of benefit in lateral epicondylalgia (Mishra & Pavelko, 2006), but of no benefit for Achilles tendinopathy (De Vos et al., 2010). Another procedure based upon autologous blood injections following dry needling of the tendon to insult the tendon structure, have been reported to improve pain compared to baseline for a variety of tendinopathies (Connell et al., 2006; Edwards & Calandruccio, 2003; James et al., 2007; Suresh, Ali, Jones, & Connell, 2006); however, none of these were controlled studies, and thus high level clinical evidence to support this therapy is lacking. Injection of dextrose into the tendon (prolotherapy) has also yielded positive results in patients with Achilles pain and lateral epicondylalgia (Maxwell, Ryan, Taunton, Gillies, & Wong, 2007; Scarpone, Rabago, Zgierska, Arbogast, & Snell, 2008), but once again, given the limited quality of the studies to date, robust evidence is lacking to support the clinical use of this modality. Aprotinin, used in open heart surgery for its protease inhibition qualities has been investigated in the treatment of Achilles and patellar tendinopathy, again with mixed results. One study reported no benefit for Achilles patients (Brown, Orchard, Kinchington, Hooper, & Nalder, 2006), whereas another group of researchers reported positive results for both Achilles and patellar...
tendinopathy patients (Capasso, Maffulli, Testa, & Sgambato, 1993; Capasso, Testa, Maffulli, & Bifulco, 1997). Other authors performed a retrospective case review of 430 patients suffering from Achilles or patellar tendinopathy who had received aprotinin injection and achieved a 72% response rate (310 patients); this group reported substantial benefits, in some cases lasting years (Orchard, Massey, Brown, Cardon-Dunbar, & Hofmann, 2008). This is surprising, given the negative effects outlined above that arise from using broad spectrum MMP inhibitors. There have also been reports of patients suffering a systemic allergic reaction after aprotinin treatment for Achilles tendinopathy resulting in hospital admission (Rukin & Maffulli, 2007); this is obviously a serious risk which needs to be considered when using this form of treatment. Rates for severe allergic reaction to aprotinin have been reported as 1-3% (Orchard, Hofman, & Brown, 2005).

Although there is some limited evidence to support the effectiveness of injection therapies, a lot more research is needed before such interventions can be considered for routine practice.

3.5.6 Glyceryl Trinitrate Patches

As discussed above, nitric oxide can enhance collagen synthesis and promote tendon healing (Murrell, 2007; Xia et al., 2006). Glyceryl trinitrate patches (GTN) provide a means of delivering nitric oxide, and for treatment of tendinopathy are placed over the tender spot on the tendon. Three recent clinical trials on supraspinatus, Achilles, and lateral elbow tendinosis have all shown positive results from the use of GTN patches when combined with a tendon rehabilitation programme (Paoloni et al., 2003, 2004, 2005). However, another recent randomised controlled trial on Achilles tendinosis found
no added benefit from GTN patches (Kane et al., 2008). In this trial, participants completed the eccentric exercise regime as described by Alfredson et al (1998) and were given GTN or placebo patches. Outcome measures were pain and disability scores; four participants from the GTN group went on to have surgery, and biopsies where taken to measure NOS to assess evidence of nitric oxide production. For all outcome measures, this study reported no differences between the groups.

Although GTN patches have been demonstrated to be of benefit in some trials, more robust trials with larger numbers of patients need to be carried out to fully assess the effectiveness of this modality.

3.5.7 Extracorporeal Shock Wave Therapy

Extra corporeal shock wave therapy (ESWT) is a new technology using intense, but very short energy waves to treat chronic, painful conditions of the musculoskeletal system and as with other modalities described, variable evidence exists for the effectiveness of ESWT. A number of studies have shown benefit in the treatment of calcification of the supraspinatus tendon (Albert et al., 2007; Cacchio et al., 2006; Cosentino et al., 2003), but for non-calcified tendons the results were less encouraging (Schmitt et al., 2001; Speed et al., 2002b). Evidence for the treatment of lateral epicondylalgia is similar: there are some positive reports (Pettrone & McCall, 2005; Rompe, Decking, Schoellner, & Theis, 2004; Spacca et al., 2005), and some reports of no extra benefit compared to controls (Chung & Wiley, 2004; Haake et al., 2002; Speed et al., 2002a; Staples, Forbes, Ptasznik, Gordon, & Buchbinder, 2008). One group of researchers conducted a number of trials on the Achilles tendon evaluating ESWT and eccentric exercises: one study found the two approaches to be comparable (Rompe,
Nafe, Furia, & Maffulli, 2007); a second reported that ESWT gave better results than eccentric exercises (Rompe, Furia, & Maffulli, 2008); the final study concluded that a combined approach was better than eccentric exercise alone (Rompe, Furia, & Maffulli, 2009). Systematic reviews on the topic have also concluded that there is little or no evidence to support the use of ESWT in lateral epicondylalgia (Bisset, Paungmali, Vicenzino, & Beller, 2005; Buchbinder et al., 2006; Faro & Wolf, 2007) and other reviews also fail to provide strong recommendations for its use for other tendinopathies (Andres & Murrel, 2008; Rees, Maffulli, & Cook, 2009). This is due in part to variation in application and treatment protocols, and more work is needed to define the optimum treatment regime before the usefulness of ESWT to treat non-calcified tendinopathies can be properly evaluated.

3.6 Summary

A healthy functioning tendon relies on a complicated interaction between biomechanical load and biochemical stimulation of a process designed to constantly remodel and adjust the structure of the tendon, and therefore maintain the viscoelastic properties to enable the tendon to cope with the mechanical loads placed upon it. The viscoelastic properties can be altered due to trauma, overuse or underuse, and these changes in turn have an effect on gene expression. This altered gene expression disrupts the constant cycle of remodeling, and leads to degeneration or susceptibility to overload and injury. This weakening of the tendon not only decreases its ability to withstand forces, but can also lead to heating, which in turn can disrupt cell metabolism of matrix components. This further weakens the tendon structure, increasing hysteresis, which increases heating and a vicious circle is formed (Figure 3-4). As discussed above, the
production and regulation of enzymes and chemical messengers relies on a complex interaction with each other, and although this delicate balance of synthesis and degradation is the normal reaction of the structure to repetitive loading, it can be thrown into disarray by over or underproduction of any one of these chemicals.

Figure 3-4: Schematic of a Model of Tendinopathy.
Pathogenesis of tendinopathy is multifactorial and despite the myriad of treatment options available there is not one modality or approach that stands out as the definitive solution based upon the current evidence. Negative changes in viscoelastic properties along with abnormal biochemical responses seem to be at the center of the problem (Figure 3-4). Therefore logic suggests that some form of reconditioning of the tendon to withstand the loads put upon it and resist negative changes in viscoelastic properties, thus providing greater resistance to trauma, must be included in any rehabilitation process; heavy load eccentric exercises, as opposed to other forms of exercise, provide the best evidence for their inclusion in any such regime.

All the other approaches identified above attempt to influence the repair/remodeling process at various stages, and stimulate the synthesis of proteins and other extracellular components. However, the evidence from the literature is mixed, and in the case of dose dependant modalities it is often the case that the most efficacious dose has yet to be found. Low level laser therapy is one such modality: positive evidence from cellular and animal studies suggests that beneficial effects upon tendinopathy should be forthcoming; however, in the clinical setting research shows that the success of the lab based studies cannot always be replicated. More work is needed to establish the clinical effectiveness of low level laser therapy and to define the optimum treatment application and parameters.

The combination of eccentric exercise and low level laser therapy, because of the evidence as to their effects discussed previously in Chapters 2 and 3, may be beneficial in treating Achilles tendinopathy. These two modalities in combination should enhance the
healing response and also recondition the tendon to enable the patient to return to previous levels of activity.
4 Low Level Laser Treatment of Tendinopathy: A Systematic Review with Meta-analysis

4.1 Introduction

In previous chapters (Chapter 2 and 3) the published literature on tendinopathy and low level laser therapy has been reviewed. There are a number of points that are worth highlighting. In recent times, the term “tendinopathy” has been used as a general clinical descriptor to indicate pain in the region of the tendon without any indication of the underlying cause (Maffuli et al., 1998). Regardless of the cause, the prevalence of tendinopathies is increasing: for example in New Zealand the incidence of Achilles tendon ruptures more than doubled between the years 1998 to 2003, from 4.7/100,000 to 10.3/100,000, a phenomenon that follows international trends (Tumilty, 2007). Patellar tendinopathy accounted for 20% of all knee injuries reported over a 6 month period at a sports injury clinic, (Kannus et al., 1987) while tennis elbow affects approximately 1%-2% of the population (Gabel, 1999). Other common sites of tendinopathy are golfer’s elbow at the medial side of the elbow, and the rotator cuff tendons in the shoulder.

Perhaps because of the multifactorial nature of the pathogenesis of tendinopathy, (Riley, 2004; Sharma & Maffulli, 2005) there is a plethora of treatment modalities available to reduce symptoms and to attempt to control or enhance the tendon healing response. These modalities, (which include various electrotherapy modalities; eccentric exercise; a variety of injection techniques and cross-fiber massage), have been reported to provide mixed or uneven benefit, with conflicting evidence from randomised
controlled trials in patient populations with rotator cuff, Achilles tendon, patellar tendon, iliotibial band, and extensor carpi radialis tendinopathies. As a result the ideal treatment for tendinopathy remains unclear (Andres & Murrel, 2008; Brosseau et al., 2002; Green et al., 2003; McLauchlan & Handoll, 2001; Stasinopoulos & Stasinopoulos, 2004).

Low level laser therapy (LLLT) or the use of laser sources at powers too low to cause clinically measurable temperature increases (<1W output power, but typically 30mW-300mW), have been used to treat soft tissue injuries and inflammation since the 1960s, and studies from as early as the 1980s reported benefits in a variety of tendon and sports injuries (Emmanoulidis & Diamantopoulos, 1986; Roumeliotis, Emmanoulidis, & Diamantopoulos, 1987). More recently the term LLLT has been used to describe not only the use of low power laser sources, but also narrow band superluminous diodes. Both types of system have been used in the treatment of various musculoskeletal conditions including tendon injuries, each apparently with success (Corazza et al., 2007; Klebanov et al., 2005; Klebanov et al., 2006; Vinck et al., 2005; Vinck et al., 2003). Such applications are supported by experimental evidence of the biological effects of LLLT, including increased ATP production, as well as enhanced cell function and increased protein synthesis (Karu, 1989); superluminous diodes have also been shown to have positive effects on reduction of inflammation (Bjordal et al., 2006), increase of collagen synthesis (Reddy et al., 1998), and angiogenesis (Salate et al., 2005).

While LLLT is promoted as a safe and effective form of treatment for a variety of conditions, in today’s health care climate there is a necessity to practice evidence based medicine, and a need to provide high level evidence to support the use of any treatment modality (Chapter 1). Whether previous research into the clinical effectiveness of LLLT
has accomplished this is debatable due to the varying quality of the available research. As discussed in Chapter 2, synthesizing the evidence from many reviews fails to provide conclusive recommendations for the effectiveness of this modality: problems cited include methodological weaknesses and heterogeneity of the included studies (Bjordal, 2007; Bjordal et al., 2007; Chow & Barnsley, 2005; Enwemeka et al., 2004; Green et al., 2003; Jamtvedt et al., 2008; Stasinopoulos & Johnson, 2005; Yousefi-Nooraie et al., 2008). Clinical heterogeneity is caused by differing applications of the laser, such as contact, non-contact, or scanning; trigger point treatments, acupuncture point treatments, or treatment over the lesion. Apart from application techniques, clinical heterogeneity is also caused by variation in the patient population due, for example to variation in the health of individual patients and the presence of co-morbidities. Specifically for tendinopathy, reviews provide a mixed message and often conclude that the optimum dose has yet to be indentified (Bjordal et al., 2001; Bjordal et al., 2008; McLauchlan & Handoll, 2001; Smidt et al., 2003; Stasinopoulos & Johnson, 2005).

With this in mind, a systematic review with a meta-analysis of the data was undertaken to answer the question: “Is low level laser therapy effective in the treatment of tendinopathy?” Three main objectives were set:

I. To determine the clinical effectiveness of LLLT in the treatment of tendinopathy when compared to placebo, no treatment, or other types of intervention.

II. To determine the relevance of irradiation parameters to reported positive outcomes.
III. To determine the validity of current dosage recommendations for the treatment of tendinopathy.

4.2 Methodology

A search of common medical databases was carried out on 1\textsuperscript{st} August 2008; the search covered the period of the individual database inception until 1\textsuperscript{st} August 2008.

Search Strategy: The MEDLINE, PubMed, CINAHL, AMED, EMBASE, All EBM (Evidence Based Medicine) reviews, PEDro (Physiotherapy Evidence Database), SCOPUS databases were searched (Table 4-1.).

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Selection Criteria

The Selection Criteria for this Review were as follows:

- **Types of Studies:** Fully reported randomized controlled trials (RCTs) and controlled clinical trials (CCTs) from peer reviewed journals. No language restrictions were made.

- **Types of Participants:** Human participants who had been diagnosed with tendinopathy and exhibited pain and/or functional disability. There was no distinction made with regards to age, gender, level of activity, or chronicity of the injury.

- **Types of interventions:** One group in the controlled trial must have involved participants treated with active LLLT. Comparisons were made with either: placebo, no treatment, or other treatments such as medication, exercise therapy, or other electrotherapy modalities. Interventions based upon combinations of LLLT and other modalities were not considered for the review.

- **Types of outcome measure:** Trials which assessed pain or function for at least one of the outcome measures were considered for inclusion.

**Retrieval of relevant articles:** Two independent reviewers (ST and JM) applied the selection criteria to the titles and abstracts of articles retrieved by the electronic search. All trials classified as relevant by either of the reviewers were retrieved. When there was insufficient information in the title or abstract to determine eligibility, the full text of the article was retrieved. Where there was disagreement between the two reviewers about
a trial’s eligibility, the retrieved trial was re-examined against the selection criteria, and 
disagreement resolved by consensus. For studies published in languages other than 
English, a translation was obtained.

**Quality Assessment:** Three independent reviewers (ST, SM & DH) assessed included 
articles for methodological quality against the PEDro scale (PEDro, 2007; appendix III).

**Data Extraction:** Three reviewers (ST, JB & DB) independently extracted and recorded the 
necessary details about diagnosis, interventions, and LLLT parameters, in line with 
recommendations by the World Association for Laser Therapy (WALT) (WALT, 2005) to 
determine the parameters and method of delivery of laser therapy.

**Analysis:** The recommendations of van Tulder et al., 2003 regarding levels of evidence 
were used to interpret the results:

- **Strong evidence:** consistent findings among multiple higher quality RCTs;

- **Moderate evidence:** consistent findings among multiple lower quality RCTs 
  and/or one higher quality RCT;

- **Limited evidence:** one lower quality RCT;

- **Conflicting evidence:** inconsistent findings among multiple RCTs;

- **No evidence:** no RCTs.

**Pooling of Data:** Where available, data were pooled as follows:

- **Pain:** using a visual analogue scale (VAS), for both final scores and change 
in scores.
- **Site of injury:** i.e. for Lateral epicondylitis, Achilles tendinopathies, Rotator Cuff injuries.

- **Grip Strength.**

  To investigate the relevance of parameters to reported benefits, studies were also grouped as those reporting positive effects, and those reporting inconclusive or no effect.

**Statistical Analysis:** Where pooling of data was justified, results were expressed as relative risks (RR) and 95% confidence intervals (CI) for dichotomous outcomes, and weighted mean difference (WMD) and 95% confidence intervals calculated for continuous outcomes. Testing for heterogeneity was done using the chi-squared test. Tested heterogeneity determined whether a random or fixed effects model was used with the “p” value set to 0.10 as per Review Manager Software guidelines, resulting in the random effects model being used for statistical heterogeneity. The Review Manager software, version 4.2 (Cochrane Collaboration, Copenhagen "Review Manager (RevMan)," 2003) was used to perform the analysis. Sensitivity analyses were conducted where appropriate, to check the robustness of the review, and to assess if there were any magnitude or directional changes in the pooled results. Sensitivity analyses were attempted using only two groups per study for trials with multiple intervention groups, as a unit-of-analysis error occurs when using data from the same group of participants twice; i.e. the placebo group (LLLT versus placebo; or LLLT versus the group with the most conservative score, so as not to introduce bias to the review). Other sensitivity analyses where carried out using only studies scoring ≥6 on the PEDro scale to ensure only high quality RCTs where included, or by using both a fixed and random effects model when
analysing small numbers of studies where reduced confidence in the chi-squared test might have been an issue.

Disagreements between reviewers were settled by consensus. Where insufficient data were provided in the published article, every attempt was made to contact the corresponding authors to obtain the relevant information by the use of emails and letters (see Appendix IV for examples).

### 4.3 Results

The Quality of Reporting of Meta-Analysis (QUOROM) statement flow diagram (Moher et al., 1999) (Figure 4-1) displays the results of the search conducted on 1st August 2008. As shown, 663 investigations were identified as being potentially relevant according to the initial search criteria. Of these, 638 reports were excluded at various stages of the process for a variety of reasons, including: they were review articles; involved surgery or did not involve LLLT; did not address tendinopathy; inappropriate LLLT intervention/application technique; were not an RCT/CCT; were not full reports or did not appear in peer-reviewed journals. Twenty five articles were included in the review (Table 4-2 and Table 4-3) (Basford et al., 2000; Bjordal et al., 2006; Costantino et al., 2005; Darre et al., 1994; England et al., 1989; Haker & Lundeberg, 1991a; Haker & Lundeberg, 1991b; Hernandez Herrero et al., 2006; Konstantinovic et al., 1997; Krasheninnikoff et al., 1994; Lam & Cheing, 2007; Melegati et al., 1994; Muller et al., 1993; Oken et al., 2008; Papadopoulos et al., 1996; Saunders, 1995, 2003; Sharma et al., 2002; Siebert et al., 1987; Stergioulas, 2007; Stergioulas et al., 2008; Tumilty et al., 2008; Vasseljen, 1992; Vasseljen et al., 1992; Vecchio et al., 1993). The pilot study (Chapter 5) was included, as it was published at the time of the review.
Figure 4-1: Search Strategy Flow Diagram.
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Diagnosis</th>
<th>n</th>
<th>Interventions</th>
<th>Outcomes Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basford</td>
<td>2000</td>
<td>Lat epicondylitis</td>
<td>47</td>
<td>Laser V Placebo All participants were instructed in conservative treatment options (i.e., ice massage, cross-fibre friction massage, wrist extensor stretching)</td>
<td>VAS; pain in last 24 hours, VAS; tenderness to palpation, VAS; patient’s perception of change (benefit). Grip strength; pinch strength VAS; pain on grip; pain on pinch</td>
</tr>
<tr>
<td>Haker</td>
<td>1991a</td>
<td>Lat epicondylalgia</td>
<td>49</td>
<td>Laser V Placebo</td>
<td>Grip strength</td>
</tr>
<tr>
<td>Haker</td>
<td>1991b</td>
<td>Lat epicondylalgia</td>
<td>58</td>
<td>Laser V Placebo As well as the painful area, LI 11 &amp; LI 12 acupuncture points were also Irradiated.</td>
<td>Patient satisfaction (5 point scale)</td>
</tr>
<tr>
<td>Hernandez-Herrero</td>
<td>2006</td>
<td>Elbow Tendinosis</td>
<td>46</td>
<td>Laser V Other electrotherapy modalities</td>
<td>VAS; pain</td>
</tr>
<tr>
<td>Konstantinovic</td>
<td>1997</td>
<td>Radiohumeral epicondylitis</td>
<td>32</td>
<td>Laser V Corticosteroid injection V combination of both</td>
<td>McGill pain questionnaire</td>
</tr>
<tr>
<td>Krasheninnikoff</td>
<td>1994</td>
<td>Lat epicondylitis</td>
<td>36</td>
<td>Laser V Placebo</td>
<td>Pain 4 point scale</td>
</tr>
<tr>
<td>Lam</td>
<td>2007</td>
<td>Lat epicondylitis</td>
<td>39</td>
<td>Laser V Placebo</td>
<td>Dynamic muscle test Number of tender points</td>
</tr>
<tr>
<td>Melagati</td>
<td>1994</td>
<td>Humeral epicondylitis</td>
<td>32</td>
<td>Laser V Cryotherapy &amp; Iontophoresis</td>
<td>VAS; pain</td>
</tr>
<tr>
<td>Oken</td>
<td>2008</td>
<td>Lat epicondylitis</td>
<td>58</td>
<td>Laser V Ultrasound V Brace</td>
<td>VAS; pain; Telethermography</td>
</tr>
<tr>
<td>Papadopoulos</td>
<td>1996</td>
<td>Tennis Elbow</td>
<td>29</td>
<td>Laser V Placebo</td>
<td>VAS; pain; Endurance score</td>
</tr>
<tr>
<td>Stergiouls</td>
<td>2007</td>
<td>Lat epicondylitis</td>
<td>50</td>
<td>Laser V Placebo</td>
<td>VAS; pain; Grip Strength</td>
</tr>
<tr>
<td>Vasseljen et al</td>
<td>1992</td>
<td>Tennis Elbow</td>
<td>30</td>
<td>Laser V Placebo</td>
<td>Wrist extension strength Grip strength Lifting test 1, 2, &amp; 3 Kg Goniometric measure of wrist flex VAS; pain</td>
</tr>
<tr>
<td>Vasseljen</td>
<td>1992</td>
<td>Tennis Elbow</td>
<td>30</td>
<td>Laser V Deep friction massage &amp; pulsed ultrasound</td>
<td>VAS; pain; Verbal rating scale</td>
</tr>
<tr>
<td>England</td>
<td>1999</td>
<td>Shoulder Tendinitis</td>
<td>30</td>
<td>Laser V Placebo V Drug treatment</td>
<td>VAS; pain; Goniometry of flex, ext, abd</td>
</tr>
<tr>
<td>Saunders</td>
<td>1995</td>
<td>Supraspinatus Tendinitis</td>
<td>24</td>
<td>Laser V Placebo Self help advice given to</td>
<td>VAS; pain; stiffness, function</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Condition</td>
<td>Sample Size</td>
<td>Treatment 1</td>
<td>Treatment 2</td>
</tr>
<tr>
<td>--------------</td>
<td>------</td>
<td>------------------------------</td>
<td>-------------</td>
<td>----------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Saunders</td>
<td>2003</td>
<td>Supraspinatus Tendinitis</td>
<td>36</td>
<td>Laser V Ultrasound V Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Vecchio</td>
<td>1993</td>
<td>Rotator Cuff Tendinitis</td>
<td>35</td>
<td>Laser V Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Bjordal</td>
<td>2006</td>
<td>Achilles Tendinitis</td>
<td>14</td>
<td>Laser V Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Darre</td>
<td>1994</td>
<td>Achilles Tendinitis</td>
<td>89</td>
<td>Laser V Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Stergioulas</td>
<td>2008</td>
<td>Achilles Tendinopathy</td>
<td>52</td>
<td>Laser V Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Tumilty</td>
<td>2008</td>
<td>Achilles Tendinopathy</td>
<td>20</td>
<td>Laser V Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Costantino</td>
<td>2005</td>
<td>Achilles Tendinitis, epicondylitis</td>
<td>45</td>
<td>Cryoultrasound V Laser V T.e.c.a.r. therapy</td>
<td>Placebo</td>
</tr>
<tr>
<td>Muller</td>
<td>1993</td>
<td>Various Tendinopathies</td>
<td>48</td>
<td>Laser V Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Siebert</td>
<td>1987</td>
<td>Med &amp; Lat epicondylitis, Other Tendinopathies</td>
<td>64</td>
<td>Laser V Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Sharma</td>
<td>2002</td>
<td>De Quervains Tenosynovitis</td>
<td>30</td>
<td>Laser V Placebo</td>
<td>Placebo</td>
</tr>
</tbody>
</table>
### Table 4-3: Itemised Methodology Scores of Included Studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Diagnosis</th>
<th>PEDro</th>
<th>Score/10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basford</td>
<td>2000</td>
<td>Lat epicondylitis</td>
<td>1,2,4,5,6,8,10,11</td>
<td>7</td>
</tr>
<tr>
<td>Haker</td>
<td>1991a</td>
<td>Lat epicondylalgia</td>
<td>1,2,4,5,6,7,8,10</td>
<td>7</td>
</tr>
<tr>
<td>Haker</td>
<td>1991b</td>
<td>Lat epicondylalgia</td>
<td>1,2,4,5,6,7,8,10</td>
<td>7</td>
</tr>
<tr>
<td>Hernandez-Herrero</td>
<td>2006</td>
<td>Elbow Tendinosis</td>
<td>1,2,3,4,7,11</td>
<td>5</td>
</tr>
<tr>
<td>Konstantinovic</td>
<td>1997</td>
<td>Radiohumeral epicondylitis</td>
<td>1,2</td>
<td>1</td>
</tr>
<tr>
<td>Krasheninnikoff</td>
<td>1994</td>
<td>Lat epicondylitis</td>
<td>1,2,4,5,6,10,11</td>
<td>6</td>
</tr>
<tr>
<td>Lam</td>
<td>2007</td>
<td>Lat epicondylitis</td>
<td>1,2,4,5,6,8,9,10,11</td>
<td>7</td>
</tr>
<tr>
<td>Melegati</td>
<td>1994</td>
<td>Humeral epicondylitis</td>
<td>1,4,7,8,10</td>
<td>4</td>
</tr>
<tr>
<td>Oken</td>
<td>2008</td>
<td>Lat epicondylitis</td>
<td>1,2,4,7,8,10,11</td>
<td>6</td>
</tr>
<tr>
<td>Papadopoulos</td>
<td>1996</td>
<td>Tennis Elbow</td>
<td>1,2,5,6,8,9,10</td>
<td>6</td>
</tr>
<tr>
<td>Stergioulas</td>
<td>2007</td>
<td>Lat epicondylitis</td>
<td>1,2,4,5,7,10,11</td>
<td>6</td>
</tr>
<tr>
<td>Vasseljen et al</td>
<td>1992</td>
<td>Tennis Elbow</td>
<td>1,2,4,5,6,8,9,10,11</td>
<td>8</td>
</tr>
<tr>
<td>Vasseljen</td>
<td>1992</td>
<td>Tennis Elbow</td>
<td>1,2,4,8,9,10,11</td>
<td>6</td>
</tr>
<tr>
<td>England</td>
<td>1999</td>
<td>Shoulder Tendinitis</td>
<td>1,2,5,7,8,10,11</td>
<td>6</td>
</tr>
<tr>
<td>Saunders</td>
<td>1995</td>
<td>Supraspinatus Tendinitis</td>
<td>1,2,4,5,6,7,8,9,10,11</td>
<td>9</td>
</tr>
<tr>
<td>Saunders</td>
<td>2003</td>
<td>Supraspinatus Tendinitis</td>
<td>1,2,4,7,8,9,10</td>
<td>6</td>
</tr>
<tr>
<td>Vecchio</td>
<td>1993</td>
<td>Rotator Cuff Tendinitis</td>
<td>1,2,4,5,6,7,8,9,10,11</td>
<td>9</td>
</tr>
<tr>
<td>Bjordal</td>
<td>2006</td>
<td>Achilles Tendinitis</td>
<td>1,2,3,4,5,6,7,8,9,10,11</td>
<td>10</td>
</tr>
<tr>
<td>Darre</td>
<td>1994</td>
<td>Achilles Tendinitis</td>
<td>1,2,5,6,8,10</td>
<td>5</td>
</tr>
<tr>
<td>Stergioulas</td>
<td>2008</td>
<td>Achilles Tendinopathy</td>
<td>1,2,4,5,7,9,10,11</td>
<td>7</td>
</tr>
<tr>
<td>Tumilty</td>
<td>2008</td>
<td>Achilles Tendinopathy</td>
<td>1,2,3,4,5,6,7,8,9,10,11</td>
<td>10</td>
</tr>
<tr>
<td>Costantino</td>
<td>2005</td>
<td>Achilles Tendinitis, patella Tendinitis, epicondylitis</td>
<td>4,7,8,9,10,11</td>
<td>6</td>
</tr>
<tr>
<td>Muller</td>
<td>1993</td>
<td>Various Tendinopathies</td>
<td>2,3,5,6,8,9</td>
<td>6</td>
</tr>
<tr>
<td>Siebert</td>
<td>1987</td>
<td>Med &amp; Lat epicondylitis, other tendinopathies</td>
<td>1,2,5,7,11</td>
<td>4</td>
</tr>
<tr>
<td>Sharma</td>
<td>2002</td>
<td>De Quervains Tenosynovitis</td>
<td>1,5,6,7,8,9,11</td>
<td>6</td>
</tr>
</tbody>
</table>

*Item 1 does not count towards the final score*

### 4.3.1 Clinical Effectiveness

Assessing the level of evidence for the effectiveness of LLLT in the treatment of tendinopathy based upon van Tulder’s recommendations (considering quality scores from Table 4-3) (van Tulder et al., 2003), the evidence for the effectiveness of LLLT in the treatment of tendinopathy is inconclusive, as there are conflicting findings among multiple RCTs: 12 studies reported a positive effect (Table 4-4), and 13 studies reported no effect or inconclusive results (Table 4-5).
### Table 4-4: Studies Reporting Positive Effects of LLLT.

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis</th>
<th>Power Density mW/cm²</th>
<th>Dose J/cm²</th>
<th>Wavelength nm</th>
<th>PEDro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haker (1991a)</td>
<td>Lat epicondylalgia</td>
<td>60</td>
<td>1.8</td>
<td>904</td>
<td>7</td>
</tr>
<tr>
<td>Konstantinovic</td>
<td>Radiohumeral epicondylitis</td>
<td>*</td>
<td>*</td>
<td>904</td>
<td>1</td>
</tr>
<tr>
<td>Lam **</td>
<td>Lat epicondylitis</td>
<td>*</td>
<td>*</td>
<td>904</td>
<td>7</td>
</tr>
<tr>
<td>Melagioti</td>
<td>Humeral epicondylitis</td>
<td>*</td>
<td>2.4</td>
<td>904</td>
<td>7</td>
</tr>
<tr>
<td>Stergioulas (2007) **</td>
<td>Lat epicondylitis</td>
<td>*</td>
<td>150</td>
<td>1064</td>
<td>4</td>
</tr>
<tr>
<td>Vasseljen et al (1992)</td>
<td>Tennis Elbow</td>
<td>*</td>
<td>5</td>
<td>904</td>
<td>8</td>
</tr>
<tr>
<td>England</td>
<td>Shoulder Tendinitis</td>
<td>*</td>
<td>*</td>
<td>904</td>
<td>6</td>
</tr>
<tr>
<td>Saunders (95) **</td>
<td>Supraspinatus Tendinitis</td>
<td>320</td>
<td>19.2</td>
<td>820</td>
<td>9</td>
</tr>
<tr>
<td>Saunders (2003) **</td>
<td>Supraspinatus Tendinitis</td>
<td>320</td>
<td>19.2</td>
<td>820</td>
<td>6</td>
</tr>
<tr>
<td>Bjordal</td>
<td>Achilles Tendinitis</td>
<td>20</td>
<td>3.6</td>
<td>904</td>
<td>10</td>
</tr>
<tr>
<td>Stergioulas (2008) **</td>
<td>Achilles Tendinopathy</td>
<td>60</td>
<td>1.8</td>
<td>820</td>
<td>7</td>
</tr>
<tr>
<td>Sharma</td>
<td>De Quervains</td>
<td>32</td>
<td>4</td>
<td>830</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Tenosynovitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Parameters not provided or insufficient information to calculate missing parameter  
** These studies are included in the RevMan analysis

### Table 4-5: Studies Reporting Inconclusive or No Effect of LLLT (Not Statistically Significant).

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis</th>
<th>Power Density mW/cm²</th>
<th>Dose J/cm²</th>
<th>Wavelength nm</th>
<th>PEDro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basford **</td>
<td>Lat epicondylitis</td>
<td>204</td>
<td>12.24</td>
<td>1060</td>
<td>7</td>
</tr>
<tr>
<td>Haker (1991b)</td>
<td>Lat epicondylalgia</td>
<td>*</td>
<td>*</td>
<td>904 &amp; 632.8</td>
<td>7</td>
</tr>
<tr>
<td>Hernandez-Herrero **</td>
<td>Elbow Tendinitis</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>5</td>
</tr>
<tr>
<td>Krasheninnikoff</td>
<td>Lat epicondylitis</td>
<td>114</td>
<td>13.68</td>
<td>830</td>
<td>6</td>
</tr>
<tr>
<td>Oken **</td>
<td>Lat epicondylitis</td>
<td>*</td>
<td>*</td>
<td>632.8</td>
<td>6</td>
</tr>
<tr>
<td>Papadopoulos **</td>
<td>Tennis Elbow</td>
<td>400</td>
<td>24</td>
<td>820</td>
<td>6</td>
</tr>
<tr>
<td>Vasseljen (1992)</td>
<td>Tennis Elbow</td>
<td>*</td>
<td>3.5</td>
<td>904</td>
<td>6</td>
</tr>
<tr>
<td>Vecchio **</td>
<td>Rotator cuff Tendinitis</td>
<td>422</td>
<td>14</td>
<td>830</td>
<td>9</td>
</tr>
<tr>
<td>Darre</td>
<td>Achilles tendinitis</td>
<td>150</td>
<td>20.1</td>
<td>830</td>
<td>5</td>
</tr>
<tr>
<td>Tumilty **</td>
<td>Achilles tendinopathy</td>
<td>2375</td>
<td>82.4</td>
<td>810</td>
<td>10</td>
</tr>
<tr>
<td>Costantino **</td>
<td>Various Tendinopathies</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>6</td>
</tr>
<tr>
<td>Muller</td>
<td>Various Tendinopathies</td>
<td>*</td>
<td>*</td>
<td>904</td>
<td>6</td>
</tr>
<tr>
<td>Siebert</td>
<td>Med &amp; Lat epicondylitis</td>
<td>7500</td>
<td>*</td>
<td>904</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Other Tendinopathies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Parameters not provided or insufficient information to calculate missing parameter  
** These studies are included in the RevMan analysis
4.3.2 Studies Included in the Meta-Analysis

Twelve studies provided sufficient detailed data to input into RevMan 4.2 (Cochrane Collaboration, Copenhagen "Review Manager (RevMan)," 2003) to calculate effect sizes for the outcome measures of final pain scores, pain change scores measured on a VAS (Figure 4-2), or for lateral epicondylitis - grip strength (Figure 4-3). These twelve studies are indicated by** in Tables 4-4 & 4-5.

Attempts to pool data from multiple studies were not valid as the test for heterogeneity was significant (p<0.10) for most of the analyses; however, to show the effect of individual comparisons, studies that compared LLLT against more than one other group have had data comparing LLLT against all other modalities included in the analysis (Figure 4-2). For example, in the poorly powered study by Hernandez Herrero et al., 2006, where LLLT was compared against four other modalities for the treatment of elbow tendinosis, it can be seen that there was very little difference between LLLT and the other forms of treatment. Of the studies that showed a positive result of LLLT for pain in Figure 4-2, the effects ranged from 2.1-28mm on a 100mm VAS.
Review: LLLT in the Treatment of Tendinopathy
Comparison: 01 Laser V control
Outcome: 01 Pain

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Laser Mean (SD)</th>
<th>N</th>
<th>Control Mean (SD)</th>
<th>N</th>
<th>WMD (random)</th>
<th>Weight %</th>
<th>95% CI</th>
<th>WMD (random)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basford</td>
<td>34.30 (28.00)</td>
<td>23</td>
<td>25.10 (21.00)</td>
<td>24</td>
<td>8.14</td>
<td></td>
<td>9.20 [-5.00, 23.40]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costantino V Cryo</td>
<td>24.70 (6.40)</td>
<td>15</td>
<td>13.30 (8.20)</td>
<td>15</td>
<td>9.93</td>
<td></td>
<td>11.40 [6.14, 16.66]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costantino V TECAR</td>
<td>24.70 (6.40)</td>
<td>15</td>
<td>19.30 (4.60)</td>
<td>13</td>
<td>10.08</td>
<td></td>
<td>5.40 [1.41, 9.39]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hernandez V Cryo</td>
<td>32.10 (34.78)</td>
<td>7</td>
<td>32.00 (18.82)</td>
<td>7</td>
<td>8.08</td>
<td></td>
<td>0.10 [-22.84, 23.04]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hernandez V Electro</td>
<td>32.10 (34.78)</td>
<td>7</td>
<td>31.00 (28.20)</td>
<td>7</td>
<td>2.99</td>
<td></td>
<td>1.10 [-42.02, 44.22]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hernandez V Sonoro</td>
<td>32.10 (34.78)</td>
<td>16</td>
<td>32.00 (32.00)</td>
<td>16</td>
<td>5.85</td>
<td></td>
<td>-0.40 [-24.44, 23.64]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hernandez V US</td>
<td>32.10 (34.78)</td>
<td>7</td>
<td>33.00 (26.50)</td>
<td>7</td>
<td>5.30</td>
<td></td>
<td>-0.90 [-27.68, 25.88]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lam</td>
<td>14.80 (13.60)</td>
<td>18</td>
<td>42.80 (21.10)</td>
<td>2</td>
<td>8.80</td>
<td></td>
<td>-28.00 [-39.35, -16.65]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stergioulas 2007</td>
<td>6.21 (7.70)</td>
<td>25</td>
<td>19.67 (9.28)</td>
<td>25</td>
<td>10.00</td>
<td></td>
<td>-13.46 [-18.15, -8.73]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oken V Brace</td>
<td>43.00 (12.00)</td>
<td>20</td>
<td>67.00 (9.00)</td>
<td>20</td>
<td>9.74</td>
<td></td>
<td>-24.00 [-30.57, -17.43]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oken V US</td>
<td>43.00 (12.00)</td>
<td>18</td>
<td>70.00 (22.00)</td>
<td>18</td>
<td>8.78</td>
<td></td>
<td>-14.00 [-25.44, -2.56]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stergioulas 2008</td>
<td>33.00 (29.80)</td>
<td>20</td>
<td>53.00 (19.50)</td>
<td>20</td>
<td>7.80</td>
<td></td>
<td>-20.00 [-35.61, -4.39]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumilty</td>
<td>16.90 (21.92)</td>
<td>10</td>
<td>19.00 (25.88)</td>
<td>10</td>
<td>6.51</td>
<td></td>
<td>-2.10 [-23.12, 18.92]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>225</td>
<td>197</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 132.96, df = 12 (P < 0.00001), I² = 91.0%
Test for overall effect: Z = 1.48 (P = 0.14)

Figure 4-2: RevMan Charts: Pain Analysis with All Groups in All Studies.
It was valid to pool data in two instances: the first for participants’ grip strength in studies of lateral epicondylitis that scored ≥6 on the PEDro scale (Figure 4-3); in the second instance for pain scores in Achilles tendinopathy (Figure 4-5). Effect sizes corresponded to a value of greater than 9.61Kg for grip strength than the control group for participants with lateral epicondylitis. Of the two studies which investigated Achilles tendinopathy (Stergioulas et al., 2008; Tumilty et al., 2008), both showed positive effects in terms of pain scores at the final assessment, with a pooled effect size 13.64mm in favour of the LLLT groups.

Sensitivity analyses were performed for these two instances due to the low number of studies in each analysis; these are presented in Figure 4-4. The random effects model was used instead of the fixed effects model, but there were no great changes in magnitude or direction of effect, therefore the results are robust.
## Review: LLLT in the Treatment of Tendinopathy

### Comparison: 01 Laser V control

### Outcome: 06 Lat Epicondylitis (Grip Strength)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>N</th>
<th>Laser Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>WMD (random)</th>
<th>Weight %</th>
<th>WMD (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basford</td>
<td>23</td>
<td>30.90 (30.10)</td>
<td>24</td>
<td>35.40 (36.10)</td>
<td>7.38</td>
<td>-4.50 [-23.47, 14.47]</td>
</tr>
<tr>
<td>Lam</td>
<td>21</td>
<td>29.57 (8.96)</td>
<td>18</td>
<td>21.61 (9.70)</td>
<td>23.84</td>
<td>7.96 [2.06, 13.86]</td>
</tr>
<tr>
<td>Stergioulas 2007</td>
<td>25</td>
<td>40.22 (10.45)</td>
<td>25</td>
<td>29.31 (8.98)</td>
<td>24.90</td>
<td>10.91 [5.51, 16.31]</td>
</tr>
<tr>
<td>Oken V Brace</td>
<td>20</td>
<td>56.30 (11.20)</td>
<td>20</td>
<td>36.20 (5.20)</td>
<td>24.88</td>
<td>20.10 [14.69, 25.51]</td>
</tr>
<tr>
<td>Oken V US</td>
<td>20</td>
<td>56.30 (11.20)</td>
<td>18</td>
<td>43.60 (15.20)</td>
<td>18.90</td>
<td>12.70 [4.13, 21.27]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>109</td>
<td></td>
<td></td>
<td>105</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 13.24$, df = 4 (P = 0.01), I² = 69.8%  
Test for overall effect: $Z = 3.89$ (P < 0.0001)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>N</th>
<th>Laser Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>WMD (fixed)</th>
<th>Weight %</th>
<th>WMD (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basford</td>
<td>23</td>
<td>30.90 (30.10)</td>
<td>24</td>
<td>35.40 (36.10)</td>
<td>3.74</td>
<td>-4.50 [-23.47, 14.47]</td>
</tr>
<tr>
<td>Lam</td>
<td>21</td>
<td>29.57 (8.96)</td>
<td>18</td>
<td>21.61 (9.70)</td>
<td>36.08</td>
<td>7.96 [2.06, 13.86]</td>
</tr>
<tr>
<td>Stergioulas 2007</td>
<td>25</td>
<td>40.22 (10.45)</td>
<td>25</td>
<td>29.31 (8.98)</td>
<td>42.38</td>
<td>10.91 [5.51, 16.31]</td>
</tr>
<tr>
<td>Oken V US</td>
<td>20</td>
<td>56.30 (11.20)</td>
<td>18</td>
<td>43.60 (15.20)</td>
<td>17.80</td>
<td>12.70 [4.13, 21.27]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>89</td>
<td></td>
<td></td>
<td>85</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 3.15$, df = 3 (P = 0.37), I² = 4.7% 
Test for overall effect: $Z = 5.10$ (P < 0.00001)

---

**Figure 4-3: RevMan Charts: Lateral Epicondylitis grip Strength.**

**Top:** Figure 4-3a; comparison of both groups from Oken study with laser group.  
**Bottom:** Figure 4-3b; comparison from the Oken study of laser group with US group only.
Figure 4-4: RevMan Charts: Sensitivity Analysis for Valid Pooled Data.

Sensitivity analyses using random effects model instead of fixed effects model
4.3.3 Effect of LLLT on Pain at Specific Sites of Injury

Results for pain scores categorised by site of injury are displayed in Figure 4-5.

The positive effect of LLLT for Achilles tendinopathy has been reported above. Three studies reported pain change scores for rotator cuff injuries treated with LLLT (Saunders, 1995, 2003; Vecchio et al., 1993); of these, two compared LLLT to placebo (Saunders, 1995; Vecchio et al., 1993), while Saunders, 2003 included three groups LLLT, placebo, and ultrasound. Assessment by change in pain between initial and final assessments, all showed a positive effect in favour of LLLT.
### Review: LLLT in the Treatment of Tendinopathy
#### Comparison: 01 Laser V control
#### Outcome: 03 Rotator cuff, Pain change scores

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Laser N</th>
<th>Laser Mean (SD)</th>
<th>Control N</th>
<th>Control Mean (SD)</th>
<th>WMD (random)</th>
<th>Weight %</th>
<th>WMD (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>95% CI</td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td>Vecchio</td>
<td>19</td>
<td>36.00 (9.00)</td>
<td>16</td>
<td>18.00 (12.00)</td>
<td>-</td>
<td>16.02</td>
<td>18.00 [10.86, 25.14]</td>
</tr>
<tr>
<td>Saunders 1995</td>
<td>12</td>
<td>18.70 (4.39)</td>
<td>12</td>
<td>-6.30 (5.56)</td>
<td>-</td>
<td>27.99</td>
<td>25.00 [20.99, 29.01]</td>
</tr>
<tr>
<td>Saunders 2003 V PI</td>
<td>12</td>
<td>29.80 (5.82)</td>
<td>12</td>
<td>1.10 (3.37)</td>
<td>-</td>
<td>28.47</td>
<td>28.70 [24.69, 32.51]</td>
</tr>
<tr>
<td>Saunders 2003 V US</td>
<td>12</td>
<td>29.40 (5.82)</td>
<td>12</td>
<td>2.10 (4.64)</td>
<td>-</td>
<td>27.02</td>
<td>27.70 [23.49, 31.91]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>55</td>
<td></td>
<td>52</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 3.35, df = 3 (P = 0.56), I² = 0.0%
Test for overall effect: Z = 13.92 (P < 0.0001)

---

### Review: LLLT in the Treatment of Tendinopathy
#### Comparison: 01 Laser V control
#### Outcome: 05 Lat Epicondylitis pain

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Laser N</th>
<th>Laser Mean (SD)</th>
<th>Control N</th>
<th>Control Mean (SD)</th>
<th>WMD (random)</th>
<th>Weight %</th>
<th>WMD (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>95% CI</td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td>Basford</td>
<td>23</td>
<td>34.30 (28.00)</td>
<td>24</td>
<td>25.10 (21.00)</td>
<td>12.16</td>
<td>9.20</td>
<td>5.00 [10.86, 25.14]</td>
</tr>
<tr>
<td>Hernandez V Cryo</td>
<td>14</td>
<td>32.10 (34.78)</td>
<td>7</td>
<td>32.00 (18.82)</td>
<td>7.46</td>
<td>1.10</td>
<td>-22.84, 23.04</td>
</tr>
<tr>
<td>Hernandez V Electro</td>
<td>14</td>
<td>32.10 (34.78)</td>
<td>2</td>
<td>31.00 (28.20)</td>
<td>2.89</td>
<td>1.00</td>
<td>-42.02, 44.22</td>
</tr>
<tr>
<td>Hernandez V Sono</td>
<td>14</td>
<td>32.10 (34.78)</td>
<td>16</td>
<td>32.50 (32.00)</td>
<td>7.03</td>
<td>0.40</td>
<td>-24.44, 23.64</td>
</tr>
<tr>
<td>Hernandez V US</td>
<td>14</td>
<td>32.10 (34.78)</td>
<td>7</td>
<td>33.00 (26.50)</td>
<td>6.08</td>
<td>0.90</td>
<td>-27.68, 25.88</td>
</tr>
<tr>
<td>Lam</td>
<td>21</td>
<td>14.80 (13.60)</td>
<td>18</td>
<td>42.80 (21.10)</td>
<td>14.15</td>
<td>-0.90</td>
<td>-39.35, -16.65</td>
</tr>
<tr>
<td>Oken V Brace</td>
<td>20</td>
<td>43.00 (12.00)</td>
<td>20</td>
<td>67.00 (9.00)</td>
<td>17.54</td>
<td>24.00</td>
<td>-30.57, -17.43</td>
</tr>
<tr>
<td>Oken V US</td>
<td>20</td>
<td>43.00 (12.00)</td>
<td>18</td>
<td>57.00 (22.00)</td>
<td>14.08</td>
<td>14.00</td>
<td>-25.44, -2.56</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>165</td>
<td></td>
<td>137</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 28.48, df = 8 (P = 0.0004), I² = 71.9%
Test for overall effect: Z = 2.86 (P = 0.004)

---

### Review: LLLT in the Treatment of Tendinopathy
#### Comparison: 01 Laser V control
#### Outcome: 04 Achilles tendinopathy, Pain

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Laser N</th>
<th>Laser Mean (SD)</th>
<th>Control N</th>
<th>Control Mean (SD)</th>
<th>WMD (fixed)</th>
<th>Weight %</th>
<th>WMD (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>95% CI</td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td>Stergioulas 2008</td>
<td>20</td>
<td>33.00 (29.80)</td>
<td>20</td>
<td>53.00 (19.50)</td>
<td>64.46</td>
<td>-20.00</td>
<td>-35.61, -4.39</td>
</tr>
<tr>
<td>Tumilty</td>
<td>10</td>
<td>16.90 (21.92)</td>
<td>10</td>
<td>19.00 (25.88)</td>
<td>35.54</td>
<td>-2.10</td>
<td>-23.12, 18.92</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>30</td>
<td></td>
<td>30</td>
<td></td>
<td>100.00</td>
<td>-13.64</td>
<td>-26.17, -1.11</td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 1.80, df = 1 (P = 0.18), I² = 44.3%
Test for overall effect: Z = 2.13 (P = 0.03)

---

Figure 4-5: RevMan Charts: LLLT Effects on pain Scores Categorised into Site of Injury.
Final pain scores were analysed for participants with lateral epicondylitis. Figure 4-5 shows multiple comparisons from single studies so, as already pointed out, determination of a pooled effect size was not possible. Of the five studies, two showed no effect of LLLT on participants’ pain (Basford et al., 2000; Hernandez Herrero et al., 2006), and three resulted in a positive effect on pain (Lam & Cheing, 2007; Oken et al., 2008; Papadopoulos et al., 1996).

4.3.4 Relevance of Irradiation Parameters and Dosage Recommendations

Table 4-4 displays those studies reporting positive effects of LLLT, as concluded by the authors of the individual studies, and the parameters used in these studies. Table 4-5 displays studies reporting inconclusive results or no effect from LLLT. It should be noted, that even though three studies (Oken et al., 2008; Tumilty et al., 2008; Vecchio et al., 1993) reported no significant differences between groups, in the RevMan analysis the effect sizes of these studies favoured the group treated with laser.

Using the parameters reported in Table 4-4, a range of effective dosages can be calculated for each injury site. These can then be compared to the current recommendations from WALT, 2005) and from Bjordal et al., 2001) (Table 4-6). These guidelines state power densities below 100mW/cm² should be used for superficial tendons, along with an energy dose of between 1-8J. For the deeper tendons of the rotator cuff, power densities are allowed to go as high as 600mW/cm² and energy dosages of between 3-9J.
Table 4-6: Effective Parameters.

<table>
<thead>
<tr>
<th>Injury Site</th>
<th>Number of Studies</th>
<th>Parameters</th>
<th>W.A.L.T.</th>
<th>Bjordal et al 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epicondylitis</td>
<td>6</td>
<td>904nm 1064 nm 60-80mW/cm² 1.8-3.5J/cm²</td>
<td>780-860nm: 4J 904nm: 1J &lt;100mW/cm²</td>
<td>830nm; 5-100mW/cm² 0.7-7J/cm² 904nm; 2-100mW/cm² 0.3-3J/cm²</td>
</tr>
<tr>
<td>Rotator-cuff</td>
<td>3</td>
<td>820nm 904nm 320mW/cm² 19.2J/cm²</td>
<td>780-860nm: 9J 904nm: 3J</td>
<td>830nm; 30-600mW/cm² 4.2-42J/cm² 904nm; 12-600mW/cm² 0.4-4J/cm²</td>
</tr>
<tr>
<td>Achilles</td>
<td>2</td>
<td>820nm 904nm 20-60mW/cm² 1.8-3.6J/cm² &lt;100mW/cm²</td>
<td>780-860nm: 8J 904nm: 2J</td>
<td>830nm; 5-100mW/cm² 0.7-7J/cm² 904nm; 2-100mW/cm² 0.3-3J/cm²</td>
</tr>
<tr>
<td>Wrist</td>
<td>1</td>
<td>830nm 32mW/cm² 4J/cm²</td>
<td>780-860nm: 8J 904nm: 2J</td>
<td>No guideline</td>
</tr>
</tbody>
</table>

**Epicondylitis:** Thirteen studies investigated the effectiveness of LLLT for epicondylitis; six showed positive results (Haker & Lundeberg, 1991a; Konstantinovic et al., 1997; Lam & Cheing, 2007; Melegati et al., 1994; Stergioulas, 2007; Vasseljen et al., 1992). Ten of the thirteen scored 6 points or more on the PEDro scale and would be considered of high quality. The positive studies used a wavelength of 904nm and power densities that lay between 2-100mW/cm² as recommended by the WALT and Bjordal et al guidelines. However, one study (Vasseljen et al., 1992) used a dosage slightly higher than the recommended value (3.5J/cm² instead of 3J/cm²), while another (Melegati et al., 1994) used a wavelength (1064nm) and energy density (150J/cm²) that do not appear in any of the guidelines. Those studies demonstrating no effect (Basford et al., 2000; Haker & Lundeberg, 1991b; Hernandez Herrero et al., 2006; Krasheninnikoff et al., 1994; Oken et al., 2008; Papadopoulos et al., 1996; Vasseljen, 1992) all used power densities and dosage parameters outside of the guidelines, regardless of wavelength employed.
**Rotator Cuff:** Four high quality studies examined the effects of LLLT on tendinopathy around the shoulder region (England et al., 1989; Saunders, 1995, 2003; Vecchio et al., 1993); three studies (England et al., 1989; Saunders, 1995; 2003) used parameters that lay within the guidelines (30-600mW/cm² & 4.2-42 J/cm²) but the four provided conflicting results (two positive {Saunders, 1995 #2461Saunders, 1995; 2003; and one negative Vecchio et al., 1993). The positive study by England et al., 1989) failed to provide enough detail on irradiation parameters (Table 4-4).

**Achilles Tendinopathy:** Four studies investigated LLLT for Achilles tendinopathy (Bjordal et al., 2006; Darre et al., 1994; Stergioulas et al., 2008; Tumilty et al., 2008); two showed beneficial outcomes (Bjordal et al., 2006; Stergioulas et al., 2008), and two were inconclusive (Darre et al., 1994; Tumilty et al., 2008). The two positive studies used parameters that lay within recommended guidelines (Bjordal et al., 2006; Stergioulas et al., 2008), the others used power and energy densities that are deemed to be too high (Darre et al., 1994; Tumilty et al., 2008). One of the negative studies was deemed of low methodological quality (less than 6 on the PEDro scale) (Darre et al., 1994).

**De Quervains Tenosynovitis:** One high quality study (Sharma et al., 2002) used LLLT to treat tendinopathy at the wrist (Table 4-6); however there are no recommended guidelines published for that condition. The parameters used are provided in the table.
4.4 Discussion

This systematic review and meta-analysis was designed to assess the evidence for the clinical effectiveness of LLLT in the treatment of tendinopathy. Its secondary objectives were to determine the relationship of irradiation parameters to outcomes, and to compare these with dosage recommendations provided by WALT, 2005) and from Bjordal et al., 2001). Findings provide conflicting evidence of the effectiveness of LLLT for the treatment of tendinopathies; however there was a clear relationship between positive findings and use of recommended dosages.

Conflicting evidence was provided from a similar number of studies reporting positive effects (n=12) as those that found no benefit (n=13). The methodological quality scores of studies were generally good (6 or higher on the PEDro scale), with only two positive studies scored as low (Konstantinovic et al., 1997; Melegati et al., 1994), compared to three inconclusive studies (Darre et al., 1994; Hernandez Herrero et al., 2006; Siebert et al., 1987). Perhaps the most important finding of this review was that 12 RCTs (10 high quality and 2 low quality) demonstrated that LLLT is potentially effective in the treatment of tendinopathy when the recommended irradiation parameters are used. However, it should be noted, that the recommended irradiation parameters do not include the duration of each treatment, although it could be argued that time is implied, as the guidelines include energy density which is a product of power density (irradiance) multiplied by time. The “time” parameter determines how much of the circulating blood is exposed to LLLT intracutaneously and subcutaneously, modulating the systemic effects of LLLT and activating the immune system.
This finding is perhaps not surprising as a dosage-dependent effect should not be unexpected for any effective therapeutic modality. Furthermore, as the body of research grows for a new modality and researchers seek to establish an effective dosage window, there will be conflicting evidence from an ever increasing number of studies: as seen in the therapeutic ultrasound literature (Crawford & Thomson, 2003; Robertson, 2003). Under these circumstances, it becomes important to look at the available evidence using methods other than van Tulder’s best evidence synthesis, which does not take account of the validity of the intervention used (van Tulder et al., 2003).

Twelve studies provided sufficient data to undertake a meta-analysis of effects. Unfortunately, given the variation in interventions used (including different manufacturers, devices, variations in delivery and calculations of dosages) there was clinical heterogeneity between studies. This can result in misleading conclusions as treatment parameters and application are important (Tuner & Hode, 1998), and can lead in turn to statistical heterogeneity. Indeed only two of the meta-analyses resulted in studies that were homogenous (see Figures 4-2, 4-3 & 4-5) and thus allowed calculation of pooled effect results (the effect on Achilles tendon pain; the effect on grip strength for lateral epicondylitis). Other meta-analyses resulted in statistical heterogeneity, thus limiting any conclusions from these data (Herbert & Bø, 2005). Given such clinical and statistical heterogeneity from the studies included in this review, no attempt was made to report these combined data.

However, useful information can still be derived from the RevMan analysis by calculating effect sizes from individual studies and making multiple comparisons when studies include more than one other intervention or control group. For this reason,
results displayed in Figures 4-2, 4-3 & 4-5 include effect size calculations for all studies comparing LLLT to all other groups. Data presented this way allows a visual estimate to be made of whether sensitivity analyses are necessary to explore any changes in the pooled results. Sensitivity analyses were attempted as described in the methodology in two instances (the effect of LLLT on Achilles tendon pain, and on grip strength for patients suffering from lateral epicondylitis). For both examples, outcomes changed very little in magnitude, or in the direction of effect (pro or contra LLLT) which also remained constant, suggesting the results of these two meta-analyses are robust.

When interpreting these results it should be borne in mind that what is important is whether the effect size is greater than the relevant minimal clinical important difference (MCID) for the outcome measure. A search of the literature failed to find any articles discussing an MCID for tendinopathies. However, from studies using similar pain scales as an outcome measure, both a 2 point reduction on a 10 point scale (Chow et al., 2006; Farrar, Portenoy, Berlin, Kinman, & Strom, 2000; Farrar, Young, LaMoreaux, Werth, & Poole, 2001) and 13mm reduction on a 100mm scale (Todd, Funk, Funk, & Bonacci, 1996) have been reported as a minimal clinical important difference (Chow, Barnsley, Heller, & Siddall, 2004). From Figures 4-2, 4-3 and 4-5, it can be seen that there are several instances of effects sizes for LLLT treatments which meet or exceed this MCID, even though pooling of effect sizes was not always possible: e.g. for participants with rotator cuff injury (Figure 4-5).

The present study also aimed to assess the relevance of treatment/irradiation parameters to reported effectiveness. Assessment of results from positive studies
provide interesting insights: Table 4-6 summarises current results by anatomical site in comparison to guidelines from WALT, 2005) and Bjordal et al., 2001) as detailed below.

**Epicondylitis:** Four high quality studies provided enough information to allow comparison with guidelines; whereas power densities were within recommendations, dosages (J/cm$^2$) used in these studies suggest that for epicondylitis the effective dosage window could be widened. Interestingly, of the inconclusive studies, Oken et al., 2008) actually shows a WMD in favour of laser for both pain and grip strength (Figures 4-2 to 4-4). While the wavelength used by Oken et al., 2008) was not one identified in the guidelines, nevertheless it would be potentially beneficial for the treatment of epicondylitis.

**Rotator Cuff:** There were a range of dosages and methods of application used for treatment of rotator cuff injuries, which may explain the conflicting results: two studies by Saunders et al (Saunders, 1995, 2003) used standardised treatment points and applied laser three times per week for three weeks; Vecchio et al., 1993) treated up to 5 tender points per session and gave two sessions per week for 8 weeks. Once again, even though Vecchio et al., 1993) reported no benefit from laser, the effect size expressed as WMD (Figure 4-5) for pain change scores favoured the LLLT group. The mean change in pain for the laser group over the time period studied was twice that of the control group, which would suggest that the analysis of results in the original paper was flawed. On the whole, the effective dose for rotator cuff tendinopathies was found to lie within that recommended by Bjordal et al., 2001).

**Achilles Tendinopathy:** Three high quality studies (Bjordal et al., 2006; Stergioulas et al., 2008; Tumilty et al., 2008) and one of low quality (Darre et al., 1994)
were included in the review. Bjordal et al., 2006) measured prostaglandin E$_2$ (PGE2) over the first two hours following treatment using parameters within his own recommended guidelines (Bjordal et al., 2001); results showed that LLLT was effective in reducing this proxy for inflammation over that time period. Stergioulas et al., 2008) also used parameters from within the recommended guidelines. Darre et al., 1994) studied treatment of Achilles tendinopathy in Danish Army recruits, however there was no standardisation of the number of treatments given, and insufficient detail on participants, or how the decision was made to end treatment. The power density and the dose delivered were significantly above what would be considered appropriate by Bjordal et al., 2001), and may explain the lack of reported differences between treatment and control groups. Stergioulas et al., 2008) and Tumilty et al., 2008) were studies of very similar design, in that both looked at LLLT as an adjunct therapy to heavy load eccentric exercise; both used similar wavelengths (810nm & 820nm) but the power and energy densities differed. The pilot study (Tumilty et al., 2008) was underpowered as the aim was to gather data to inform a larger RCT in the future, therefore these results need to be interpreted with this in mind. Once again, the studies reporting beneficial effects support the already published guidelines.

Three other studies reported negative outcomes (Costantino et al., 2005; Muller et al., 1993; Siebert et al., 1987), but the design of these studies, namely the grouping of different tendinopathies together, and the lack of adequate reporting of parameters or outcome data, precluded comparison of these findings with other work.
4.4.1 Effect Sizes versus Statistical Tests

As mentioned earlier a number of studies that reported no significant difference between experiment and control groups, actually showed effect sizes that favoured the group treated with laser (Oken et al., 2008; Tumilty et al., 2008; Vecchio et al., 1993). This may cause confusion for the reader, as which result is correct? Consider that when performing a meta-analysis, the aim, which is totally different to normal statistical tests, is to compare outcomes across a range of studies and these data are displayed in the forest plots. Traditional statistical tests are partially a function of the sample size, and effect size estimates are independent of sample size. Studies with similar differences between treatment and control groups but with dissimilar sample sizes can have very diverse “t” and “F” statistics, therefore it would be inappropriate to include group numbers. Any study that stands out because of this phenomenon must be further analysed to determine why there is such a mismatch.

Pilot studies are performed to provide information on procedures and provide data for power calculations, therefore it is not unusual to have non-significant results due to insufficient power, and even positive effect size estimates may not be large enough for the size of the groups to be statistically significant (Tumilty et al., 2008). In one study, where LLLT was evaluated against ultrasound and a brace, the authors reported “there were no significant differences between the groups on VAS and grip strength at baseline and follow-up assessments”. However, the reported “p” statistic which the authors based their statement on, was an analysis of the changes between three groups and in the RevMan analysis comparisons are made with only two groups (LLLT V US; & LLLT V Brace); the resulting “p” statistic for these comparisons is not known (Oken et al., 2008).
The final study of the three (Vecchio et al., 1993) may well have been underpowered, as reported by the authors, reducing the likelihood of detecting statistical significance. The Mann-Whitney test was performed on the data suggesting that the data were skewed and subsequently ranked, but the available data that were extracted from the article and entered into the RevMan analysis were the change in scores between baseline and end point; a continuous variable. This may explain the conflicting result of effect size estimate against the statistical test.

It should be noted that it is important to take into account the context in which results are reported, whether these are statistical tests, forest plots without meta-analysis, or forest plots with meta-analysis, and any discrepancies further investigated.

4.4.2 Results of Other Reviews

There have been few reviews that have focussed on the evaluation of the evidence for LLLT in the treatment of tendinopathies. Two Cochrane reviews have looked at interventions for rotator cuff tears and shoulder pain (Ejnisman et al., 2004; Green et al., 2003) and made no or weak recommendations as to the effectiveness of LLLT. The rotator cuff review (Ejnisman et al., 2004) evaluated physiotherapy interventions but did not adequately define what was included in such an intervention; therefore no comparison could be made with the current work. The shoulder pain review (Green et al., 2003) came to the conclusion that LLLT was more effective than placebo for adhesive capsulitis but not for rotator cuff tendinopathy, based on the finding of only one study for each condition, apparently due to an inability to determine sufficient detail from two of the other included studies. Another Cochrane review on interventions for treating acute and chronic Achilles tendonitis (McLauchlan & Handoll,
2001) concluded there was insufficient evidence for effectiveness of LLLT, based on one study.

Two reviews looked at lateral epicondylitis (Maher, 2006; Stasinopoulos & Johnson, 2005); both reported weak or negative conclusions for the effectiveness of LLLT to treat this condition. The earlier review (Stasinopoulos & Johnson, 2005) had many methodological weaknesses, which were acknowledged by the authors, but they still recommended that LLLT should not be used as a sole treatment for lateral epicondylitis. However, these authors acknowledged that LLLT is a dose-response modality and their view that the optimum dose had yet to be found. The later review (Maher, 2006) was a synthesis of other reviews, as well as clinical and randomised controlled trials. Again, and as noted elsewhere (Bjordal, 2007), the review methodology had many shortcomings (inadequate coverage of relevant databases; studies rejected because they are “old”; insufficient analysis of dosage and knowledge of dosage recommendations); the final conclusion that LLLT was ineffective seemed to be based on the evidence from only two studies, and relied strongly on the result of one study with a good methodology score.

It is concerning that these reviews turned up relatively low numbers of studies on which to base their recommendations, considering that the present review included 25 articles and had stringent inclusion criteria. It also brings into question the validity of holding up systematic reviews as the gold standard of evidence based practice, when there is such a variation in methodology, numbers of included studies and results.

In contrast to the above reviews, a recent review by Bjordal et al., 2008) evaluated the evidence from 18 RCTs of LLLT to treat lateral epicondylitis, and assessed the validity of treatment procedures and doses. Bjordal et al (2008) concluded that the
use of optimal wavelengths and doses resulted in beneficial effects of LLLT, either alone or in conjunction with an exercise programme.

Such apparent differences in conclusions are explained in part by Bjordal’s approach in scrutinising application and dosage information included in RCTs. As part of this, it is important to make an independent analysis of reported dosages as miscalculations are not uncommon in the literature. This problem is not unique to the laser field, as poor reporting of interventions has been noted in the field of manual therapy concerning descriptions of manipulation and mobilization (Kotoulas, 2002) making accurate synthesis of information difficult. It is noteworthy that negative reviews of laser therapy for musculoskeletal conditions can be challenged, at least in part, on the basis of inaccurately reported or inappropriate dosages (Bjordal & Greve, 1998).

The current review reinforces the validity of this approach, as analysis of results from positive studies can provide evidence of a therapeutic window for effective treatment of tendinopathies.

**Limitations of the Review:** Despite the rigorous procedures put in place to minimize any potential biases and ensure a high quality of methodology for this review, synthesis of the evidence proved difficult due to a number of reasons: although individual studies scored well in terms of methodological quality (>5 on the PEDro scale), poor blinding procedures, lack of randomisation, and lack of intention to treat analysis may have increased potential biases and weakened the scientific merit of the works reviewed. Lack of use of valid and reliable outcome measures, and inadequate detail in the reporting of these measures, made it difficult to pool data from numerous studies and thus provide any measure of estimated overall effect. The clinical application of LLLT
was either poorly reported or varied between studies, adding to the difficulties. Contact was attempted with the corresponding authors of 22 articles by email and/or letter; only five replied with three sending partially useful data. The age of some of the articles, and the different institutions’ regulations on the storage of research data prevented adequate retrieval of information. All appropriate and available data was used in the analysis.

4.5 Conclusion

This study found conflicting evidence as to the effectiveness of LLLT in the treatment of tendinopathy: 10 high quality RCTs and 2 low quality with positive outcomes, compared to 10 high quality RCTs and 3 low quality with negative outcomes. However there is evidence from the 12 positive studies of a correlation between use of recommended dosages and a positive outcome.

The quality of reporting of clinical application techniques and parameters and results needs to be improved in future studies, as recommended by WALT guidelines (WALT, 2005); this would facilitate the pooling of data for a meta-analysis. At present, the heterogeneity of studies often precludes the ability to assess the overall effect of LLLT. Furthermore, for LLLT as for any electrotherapy modality, the application technique and dose must be considered as part of any systematic review. Finally, the quality of systematic reviews needs to follow guidelines such as the QUORUM statement (Moher et al., 1999) which has since been reviewed and updated in 2009 and renamed PRISMA (Preferred reporting items of Systematic Reviews and Meta-analyses) (PRISMA, 2009) to ensure a fair and robust evaluation of the evidence. Like any other piece of research, systematic reviews must be critically appraised to assess the strengths and weaknesses of
the said reviews. There are now quality measures (e.g. such as AMSTAR) to aid in the evaluation of systematic reviews and meta-analyses (Shea et al., 2009).
5 Laser Therapy in the Treatment of Achilles Tendinopathy: A Pilot Study.

5.1 Introduction

The literature relating to tendinopathy and LLLT has been reviewed and discussed in previous chapters (Chapters 2-4). The exact pathogenesis of tendinopathy is multifactorial and not yet fully understood. Tenocytes, reacting to mechanical loading produce signal substances which have an effect on pain signaling, tissue maintenance/repair processes and vascular regulation, which in turn could lead to structural damage to the tendon, a failed healing response and degeneration of the tendon (Danielson, 2009; Wang et al., 2006). The tendon structure has been investigated extensively (for review see Kibler, 2003). Another hypothesis on the cause of tendon injuries is repetitive micro trauma or overuse pathology; this is primarily associated with collagen separation, matrix damage, and changes in the biomechanical properties of tendon. This matrix damage is considered to be the primary event, temporarily overwhelming the ability of the relevant cells to repair structural damage (Jozsa & Kannus, 1997). It is then plausible that any modality that can stimulate cell metabolism and enhance cell proliferation may aid in the repair or recovery of the tendon.

As the Achilles tendon is relatively superficial and application of LLLT to the tendon structure through the intact skin is easily achievable, it was decided to use this tendon in a pilot study to develop and test a protocol to investigate the efficacy of LLLT to treat Achilles tendinopathy. The feasibility of progressing on to conduct an adequately powered RCT could then also be assessed.
The Achilles tendon is a large thick fibrous structure that attaches to the calcaneus and is formed by the confluence of the gastrocnemius and soleus muscles. It is one of two tendons (together with the patellar tendon) most susceptible to overuse injury and rupture (Wren, Yerby, Beaupre, & Carter, 2001). The term “tendinopathy” indicates pain in the region of the tendon without any indication of the cause. Maffulli, Wong, & Almekinders, 2003c, advocate the use of this term as a general descriptor of tendon injuries, as “tendonitis” implies that inflammation is present, and “tendinosis” suggests degeneration of the tendon.

Tendon injuries are becoming an ever increasing burden on the health system. For example in New Zealand in 2003, 412 Achilles tendon ruptures cost the Accident Compensation Corporation (ACC) approximately NZ$2 million; furthermore, the incidence is rising; 4.7/100,000 in 1998 to 10.3/100,000 in 2003 (Tumilty, 2007).

Low level laser therapy (LLLT) is the term used to describe the use of low power laser and superluminous diodes for the treatment of a variety of medical conditions and has emerged as a possible treatment modality for tendon injuries (Chapter 3). Accepted effects of LLLT are enhanced ATP production, enhanced cell function and increased protein synthesis (Karu, 1989). It has also been shown to have positive effects on reduction of inflammation (Bjordal et al., 2006), increase of collagen synthesis (Reddy et al., 1998) and angiogenesis (Salate et al., 2005). However, the effectiveness of LLLT for the treatment of Achilles tendinopathy in the clinical setting has not been adequately established: since 1988 there have been only four trials investigating the effectiveness of LLLT for the treatment of Achilles tendinopathy (Bjordal et al., 2006; Darre et al., 1994; Meier & Kerkour, 1988; Stergioulas et al., 2008) (Table 5-1). The most recent study was
published after the current pilot study was completed (Stergioulas et al., 2008). Poor methodology (possible sources of bias and poor reporting of laser parameters) in the earlier two trials (Darre et al., 1994; Meier & Kerkour, 1988), weaken the results and therefore the evidence from these two trials must be judged with this in mind. The Darre et al trial (1994) was inconclusive and showed no significant difference between the treatment and control groups, and Meier and Kerkour (1988) compared LLLT against LLLT and infrared (IR) concluding that LLLT and IR were significantly better than LLLT alone. The two most recent trials (Bjordal et al., 2006; Stergioulas et al., 2008) employed robust methodology and followed the guidelines recommended by the World Association of Laser Therapy (W.A.L.T.) (WALT, 2005, 2006).

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Interventions</th>
<th>Outcomes reported</th>
<th>Pro LLLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meier</td>
<td>1988</td>
<td>52</td>
<td>LLLT V LLLT &amp; IR</td>
<td>Length of treatment</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patient benefit</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Return to sport</td>
<td></td>
</tr>
<tr>
<td>Darre</td>
<td>1994</td>
<td>89</td>
<td>Laser V placebo</td>
<td>VAS for pain</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Morning stiffness</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Swelling</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tenderness</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Crepitation</td>
<td></td>
</tr>
<tr>
<td>Bjordal</td>
<td>2006</td>
<td>14</td>
<td>Laser V Placebo</td>
<td>Inflammatorvmarkers (PGE2)</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pressure pain threshold</td>
<td></td>
</tr>
<tr>
<td>Stergioulas</td>
<td>2008</td>
<td>52</td>
<td>Laser V Placebo</td>
<td>VAS for pain</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Crepitation</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Morning stiffness</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Tenderness to palpation</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Active dorsiflexion</td>
<td></td>
</tr>
</tbody>
</table>

Bjordal’s group (Bjordal et al., 2006) studied the effects of LLLT over the first two hours after a single application and concluded that LLLT was effective in reducing the
inflammation and pain associated with Achilles tendonitis. Stergiouls et al., 2008) used LLLT in addition to eccentric exercises and reported significant differences for the outcome measures of pain, morning stiffness, active dorsiflexion, palpation tenderness, and crepitation. Clinical evidence obtained through high quality RCTs is thus sparse: LLLT would appear to be effective in the first two hours after treatment (Bjordal et al., 2006), and there is an effect on pain, morning stiffness, active dorsiflexion, palpation and crepitation (Stergiouls et al., 2008); however, this evidence is derived from only two studies. Therefore there is a need for further well conducted randomized controlled trials to assess the effectiveness of LLLT for the treatment of Achilles tendinopathy in the clinical setting with robust objective outcome measures.

The primary aim of this study was to test the feasibility of the protocol for a Randomized Controlled Trial (RCT) to assess the clinical effectiveness of LLLT as an adjunct to eccentric exercise therapy in the management of Achilles tendinopathy. Data from the feasibility study were used to conduct a power analysis for the main RCT. To determine the feasibility, the following objectives were set;

I. Assess the effectiveness of the advertising to aid recruitment by measuring the number of volunteers over the time frame required to achieve group numbers.

II. Determining the actual numbers recruited, adherence, and dropout rates.

III. Piloting the methodological procedures.
5.2 Methods

This was a feasibility study for a prospective, randomised, placebo controlled, double-blinded trial, performed at the Otago School of Physiotherapy Clinics, Dunedin, New Zealand. The Lower South Regional Ethics Committee of New Zealand gave approval for this study (Appendix I).

Patients were recruited by placing an advertisement in the local newspaper. Forty-five people registered interest and all were assessed against the inclusion and exclusion criteria by the principal investigator (ST). The first 20 consecutive patients who met the inclusion criteria were included in the study; written informed consent was obtained from all participants prior to commencing the trial. The principal investigator, blinded to group allocation, performed the initial assessment and evaluation of baseline and follow-up outcome measures at 4 and 12 weeks. A different physiotherapist, blinded to group allocation, performed the 12 treatment sessions over the first 4 weeks (the treatment period). All participants were instructed to undertake a programme of heavy load eccentric exercises, and to complete a compliance log over the 12 week period. In addition, participants were randomly allocated to one of two groups, and were irradiated 3 times per week for 4 weeks with either a placebo or active laser device. The exercises and laser treatment were given in conjunction with each other over the first 4 weeks. The laser treatment was given on completion of the exercises for the 12 sessions the patient spent with the treating therapist. Participants were also asked to complete an exit questionnaire at the completion of the 12 week intervention.

Inclusion criteria: Patients between 18-65 years with a diagnosis of Achilles tendinopathy based upon accepted diagnostic criteria (Maffulli et al., 2003a), and assessed by an
experienced physiotherapist or physician; and who had not received treatment for tendinopathy within the last 3 months.

**Exclusion criteria:** These were: contraindications to LLLT to the area of the Achilles tendon (Baxter, 2002); co-morbid musculoskeletal or serious conditions which may have confounded treatment or anticipated recovery; NSAIDs use; steroid injections or surgery for the condition; insertional tendinopathy or bursitis (retrocalcaneal or Achilles; determined by clinical examination); neurological signs; adverse neural tension (Butler, 2000) affecting the sciatic or sural nerves.

**Randomisation:** A computer-generated random numbers list was produced and the clinic receptionist randomized participants into one of two groups by asking them to select any one of twenty identical opaque sealed envelopes. The envelopes contained a study number and a group number: 1 (Placebo) or 2 (Laser). The group number corresponded to the setting of a switch on the laser unit. Neither the principal investigator, the treating physiotherapist, nor the participant had any knowledge of which group was receiving the active laser treatment.

**Laser protocol:** The laser therapy system used in this trial was the Thor DD Laser Therapy Unit, a class 3B laser with an 810nm 100mW infra red probe, spot size 0.0364cm² and power density of 2.375W/cm² (as reported in the manufacturer’s handbook; Thor use the 1/e2 value to calculate power density as they take into account that the laser beam is not uniform in size and shape, Carroll, 2009). Laser treatment was delivered with the subject prone with their foot over the end of the treatment plinth, and the ankle plantar-grade. The contact method was applied to three standardized points either side of the Achilles tendon (six in all: at the insertion, 2cm proximal, and 4cm proximal) for 30 seconds giving
a dose of 3J per point and 18J per session. Treatment was given 3 times per week for 4 weeks.

**Exercise protocol:** Participants were instructed on how to perform a unilateral heavy load eccentric plantar flexion training programme for 6 sets of 15 repetitions, twice per day, 7 days per week, for 12 weeks (Alfredson, Pietila, Jonsson, & Lorentzon, 1998). Exercises were performed on a step, and individually targeted the gastrocnemius and soleus muscles by being performed (for 3 sets of the exercise) with knee held in extension, and (for 3 sets) in slight knee flexion. Load was added so that the patient’s symptoms were provoked during the exercise. This programme is unique as it encourages patients to complete the exercise even if they experience pain, and they are only allowed to stop (or decrease the applied load) if the pain becomes disabling. When participants could complete the exercise without pain, the load was increased by the addition of extra weight until pain was again experienced (see Appendix VII).

**Outcome measures:** All of the outcomes were measured before treatment 1, after treatment 12 (4 weeks), and at the 12 week follow-up. The primary outcome measure was the VISA-A questionnaire (Robinson et al., 2001; see Appendix VIII), developed by the Victoria Institute of Sport and designed specifically for Achilles tendon problems, resulting in a score between 0-100 (“100” being a totally healthy tendon, and “0” being a painful tendon severely impacting on function). The amount of pain first thing in the morning (worst pain) evaluated by the participants on a 100mm visual analogue scale (VAS), (with “0” being no pain and “100” being the worst pain imaginable) was also assessed. Isokinetic measurement of muscle strength (Nm) was also undertaken (using a Biodex dynamometer, Biodex Medical Systems Inc, New York) at the point when pain
started. For this, participants were seated with 40° knee flex and hip at 110°; strength was measured between 20° of dorsiflexion and 30° of plantarflexion, at a speed of 90°/s (Alfredson et al., 1998).

**Statistical analysis:** Statistical analysis was performed using the Statistical Package for the Social Sciences software (SPSS 14.0, SPSS Inc Chicago); alpha set to 0.05. Normal descriptive statistics for the two groups, such as means and standard deviations, were calculated. Analysis was performed on an intention to treat basis using ANCOVA with base line scores as the covariate (Van Breukelen, 2006; Vickers & Altman, 2001) to assess the difference between groups at the 4 week mark and the 12 week mark.

### 5.3 Results

The pilot study data was collected between 11th September 2006 and 7th March 2007. A total of 45 participants initially expressed interest in the trial; of these, 45 were screened and 20 recruited to the trial within 3 months; this demonstrated the effectiveness of the advertising and recruitment strategy, with a success rate of 45% of volunteers meeting the inclusion criteria. All of these 20 consenting participants completed the course of treatment and follow-up assessment as described in the methodology according to group allocation, and were therefore eligible to be included in the statistical analysis (Figure 5-1). Therefore recruitment, adherence, and retention were also shown to be excellent.
Figure 5-1: Feasibility Study: Participant Flow through the Study.
Demographic and baseline data are presented in Table 5-2; there were no statistically significant differences in baseline data observed between the groups (independent T test).

### Table 5-2: Participants Demographic Data and Baseline Measurements.

<table>
<thead>
<tr>
<th></th>
<th>Laser Group (n=10) Mean (SD)</th>
<th>Placebo Group (n=10) Mean (SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41.4 (7.6)</td>
<td>42.5 (8.5)</td>
<td>0.736</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>7/3</td>
<td>4/6</td>
<td></td>
</tr>
<tr>
<td>VISA-A</td>
<td>57 (16.7)</td>
<td>56 (19.8)</td>
<td>0.933</td>
</tr>
<tr>
<td>Pain (mm)</td>
<td>47.8 (25.9)</td>
<td>39 (20.2)</td>
<td>0.409</td>
</tr>
<tr>
<td>Con Strength (Nm)</td>
<td>137.8 (48.4)</td>
<td>124.1 (55.0)</td>
<td>0.564</td>
</tr>
<tr>
<td>Ecc Strength (Nm)</td>
<td>190.9 (58.5)</td>
<td>180.1 (67.2)</td>
<td>0.708</td>
</tr>
</tbody>
</table>

Con = concentric; Ecc = eccentric.

Although the difference between groups in pain and VISA-A scores are not significantly different, exploring the group means showed a possible trend at the 12 week point in favour of the group treated with LLLT (Figures 5-2 and 5-3). Within groups, there was a significant difference (p < 0.05) between baseline scores and the two evaluation periods of 4 and 12 weeks for all of the outcome measures, except for eccentric strength in the Placebo group at 4 weeks (p = 0.11) (Table 5-3).
Figure 5-2: VISA-A Scores at the Three Measurement Periods (Group Means).
Init = baseline score: 4 weeks = end of LLLT phase: 12 weeks = end of exercise phase

Figure 5-3: Pain Scores at the Three Measurement Periods (Group Means).
Init = baseline score: 4 weeks = end of LLLT phase: 12 weeks = end of exercise phase
Table 5-3: Within Group Mean Differences for Outcomes Between Baseline and Follow-Up Periods.

<table>
<thead>
<tr>
<th></th>
<th>4 weeks Difference between Means (95% CI)</th>
<th>p</th>
<th>12 Weeks Difference between Means (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VISA-A</td>
<td>Placebo</td>
<td>-21.4</td>
<td>(-30.4 to -12.4)</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Laser</td>
<td>-18.9</td>
<td>(-34.8 to -3.1)</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>Placebo</td>
<td>17.2</td>
<td>(4.5 to 29.9)</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>Laser</td>
<td>22.6</td>
<td>(1.2 to 44.0)</td>
<td>0.040</td>
</tr>
<tr>
<td>Con Strength (Nm)</td>
<td>Placebo</td>
<td>-43.0</td>
<td>(-79.0 to -7.1)</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td>Laser</td>
<td>-34.0</td>
<td>(-62.4 to -5.2)</td>
<td>0.025</td>
</tr>
<tr>
<td>Ecc Strength (Nm)</td>
<td>Placebo</td>
<td>-31.5</td>
<td>(-71.8 to 8.7)</td>
<td>0.110</td>
</tr>
<tr>
<td></td>
<td>Laser</td>
<td>-33.1</td>
<td>(-62.4 to -3.7)</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Con = concentric; Ecc = eccentric. For VISA-A, Con Strength and Ecc Strength, negative values denote improvement. For Pain, positive values denote improvement.

Analysis of differences between groups using ANCOVA (change scores with the baseline score as the covariate) indicated there were no clinically or statistically significant differences between the groups at either 4 or 12 weeks (Table 5-4).

Table 5-4: Mean Differences between Groups for Outcomes at the Two Follow-Up Periods.

<table>
<thead>
<tr>
<th></th>
<th>Week 4 Difference between Group Means (95% CI)</th>
<th>p</th>
<th>Week 12 Difference between Group Means (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VISA-A</td>
<td>-2.0 (~-14.9 to 10.9)</td>
<td>0.743</td>
<td>4.6 (~-11.7 to 20.8)</td>
<td>0.563</td>
</tr>
<tr>
<td>Pain (VAS)</td>
<td>0.5 (~-18.9 to 19.3)</td>
<td>0.955</td>
<td>-5.5 (~-27.5 to 16.6)</td>
<td>0.609</td>
</tr>
<tr>
<td>Con Strength (Nm)</td>
<td>-3.2 (~-42.2 to 35.9)</td>
<td>0.865</td>
<td>-19.8 (~-62.9 to 23.3)</td>
<td>0.347</td>
</tr>
<tr>
<td>Ecc Strength (Nm)</td>
<td>6.3 (~-33.2 to 45.8)</td>
<td>0.740</td>
<td>-25.2 (~-77.7 to 27.4)</td>
<td>0.326</td>
</tr>
</tbody>
</table>

Covariates appearing in the model are evaluated at the following values, VISA-A initial 56.65; pain initial 43.4; con strength initial 130.95; eccentric strength initial 185.56. For pain, negative values favour the laser group; for all other measures negative values favour placebo group.
The variability of scores within groups was quite large for all of the outcome measures, and therefore any apparent trend in the data recognised earlier (Figures 5-2 and 5-3) is weakened. This is illustrated in Figure 5-4 which shows the individual scores for pain and the VISA-A.
Figure 5-4: Individual Scores for Pain and VISA-A Divided into Placebo and Laser Groups.
5.4 Discussion

This study was designed to test the feasibility and provide data for a power analysis for an RCT that would assess the effectiveness of LLLT in the treatment of Achilles tendinopathy. This was achieved, and the current research protocol was demonstrated to be feasible for a fully-powered study with regards to recruitment, adherence, and retention. The piloting of the methodology was also successful and is discussed below. While comparison between treatment and control groups is of secondary importance at this stage, the ensuing study (and current results) should contribute to the body of evidence surrounding the use of LLLT for the treatment of Achilles tendinopathy.

Using the current data it was possible to perform a power analysis for a future adequately powered RCT with the same methodology. However, given the lack of clear differences between groups (not unexpected findings for a pilot study), this was based on the Minimal Clinical Important Difference (MCID) rather than the results of this study. For VISA-A, Khan et al., 2003 state 25 points is clinically significant, based upon previous work of Robinson et al., 2001). However, the Robinson et al (2001) article describes the development of the VISA and has no mention of a clinically significant change value. As for the VAS for pain, Chow et al., 2006 cites a range of previous studies which found between 13mm on a 100mm scale(Todd et al., 1996) to 2 points on a 10 point scale to be significant (Chow et al., 2004; Farrar et al., 2000; Farrar et al., 2001). Nevertheless, MCID has minimal generalisability across groups and it has been suggested that it may be best derived from the clinical data (e.g. 75% of the patient population scored a change of 20 points or more Hayley & Fragala-Pinkham, 2006). Using this approach with the pilot data, a MCID of 15mm on VAS for pain and 16 points for VISA-A was calculated; i.e. 75%
of participants achieved these scores or better. Therefore, for an adequately powered RCT using the same research design and VISA-A as the primary outcome measure, the number of participants needed in each group for final data analysis is 16; allowing for 20% dropout, 20 per group would need to be recruited (SD 20.25, power 80%, type I error 0.05).

Such a randomized controlled trial is urgently required within this field, as the clinical effectiveness of LLLT for the treatment of tendinopathy is still somewhat controversial. It is widely accepted that the underlying problem in the tendon is one of degeneration and not inflammation (Khan et al., 1999). Lind et al., 2006) have shown positive results by reducing or eliminating neovascularisation. Some of the known effects of LLLT are anti-inflammatory (Bjordal et al., 2006) and increased neovascularisation (Salate et al., 2005), which would seem to be contrary to the desired effects needed to treat the condition. Other effects that may contribute to beneficial outcomes are increased collagen synthesis, (Reddy et al., 1998) which would help to address degeneration, and pain relief (Enwemeka et al., 2004) which would also be beneficial. To date the clinical evidence with regards to LLLT in the treatment of tendinopathy is mixed; there is a paucity of good quality RCTs upon which to base any decision. Bjordal et al., 2001) found only 16 studies for inclusion in their review, of which only nine were considered to have used optimal treatment parameters. In particular, there are only four human studies on LLLT in the treatment of Achilles tendinopathy (Bjordal et al., 2006; Darre et al., 1994; Meier & Kerkour, 1988; Stergioulas et al., 2008) and the evidence provided by these is variable. Darre et al., 1994) examined only soldiers (18-22 years), which would be considered an atypical group; in contrast the participants in the current
study had a mean age of 42 years and therefore were a closer fit to the archetypal profile for the age of peak incidence from epidemiology data (Tumilty, 2007). Any comparison with two of the other studies is limited as Meier & Kerkour, 1988) compared two different protocols of laser and infra-red treatments, and Bjordal et al., 2006) examined the anti-inflammatory effects over the first two hours after application of laser. The fourth and most recent study by Stergioulas et al., 2008) used a protocol very similar to this pilot study; differences included the laser parameters, subject demographics, and larger numbers per group where 40 participants completed the 4 weeks of laser and 12 weeks of eccentric exercise. This pilot study matched the trend in favour of laser reported by Stergioulas et al (2008) but the results were not matched statistically, further demonstrating the need to conduct an adequately powered RCT.

As the aim of this study was to test the feasibility of the research design it is pertinent to consider the methodology and the reasoning behind the decisions made. Heavy load eccentric exercise (Alfredson et al., 1998) has emerged as the treatment of choice for Achilles tendinopathy and it was decided to use this as a common intervention for everyone who participated in the study regardless of group allocation. However, this design measures the effect of the adjunct intervention (in this case LLLT) over and above that of eccentric exercises, and is appealing because, unlike a placebo-controlled explanatory trial, half of the participants were not being denied treatment. Other authors have used this approach: Brown et al., 2006) investigated the effectiveness of aprotinin injection in the management of Achilles tendinopathy and had all participants perform eccentric exercises. However, as in the current study, while there were improvements in both groups, Brown et al (2006) failed to show any significant
differences between groups, indicating that there was no added benefit from the adjunct therapy.

The selection of optimal dose in clinical trials of LLLT (or indeed for routine clinical use) is controversial, as often the reporting of parameters has varied in previous studies. However, there is enough information from a previous detailed review by Bjordal et al., 2001 to indicate an optimal dose range (or window); in addition, the World Association of Laser Therapy (WALT) website (WALT, 2005) provides dosage recommendations on the energy to be delivered to the skin over the target tendon, and also recommends irradiating most of the pathological tissue in the tendon. These two sources of information thus provide the clinician or clinical researcher a therapeutic window from which to choose. For the current feasibility study, it was decided to use a dose that lay in the middle of that recommended by Bjordal et al (2001) (0.7-7J/cm²): thus 3J per point were delivered to the skin on 6 points along the affected tendon. However, the Thor laser system employed here had a 100mW probe, which although commonly used in routine clinical practice, provided irradiance significantly higher than that recommended by Bjordal et al., 2001). This is then an important consideration for the future RCT, for which it was planned to employ a different probe with a lower irradiance (Chapter 6).

The main outcome measures used in this feasibility study were found to be useful and reliable. The primary outcome measure was the VISA-A questionnaire developed by the Victoria Institute of Sport and designed specifically for Achilles tendon problems. It has been shown to be valid and reliable (Robinson et al., 2001; Silbernagel, Thomee, & Karlsson, 2005), and is often used in Achilles tendon studies (Maffulli, Tallon, Wong, Lim, & Bleakney, 2003b; Maffulli, Testa, Capasso, & Sullo, 2004). It takes only a few minutes
to complete, and although one or two questions are a little ambiguous, explanations provided with the form cleared up any misunderstanding. Visual analogue scales (VAS) have become an acceptable measurement tool (De Boer et al., 2004) and the use of a VAS to measure pain has been shown to have a high interclass correlation of 0.95 (McCarthy Jr et al., 2005).

This study used a 12 week follow up period, which was chosen because after three months of heavy load eccentric exercises, it is expected that the majority of participants would have returned to sport (Alfredson et al., 1998); also the turnaround for collagen synthesis is approximately 100 days (Vailas, Tipton, & Laughlin, 1978), therefore it was considered relevant to compare the groups at this stage.

When attempting to measure a treatment effect between a treated and untreated group on a quantitative outcome measured before and after treatment, one must be aware that baseline values are negatively correlated with change, and more often than not participants with a low score at baseline will improve more than participants with a high score at baseline. In randomised trials analysis of covariance (ANCOVA) using baseline scores as the covariate is the preferred test (Vickers & Altman, 2001) and gives more statistical power to the analysis (Van Breukelen, 2006). This is therefore considered the most appropriate means of analysis for the main study.

5.5 Conclusion

The current methodology has been shown to be feasible, and the study has provided data to design a future adequately powered RCT. As this study had low numbers, it could not be used to make any definitive conclusions regarding the effectiveness of LLLT for the treatment of Achilles tendinopathy. This notwithstanding,
the treatment package as a whole provided a significant improvement in all outcome measures (p < 0.05) for both groups, a positive note for the physiotherapy management of this condition. The fact that in the past there have been few human studies on LLLT for Achilles tendinopathy, and no other studies investigating the additional benefit of LLLT to a programme of eccentric exercise therapy, justifies further investigation to assess the effectiveness of this modality.
6 Clinical Effectiveness of Low Level Laser Therapy for the Treatment of Achilles Tendinopathy: A Randomised Controlled Trial.

6.1 Introduction

Previous chapters have reviewed the literature regarding LLLT and tendinopathy with a focus on the Achilles tendon. Pathogenesis of tendinopathy is considered multifactorial and is not yet fully understood; the problem in the tendon is one of a failed healing response resulting in degeneration of the tendon structure and can be explained, at least in part by the biochemical hypothesis (Danielson, 2009) and the biomechanical hypothesis (Wang et al., 2006). Apart from any structural damage to the tendon, tenocytes reacting to mechanical loading produce signal substances that may have effects on pain signaling, tissue maintenance/repair processes and vascular regulation, but whether the increase in these substances are causative or a byproduct of the condition has yet to be determined.

The effects of LLLT have been shown in cellular and animal studies to include decreased pain, decreased inflammation, increased collagen synthesis leading to increased tensile strength, altered cell membrane potential, and increase of ATP production (Bjordal et al., 2006; Demir et al., 2004; Enwemeka et al., 2004; Karu et al., 1995; Reddy et al., 1998). These effects make LLLT ideal for increased tissue repair and are postulated to aid the recovery of someone with a tendinopathy.

Heavy load eccentric exercise has emerged as the treatment of choice for Achilles Tendinopathy (Alfredson et al., 1998) and the combination of exercise and laser
treatment in an animal model has been studied with positive results (Ng & Fung, 2008) thus adding to the evidence supporting the use of such a treatment approach. However, the evidence from clinical trials on humans is contradictory for a variety of reasons that have been previously discussed (Chapters 3 and 4); thus the need for more robust evidence has been established.

Results of the pilot study reported in the previous chapter demonstrated the feasibility of conducting an adequately powered RCT to assess the clinical effectiveness of LLLT when used as an adjunct treatment to eccentric exercise. Although differences between groups in pain and VISA-A scores were not significantly different (Chapter 5, Table 5-4), a possible trend emerged at the 12 week review in favour of the group treated with LLLT (Chapter 5, Figures 5-2 and 5-3); this warranted further investigation with adequate numbers in each group. Such lack of (statistically significant) difference is not unexpected from pilot data; therefore it was decided to base power calculations on an expected minimal clinical important difference (MCID). To ensure a robust calculation of the numbers needed for each group, two different approaches were used to validate MCID, which resulted in similar figures. The first approach was based upon recommendations by Hayley & Fragala-Pinkham, 2006 and setting MCID at a level where at least 75% of patients achieved an improvement: i.e. 15mm on VAS for pain and 16 points for the VISA-A. The second approach was based upon using the data from the pilot study exit questionnaire, and dividing patients into those who reported a “great deal better” (n=13) from those who reported “some” or “no change” (n=7), and then using the corresponding VISA-A change scores to plot a receiver operating characteristic (ROC) curve (see Appendix VI). MCID was determined to be the magnitude of change
associated with the uppermost left-hand corner of the curve, where both sensitivity and 1-specificity are maximized, resulting in 16 points on the VISA-A scale, with a sensitivity of 92.3% and a specificity of 85.7%. Finally, power calculations were performed for an ANCOVA with two follow-up measurements, alpha 0.05 and power of at least 80% (correlation value 0.03, pooled SD 20.25). Therefore, to adequately power this RCT using the same research design and VISA-A as the primary outcome measure, the number of participants needed in each group (allowing for 20% dropout) would be 20.

There is little evidence in the literature to suggest that differential diagnosis of Achilles tendinopathy has been subject to detailed scientific assessment. A detailed history combined with a clinical examination is the accepted path to diagnosis; augmentation of findings with diagnostic imaging (MRI and US) may also aid differentiation. However, MRI and US are costly and time consuming and many tendons with intra-tendinous pathology shown on imaging are not painful or symptomatic (Cook et al., 2000a; Cook, Khan, Kiss, Purdam, & Griffiths, 2000b; Kayser et al., 2005; Khan et al., 2003). Maffulli et al., 2003a have attempted to validate a series of tests to increase the detection of Achilles tendinopathy; as part of this, they evaluated three tests: palpation, the Arc sign, and the Royal London Hospital test, and advocate the use of all three tests together reporting overall sensitivity of 0.586 and overall specificity of 0.833. For the purpose of this RCT it was decided to use these tests as diagnostic criteria.

The pilot study reported in the previous chapter resulted in a publication (Tumilty et al., 2008); certain comments received during the review process for this paper prompted a change in the methodology for the main study. The primary criticism was around the parameter of power density, which was reported for the purpose of the
publication from data provided in the manufacturer’s handbook. The therapy system used for this main study was the Thor DD Laser Therapy Unit (Thor International Ltd, Chesham, Buckinghamshire, England), a class 3B laser with an 810nm 100mW infrared probe, with a specified spot size of 0.0364cm$^2$ and thus resulting power density of 2.375W/cm$^2$. Current guidelines recommend <100mW/cm$^2$ (Bjordal et al., 2001; WALT, 2005) when treating Achilles tendons. After consultation with prominent scientists in the field, and taking into consideration the results of the systematic review (Tables 4-4 & 4-5), it was decided to modify the output of the probe. The Physics Department of the University of Otago manufactured an opaque tube to fit over the end of the laser probe (Figure 6-1.) which modified the output of the device to produce a power density of 100mW/cm$^2$. This was achieved by altering the spot size, and having the aperture 46mm from the end of the probe.

![Modification to the Laser Probe](image-url)
Patients suffering from Achilles tendinopathy can have varying pain experiences throughout the day or depending upon behaviour of symptoms. It was thought that a more accurate measure of pain would be to use the eleven point numeric pain rating scale NPRS (see Appendix IX) to measure the current, best, and worst pain over the last 24 hours instead of a single instance; the average of the three scores was used to represent the overall intensity of pain (Childs, Piva, & Fritz, 2005).

The primary endpoint was set at the 12 week follow-up, as after 3 months of heavy load eccentric exercise it is expected that the majority of patients would have returned to normal activities (Alfredson et al., 1998). Tendons are notoriously slow to heal and remodel, given the turnaround for collagen synthesis to be in excess of 100 days (Vailas et al., 1978), therefore adding to the weight of evidence for the 12 week point to be the primary assessment stage. A follow-up assessment at 52 weeks using postal questionnaires was added to the methodology to ascertain any long term benefits of the treatment, and, where appropriate, whether patients were able to self manage any recurrence of their injury.

The primary aim of this current study was to investigate the clinical effectiveness of LLLT as an adjunct to a programme of eccentric exercises for the treatment of Achilles tendinopathy, and decide if any additional benefit is derived from the use of this modality. Secondary to this, a follow-up at one year was included to assess any long-term benefits of the treatment. Data for this study were collected between 9th April 2008 and 30th August 2009.
6.2 Methods

This was a randomised, placebo controlled, double-blinded trial, performed at the Otago School of Physiotherapy Clinics, Dunedin, New Zealand. The Lower South Regional Ethics Committee of New Zealand gave approval for this study (Appendix I).

Patients were recruited through advertisement in the local newspaper. Seventy three people registered interest, and all were assessed against the inclusion and exclusion criteria by the principal investigator (ST). The first 40 consecutive patients who met the inclusion criteria were included in the study; informed consent was obtained from all participants prior to commencing the trial. The principal investigator, blinded to group allocation, performed the initial assessment, and evaluation of baseline and follow-up outcome measures at 4, 12, and 52 weeks. A different physiotherapist, blinded to group allocation, performed the 12 treatment sessions over the first 4 weeks (the treatment period). All participants were instructed to undertake a programme of heavy load eccentric exercises and to complete a compliance log over the 12 week period. In addition, participants were randomly allocated to one of two groups and were irradiated 3 times per week for 4 weeks with either a placebo or active laser treatment. Exercises and laser treatment were given in conjunction with each other over the first 4 weeks. During each attendance, laser treatment was performed on completion of the exercises for the 12 sessions the participant spent with the treating therapist. After 12 weeks, the participants were informed that an assessment at 52 weeks would be performed by postal questionnaires, but that there was no restriction on their activities or any requirements they may have for treatment during this time.
Inclusion criteria: Patients between 18-65 years with a diagnosis of Achilles Tendinopathy based upon accepted diagnostic criteria (Maffulli et al., 2003a), and assessed by an experienced physiotherapist or physician; and who had not received treatment within the last 3 months.

Exclusion criteria: These were: contraindications to LLLT to the area of the Achilles tendon (Baxter, 2002); co-morbid musculoskeletal or serious conditions which may have confounded treatment or anticipated recovery; NSAIDs use; steroid injections or surgery for the condition; insertional tendinopathy or bursitis (retrocalcaneal or Achilles; determined by clinical examination); neurological signs; adverse neural tension (Butler, 2000) affecting the sciatic or sural nerves.

Randomisation: The clinic receptionist randomized participants into one of two groups by asking them to select any one of forty identical opaque sealed envelopes. The envelopes contained a study number and a group number, 1 (Placebo) or 2 (Laser), based upon a computer generated random number list. The group number corresponded to the setting of a switch on the laser unit. Neither the principal investigator, nor the treating physiotherapist, nor the participant had any knowledge of which group was receiving the active laser treatment.

Laser protocol: The therapy system used in this trial was the Thor DD Laser Therapy Unit; this is a class 3B laser with an 810nm, 100mW, infra red probe. The laser was modified by the Physics Department at Otago University to give a power density of 100mW/cm². This was achieved by the addition of an opaque tube 46mm long, attached over the end of the laser probe, which provided a spot size of 0.07cm² (Figure 6-1). Laser treatment was delivered with the patient lying prone, with their foot over the end of the treatment
plinth, and the ankle plantar-grade. The contact method was used to apply the laser treatment probe to three standardized points either side of the Achilles tendon (six in all: at the site of the lesion, 2cm proximal and 2cm distal [Figure 6-2.]) for 30 seconds, giving a dose of 3J per point and 18J per session. Treatment was given 3 times per week for 4 weeks.

![Figure 6-2: Treatment Points on the Achilles Tendon.](image)

**Exercise protocol:** Participants were instructed on how to perform a unilateral heavy load eccentric plantar flexion training programme for 6 sets of 15 repetitions, twice per
day, 7 days per week, for 12 weeks (Alfredson et al., 1998; see Appendix VII). Exercises were performed on a step, and individually targeted gastrocnemius and soleus by being performed (for 3 sets of the exercise) with knee held in extension, and (for 3 sets) in slight knee flexion. Load was added so that the participant’s symptoms were provoked during the exercise. This programme is unique as it encourages patients to complete the exercise even if they experience pain, and are only allowed to stop (or decrease the applied load) if the pain becomes disabling. When participants can complete the exercise without pain the load was increased by the addition of extra weight until pain was again experienced.

**Outcome measures:** All of the outcomes were measured by the principal investigator before treatment 1, at the end of the laser treatment phase (4 weeks), and at the end of the exercise phase (12 weeks). At 52 weeks, an assessment of outcomes was made via post. Participants were sent the appropriate forms and asked to complete and return these in envelopes provided. The primary outcome measure was the VISA-A questionnaire (Robinson et al., 2001), developed by the Victoria Institute of Sport and designed specifically for Achilles tendon problems, resulting in a score between 0-100 (“100” being a totally healthy tendon, and “0” being a painful tendon severely impacting on function). Pain was assessed on a 11 point visual analogue scale (VAS) using an average of three scores: pain now; best pain in the last 24 hours; worst pain in the last 24 hours; resulting in a score between 0-10 (NPRS) (Childs et al., 2005; see Appendix IX). The primary outcome time point was at the end of the intervention phase, when both laser treatment and eccentric exercises are concluded (the 12 week point).
**Statistical analysis:** Statistical analysis on an intention to treat basis was performed using the Statistical Package for the Social Sciences software (SPSS 16.0, SPSS Inc Chicago); alpha was set to 0.05. To mirror what is observed in actual clinical practice, and answer the public health question of how the public would respond to any given treatment regime, intention to treat analyses (ITT) are recommended as the preferred method of analyzing data from clinical trials (Bubbar & Kreder, 2006; PRISMA, 2009; Whittaker, Sutton, & Burton, 2006; Wright & Sim, 2003). The treatment allocation code was broken after all the participants had completed all assessments. Normal descriptive statistics for the two groups (such as means and standard deviations) were calculated. When attempting to measure a treatment effect between a treated and untreated group on a quantitative outcome which has been measured before and after treatment, one must be aware that baseline values are negatively correlated with change and commonly participants with a low score at baseline will improve more than patients with a high score at baseline. Analysis of covariance (ANCOVA) using baseline scores as the covariate was therefore considered the most appropriate test for the current data (Vickers & Altman, 2001), and would give more statistical power to the analysis (Van Breukelen, 2006). Missing values were replaced using the “Group Mean” (Armijo-Olivo, Warren, & Magee, 2009).

**6.3 Results**

Volunteers were screened and the first 40 consecutive participants who met the inclusion criteria were included in the study. Thirty six participants completed the treatment phase of 4 weeks of LLLT and 12 weeks of eccentric exercises; there were 4 dropouts before the end of the first 4 weeks: two between randomisation and start of
treatment, and two after the second treatment session. The twelve month follow-up outcomes were returned by 33 participants. Figure 6-3 displays the participants’ flow through the study. Following the “Intention to Treat” protocol, missing values were replaced by the group mean (see Chapter 7), giving a final analysis of 20 participants in each group. Demographic and baseline data from all 40 participants are presented in Table 6-1; there were no statistical differences in baseline data observed between groups, but the VISA-A scores came close to being significant (p=0.051). As indicated above, to minimise any impact of baseline differences, an ANCOVA was performed using baseline data as the covariate.
Figure 6-3: Main RCT: Participant Flow through the Study.

Participants Randomised (n = 40)

- Ecc Exs & LLLT (n = 20)
  - 4 weeks, End of LLLT (n = 19)
  - 12 weeks, End of Ecc Exs (n = 19)
  - 52 weeks follow-up (n = 17)

- Ecc Exs & Placebo LLLT (n = 20)
  - 4 weeks, End of Placebo LLLT (n = 17)
  - 12 weeks, End of Ecc Exs (n = 17)
  - 52 weeks follow-up (n = 16)
Table 6-1: Main RCT: Participants’ Demographic Data and Baseline Measurements.

<table>
<thead>
<tr>
<th></th>
<th>Laser Group (n=20) Mean (SD)</th>
<th>Placebo Group (n=20) Mean (SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>45.6 (9.1)</td>
<td>46.5 (6.4)</td>
<td>0.705</td>
</tr>
<tr>
<td><strong>Gender (F/M)</strong></td>
<td>12/8</td>
<td>10/10</td>
<td></td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>169.5 (7.3)</td>
<td>169.2 (8.8)</td>
<td>0.909</td>
</tr>
<tr>
<td><strong>Weight (Kg)</strong></td>
<td>78.6 (15.6)</td>
<td>77.8 (13.6)</td>
<td>0.870</td>
</tr>
<tr>
<td><strong>VISA-A</strong></td>
<td>53.5 (12.7)</td>
<td>61.0 (10.8)</td>
<td>0.051</td>
</tr>
<tr>
<td><strong>Pain (NPRS)</strong></td>
<td>2.11 (1.17)</td>
<td>1.93 (0.94)</td>
<td>0.589</td>
</tr>
</tbody>
</table>

Differences between the groups at the three follow-up points (4, 12, and 52 weeks) are presented in Table 6-2. At the primary outcome point (12 weeks) VISA-A scores for the placebo group were superior to the group treated with the active laser, although this was not statistically significant (p = 0.082). The difference in VISA-A scores at the 4 week mark significantly favoured the placebo group (p = 0.016); all other results showed no significant difference between the groups, although the laser group consistently showed inferior scores at all follow-up time points, and for both outcome measures.
Table 6-2: Mean Differences between Groups for Outcomes at the Follow-Up Periods.

<table>
<thead>
<tr>
<th>Follow-up period</th>
<th>VISA-A Difference between Group Means (95% CI)</th>
<th>p</th>
<th>Pain (NPRS) Difference between Group Means (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>-9.3 (-16.8 to -1.9)</td>
<td>0.016*</td>
<td>0.5 (-0.2 to 1.2)</td>
<td>0.131</td>
</tr>
<tr>
<td>Week 12</td>
<td>-6.4 (-13.7 to 0.86)</td>
<td>0.082</td>
<td>0.2 (-0.3 to 0.7)</td>
<td>0.436</td>
</tr>
<tr>
<td>Week 52</td>
<td>-6.9 (-15.4 to 1.5)</td>
<td>0.106</td>
<td>0.4 (-0.1 to 0.9)</td>
<td>0.097</td>
</tr>
</tbody>
</table>

Covariates appearing in the model are evaluated at the following values, VISA-A initial 57.20; pain initial 2.02. For pain, negative values favour the laser group; for all other measures negative values favour placebo group. * Significant at the 0.05 level.

Figure 6-4 depicts group mean scores at all of the assessment points throughout the study. The group treated with active laser displayed inferior scores for both VISA-A and pain NPRS initially, justifying the use of ANCOVA, but failed to demonstrate any superior gains that may have resulted from the adjunct laser treatment at all other assessment points. This point is further reinforced in Figure 6-5, which shows change in scores between initial assessment and the three follow-up periods, where the differences between the two groups are minimal. Both groups maintained significant changes (p < 0.000) at the 52 week point compared with initial scores for both outcome measures.
Figure 6-4: VISA-A and NPRS Scores at Baseline and at Follow-Up Periods.

INIT = baseline score: 4 weeks = end of LLLT phase: 12 weeks = end of exercise phase: 52 weeks:

postal follow-up
Figure 6-5: Change Scores for VISA-A and Pain NPRS between Initial Assessment and the Three Follow-Up Periods.
Compliance logs were returned from 28 participants (70%), 12/20 (60%) from the Placebo group and 16/20 (80%) from the Laser group. Out of a possible 168 exercise sessions over the 3 month period, the mean number of completed sessions for each group were: Placebo 106; Laser 81. The experimental design was not set up to investigate the relationship between compliance and outcome, therefore any robust statistical analysis of these data was not possible. However, descriptive statistics and a more complete version of the data are presented in Appendix XI, and it can be observed from these data that there was no statistically significant relationship established between change in VISA-A scores and adherence to the exercise protocol. Further discussion around the issue of compliance takes place in Chapter 7.

6.4 Discussion

This study was designed to investigate the clinical effectiveness of LLLT used as an adjunct to a programme of eccentric exercises for the treatment of Achilles tendinopathy. This was shown not to be the case at the primary end point of 12 weeks, as there was no significant difference between treatment and placebo groups. The secondary concern of whether benefits could be maintained over the long term was demonstrated by the 52 week follow-up results, which although slightly less than the 12 week scores, showed that both groups maintained approximately a 30 point improvement on the primary outcome measure VISA-A when compared with initial assessments. Considering a MCID of 16 points, this continued improvement is noteworthy for the treatment package as a whole.

There are only five other published human studies, including the pilot study reported in the previous chapter, that have investigated the effect of LLLT on the healing
of Achilles tendinopathy (Bjordal et al., 2006; Darre et al., 1994; Meier & Kerkour, 1988; Stergioulas et al., 2008; Tumilty et al., 2008). Results are mixed and two of these studies (Bjordal et al., 2006; Meier & Kerkour, 1988) are unsuitable to compare because of vastly different designs intended to answer different research questions than the present study. One study (Darre et al., 1994) investigated the effect of LLLT on Danish Army recruits with Achilles tendinopathy and reported no benefit from the laser treatment. However, there were a number of methodological inadequacies that weaken the results: the number of treatments given were not standardised; detail on participants was insufficient; criteria for the differing numbers of treatments was not specified; the power density and dose delivered were significantly above what would be considered appropriate by today’s recommendations.

The earlier pilot study (Chapter 5) was under powered, thus although there was a difference in favour of LLLT, it was not large enough to be significant. The study by Stergioulas et al., 2008) closely resembled the present study but in contrast reported significant benefits for the group treated with LLLT. The main difference between the present study and that of Stergioulas et al., 2008) is in the parameters of the laser treatment. In the present study the tendon was irradiated at 6 points with 3J per point from an 810nm, 100mW probe, and power density of 100mW/cm²; compared to irradiation at 6 points with 0.9J per point from an 820nm, 30mW probe, and power density of 60mW/cm² (Stergioulas et al., 2008). Both sets of parameters fall within recommended guidelines (Bjordal et al., 2001; WALT, 2005), and the findings from the systematic review (Chapter 4), but produced different results. Considering the results of the earlier pilot study (Chapter 5) and that of Stergioulas et al., 2008), in this present
study, differences between groups could be expected but may or may not have been significant; the fact that the change scores, especially of the primary outcome measure (VISA-A), were so similar raises a question about the methodology of the present study. The only notable difference in methodologies between the three studies is the application of the laser.

During the review process for publication of the pilot study, criticism was made over the power density being too high, and as a consequence, the results of that study might have been insignificant. Although the issue of parameter use and reporting is a contentious one, it was decided to alter the probe supplied with the machine to achieve a power density that fell within guidelines. Acting on advice from a physicist specialising in laser technology, modifications were made as described in the methodology and shown in Figure 6-1. These modifications resulted in a spot size of 0.07cm$^2$, 46mm distant from the probe, delivering a power density of 100mW/cm$^2$; to achieve this, the power output at the skin was 7mW, resulting in 0.021J per point after 30 seconds, and requiring irradiation of 429 seconds to achieve the 3J reported.

This highlights the central controversy in such cases: if dose is calculated using the power density and irradiation time of 30 seconds, then the applied dose (3J/cm$^2$) falls within guidelines. However, after modification of the laser probe the output power at the skin surface is 7mW instead of 100mW as in the pilot study, resulting in a dose at the surface of 0.021J/cm$^2$. In view of this, the depth of the target tissue must be taken into consideration. Wavelength governs the depth of penetration and at 810nm approximately 80% of the energy is absorbed within the dermis (Baxter, 1994 table 4.1 p.80; Karu, 1989). Estimation of the depth to the tendon and the sagittal cross-sectional
diameter of the Achilles tendon are 1.5-3.0mm and 4-6mm respectively (Bjordal et al., 2001); therefore in this study a resultant decrease in energy is 0.021J/cm² down to 0.004J/cm² reaching the most superficial part of the tendon, compared to figures of 3J/cm² and 0.6J/cm² respectively in the pilot study. In these circumstances, one must conclude that much of the delivered energy fails to reach the target. Calderhead, 2007) states that, “wavelength is thus probably the single most important consideration in phototherapy”. He comes to this standpoint because of two main criteria; wavelength specificity of the target chromophore, the structure that absorbs the energy from the laser, and the depth of the target chromophore. However, he also takes into consideration a third criterion, that the light reaching the target must have a high enough photon density to induce the desired reaction. Based upon this, it is important to consider whether < 0.004J/cm² is enough in this case? Indeed, this debate over incident energy at the skin surface and desired energy reaching the target tissue is not new; other authors have commented on this point (Chow, 2001) and cite studies that have produced negative results because of insufficient power density (Basford, Malanga, Krause, & Harmsen, 1998). Current recommendations (Bjordal et al., 2001) suggest that the effective dose at the target is within 0.1-3J/cm² and thus do not support such a low dose as was eventually used in the present study.

Independent alteration of one parameter seems not to be possible; considering results of previous work (Stergioulas, 2008; Chapter 5), one could expect some effect from the laser treatment (if not necessarily an optimum or significant effect), and therefore it is strange that these current results show no effect. More discussion around this point appears in Chapter 7.
Change scores in the VISA-A were maintained at levels above what was deemed to be a MCID at 4, 12 and 52 weeks. The fact that both groups maintained approximately 30 points improvement over initial scores for nine months after intervention ceased; adds to the growing body of evidence to support the use of eccentric exercise, and is comparable with a study using similar methodology to evaluate aproptinin injection as the additional therapy (Brown, 2006). Comparison with other Achilles tendon studies is difficult because of methodological differences in such areas as different outcome measures, assessment times, non RCT and cross-over designs (Chester, Costa, Shepstone, Cooper, & Donell, 2008; De Vos, Weir, Visser, De Winter, & Tol, 2007; Herrington & McCulloch, 2007; Jonsson, Alfredson, Sunding, Fahlstrom, & Cook, 2008; Mafi et al., 2001; Nørregaard, Larsen, Bieler, & Langberg, 2007; Richards, McCall, Day, Belcher, & Maffulli, 2009; Rompe et al., 2009; Roos, Engstrom, Lagerquist, & Soderberg, 2004; Sayana & Maffulli, 2007). This heterogeneity makes it difficult to combine results, and thus use of standardised methodologies, outcome measures and follow-up times would add weight to the evidence provided by such studies.

The intention to treat analysis provides the most unbiased answer to the clinical effectiveness question, even though it could be criticised as changing the research question from one of efficacy to one of adherence. The present study was adequately powered to allow for 20% dropouts; thirty six participants completed the treatment as allocated up to the 12 week point and thirty three completed the 52 week follow-up questionnaires. Thus the dropout rate was less than 20% and a per-protocol analysis would still be adequately powered. However to satisfy the intention to treat protocol, missing data needs to be replaced. Using the group mean values to replace missing data
was considered to be the method that would introduce the least bias. Sensitivity analysis was performed using the last observation carried forward (LOCF) to replace missing values; the result for the primary outcome measure at the primary endpoint (VISA-A at 12 weeks) did not alter the effect of the intervention (LOCF; p= 0.391: Group mean; p=0.082).

6.5 Conclusion
The clinical effectiveness of adding LLLT to heavy load eccentric exercises for the treatment of Achilles tendinopathy has not been demonstrated using the parameters in this study. It would appear, based on these results, caution needs to be exercised when altering any of the output parameters of the laser device as interaction between parameters may render the energy delivered at the skin to be of too low a value to cause an effect. Patients suffering from Achilles tendinopathy may benefit from 12 weeks of heavy load eccentric exercises, and have been shown to be able to maintain improvement for up to one year.
7 General Discussion

This thesis has investigated the clinical effectiveness of Low level laser therapy (LLLT) for the treatment of tendinopathy using systematic review and randomised controlled trial (RCT) methodologies, both of which are robust, evidence based approaches within the hierarchy of evidence. With regard to the main aim of the thesis: there is evidence from the systematic review (Chapter 4) that LLLT is effective if appropriate (i.e. currently recommended) dosage guidelines are followed. Conversely, results of the pilot study (Chapter 5) and the main RCT (Chapter 6) do not support the use of LLLT where it is used as an adjunct with eccentric exercise. While these results may appear contradictory, questions remain over whether the parameters used in these two clinical studies fall within current recommendations. These findings raise a number of important issues which require further consideration, not least as some are contentious. To put the findings of this work into perspective with regards to current knowledge surrounding LLLT for the treatment of tendinopathy, a number of the points and issues raised during the completion of this thesis are considered further in the subsequent pages.

7.1 Overview of Thesis

Despite the apparently widespread and longstanding use of low level laser therapy to treat musculoskeletal conditions, it still remains on the fringes of mainstream medicine. Evidence from laboratory studies on cell cultures and animals support the beneficial effects of this modality on pain attenuation and the healing process in general (see Chapters 1 and 2). However, the positive results obtained in the laboratory setting have not been consistently reproduced in the clinical setting, and consequently
acceptance as a worthwhile intervention is not yet forthcoming, at least in some quarters. The review of the literature in Chapter 2 highlighted a number of shortcomings in the research to date on LLLT; this includes poor methodology (which is of course not unique to the field of laser therapy), poor reporting of parameters, and varying application techniques. In particular, methods of calculating parameters and dosage have caused contention among scientists and clinical researchers within the field of LLLT (Chapter 2). Such contention was the stimulus for the World Association of Laser Therapy (WALT) to produce guidelines not only on dosage recommendations, but also on reporting of clinical trials involving LLLT (WALT, 2005, 2006). However, although this has been a positive development, there is not universal use of the guidelines as some studies still report parameters poorly, and many fail to use dosage recommendations (Bjordal, 2007; Bjordal & Baxter, 2006; Bjordal et al., 2005; Darre et al., 1994). This notwithstanding, low level laser therapy is (like many other electrophysical agents) a dose dependant modality, and thus many more studies are required to refine dosage guidelines, and to determine effectiveness.

Chapter 3 reviewed the current literature on the epidemiology, aetiology and current management of tendinopathy, which has become the scourge of the musculoskeletal practitioner because of the multifactorial nature of the pathogenesis of the condition. Based upon this review, it was concluded that tendinopathy is the result of a failure of one of two processes: the healing response, or the normal turnover/remodeling response, but the definitive solution to the problem remains an enigma. One intervention that has gained in popularity, especially for the Achilles and patellar tendons, is heavy load eccentric exercises; this is, however, despite varying
results and recommendations from clinical trials and systematic reviews (Meyer et al., 2009; Woodley et al., 2007).

Subsequently, the next logical step in the development of the work for the current thesis was to conduct a systematic review with meta-analysis of the literature surrounding the use of LLLT to treat any type of tendinopathy (Chapter 4). The systematic review found 12 studies that supported the use of LLLT for tendinopathy, and 13 studies that failed to show an effect. In particular, the 12 positive studies provided evidence to support the relationship between positive outcomes and the current dosage recommendations (see Chapter 4; also Bjordal et al., 2001; WALT, 2005).

Considering issues raised from the previous three chapters (Chapters 2-4) it was decided to use the Achilles tendon, a superficial tendon which is easy to locate and treat, as a basis for a controlled clinical trial to test the robustness of the current guidelines and to assess the effectiveness of LLLT in the clinical setting (Chapters 5 and 6). Given the popularity of eccentric exercise as the current treatment (see above), and that it would be unethical to include a control group with “no treatment” (WMA, 2002), both groups in the trials in Chapters 5 and 6 received eccentric exercises, i.e. such exercises were given across the board to every participant. The design was thus based upon a pragmatic control, and therefore the effect of LLLT as an adjunct treatment was assessed. A pilot RCT study (Chapter 5) was conducted using current dosage recommendations (i.e. 810nm, 100mW applied transcutaneously to six points on the tendon for 30s, for a total of 3J per point and 18J per session) to assess the feasibility of a larger controlled trial, to provide information on procedures, and to provide data for the power calculation for the proposed main trial. Although the results of the pilot study were not statistically
significant, an expected and not unusual finding for a pilot study (Tumilty et al., 2008),
the treatment group did demonstrate superior change scores for both pain, measured on a visual analogue scale, and function, measured with the VISA-A questionnaire. Along with the positive results of testing the protocol and patient recruitment, and retention over the 3 month period (indicating the feasibility of the main trial), this trend in favour of the group treated with LLLT provided further justification of a need for the further completion of a larger, adequately powered main RCT.

The pilot study was presented and published prior to commencement of the main RCT, with the parameters reported following the guidelines from WALT and information provided in the manufacturer’s handbook. Interestingly, this attracted criticism from some colleagues as the power density (irradiance) specified in the manufacturer’s handbook exceeded the 100mW/cm² (maximum) recommendation from WALT. In the light of this feedback, the decision was made to alter (reduce) the output of the laser probe to meet this 100mW/cm² limit for the main RCT. It was also decided to extend the follow-up period to one year to assess any potential long term benefits that might have resulted from laser treatment as an adjunct to eccentric exercise.

As for the pilot study, excellent recruitment and retention rates were achieved for the main RCT. However, and although participants showed improvements in their VISA-A scores at 3 months (greater than 30 points), which were maintained for a further 9 months, there was no difference in change scores between the groups at either time point (Chapter 6). These findings provide additional evidence for the effectiveness of heavy load eccentric exercises, but suggest that LLLT treatment, at least where used as an adjunct and at the parameters indicated, provided no additional benefit for
participants in the treatment group. While the precise reasons for this are unclear, the fact that the output of the laser probe was altered for the purposes of the main RCT to meet one recommended parameter (power density or irradiance) may well have influenced another parameter (peak power) rendering the probe ineffectual. This is a potentially interesting point, and possible explanations and implications of these findings are discussed below.

7.2 Laser Parameters and Guidelines

Which laser irradiation parameters are important in defining LLLT treatment and in determining its clinical effectiveness, and how should these be reported? Wavelength is unanimously accepted as important as it targets specific chromophores (wavelength-specific absorption) and in turn determines depth of penetration (Chapter 2). Power output is also critically important, as without sufficient power delivered to the target tissue to cause a reaction, the intervention will be useless. Beyond this, adequate power and (particularly) energy density have also been described as necessary components of an effective treatment (Calderhead, 1991; Calderhead, 2007; Enwemeka, 2009). For both these latter parameters, the specification is based upon the area of irradiation: energy density or dosage is often expressed as J/cm²; subsequently the irradiated area and how it is calculated then becomes a very important consideration (Nussbaum, Lilge, & Mazzulli, 2003b). While it stands to reason that the area of the spot size is relevant when using the contact method of application for treatment, there is currently not an agreed method within the LLLT research community (or even among manufacturers) to define beam area. Laser beams are rarely circular in shape, are rarely of uniform density, and once they enter the tissue the light forms a ball or egg shape in three dimensions (Tuner
& Hode, 2007b). The question then remains, should power or energy density be described as the output power over the area of the spot irradiated, over a 1cm$^2$ area of tissue, or more accurately, should volume be considered, as in 1cm$^3$? There is currently no consensus or consistency on this point and the associated variation in reporting of parameters which depend upon area of irradiation in the literature makes it difficult to replicate dose accurately.

Even currently published guidelines differ in how parameters are described (Bjordal et al., 2001; WALT, 2005; see Appendix II). Despite criticism of reporting dosage in Joules (i.e. total energy; 20 joules can be delivered with 20W for 1 second or 1W for 20 seconds), the WALT dosage guidelines for Achilles tendons (WALT, 2005) are expressed as 2-3 points of application and 8J of dosage. Other guidelines report power or energy density: e.g. Bjordal reports for the Achilles 5-100mW/cm$^2$ or 0.7-7J/cm$^2$ (Bjordal et al., 2001). This is despite contrary opinions “that dosage expressed as J/cm$^2$ is inadequate” (Carroll, 2009). The relevance of this debate can be illustrated with the following example: three laser treatment probes of differing output power (1000mW; 300mW; 30mW) and different spot sizes (0.25cm$^2$; 0.15cm$^2$; 0.015cm$^2$ respectively); all give a power density of 200mW/cm$^2$. If these three probes were applied for 20 seconds, the resulting dosage specified in terms of energy density would be 40J/cm$^2$. Although the dosage is consistent, the energy delivered is quite different (20J; 6J; 0.6J respectively). In this case, the resultant clinical results are likely to be diverse; it is noteworthy that the rule of reciprocity does not apply in such cases (Schindl, Rosado-Schlosser, & Trautinger, 2001). This would then suggest that dosage should be reported in Joules.
Nussbaum et al., 2003b) proposes a solution to this dilemma: “if the diameter of the laser beam is equal to or less than one penetration depth of the radiation, that is approximately less than 1mm, the effect will be as for a point source, and one should no longer try to define irradiance or radiant exposure, but rather the power (W) or total energy (J) of the treatment”. Of course, another solution would be to report all the relevant parameters, as per the consensus agreement reached by WALT (WALT, 2006) regardless of whether the treatment is performed in the normal clinical setting, as part of a clinical trial, or as guidelines for clinicians.

To further highlight this controversy over dosage and how it is reported, and with particular relevance to the central topic of this thesis, consider the published dosage guidelines for the Achilles tendon, when applied at the skin over the target tendon (Table 7-1) and two studies with very similar methodology but different outcomes, one supporting LLLT (Stergioulas et al., 2008), and one that showed no benefit (i.e. main RCT from Chapter 6).

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Power Density</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bjordal (2001)</td>
<td>5-100mW/cm²</td>
<td>0.7-7J/cm²</td>
<td></td>
</tr>
<tr>
<td>WALT (2005)</td>
<td>&lt;100mW/cm²</td>
<td>8J</td>
<td>Minimum 2-3 points</td>
</tr>
</tbody>
</table>

The parameters used in the main RCT for this thesis (Chapter 6), adjusted in the light of feedback through modification to the laser probe, were: 7mW X 30s = 0.21J per point, with spot size 0.07cm² = 3J/cm² and power density of 100mw/cm²; these fall within
guidelines. The study by Stergioulas et al., 2008) used a similar wavelength (820nm instead of 810nm) and the following parameters: 30mW X 30s = 0.9J per point with spot size 0.5cm$^2$ = 1.8J/cm$^2$ with a power density of 60mW/cm$^2$; these also fall within parameters. Both studies treated 6 points on the tendon at each session.

The differences in irradiation delivered between these studies are 3J/cm$^2$ compared to 1.8J/cm$^2$, and 100mW/cm$^2$ compared to 60mW/cm$^2$; both of which should have worked as combinations of parameters according to guidelines. However, accounting for 80% power loss through the dermis (Figure 2-1 from Chapter 2, Karu, 1989), (and ignoring the three dimensional nature of the light flux once in the tissue) one study delivered 6mW to the target tendon (Stergioulas et al., 2008) and the other delivered only 1.4mW to the target (main RCT from Chapter 6). It thus would appear in this instance that power was the most important parameter in determining clinical response and effectiveness, as 7mW applied at the surface produced no measurable effect on pain or function. Therefore, for future research and clinical application... exercise extreme caution when contemplating modification of your laser and ensure sufficient power is absorbed by the target tissue.

### 7.3 Evidence Based Medicine

As stated previously (Chapter 1), although Evidence based Medicine (EBM) has been an important development in the field of medicine and health care, it is not without its critics. One of the main areas of critique has been the lack of evidence that it automatically leads to better health care (Miles, Loughlin, & Polychronis, 2008), as empirical evidence from research using population based studies does not necessarily fit the clinical environment and benefit the individual patient; in other words, while the
internal validity for the research studies which represent the underlying evidence is strong, the external validity is less so. EBM tends to lead to the production of guidelines and recommendations, as evidenced by the myriad of guideline groups that have sprung up around the world (including the Cochrane Collaboration, the US Preventative Services Task Force, the UK National Institute for Clinical Excellence, and the Scottish Intercollegiate Guideline Network). However, critics argue that these guidelines apply to the ‘average patient’ and such empirical evidence does not provide concrete answers regarding the care of the individual patient; rather such approaches only provide typical or baseline information which needs to be compared with the patient-at-hand (Feinstein & Horwitz, 1997).

The hierarchy of evidence associated with EBM puts meta-analysis and RCTs above opinion of the expert, who uses knowledge from a variety of sources, including knowledge of pathophysiological mechanisms, and knowledge derived from clinical experience, to inform decisions. The evolution of EBM has seen a softening of strict adherence to “evidence from research is the best evidence”, to include clinicians’ experiential evidence, and the patient’s goals and values. Therefore, the definition that EBM is “the explicit, judicious, and conscientious use of current best evidence from healthcare research in decisions about the care of individuals and populations” (Sackett et al., 2000) has more recently been modified to; “the integration of individual clinical expertise and patient preferences with the best available external clinical evidence from systematic research and consideration of available resources” (Tonelli, 2006). Tonelli (2006) goes further by breaking down the issues and processes underlying any clinical decision into five distinct areas:

2. Experiential evidence: derived from personal clinical experience or the clinical experience of others (i.e. expert opinion).

3. Pathophysiologic rationale: based on underlying theories of physiology, disease, and healing.

4. Patient values and preferences: derived from personal interaction with individual patients.

5. System features: including resource availability, societal and professional values, legal and cultural concerns.

It is proposed that any good clinician who considers information from these five domains to make an informed decision to administer a treatment, despite what the empirical evidence (alone) might suggest, by definition, is also practicing EBM. Herein lies part of the problem of how to evaluate EBM; how to prevent “contamination” among participants involved in a trial to assess the effectiveness of EBM. Participants (clinicians) in any study would not be immune to the evidence that is freely available through journals, the internet or other forms of media and therefore a true “no intervention/treatment” control group would be difficult to establish.

Some other criticisms around EBM are aimed at the individual methodologies used to conduct systematic review with meta-analysis and RCTs. The work conducted as part of this thesis was designed with the intention of minimizing any potential bias (and thus achieving high scores on relevant methodology scales). The pilot RCT study (Chapter 5) received a score of 10/10 on the PEDro database when published (PEDro, 2007), and it is to be expected that once the main RCT is published it would receive a similar score as it followed the same protocol and had only a 10% dropout. Therefore, due to lack of bias in methodology, it would more likely to be included in reviews assessing high quality studies and thus reported results/findings would be included in any meta-analyses.
Other scales are also used to assess the quality of RCTs. Olivo et al., 2008) identified seven such scales which are applied in research for physiotherapy (Jadad, Maastricht, Delphi, van Tulder, Maastricht-Amsterdam, PEDro and Bizzini). The Jadad scale appears to be the most valid to assess RCTs,(Olivo et al., 2008); however, in the stroke rehabilitation literature the PEDro scale exceeds the Jadad scale in terms of evaluating the methodological quality (Bhogal, Teasell, Foley, & Speechley, 2005). The PEDro scale was developed specifically for use in physiotherapy (Sherrington et al., 2000) and addresses important quality criteria such as intention to treat analysis, concealed allocation, adequate follow up, and the use of objective outcome measures. Reviewers might interpret differently the methodology used in RCTs, or the notes on administration of the PEDro scale, and therefore, provide inconsistent ratings when assessing the methodological quality of RCTs. This is evident when articles receive varying scores in different published systematic reviews, or have scores reported other than that posted on the PEDro website. For this thesis, three independent reviewers scored the articles included in the systematic review and came to a consensus. Although scales to analyse the methodological quality of RCTs in physiotherapy still need to be validated, or a new scale developed, the PEDro scale remains one of the most reliable and valid measures for this purpose (Maher et al., 2003; Olivo et al., 2008). Therefore, until a universally accepted scale is developed, researchers need to evaluate the current available methods for assessing methodological quality and select a scale that best suits their purpose and the data to be analysed.

The systematic review conducted as part of this thesis followed the QUOROM statement (Moher et al., 1999) and in the light of criticisms of other reviews (Bjordal et
al., 2005; Chou, 2008; Herbert & Bø, 2005) the actual interventions used in each study were also evaluated by three independent reviewers to improve the quality, particularly in respect of the external validity (or clinical applicability) of the findings. One group (Bjordal et al., 2005) has identified a number of biases in a Cochrane review of LLLT for osteoarthritis, and through the use of sensitivity analyses with the same data produced very different results and conclusions. As reported in Chapter 4, a best evidence synthesis can give a different result to effect size calculations or pooling of data. It must also be borne in mind that RevMan’s use of individual study effect sizes are a simplistic way of looking at data and are really only useful when considering pooling of data. Chou, 2008) recommend that conclusions of systematic reviews should not be taken at face value, and provides a list of factors to consider that help distinguish a high quality piece of work, such as:

1. Was the search comprehensive?

2. Was selection of studies unbiased?

3. Is the systematic review current?

4. Was quality of included studies appropriately assessed?

5. Was evidence combined and summarized appropriately?

6. Was publication bias assessed?

7. Are the conclusions justified?

There are conflicting views as to whether systematic reviews should include “grey” literature (that is literature from unpublished studies or obscure journals); it has
been found that only 33% of meta-analyses contained grey literature (McAuley, Ba'Pham, Tugwell, & Moher, 2000). The impact of grey literature on the estimates of treatment effects is said to be in the region of 9%-15% (Hopewell, McDonald, Clarke, & Egger, 2007; McAuley et al., 2000; Moyer, Schneider, Knapp-Oliver, & Sohl, 2010), and can constitute between 4.5% and 75% of the included articles in a review (McAuley et al., 2000). The fact that studies from journals with higher impact factors and studies with statistically significant results were more likely to be published are factors to consider (Koletsi et al., 2009). A comparison was made between the quality of unpublished PhD theses and published theses that studied psychosocial interventions for cancer; findings showed that the unpublished work was not of a vastly inferior quality, and dissertations with significant findings were more likely to be published than those with non-significant findings (Moyer et al., 2010). These factors must be taken into account when reading Chapter 4 (systematic review) as criteria were set to include only articles that had met peer review to ensure a higher quality. Thus it may be that in the two instances where pooling of data was appropriate (pain scores for Achilles tendinopathy, and participants’ grip strength in lateral epicondylitis), the estimates of effect size may be overestimated. However, from the above comment on the impact of grey literature on the estimate of effect size (9%-15%), the 95% confidence intervals from the data would include any change of this magnitude.

A myriad of published research evidence exists, some of it conflicting, which can lead to confusion for the clinician; however it is only another piece of evidence to consider when making clinical decisions and should be evaluated and critiqued like any
other. Therefore, the task-at-hand is to provide high quality research evidence that the clinician can evaluate and decide whether it fits the scenario in front of them at the time.

### 7.4 Efficacy versus Effectiveness

The concepts of efficacy and effectiveness are often confused among researchers and clinicians, and are often used interchangeably when describing the effects of a treatment (Armijo-Olivo et al., 2009). Basically efficacy is concerned with cause and effect and asks the question ‘does it work’ (albeit in a controlled setting); this controlled setting enables an evaluation of what happens when the participant receives the treatment. Effectiveness on the other hand asks the question, ‘does it work in the real world’ (clinical situation) and is more concerned with clinical applicability. This more pragmatic design can answer the question: what happens to the participants who are prescribed the treatment. In the real world, patients often fail to adhere to a treatment regime and can drop-out due to perceived lack of effect, adverse reactions, or even that they consider the treatment to work and don’t need further treatment. This latter form of study design (i.e. concerned with effectiveness in the clinical setting) is of particular interest to policy makers and funders who have to decide whether to fund a novel and promising treatment, which, while it might be promoted as “the cure”, is so painful or has such side effects that few patients finish the course of treatment. Considering the above comments, the importance of research to assess effectiveness becomes evident, and study design needs to include the appropriate analysis to answer either the efficacy or effectiveness question; more on this topic follows below.

The efficacy approach to analysing RCTs is to use an “as treated” analysis, or a “per protocol” analysis (Armijo-Olivo et al., 2009). This method only analyses data from
participants who completed at least a certain agreed percentage of treatment (e.g. 80% of the treatment) and ignores data from drop-outs; however, this may weaken the statistical power of the study. Furthermore, considering that participants experiencing positive effects from an intervention are more likely to stay in a trial (Horwitz et al., 1990; Montori & Guyatt, 2001) this form of analysis may also inflate the apparent treatment effect and thus increase the probability of a type I error (Portney & Walkins, 2000). A per protocol analysis is very similar as it counts only participants who are assigned to the treatment and who complied perfectly with the protocol (Sheiner & Rubin, 1995). In such situations, the effects on participants who are non-compliers are not known, and any adverse effects may be underestimated (Tillmann, Sharpe, Sponer, & Wehling, 2001).

The question posed at the beginning of this thesis was one of clinical effectiveness (what happens to participants who are prescribed a particular treatment) and thus analysis of data needed to take into account the fact that in the real world patients do not always comply with treatment regimes (for whatever reason). At the beginning of a trial, participants are randomised to ensure baseline homogeneity, but drop-outs can introduce bias, as seen in the previous two examples above. The way to deal with such missing data and preserve the power of the study is to use intention to treat (ITT) analysis.

7.5 Intention to Treat Analysis

To mirror what is observed in actual clinical practice and answer the public health question of how the public would respond to any given treatment regime, intention to treat analyses (ITT) are recommended as the preferred method of analyzing data from clinical trials (Bubbar & Kreder, 2006; PRISMA, 2009; Whittaker et al., 2006; Wright &
Sim, 2003). ITT is more suited to trials exploring clinical effectiveness rather than trials investigating efficacy (Hollis & Campbell, 1999) and comes with its own set of advantages and limitations (Armijo-Olivo et al., 2009). ITT is a way of minimizing bias that may occur in a “per protocol” or an “as treated” analysis due to post hoc exclusions, and of dealing with the issues of adherence and missing data. However, it may introduce other forms of bias, such as the method used to replace missing data, which may then serve to dilute or inflate the observed treatment effect. A simulated sensitivity analysis undertaken by Wright & Sim, 2003) comparing ITT with an “as treated” analysis demonstrated that the treatment effect was weakened in ITT and exaggerated in an “as treated” analysis; the authors also concluded that the methods of imputation failed to properly account for the missing data.

Many methodology quality scales often include ITT analysis as a criterion (e.g. item 9 on the PEDro scale Olivo et al., 2008; PEDro, 2007). However, such an approach does not have universal support, the main problem being the replacement of missing data: logic would suggest that if data is missing it cannot be replaced without some form of bias; the replaced data is an estimate by whatever means, and the actual value cannot be known.

Data that are not missing completely at random (MCAR) must be replaced according to ITT protocols, but all methods used to replace data can be criticised. The methods considered during this thesis were: last observation carried forward (LOCF), straight line trend from observations previous to dropout, and propensity scores (multivariate analysis to identify prognostic factors); however, the sample size was deemed too small (n=36) and unlikely to yield any meaningful prognostic indicators, so
this last method was excluded (Hollis & Campbell, 1999). Using the straight line trend from prior observations makes the assumption that participants will continue on the same trajectory after the intervention has ceased (improving; getting worse; staying the same). The four participants who dropped out of the main RCT (Chapter 6), did so before treatment began (2 due to travel required; 1 due to shift work; 1 was unable to be contacted again), therefore only the baseline data was available and a straight line trajectory was impossible to calculate. LOCF disadvantages are that it assumes there is no improvement after the last observation and ignores the trajectory of any change prior to dropout (Streiner & Geddes, 2001). Thus, all methods make assumptions and in reality there is no guarantee that participants’ reaction to a treatment while under observation will stay the same after observations stop. As indicated above, four participants dropped out before treatment began; it was deemed inappropriate to use LOCF for these missing data as three dropped out from the control group and one from the laser group, and this may have biased the results by weakening the effects experienced by the control group.

It was decided to use the group means to replace the missing data (Armijo-Olivo et al., 2009) as it was thought that this would have the least effect on the results considering that power calculations were made allowing for 20% drop-outs and 90% of randomised participants were still in the trial. This notwithstanding, a sensitivity analysis was conducted using group means and LOCF; based upon this, there was no marked change in the statistical significance observed (Chapter 6).

Essentially, ITT analysis is the preferred method to analyse data from an RCT that is attempting to answer the clinical effectiveness question. However, there is no agreed solution to dealing with missing data that may not be MCAR, therefore warranting a
sensitivity analysis as mentioned above. Considering the ongoing debate around the topic, the challenge throughout the data collection phase of this thesis was to come up with strategies to minimise missing data: however, this raises its own issues as it seemed to be in conflict with participants’ right to withdraw at any time when, as one person put it during a phone call follow-up, “I thought I could withdraw and now you are pressing me to return”. Although retention was on the whole very good for both the pilot study and the main RCT, the numbers needed for each study were relatively small; in larger studies with perhaps hundreds in each group, retention is more likely to be a problem. Strategies must be used to minimise missing data as much as possible, and explanations for drop-outs provided. To further strengthen any conclusions made from the results, sensitivity analyses should be performed where possible.

7.6 Patient Adherence

When a dose of treatment is prescribed to a patient, an assumption is made that the patient will comply with the protocol, and that the total dose will be administered. In reality this is not the case: when left to their own volition, patients often fail to complete a package of care. In the case of clinical trials, such lack of adherence can ultimately call into question the (apparent) effectiveness of the prescribed dose. Often researchers will add, as in the work completed for this thesis, compliance logs to monitor adherence to a programme to enable explanations to be formed regarding the results. Reporting of compliance varies among studies, as often the question to be answered doesn’t involve exploring the relationship between compliance and outcomes.

A recent review of the literature looking at high quality RCTs that have investigated eccentric exercise in the treatment of Achilles tendinopathy found that
detailed reporting of compliance data was lacking (Meyer et al., 2009). Of the three studies included in the review two failed to report compliance (Herrington & McCulloch, 2007; Rompe et al., 2007); the third study (Roos et al., 2004) provided information on participants’ compliance rates on a weekly basis and classed completion of the recommended exercises of over 75% as ‘good’ compliance. From week one, when 95% of participants achieved good compliance, the numbers dropped to only 50% by week 13. Therefore, adherence to the dose prescribed varied among these studies, and no relationship could be demonstrated between compliance and outcomes. Especially with regards to home exercise programmes, when compliance is not known, then the usefulness of the prescribed dose is also unclear.

The data on compliance collected from the main RCT as part of this thesis (Appendix XI) also fails to display any strong relationships between the number of exercise sessions, and the change in scores on the VISA-A questionnaire or the NPRS at 12 weeks (Table 7-2). Regression analysis was performed on these data but due to the low numbers of completed compliance logs, it was considered invalid to present this data as robust. Even ignoring the possible effect of the laser therapy treatment and forming a single cohort (which is possible due to the near identical change scores between groups and the non-significant statistical test; see Table 7.2), the data displayed little relationship between compliance and outcomes.
Table 7-2: Change Scores and Compliance (number of exercise sessions completed) at 12 Weeks.

<table>
<thead>
<tr>
<th></th>
<th>VISA-A Mean (SD)</th>
<th>NPRS Mean (SD)</th>
<th># Exercise Sessions Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Group (n=28)</td>
<td>32.9 (15.2)</td>
<td>1.4 (1.2)</td>
<td>91.9 (44.7)</td>
</tr>
<tr>
<td>Placebo (n=12)</td>
<td>33.0 (11.0)</td>
<td>1.5 (1.1)</td>
<td>106.3 (44.9)</td>
</tr>
<tr>
<td>Laser (n=16)</td>
<td>32.8 (18.1)</td>
<td>1.4 (1.3)</td>
<td>81.0 (42.7)</td>
</tr>
</tbody>
</table>

Sub-groups were formed to explore the results from participants who completed more than one exercise session per day, less than one exercise session per day, and less than one exercise session every 2 days (Table 7-3). These sub-groupings would suggest that the optimum dose for the eccentric exercise protocol used here has yet to be defined, as similar changes in scores over the 12 week period were achieved regardless of the number of sessions completed. Due to the risk of muscle injuries through eccentric exercise (Roig Pull & Ranson, 2007), and given that strength recovery may take up to 24 hours post exercise (Clarkson & Hubal, 2002), it is important to define a regime with the minimum (or optimum) number of sessions necessary to achieve positive effects in terms of VISA-A and NPRS change scores.

It is to be noted that during the first 4 weeks, full adherence to the laser protocol was achieved by 36 participants who all received 12 treatments with either the laser or placebo laser.
Table 7-3: Change Scores and Compliance at 12 Weeks by Sub-grouping.

<table>
<thead>
<tr>
<th></th>
<th>Whole group (n=28)</th>
<th>Placebo group (n=12)</th>
<th>Laser group (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VISA-A Mean (SD)</td>
<td>NPRS Mean (SD)</td>
<td># Exercise Sessions Mean (SD)</td>
</tr>
<tr>
<td>&gt; once per day (n=16)</td>
<td>36.2 (11.3)</td>
<td>1.6 (1.0)</td>
<td>123 (23.5)</td>
</tr>
<tr>
<td>&lt; once per day (n=12)</td>
<td>28.5 (18.9)</td>
<td>1.2 (1.3)</td>
<td>50.3 (29.1)</td>
</tr>
<tr>
<td>&lt; once every 2 days (n=6)</td>
<td>30.8 (9.8)</td>
<td>1.6 (1.6)</td>
<td>23.5 (9.7)</td>
</tr>
</tbody>
</table>

|                      | VISA-A Mean (SD)   | NPRS Mean (SD)       | # Exercise Sessions Mean (SD) |
| > once per day (n=10)| 30.6 (15.3)        | 1.4 (1.2)            | 112.3 (42.6)         |
| < once per day (n=2) | 29.5 (0.7)         | 1.3 (0.0)            | 20.5 (13.4)          |
| < once every 2 days (n=2)| 29.5 (0.7) | 1.3 (0.0)            | 20.5 (13.4)          |

|                      | VISA-A Mean (SD)   | NPRS Mean (SD)       | # Exercise Sessions Mean (SD) |
| > once per day (n=6) | 40.3 (9.5)         | 1.7 (0.8)            | 122.2 (28.3)         |
| < once per day (n=10)| 28.3 (20.9)        | 1.2 (1.5)            | 56.3 (27.9)          |
| < once every 2 days (n=4)| 31.5 (12.6) | 1.8 (2.1)            | 25.0 (9.4)           |

7.7 Implications for Clinical Practice

Although conflicting to some degree, results from this thesis add to the body of evidence surrounding the use of LLLT in the treatment of tendinopathy, which the clinician can use as part of the informed decision making process that underpins evidence based practice. Of particular relevance are the findings from the systematic review (Chapter 4), where analysis of treatment parameters from the 12 studies that showed positive effects, strengthen the validity of the published guidelines regarding dosage.
recommendations (Bjordal et al., 2001; WALT, 2005). Notwithstanding the results of the systematic review, the need for ongoing refinement of these guidelines is warranted, as negative results are still possible when parameters fit within the guidelines (as in the main RCT). As stated above, even in published guidelines, treatment parameters are described differently (Bjordal et al., 2001; WALT, 2005); a way forward to enable replication of positive outcomes, whether in the clinical or research setting, or in the way guidelines are described, would be to follow WALT recommendations on reporting of parameters in RCTs involving LLLT and include all the listed parameters (WALT, 2006).

The subsequent pilot study and main RCT were designed and undertaken to test the effectiveness of stated guidelines (and particularly recommended dosages) for the treatment of Achilles tendinopathy, and where using LLLT as an adjunct treatment. Whereas the pilot study showed a possible trend in favour of LLLT treatment when used as an adjunct to eccentric exercise, the main RCT failed to display any difference between the treatment and control group (possible reasons have been discussed previously and in Chapter 6). This highlights the importance for the clinician to exercise caution when changing any one parameter as part of laser treatment; although the irradiance used in the RCT fell well within guidelines, the power output to achieve this was apparently insufficient to cause an effect. The rule of reciprocity (Schindl et al., 2001) does not always apply in laser therapy applications as has been demonstrated by several authors (Karu & Kolyakov, 2005; Lubart, Lavi, Friedmann, & Rochkind, 2006); as indicated above, delivery of 1 Joule of energy can be achieved in different ways (5mW for 200 seconds; or 200mW for 5 seconds) but would not have the same effect in the tissues.
Formulation of clinical guidelines has been an integral part of the evidence based medicine movement since its inception. Results of this thesis could usefully contribute to the evidence used to inform guidelines for the treatment of tendinopathy, in particular the main finding of the systematic review (Chapter 4), namely the endorsement of positive effects when appropriate dosages are used. This notwithstanding, adherence to guidelines (and adoption of any recommendations therein) has been varied across professions. An example of this is the lack of adherence to the published clinical guidelines for the management of low back pain (Bishop, Foster, Thomas, & Hay, 2008; Corbett, Foster, & Ong, 2009; Fullen et al., 2007; Hay et al., 2008). Two studies surveyed UK General Practitioners and Physiotherapists (4000 participants) and analysed their attitudes and beliefs concerning low back pain guidelines (Bishop et al., 2008; Corbett et al., 2009); one study surveyed patients from nine general practitioners in Ireland over a 3 month period (Fullen et al., 2007) to assess adherence to the guidelines. All of these studies reported similar findings, in as much that observance was varied and mixed; reasons cited for lack of adherence were that clinicians don’t have confidence in the evidence base, and that there is a perception that guidelines are imposed and may become the standard protocol, causing resistance among clinicians. Hay et al., 2008) explored the rationale behind the clinical decision making of 29 physicians and members of three focus groups (n=10) and found that such decisions were primarily based on their own clinical experience, then expert opinion of peers and colleagues, while consideration of evidence based medicine came last on their list.

The problem seems to be not the formation of a guideline, with the primary intent of improving health care outcomes, but in the implementation of said guidelines.
The apparent mistrust of the evidence base by clinicians, stems from a perceived lack of external validity of the research evidence (“that doesn’t apply to my patient standing in front of me now”). Two reports investigated the problem of guideline implementation and found that different strategies resulted in varied uptake of the recommendations. Successful strategies identified were multifaceted interventions, interactive education, and clinical reminder systems; strategies found not to be so effective were didactic education, and passive dissemination (Ostelo, Croft, van der Weijden, & van Tulder, 2010; Prior, Guerin, & Grimmer-Somers, 2008). To improve the implementation of guidelines, a recommendation has been published by the Appraisal of Guidelines Research Evaluation (AGREE, 2001) collaboration and suggests that all stakeholders (patients, professional organizations, and policy makers) should be involved in the process at an early stage to develop a sense of ownership. To disseminate the findings of this thesis, and in particular the evidence from the systematic review, a strategy that showed adherence to low back pain guidelines in the Netherlands with physiotherapists, utilizing education, discussion, role play, feedback and reminders may need to be trialed in New Zealand (Bekkering et al., 2005) to heighten the awareness among physiotherapists of the possible treatment benefits of LLLT.

Despite the lack of evidence supporting the adjunct use of LLLT for the treatment of Achilles tendinopathy from the pilot study and main RCT, the intervention also included heavy load eccentric exercise, which has emerged as an effective treatment option for this condition. Possible mechanisms by which these exercises are effective, have been discussed previously, but can be grouped into the effects on mechanotransduction and the biochemical processes that mediate remodeling; as well as
the biomechanical changes in viscoelastic properties of the tendon (see Chapter 3). The challenge for the clinician with regard to this approach is to adequately instruct, mentor, and motivate the patient to perform the exercises correctly for at least 3 months. Even though an optimum dose has yet to be defined for eccentric exercise (Meyer et al., 2009), and patient compliance can be challenging, eccentric exercise should be considered as the treatment of choice for mid-portion Achilles tendinopathy.

Whether LLLT should be added as an adjunct therapy to enhance rehabilitation is something for the individual clinician to decide (principally using the evidence from the systematic review); however, strong recommendations for the inclusion of LLLT as an adjunct and at the parameters indicated cannot be made given the results of no difference in outcomes between groups in the main RCT. The only conclusion to make, particularly as there was no inclusion of a true control group, is that there is no difference in their effects; comments on the use of either laser or eccentric exercise as stand-alone therapies cannot be made from the data collected as part of this thesis.

Data from questionnaires administered to participants at 4, 12 and 52 weeks are presented in Appendix XII. Thirty six questionnaires were completed at the 4 and 12 weeks stages, and 33 completed questionnaires were returned at 52 weeks. When asked, 97% (35/36) of participants reported never having laser treatment previously; one reported previous eye surgery using laser. Asked at 12 weeks whether they would be happy to receive this form of treatment again, 83% (30/36) said they would; 86% (31/36) were satisfied or very satisfied with their treatment, and 89% (32/36) reported having some benefit or a great deal of benefit from the treatment. Between 12 weeks and 52 weeks, participants were left to manage their condition alone after receiving advice at
the 12 week stage. Participants reported in the 52 week questionnaire that their function (100%; 33/33) and participation in sports (97%; 32/33), when compared to the 12 week point, was the ‘same’, ‘better’ or ‘much better’. Only seven participants (21%) had a recurrence of their Achilles injury; five from the laser group, and two from the placebo group. When asked whether they kept up the exercise regime on a prophylactic basis, 67% (22/33) reported performing the exercises sporadically, and 12% (4) completed the eccentric exercises on a regular basis. Confidence in their ability to self-manage their Achilles tendon problem in the future was reported by 97% (32/33). The results of these questionnaires provide evidence that participants were apparently very satisfied with both packages of care given and felt that they benefited from the interventions. The fact that at 52 weeks after treatment started, the participants had, on the whole, maintained any improvement, bodes well for the physiotherapeutic package of care, and the self management strategies employed. Considering the finding of no added benefit of adding laser to exercise, the cost implications of purchasing and maintaining a laser device, along with patient and therapist’s time for administering the treatment, cannot be justified.

These results compare favourably to findings from other published evidence that suggests 24-45.5% of patients eventually require surgery (Clement, Taunton, & Smart, 1984; Leppilahti, Orava, Karpakka, & Takala, 1991; Paavola, Kannus, Paakkala, Pasanen, & Jarvinen, 2000; Vora, Myerson, Oliva, & Maffulli, 2005). Of the studies that included an eccentric exercise regime as part of the protocol and reported satisfaction data at 12 months, the range of participants who considered the intervention a success was 63%-91% (Brown et al., 2006; De Vos et al., 2007; Nørregaard et al., 2007; Silbernagel,
Thomee, Thomee, & Karlsson, 2001). The original article that describes the heavy load eccentric exercise protocol reported 100% success at 3 months (Alfredson et al., 1998). The only other study that investigated a treatment package similar to that employed in this thesis (LLLT + Eccentric Exercises, compared to Placebo LLLT + Eccentric Exercises) did not report participant satisfaction and failed to follow-up after 3 months (Stergioulas et al., 2008), therefore such direct comparisons cannot be made for these findings.

In the early 1990s surveys were completed in Northern Ireland (Baxter, 1991a); Brisbane (Lindsay, Dearness, Richardson, Chapman, & Cuskelly, 1990) and Victoria, Australia (McMeeken & Stillman, 1993), to investigate the usage of laser therapy in physiotherapy practice, with varying response rates (87.3%; 70%; and 31% respectively). Of the respondents 63.1%, 16.5%, and 100% respectively reported using laser, and tendinopathy was a common indication for the application of low level laser therapy.

There are no data on New Zealand physiotherapists’ use of this modality; from personal experience there are very few New Zealand physiotherapists attending laser conferences and requests for information regarding laser are not forthcoming. However, physiotherapy practice in New Zealand mirrors closely that of Australia, therefore consideration of relevant Australian data may shed some light on the situation in New Zealand.

Researchers have also attempted to gauge the use of this modality in Australia and have found that laser devices were available in only 12% of surveyed practices (Robertson & Spurritt, 1998). However, a very recent survey in Australia investigating the availability and use of all electrophysical agents that are taught on undergraduate curricula (Chipchase, Williams, & Robertson, 2009) reported that the availability of laser
devices had risen to over 30% and approached that found in Canada and England in the mid 1990s (Lindsay, Dearness, & McGinley, 1995; Pope, Mockett, & Wright, 1995). The response rate for this latest survey was very low (27%) but represented 3,538 physiotherapists across Australia. Given the low response rate, one must suspect that the real availability of electrotherapy (and thus laser devices) in Australian Physiotherapy practices is much less.

It can be seen that the utilization of low level laser therapy to treat tendinopathy is very difficult to measure. Despite evidence from research studies that have led to the formation of clinical guidelines, the uptake of this information into clinical practice is not guaranteed; clinicians are resistant to use guidelines, but rather rely on personal experience and expert opinion more than the evidence provided by research (Hay et al., 2008). In this part of the World (Australia & New Zealand), it is unclear whether lasers are becoming more popular among physiotherapists.

7.8 Future Directions

This thesis has generated questions as well as answers; this is common to all research projects. The relevance of power density for clinical effectiveness, particularly the 100mW/cm² upper limit for Achilles tendons, needs to be definitively established. It is hard to believe that a laser manufacturer (in this case Thor International Ltd) would produce a machine that has no effect because its parameters fall outside of guidelines; in such a situation, it would soon go out of business due to lack of sales. Even though the power density (2.375W/cm²) used in the pilot study, reported from the manufacturer’s handbook, lay outside published recommendations (< 100mW/cm²), participants
exhibited superior scores for pain and function at the primary endpoint of 12 weeks in the treatment group, compared to control.

In the systematic review (Chapter 4; Tables 4-4 and 4-5) power density was not always available from included studies. For studies concerning the Achilles tendon, power densities were: 20mW/cm$^2$ (Bjordal et al., 2006) and 60mW/cm$^2$ (Stergioulas et al., 2008) for positive outcomes; 150mW/cm$^2$ (Darre et al., 1994) and 2375mW/cm$^2$ (Tumilty et al., 2008) for negative or inconclusive outcomes. If 60mW/cm$^2$ was effective and 150mW/cm$^2$ wasn’t, the origin of the 100mW/cm$^2$ limit seems arbitrary or maybe formed from expert opinion. Bjordal et al., 2001) when formulating their recommendations cite cellular and animal studies to derive a proposal for power density of 5-21mW/cm$^2$ at the target location (Bjordal et al., 2001 page 92), and then it is unclear to the reader of the rationale behind their final recommendation of 5-100mW/cm$^2$, as the effective dosage window later in the article. One study has explored varying irradiance on humans (Hashimoto et al., 1997); this was concerned with treatment to the stellate ganglion to reduce pain due to post herpetic neuralgia and results showed that 150mW/cm$^2$ was superior to other irradiances tested. No study has yet explored the relevance of different irradiance on the treatment of human tendons. Apart from this confusion regarding published guidelines, the fact that three very similar studies in terms of design that conformed to guideline recommendations (main RCT chapter 6; pilot study chapter 5; and Stergioulas et al., 2008; Tumilty et al., 2008), failed to produce consistent results, warrants further refinement of the recommended power density parameter.

A more direct measurement of the effects of LLLT on tendon healing in humans with regards to the biochemical changes occurring in the tendon is needed. Many
authors have used microdialysis techniques to measure such things as inflammatory markers, growth factors, and collagen turnover in Achilles tendons (Alfredson et al., 2001; Langberg et al., 2001; Olesen et al., 2007); to date there has been only one study that used microdialysis to measure the effects of LLLT on inflammatory markers in the Achilles tendon (Bjordal et al., 2006). This approach, running in parallel with more pragmatic clinical trials exploring the effectiveness of LLLT for the treatment of tendinopathy, would add greatly to the body of evidence surrounding this topic.

Similar to laser therapy, the optimum dose for eccentric exercises as an intervention for Achilles tendinopathy has yet to be established. Previously, the issue of compliance was discussed and the lack of detailed reporting highlighted among published articles (Meyer et al., 2009). This failure to adequately monitor compliance calls into question the apparent effectiveness of the prescribed dose (Alfredson et al., 1998); indeed, data from both the pilot study and the main RCT failed to show any relationship between number of exercise sessions completed and outcome scores (Appendix XI). As indicated above, due to the need for recovery and the risk of injury, if it is possible to achieve the same outcomes with fewer exercise sessions then that is something worth investigating. One potential study design, considering compliance data from Appendix XI, would be a study consisting of three groups: group one following the Alfredson protocol (twice per day, seven days per week for 3 months); group two performing exercises once per day, seven days per week for 3 months; and group three completing two exercise sessions per week for 3 months. To monitor participant adherence, compliance logs would be utilized throughout the study, and could be used as the basis of ITT and per protocol analysis.
The future research questions arising from this thesis, as outlined in the previous paragraphs, could be categorized into three main streams: effects and safety, efficacy, and effectiveness trials. In the field of laser therapy research, unlike the pharmaceutical industry where there are strictly controlled stages of development to bring a drug from the laboratory to the bedside (Phase I; Phase II; Phase III, Phase IV trials), research concerning LLLT has been conducted in parallel. Thus, studies exploring the question of does it work, along with studies asking how it works, and also studies of clinical effectiveness, have all occurred simultaneously. Within the current context of the need for evidence based medicine, ways to approach the problem of answering these questions are discussed below.

Trials to answer questions from the first two categories (effects and safety; efficacy) are fairly straightforward to design, and the placebo controlled RCT model fits these types of experiments well. In the laboratory setting using cells or animals there is often no conflict in using a true placebo group. The basic premise of the RCT is that it is designed to have only one dependant variable and ideally one independent variable, all other possible effects from confounding factors that may influence outcome are factored out.

The danger when attempting to evaluate efficacy for complex interventions such as physiotherapy or rehabilitation is that of falling into what has been termed the efficacy paradox (Walach, Falkenberg, Fonnebo, Lewith, & Jonas, 2006): RCTs designed to measure isolated specific effects rather than the whole treatment effect, which is due to complex interaction of specific and non-specific effects, fail to assess the full therapeutic benefit of the intervention. Walach et al., 2006) illustrate this point very well when citing
the German acupuncture trial (Diener et al., 2006) in which pharmacological prevention of migraine (already considered efficacious) was measured against acupuncture (contentious efficacy), and sham acupuncture (not efficacious). Results showed that neither drugs nor acupuncture was significantly different from sham control. Thus a known effective intervention (pharmacological prevention) was apparently shown to be ineffective due to the strong non-specific effects of sham acupuncture.

Once human subjects become the subject of research, the “Declaration of Helsinki” adopted by the World Medical Association (WMA) provides guidance regarding such research (WMA, 2002). Particularly paragraph 29 of the declaration makes it increasingly difficult to obtain ethical approval for inclusion of a placebo group in studies assessing physiotherapy interventions. A note from the declaration clarifies the WMA’s standpoint;

**Footnote: Note of clarification on paragraph 29 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

(WMA, 2002)
During the work conducted as part of this thesis, eccentric exercise was considered to be the existing proven therapy for Achilles tendinopathy, and all participants performed these exercises. When the effect of an intervention is measured alongside an existing proven therapy, as in the pilot and main RCT studies of this thesis, the effect is diluted. Trials of effectiveness, and particularly physiotherapy interventions, due to their interaction of specific and non-specific effects, do not fit this simplistic model of investigation, and may be classed as complex interventions.

The hierarchical model of evidence used in EBM is not wholly supported when it comes to questions of clinical effectiveness (Dieppe, 2004; Ostelo et al., 2010; Walach et al., 2006). The conflict between internal and external validity that has to be addressed when designing a trial often leads to what some perceive as weak evidence (where either has been compromised), or creates barriers between the controlled setting and the real world. Different approaches have been proposed to improve evaluation of complex interventions (MRC, 2000; Walach et al., 2006; Walach et al., 2006) suggest that the hierarchy of evidence model should evolve into a circle of evidence, the importance being that the correct study design is used to answer the questions of efficacy, effectiveness, effects and safety, and that scientific rigor is observed at all times. All types of studies carry the same weighting and a composite of all methods contribute to form best scientific evidence. This is a strong point to make considering that systematic reviews with meta-analyses often exclude non-RCTs, and thus a large body of evidence is not considered when making recommendations or conclusions.

The Medical Research Council (MRC) in the UK has taken a different approach and suggested a framework to develop an RCT for evaluation of a complex intervention along
a continuum of increasing evidence. The phases, in ascending order are: Pre-clinical (theory); Phase I (modelling); Phase II (exploratory trial); Phase III (definitive RCT); Phase IV (long term implementation). Both of these models have their merits and a hybrid of the two would probably bring the best results for laser therapy and for physiotherapy more generally. This approach, along with less stringent exclusion criteria for articles in a systematic review, which would move evidence more towards Walach’s circle, could see huge changes in moving evidence to practice.

In summary: the questions stated earlier arising from this thesis could be confronted using a mixture of trial designs to ascertain efficacy and effectiveness, bearing in mind the constructs of internal and external validity. Following the MRC’s framework would allow the development of more robust RCTs where appropriate, depending on the question to be answered. Beyond this, following Walach’s idea of a circle of evidence, once such RCTs are completed then a single cohort study over a longer period of time would enable evaluation of clinical effectiveness in the longer term.

7.9 Conclusion

Despite the limitations and problems encountered along the way during completion of this thesis, and discussed above, this thesis has provided evidence to add to the scientific basis surrounding the use of laser therapy to treat tendinopathy. From the systematic review, it can be seen that laser is a dose dependant modality and that positive outcomes are possible when using recommended dosages. The need to refine the guidelines concerning description of parameters and dose has been highlighted by the findings of the pilot and main RCTs, as adjusting the output of the device to fall within
a recommended parameter resulted in an ineffective dosage of treatment for the Achilles tendon.

The evidence supporting the use of eccentric exercise as part of the intervention to treat mid-portion Achilles tendinopathy has been strengthened by the findings from this work. However, issues around exercise compliance and clinical effectiveness of the prescribed dose of exercise have been raised.

The complexity of accurately measuring the effectiveness of physiotherapeutic interventions in the clinical setting has also been highlighted and presents challenges for the profession in the future; possible changes in the hierarchy of evidence used in EBM have been presented and may be a way forward to more accurately assess how effective physiotherapy can be.

A final thought:

“There are two kinds of light - the glow that illuminates, and the glare that obscures.”

James Thurber

I hope this thesis has provided some illumination despite the glare from the issues around dose and parameters.
8 Appendices
Appendix I: Ethics Permission for the Pilot and Main RCTs

Main RCT:

25 September 2007

Mr Steve Tumilty
School of Physiotherapy
PO Box 56
University of Otago
Dunedin

Dear Steve,

Project Key: LRS/07/08/032
Full Title: Lower level laser therapy in the management of Achilles tendinopathy.
Investigators: Steve Tumilty, Professor G.D. Baxter, Dr. S. McDonough, Dr. J.H. Abbott, Dr. D. Hurley-Osing, Dr. J. Munn, Professor Basford.
Localities: School of Physiotherapy Clinic.

The above study has been given ethical approval by the Lower South Regional Ethics Committee. A list of members of this committee is attached.

Approved Documents

Certification
The Committee is satisfied that this study is not being conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which the trial is being carried out.

Accreditation
The Committee involved in the approval of this study is accredited by the Health Research Council and is constituted and operates in accordance with the Operational Standard for Ethics Committees, April 2006.

Progress Reports
The study is approved until 1 April 2009. The Committee will review the approved application annually and notify the Principal Investigator if it withdraws approval. It is the Principal Investigator’s responsibility to forward a progress report covering all sites prior to ethical review of the project in 25 September 2008. The report form is available on http://www.health.govt.nz/ethicscommittees. Please note that failure to provide a progress report may result in the withdrawal of ethical approval. A final report is also required at the conclusion of the study.

Requirements for SAE Reporting
The Principal Investigator will inform the Committee as soon as possible of the following:
• Any related study in another country that has stopped due to serious or unexpected adverse events
• withdrawal from the market for any reason
• all serious adverse events occurring during the study in New Zealand which result in the investigator breaking the blinding code at the time of the SAE or which result in hospitalisation or death.

Administered by the Ministry of Health
Approved by the Health Research Council
http://www.health.govt.nz/ethicscommittees
all serious adverse events occurring during the study worldwide which are considered related to the study medicine. Where there is a data safety monitoring board in place, serious adverse events occurring outside New Zealand may be reported quarterly.

All SAE reports must be signed by the Principal Investigator and include a comment on whether he/she considers there are any ethical issues relating to this study continuing due to this adverse event. It is assumed by signing the report, the Principal Investigator has undertaken to ensure that all New Zealand investigators are made aware of the event.

Amendments
All amendments to the study must be advised to the Committee prior to their implementation, except in the case where immediate implementation is required for reasons of safety. In such cases the Committee must be notified as soon as possible of the change.

Please quote the above ethics committee reference number in all correspondence.

The Principal Investigator is responsible for advising any other study sites of approvals and all other correspondence with the Ethics Committee.

It should be noted that Ethics Committee approval does not imply any resource commitment or administrative facilitation by any healthcare provider within whose facility the research is to be carried out. Where applicable, authority for this must be obtained separately from the appropriate manager within the organisation.

Yours Sincerely,

Rina Tautau-Grant
Ethics Committee Administrator
Lower South Regional Ethics Committee
email: rina_tautau-grant@moh.govt.nz
NGĀI TAHU RESEARCH CONSULTATION COMMITTEE

Te Komiti Rakahau ki Kai Tahu

21/08/2007 - 04
Wednesday, 22 August 2007

Mr Steven J Tumilty
School of Physiotherapy
Dunedin

Tēnā koe Mr Tumilty

Title: Low-Level Laser Therapy in the Management of Achilles Tendinopathy.

The Ngāi Tahu Research Consultation Committee (The Committee) met on Tuesday, 21 August 2007 to discuss your research proposition.

The Committee considers the research to be of importance to Māori health.

The Committee acknowledges that researcher is going to collect ethnicity data as part of the project.

The Committee also acknowledges that the researchers have committed to dissemination of the research findings to the Committee and would further suggest that the findings are also disseminated to relevant Māori health organisations.

The Committee would also value a copy of the research findings.

Nāhaku noa, nā

Mark Brunton
Kaitakawaenga Rangahau Māori
Facilitator Research Māori
Research Division
Te Whare Wānanga o Ōtāgo
Ph: +64 3 479 8738
Email: mark.brunton@otago.ac.nz
Web: www.otago.ac.nz

The Ngāi Tahu Research Consultation Committee has membership from:

Te Rūnanga o Ōhakowhakatū Incorporated
Kāti Huirapa Rūnaka ki Puketeraki
Te Rūnanga o Moeraki
Pilot Study:

26 June 2006

Mr Steve Tumility
School of Physiotherapy
Otago University
PO box 56
Dunedin

Dear Steve

Project Key: LRS/06/06/027
Full Title: Low level laser therapy in the management of achilles tendinopathy: A feasibility study
Investigators: Steve Tumility, Professor G.D. Baxter, Dr. S McDonough, Dr. D Hurley- Osing
Localities: School of Physiotherapy

The above study has been given ethical approval by the Lower South Regional Ethics Committee. A list of members of this committee is attached.

Approved Documents
Information sheet and consent form version 2, dated 21 June 2006

Certification
The Committee is satisfied that this study is not being conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which the trial is being carried out.

Accreditation
The Committee involved in the approval of this study is approved by the Health Research Council and is constituted and operates in accordance with the Operational Standard for Ethics Committees, March 2002.

Progress Reports
The study is approved until 01 July 2007. The Committee will review the approved application annually and notify the Primary Investigator if it withdraws approval. It is the Primary Investigator’s responsibility to forward a progress report covering all sites prior to ethical review of the project in 26 June 2007. You will be sent a form requesting this information. Please note that failure to complete and return this form may result in the withdrawal of ethical approval. A final report is also required at the conclusion of the study.

Requirements for SAE Reporting
The Primary Investigator will inform the Committee as soon as possible of the following:
- Any related study in another country that has stopped due to serious or unexpected adverse events
- withdrawal from the market for any reason
- all serious adverse events occurring during the study in New Zealand which result in the investigator or sponsor breaking the blinding code at the time of the SAE or which result in hospitalisation or death.
- all serious adverse events occurring during the study worldwide which are considered related to the study medicine.
All SAE reports must be submitted on the standard notification form, be signed by the Primary Investigator and include a comment on whether he/she considers there are any ethical issues relating to this study continuing due to this adverse event. If the adverse event is local and does not have the sponsor’s report attached, an opinion on whether the event is thought to be related to the study should be given along with any other pertinent information. It is assumed by signing the report, the primary investigator has undertaken to ensure that all New Zealand investigators are made aware of the event.

Amendments
All amendments to the study must be advised to the Committee prior to their implementation, except in the case where immediate implementation is required for reasons of safety. In such cases the Committee must be notified as soon as possible of the change.

Please quote the above ethics committee reference number in all correspondence.

The Primary Investigator is responsible for advising any other study sites of approvals and all other correspondence with the Ethics Committee.

It should be noted that Ethics Committee approval does not imply any resource commitment or administrative facilitation by any healthcare provider within whose facility the research is to be carried out. Where applicable, authority for this must be obtained separately from the appropriate manager within the organisation.

Yours Sincerely,

Riria Tautau-Grant
Administrator
Lower South Regional Ethics Committee
email: riria.tautau-grant@mohe.govt.nz
Mr Steve S.J. Tumility
School of Physiotherapy
Dunedin

Tenâ koe Mr Tumility

Title: Low level Laser Therapy in the Management of Achilles Tendinopathy: a Feasibility Study

The Ngāi Tahu Research Consultation Committee (NTRCC) met on Tuesday, April 4 2006 to discuss your research proposition.

The NTRCC consider the research to be of importance and interest.

The Committee acknowledges that this is a population-based proposition, Māori make up a significant proportion of the population and that the proposition makes note of this.

The Committee asks that the researchers consider recording ethnicity based on the Census question.

The Committee supports this research project and the potential contribution to Māori Health and recommends that relevant Māori Committees, Māori Service Providers, District Health Boards and Māori health professional organisations receive a copy of your findings. They would also value a copy of the research findings.

Please contact me if you would like an electronic copy of this letter.

Nāhaku noa, nā

Mark Brunton
Kaitakawaenga Rangahau Māori
Facilitator Research Māori
Research Division
Te Whare Wananga o Otago
Ph: +64 3 479 8738
email: mark.brunton@otago.ac.nz
Web: www.otago.ac.nz

The Ngāi Tahu Research Consultation Committee has membership from:
Te Rūnanga o Ōtākou Incorporated
Kāti Huirapa Rūnaka ki Puketeraki
Te Rūnanga o Moteaki
Appendix II: Guidelines

Bjordal et al., 2001

<table>
<thead>
<tr>
<th>Tendon</th>
<th>IR 820-830nm Power density (w/cm²)</th>
<th>IR 820-830nm Dose (J/cm²)</th>
<th>IR 904nm Power Density (W/cm²)</th>
<th>IR 904nm Dose (J/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plantar Fasciitis</td>
<td>0.010 – 0.200</td>
<td>1.4 – 14</td>
<td>0.004 – 0.200</td>
<td>4.2 - 42</td>
</tr>
<tr>
<td>Achilles</td>
<td>0.005 – 0.100</td>
<td>0.7 – 7</td>
<td>0.002 – 0.100</td>
<td>1.4 - 14</td>
</tr>
<tr>
<td>Patellar</td>
<td>0.005 – 0.100</td>
<td>0.7 – 7</td>
<td>0.002 – 0.100</td>
<td>1.4 - 14</td>
</tr>
<tr>
<td>Epicondylitis</td>
<td>0.005 – 0.100</td>
<td>0.7 – 7</td>
<td>0.002 – 0.100</td>
<td>1.4 - 14</td>
</tr>
<tr>
<td>Rotator Cuff</td>
<td>0.030 – 0.600</td>
<td>4.2 - 42</td>
<td>0.012 – 0.600</td>
<td>12.6 - 126</td>
</tr>
</tbody>
</table>
Recommended anti-inflammatory dosage for Low Level Laser Therapy

Laser classes 3 or 3 B, 780 - 860nm GaAlAs Lasers. Continuous or pulse output less than 0.5 Watt

Energy dose delivered to the skin over the target tendon or synovia

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Points or cm²</th>
<th>Joules 780 - 820nm</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tendinopathies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carpal tunnel</td>
<td>2-3</td>
<td>12</td>
<td>Minimum 6 Joules per point</td>
</tr>
<tr>
<td>Epicondylitis</td>
<td>1-2</td>
<td>4</td>
<td>Maximum 100mW/cm²</td>
</tr>
<tr>
<td>Biceps humeri c.l.</td>
<td>1-2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Supraspinatus</td>
<td>2-3</td>
<td>10</td>
<td>Minimum 5 Joules per point</td>
</tr>
<tr>
<td>Infraspinatus</td>
<td>2-3</td>
<td>10</td>
<td>Minimum 5 Joules per point</td>
</tr>
<tr>
<td>Teres major</td>
<td>2-4</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Patellar tendon</td>
<td>2-3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Tract. iliotibialis</td>
<td>2-3</td>
<td>3</td>
<td>Maximum 100mW/cm²</td>
</tr>
<tr>
<td>Achilles tendon</td>
<td>2-3</td>
<td>8</td>
<td>Maximum 100mW/cm²</td>
</tr>
<tr>
<td>Planter fascitis</td>
<td>2-3</td>
<td>12</td>
<td>Minimum 6 Joules per point</td>
</tr>
<tr>
<td>Arthritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finger PIP or MCP</td>
<td>1-2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Wrist</td>
<td>2-4</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Humeral radial</td>
<td>1-2</td>
<td>4</td>
<td></td>
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<tr>
<td>Elbow</td>
<td>2-4</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Glenohumeral joint</td>
<td>2-4</td>
<td>15</td>
<td>Minimum 6 Joules per point</td>
</tr>
<tr>
<td>Acromioclavicular</td>
<td>1-2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Temporomandibular</td>
<td>1-2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Cervical spine</td>
<td>2-4</td>
<td>15</td>
<td>Minimum 6 Joules per point</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>2-4</td>
<td>40</td>
<td>Minimum 6 Joules per point</td>
</tr>
<tr>
<td>Hip</td>
<td>2-4</td>
<td>40</td>
<td>Minimum 8 Joules per point</td>
</tr>
<tr>
<td>Knee medial</td>
<td>3-6</td>
<td>20</td>
<td>Minimum 5 Joules per point</td>
</tr>
<tr>
<td>Ankle</td>
<td>2-4</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

Daily treatment for 2 weeks or treatment every other day for 3-4 weeks is recommended.

Irradiation should cover most of the pathological tissue in the tendon/synovia.

Tendons
Start with energy dose in table, then reduce by 30% when inflammation is under control
(Does not apply for carpal tunnel tendosynovitis)

Therapeutic windows range from typically +/- 50% of given values
Recommended doses are based on ultrasonographic measurements of depths from skin surface and typical volume of pathological tissue and estimated optical penetration for the different laser types in caucasiens

Disclaimer
The list may be subject to change at any time when more research trials are being published. World Association of Laser Therapy is not responsible for the application of laser therapy in patients, which should be performed at the therapist/docotor’s discretion and responsibility

Revised August 2005
Consensus Agreement on the Design and Conduct of Clinical Studies with Low-Level Laser Therapy and Light Therapy for Musculoskeletal Pain and Disorders

WORLD ASSOCIATION OF LASER THERAPY (WALT)

DEFINITION

LOW-LEVEL LASER THERAPY (LLLT) in musculoskeletal disorders refers to monochromatic light therapy with lasers that have a mean optical output of larger than 1 mW, i.e., lasers in classes III and IIIa. A similar definition applies for light therapy with light-emitting diodes (LEDT) when the mean optical output is larger than 1 mW. Trial reports should make explicit whether LLLT or LEDT is being used.

DESIGN AND CONDUCT

1. In general, clinical trials with LLLT should have a control group where patients receive placebo LLLT or another reference treatment, and include procedures for randomization and patient-blinding.
2. The reporting of a trial should be presented according to the CONSORT guidelines from The Lancet.
3. Several leading journals require (or will in the near future require) that the trial be registered in a public trials register, prior to the start of the trial to ensure that not only positive results are being published. Several registers exist, and one such register can be found at www.controlled-trials.com.
4. In particular, item 4 in the CONSORT guidelines calls for a specific description of the intervention. A specific description of LLLT should include the number of treatment sessions and the frequency of sessions per week, and the following parameters from one treatment session are mandatory:
   1) Stationary in skin contact
   or
   2) Stationary with distance from skin described
   or
   3) Scanning mode
   Wavelength reported in nanometers
   Average output of the laser reported in milliWatts (mW)
   Treatment time in seconds
   Energy Dose delivered reported in Joules (reporting in J/cm² should be confined to studies with small animals and cell cultures)

   In addition, the following parameters should be reported
   spot size on the skin in square cm (cm²),
   and
   power density in mW/cm²
   Accumulated energy delivered from all sessions in Joules
5. Testing of optical output should be performed regularly and at least before and after the end the trial.
6. Co-intervention with steroids should be avoided as steroids block the effect of LLLT.
7. The review should explicitly state which possible biological action(s) of LLLT are intended. The site of laser exposure should be clearly stated and include either (a) the site of pathology (tendon, joint capsule, cartilage, ligament, muscle, bone, wound, etc.); (b) the nerve supplying the painful and/or paralyzed area; (c) the acupuncture or trigger points; (d) other sufficiently described locations.

WALT musculoskeletal advisory board has acknowledged that optimal doses exist for several musculoskeletal complaints when treatment is administered to the site of the pathology. Scientific evidence is graded at two levels, optimal dose and likely optimal dose, and a list of diagnoses is available at the WALT website. These parameters are based on imaging studies that provide data for estimation of energy loss and statistical testing that has verified that these parameters are significantly more effective than other parameters. Using dosage outside the optimal parameters in trials requires a detailed hypothesis and rationale for the treatment parameters used in the trial report. Authors should be aware that trials with non-optimal doses according to WALT standards should not be included or sub-grouped as non-optimal dosage in systematic reviews and meta-analyses of LLLT.
8. Outcomes should be selected from current valid and reliable measures as recommended by organizations such as the American College of Rheumatology and the European League Against Rheumatism. Approved by WALT at the 5th World Congress, in Guaruja, Brazil, November 27, 2004.

Photomedicine and Laser Surgery
Volume 24, Number 6, 2006
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DOI: 10.1089/PHO.2006.24.6W2

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Against Rheumatism. Preferably outcomes of pain, physical function, and quality of life should be provided if the material allows for this. Outcome measures should be quantified either by continuous scales or categorical scales of at least five categories. Examples of valid pain measures are pain at rest, pain during physical activities, or pain at palpation measured by a pressure algometer. Examples of physical function are pain-free muscle strength, maximal walking distance in 6 min, and the Back Performance Scale. Examples of health-related measures of quality of life is Short-Form 36. For systemic inflammatory conditions, measures of disease activity should be included. Other valid outcome measure instruments are Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC), Visual Analogue Scale (VAS) for pain, Arthritis Impact Measurement Scale 2 (AIMS2), AUSCAN for hand osteoarthritis, Shoulder Pain and Disability Index (SPADI), Roland Morris disability index, or Oswestry Pain and Disability index.

9. Statistical analysis of results should preferably be made according to current standards as used by either the European League Against Rheumatism (EULAR), Cochrane Collaboration, or British Medical Journal. As such, the reporting of means for pre-treatment and post-treatment outcomes and the mean difference in change between groups and their respective variance data and parametric tests of p-values for significance is expected for normally distributed data. For outcome data that are not normally distributed, medians and quartile should be used together with non-parametric tests.

10. This Consensus agreement is valid until further notice. Updates on optimal treatment will be continuously considered and subject to alteration if the WALT musculoskeletal advisory board finds it necessary. Such updates will be made available on the WALT website (www.walt.nu).

REFERENCES


<table>
<thead>
<tr>
<th>PAPER SECTION And topic</th>
<th>Item</th>
<th>Description</th>
<th>Reported on Page #</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE &amp; ABSTRACT</td>
<td>1</td>
<td>How participants were allocated to interventions (e.g., &quot;random allocation&quot;, &quot;randomized&quot;, or &quot;randomly assigned&quot;).</td>
<td>✓</td>
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<td>INTRODUCTION Background</td>
<td>2</td>
<td>Scientific background and explanation of rationale.</td>
<td></td>
</tr>
<tr>
<td>METHODS Participants</td>
<td>3</td>
<td>Eligibility criteria for participants and the settings and locations where the data were collected.</td>
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<tr>
<td>Interventions</td>
<td>4</td>
<td>Precise details of the interventions intended for each group and how and when they were actually administered.</td>
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</tr>
<tr>
<td>Objectives</td>
<td>5</td>
<td>Specific objectives and hypotheses.</td>
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<tr>
<td>Outcomes</td>
<td>6</td>
<td>Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors).</td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>7</td>
<td>How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.</td>
<td></td>
</tr>
<tr>
<td>Randomization Sequence</td>
<td>8</td>
<td>Method used to generate the random allocation sequence, including details of any restrictions (e.g., blocking, stratification).</td>
<td></td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>9</td>
<td>Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.</td>
<td></td>
</tr>
<tr>
<td>Randomization Implementation</td>
<td>10</td>
<td>Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.</td>
<td></td>
</tr>
<tr>
<td>Blinding (masking)</td>
<td>11</td>
<td>Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated.</td>
<td></td>
</tr>
<tr>
<td>Statistical methods</td>
<td>12</td>
<td>Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses.</td>
<td></td>
</tr>
<tr>
<td>RESULTS Participant flow</td>
<td>13</td>
<td>Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.</td>
<td></td>
</tr>
<tr>
<td>Recruitment</td>
<td>14</td>
<td>Dates defining the periods of recruitment and follow-up.</td>
<td></td>
</tr>
<tr>
<td>Baseline data</td>
<td>15</td>
<td>Baseline demographic and clinical characteristics of each group.</td>
<td></td>
</tr>
<tr>
<td>Numbers analyzed</td>
<td>16</td>
<td>Number of participants (denominator) in each group included in each analysis, and whether the analysis was by ‘intention-to-treat’. State the results in absolute numbers when feasible (e.g., 10/20, not 50%).</td>
<td></td>
</tr>
<tr>
<td>Outcomes and estimation</td>
<td>17</td>
<td>For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g., 95% confidence interval).</td>
<td></td>
</tr>
<tr>
<td>Ancillary analyses</td>
<td>18</td>
<td>Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>19</td>
<td>All important adverse events or side effects in each intervention group.</td>
<td></td>
</tr>
</tbody>
</table>

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**Appendix III: PEDro Scale**

**PEDro Scale**

1. eligibility criteria were specified
   - no □ yes □ where:
2. subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)
   - no □ yes □ where:
3. allocation was concealed
   - no □ yes □ where:
4. the groups were similar at baseline regarding the most important prognostic indicators
   - no □ yes □ where:
5. there was blinding of all subjects
   - no □ yes □ where:
6. there was blinding of all therapists who administered the therapy
   - no □ yes □ where:
7. there was blinding of all assessors who measured at least one key outcome
   - no □ yes □ where:
8. measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups
   - no □ yes □ where:
9. all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by “intention to treat”
   - no □ yes □ where:
10. the results of between-group statistical comparisons are reported for at least one key outcome
    - no □ yes □ where:
11. the study provides both point measures and measures of variability for at least one key outcome
    - no □ yes □ where:

The PEDro scale is based on the Delphi list developed by Verhagen and colleagues at the Department of Epidemiology, University of Maastricht (Verhagen AP et al (1998). *The Delphi list: a criteria list for quality assessment of randomised clinical trials for conducting systematic reviews developed by Delphi consensus. Journal of Clinical Epidemiology, 51(12):1235-41*). The list is based on "expert consensus" not, for the most part, on empirical data. Two additional items not on the Delphi list (PEDro scale items 8 and 10) have been included in the PEDro scale. As more empirical data comes to hand it may become possible to "weight" scale items so that the PEDro score reflects the importance of individual scale items.

The purpose of the PEDro scale is to help the users of the PEDro database rapidly identify which of the known or suspected randomised clinical trials (ie RCTs or CCTs) archived on the PEDro database are likely to be internally valid (criteria 2-9), and could have sufficient statistical information to make their results interpretable (criteria 10-11). An additional criterion (criterion 1) that relates to the external validity (or “generalisability” or “applicability” of the trial) has been retained so that the Delphi list is complete, but this criterion will not be used to calculate the PEDro score reported on the PEDro web site.
The PEDro scale should not be used as a measure of the “validity” of a study’s conclusions. In particular, we caution users of the PEDro scale that studies which show significant treatment effects and which score highly on the PEDro scale do not necessarily provide evidence that the treatment is clinically useful. Additional considerations include whether the treatment effect was big enough to be clinically worthwhile, whether the positive effects of the treatment outweigh its negative effects, and the cost-effectiveness of the treatment. The scale should not be used to compare the “quality” of trials performed in different areas of therapy, primarily because it is not possible to satisfy all scale items in some areas of physiotherapy practice.

**Notes on administration of the PEDro scale:**

<table>
<thead>
<tr>
<th>All criteria</th>
<th>Points are only awarded when a criterion is clearly satisfied. If on a literal reading of the trial report it is possible that a criterion was not satisfied, a point should not be awarded for that criterion.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criterion 1</td>
<td>This criterion is satisfied if the report describes the source of subjects and a list of criteria used to determine who was eligible to participate in the study.</td>
</tr>
<tr>
<td>Criterion 2</td>
<td>A study is considered to have used random allocation if the report states that allocation was random. The precise method of randomisation need not be specified. Procedures such as coin-tossing and dice-rolling should be considered random. Quasi-randomisation allocation procedures such as allocation by hospital record number or birth date, or alternation, do not satisfy this criterion.</td>
</tr>
<tr>
<td>Criterion 3</td>
<td>Concealed allocation means that the person who determined if a subject was eligible for inclusion in the trial was unaware, when this decision was made, of which group the subject would be allocated to. A point is awarded for this criteria, even if it is not stated that allocation was concealed, when the report states that allocation was by sealed opaque envelopes or that allocation involved contacting the holder of the allocation schedule who was “off-site”.</td>
</tr>
<tr>
<td>Criterion 4</td>
<td>At a minimum, in studies of therapeutic interventions, the report must describe at least one measure of the severity of the condition being treated and at least one (different) key outcome measure at baseline. The rater must be satisfied that the groups’ outcomes would not be expected to differ, on the basis of baseline differences in prognostic variables alone, by a clinically significant amount. This criterion is satisfied even if only baseline data of study completers are presented.</td>
</tr>
<tr>
<td>Criteria 4, 7-11</td>
<td>Key outcomes are those outcomes which provide the primary measure of the effectiveness (or lack of effectiveness) of the therapy. In most studies, more than one variable is used as an outcome measure.</td>
</tr>
<tr>
<td>Criterion 5-7</td>
<td>Blinding means the person in question (subject, therapist or assessor) did not know which group the subject had been allocated to. In addition, subjects and therapists are only considered to be “blind” if it could be expected that they would have been unable to distinguish between the treatments applied to different groups. In trials in which key outcomes are self-reported (eg, visual analogue scale, pain diary), the assessor is considered to be blind if the subject was blind.</td>
</tr>
</tbody>
</table>
| Criterion 8  | This criterion is only satisfied if the report explicitly states both the number of subjects initially allocated to groups and the number of subjects from whom key outcome measures were obtained. In trials in which outcomes are measured at several points in time, a key outcome
must have been measured in more than 85% of subjects at one of those points in time.

**Criterion 9**  
An *intention to treat* analysis means that, where subjects did not receive treatment (or the control condition) as allocated, and where measures of outcomes were available, the analysis was performed as if subjects received the treatment (or control condition) they were allocated to. This criterion is satisfied, even if there is no mention of analysis by intention to treat, if the report explicitly states that all subjects received treatment or control conditions as allocated.

**Criterion 10**  
A *between-group* statistical comparison involves statistical comparison of one group with another. Depending on the design of the study, this may involve comparison of two or more treatments, or comparison of treatment with a control condition. The analysis may be a simple comparison of outcomes measured after the treatment was administered, or a comparison of the change in one group with the change in another (when a factorial analysis of variance has been used to analyse the data, the latter is often reported as a group × time interaction). The comparison may be in the form hypothesis testing (which provides a “p” value, describing the probability that the groups differed only by chance) or in the form of an estimate (for example, the mean or median difference, or a difference in proportions, or number needed to treat, or a relative risk or hazard ratio) and its confidence interval.

**Criterion 11**  
A *point measure* is a measure of the size of the treatment effect. The treatment effect may be described as a difference in group outcomes, or as the outcome in (each of) all groups. *Measures of variability* include standard deviations, standard errors, confidence intervals, interquartile ranges (or other quartile ranges), and ranges. Point measures and/or measures of variability may be provided graphically (for example, SDs may be given as error bars in a Figure) as long as it is clear what is being graphed (for example, as long as it is clear whether error bars represent SDs or SEs). Where outcomes are categorical, this criterion is considered to have been met if the number of subjects in each category is given for each group.
Appendix IV: Systematic Review; Authors Letters

Template:

Date.........

Name............... 
Address..................
Address.................. 
Address.................. 
Address..................

Dear .............,

I am a physiotherapist completing a PhD on Low Level Laser Therapy (LLLT) for the treatment of tendinopathy under the supervision of Prof D. Baxter at the School of Physiotherapy, Otago University, Dunedin, New Zealand. As part of the PhD I am conducting a systematic review of the literature and a meta-analysis. Your article entitled, .................................................. .................................................. .................................................. .................................................. has been included in the final list for analysis.

However, we would appreciate clarification on the following points in order to be able to fully evaluate the level of evidence your article provides.

................................................................. ................................................................. ................................................................. ................................................................. .................................................................

Please be assured that confidentiality will be observed at all times and any data supplied will not be used outside the confines of this Systematic review and Meta-analysis.

Thanking you in anticipation,

Yours sincerely,

Steve Tumilty MPhty
School of Physiotherapy,
Otago University,
Dunedin,
New Zealand.
Tel: 0064-3-479-5757
E-mail: steve.tumilty@otago.ac.nz
Example letter:

Dear Renu Sharma,

I am a PhD candidate researching Low Level Laser Therapy (LLLT) for the treatment of tendinopathy under the supervision of Prof D. Baxter at the School of Physiotherapy, Otago University, Dunedin, New Zealand.

As part of the PhD I am currently conducting a systematic review of the literature and a meta-analysis. Your article entitled:


has been included in the final list for analysis.

We would appreciate clarification on the following points in order to be able to fully evaluate the level of evidence your article provides.

To be able to compute the effect size we require;
The mean change scores between pre & post treatment (with 95% CI) for each group for all outcome measures. Please provide this data, or failing this, the raw data from each group and we will perform the calculations.
Also, could you provide;
The frequency of the treatments
The length of time between treatment and follow-up assessment
The dose (J)
The spot size (cm2) of the laser used
The power density (mW/cm2) of the laser used
The energy delivered at each treatment
The accumulated energy from all treatments

Thanks for your assistance with this. Please be assured that any response you are able to provide will only be used for the purpose of the Systematic review and Meta-analysis, and any data will kept confidential to the research team.

Yours sincerely,

Steve Tumilty MPhty
Appendix V: Pilot Study Forms


Information sheet for Participant (July 2006)

You are invited to take part in a study to assess the effectiveness of laser to treat Achilles tendon injuries. Please read this information sheet carefully, and take as much time as you need before deciding whether or not to participate in this project. If you decide to participate, we thank you. If you decide not to take part, there will be no disadvantage to you of any kind, you will still receive the usual treatment and we thank you for considering our request. Please be aware that you may decide at any time to withdraw from the project without any disadvantage to yourself of any kind.

- Participation in the study will be stopped should any harmful effects appear or if the therapist feels it is not in the participant’s best interests to continue.
- If you need an interpreter, one can be provided.
- You may have a friend, family or whanau support to help you understand the risks/benefits of this study and any other explanation you may require.
- Your G.P. will be informed of the results of your participation in this study.
- At the end of the study ongoing treatment will be provided under the normal ACC rules if required.

The aim of the project:
This project is being undertaken to explore the effectiveness of laser therapy as part of the management of patients with Achilles tendon pain.

Participants:
Volunteers between 18-65 years old who have pain in the region of the Achilles tendon and have not had treatment over the past 3 months.

Exclusion criteria:
You will not be allowed to participate if there is a risk to your health or safety from the treatment. This will be judged by the principal investigator using a standard checklist of risk factors. You will not be allowed to participate if you have had steroid injections or surgery for the condition. If you have any other problems that may cause you difficulty in performing the exercise routine, you will also not be allowed into the study.

Study requirements:
All participants in the study receive the standard treatment of exercises and then an active or inactive laser treatment.
Should you agree to take part in this project, you will be allocated into one of two groups by use of a computer generated list. The two groups will be treated identically with the exception of the laser therapy. One group will receive placebo laser, one group active laser. A placebo laser is a dummy and the group given the placebo laser will not get any of the expected effects of the laser. Subjects will receive treatment and be assessed against the outcome measures before treatment 1 and after treatment 12, and 3 months after the first treatment. Treatment will be carried out by a clinician who will have no knowledge as to which group you belong to. Subjects will receive a set of exercises and be advised on how and when to perform the exercises. In addition you will be given laser treatment to six points around the Achilles tendon 3 times per week for 4 weeks with either a placebo or active laser probe. You will be required to keep a diary to record your exercise activity while taking part in the study.

**Exercise Routine:**
Subjects will be instructed on how to perform the exercise training by the same therapist who will also instruct them on how to fill out the diary. Subjects are to perform the exercises two times daily 7 days a week for 12 weeks. During the 12 week training regimen, running is allowed only if it can be performed with mild discomfort and no pain.

**Outcome measures:**
You will be required to complete the VISA-A questionnaire, to assess the impact of your injury on your daily activities, before treatment 1 and after treatment 12, and at the 3 month follow up. You will also be asked at every visit, to indicate the amount of pain during activity (worst pain) you have experienced by marking on an 100mm scale your level of pain. Measurement of your calf muscle strength at the point when pain starts will be taken using a computer controlled machine. The unaffected side will also be measured for comparison, using the same procedure. Calf muscle strength will be measured before treatment 1 and after treatment 12, and at the 3 month follow up.

**Follow up Procedure:** Three months after the initial treatment subjects will be asked to return for a final assessment of the 3 outcome measures listed above.

**Benefits, risks and safety:**
Laser therapy uses specific wavelengths of light to stimulate damaged cells. The cells receive energy from the light and increase their production of whatever substance they would normally produce. In this case the cells we are targeting produce the fibres that make up the tendon, thus enhancing the repair process. Prior to commencing the study you will be asked questions regarding your health and fitness and be assessed against the inclusion/exclusion criteria to determine your suitability for the study. The risks associated with the laser treatment and the exercise regime are; laser light may damage the eyes in some instances and patients and therapists will wear protective glasses during treatment; also muscle/tendon soreness
during and after the exercise may be experienced. Please be aware that every effort has been made to minimize these risks. Most patients benefit from the exercises alone and this study is designed to see if laser therapy enhances the effects of exercise. If a situation arises where you feel uncomfortable you are encouraged to mention this to the physiotherapist and your further participation in the project will be discussed with you.

**Data collection and use of information**
Results of this project may be published but any data included will in no way be linked to any specific participant. You are most welcome to request a copy of the results of the project. The data collected will be securely stored in such a way that only the principal researchers will be able to gain access to it. At the end of the project any personal information will be destroyed immediately except that, as required by the University’s research policy. Any raw data on which the results of the project depend will be retained in secure storage for ten years, after which it will be destroyed.

**Cancellation Fee:**
*In accordance with the School of Physiotherapy Clinics’ policies and procedures, patients who have booked an appointment and then fail to cancel the appointment when they cannot attend will be charged a $25 cancellation fee.*

**COMPENSATION**

In the unlikely event of a physical injury as a result of your participation in this study, you will be covered by the accident compensation legislation with its limitations. If you have any questions about ACC please feel free to ask the researcher for more information before you agree to take part in this trial.

**Health & Disability Advocacy**
If you have any queries or concerns about your rights as a participant in this study you may wish to contact a Health and Disability Services Consumer Advocate, telephone: (03) 479 0265 or 0800 37 77 66. If there is a specific Maori issue/concern please contact Linda Grennell at 0800 377 766.

If you have any questions about this project, either now or in the future, please feel free to contact:

Steve Tumilty  
Principal Investigator  
School of Physiotherapy  
Tel: (03) 479 5757

This project has been approved by the Lower South Regional Ethics Committee.

CONSENT FORM FOR PARTICIPANT

REQUEST FOR INTERPRETER

<table>
<thead>
<tr>
<th>Language</th>
<th>I wish to have an interpreter</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>English</td>
<td>I wish to have an interpreter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maori</td>
<td>E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero</td>
<td>Ae</td>
<td>Kao</td>
</tr>
<tr>
<td>Cook Island</td>
<td>Ka inangaro au I tetai tangata uri reo</td>
<td>Ae</td>
<td>Kare</td>
</tr>
<tr>
<td>Fijian</td>
<td>Au gadreva me dua e vakadewa vosa vei au</td>
<td>Io</td>
<td>Sega</td>
</tr>
<tr>
<td>Niuean</td>
<td>Fia manako au ke fakaaoaga e taha tagata fakahokohoko kupu</td>
<td>E</td>
<td>Nakai</td>
</tr>
<tr>
<td>Samoan</td>
<td>Ou te mana’o ia i ai se fa’amatalata upu</td>
<td>Ioe</td>
<td>Leai</td>
</tr>
<tr>
<td>Tokelaun</td>
<td>Ko au e fofou ki he tino ke fakaliliu te gagana Peletania kin a gagana o na motu o te Pahafika</td>
<td>Ioe</td>
<td>Leai</td>
</tr>
<tr>
<td>Tongan</td>
<td>Oku ou fiemaú ha fakatonulea</td>
<td>Io</td>
<td>Ikai</td>
</tr>
</tbody>
</table>

I have read the information sheet dated July 2006 for volunteers taking part in the study designed to assess the effectiveness of lasers to treat Achilles tendon injury. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

- I have had the opportunity to use whanau support or a friend to help me ask questions and understand the study.
- I understand that taking part in the study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way effect my future health care/continuing health care.
- I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study.
- I understand that the treatment, or investigation, will be stopped if it should appear harmful to me.
- I understand the compensation provisions for this study.
- I have had time to consider whether to take part.
- I know who to contact if I have any side effects to the study.

I wish to receive a copy of the results.  YES/NO

Participants should be advised that a significant delay may occur between data collection and publication of results. Alternatively, “I would like the researcher to discuss the outcomes of the study with me”.  YES/NO
I agree to my G.P. or other current provider being informed of my participation in this study/the results of my participation in this study. YES/NO

I .......................................................... hereby consent to take part in this study.

..........................................................  ........................................
(Signature of participant)  (Date)

Project Explained by Steve Tumilty, principal researcher Tel: 03-479-5757

..........................................................  ........................................
(Signature of researcher)  (Date)

This project has been approved by the Lower South Regional Ethics Committee.
Data Collection Protocol (Pilot Study)

1. Patient registers at the clinic.
2. Patient given information sheet and consent form. Researcher available to answer any questions.
3. Patient assessed by principal investigator against inclusion/exclusion criteria.
4. Administration of VISA-A questionnaire. Researcher available to answer any questions.
5. Administration of VAS. Researcher available to answer any questions.
6. Biodex testing of calf muscle strength (see Biodex protocol).
7. Clinic receptionist randomizes the patient to a group.
9. Clinician completes treatment sheet for each visit.
10. Application of laser (see LLLT protocol).
11. Clinician explains eccentric exercises to the patient and monitors exercise progression (see eccentric exercise protocol).
12. Explanation/instruction on how to fill in the compliance log.
13. After 12 treatments principal investigator administers VAS, VISA-A and performs Biodex testing.
14. Three months after initial visit principal investigator will once again administer VAS, VISA-A and Biodex testing. Compliance log will be collected from the patients and an exit questionnaire will be completed.
15. If a patient drops out of the study before the protocol is complete they will be asked to return and have the outcomes measured (VAS, VISA-A and Biodex test) and complete an exit questionnaire.
Biodex Protocol

Biodex machine is to be calibrated before every session and set up to test concentric plantarflexion as per manufacturer’s instructions.

1. Patients to wear shorts and T-shirt with no shoes.
2. Patient performs 10 minutes warm-up exercise on the ergocycle at a comfortable resistance and intensity.
3. The unaffected side will be measured first.
4. Isokinetic measurement of muscle strength (N) with subjects seated with 40° knee flexion and hip at 110°. Strength will be measured between 20° of dorsiflexion and 30° of plantarflexion at a speed of 90°/s.
5. Patients will be allowed up to 10 repetitions at well below maximum contraction to get used to the Biodex machine.
6. Measurement of unaffected side
7. Adjust Biodex set up to measure the opposite side.
8. Isokinetic measurement of muscle strength (N) at the point when pain starts with subjects seated with 40° knee flexion and hip at 110°. Strength will be measured between 20° of dorsiflexion and 30° of plantarflexion at a speed of 90°/s.
9. Patients will be allowed up to 10 repetitions at well below maximum contraction to get used to the Biodex machine.

The unaffected side will be measured using the same protocol for comparison. Strength measured before treatment 1 and after treatment 12, and at the 3 month follow-up.

The therapy system used in this trial will be the Thor DD Laser Therapy Unit, a class 3B laser with an 810nm, 100mW infra red probe, spot size 0.0364cm² and power density of 2.75W/cm². The laser probe has been modified to provide a power density of 100mW/cm² (7mW over a spot size of 0.07 cm²). To produce a 3J dosage, irradiation will be allowed for 30s at each point.

1. Patient checked for contraindications.
2. Patient positioned prone on the plinth with the feet over the end of the plinth; ankle at a relaxed angle near plantargrade.
3. The skin around the treatment area is to be wiped with an alcohol swab.
4. The head of the laser probe is to be wiped with an alcohol swab.
5. Therapist and Patient to wear the protective glasses provided with the machine.
6. Switch on the laser device to be positioned at “1” or “2” as per allocation from the randomization process.
7. The timer is to be set for 30s and laser to be applied to 3 points each side of the tendon (6 X 30s). The sites are; at the site of the lesion, 2cm proximal and 2cm distal.
8. Clinician to check the treated area for any abnormal signs.
9. Clinician to document the parameters (810nm, 100mW, spot size 0.07 cm², power density 100mW/cm², treatment time 30s, energy 3J per point) at each treatment session.
Appendix VI: Main RCT Forms and Power Calculations


Information sheet for Participant (July 2007)

You are invited to take part in a study to assess the effectiveness of laser to treat Achilles tendon injuries. Please read this information sheet carefully, and take as much time as you need before deciding whether or not to participate in this project. If you decide to participate, we thank you. If you decide not to take part, there will be no disadvantage to you of any kind, you will still receive the usual treatment and we thank you for considering our request. Please be aware that you may decide at any time to withdraw from the project without any disadvantage to yourself of any kind.

- Participation in the study will be stopped should any harmful effects appear or if the therapist feels it is not in the participant’s best interests to continue.
- If you need an interpreter, one can be provided.
- You may have a friend, family or whanau support to help you understand the risks/benefits of this study and any other explanation you may require.
- Your G.P. will be informed of the results of your participation in this study.
- At the end of the study ongoing treatment will be provided under the normal ACC rules if required.

The aim of the project:
This project is being undertaken to explore the effectiveness of laser therapy as part of the management of patients with Achilles tendon pain.

Participants:
Volunteers between 18-65 years old who have pain in the region of the Achilles tendon and have not had treatment over the past 3 months.

Study requirements:
All participants in the study receive the standard treatment of exercises along with an active or inactive laser treatment. Participants will be required to be free from taking any anti-inflammatory medication. Should you agree to take part in this project, you will be allocated into one of two groups. The two groups will be treated identically with the exception of the laser therapy. One group will receive placebo laser, one group active laser. A placebo laser is a dummy and the group given the placebo laser will not get any of the expected effects of the laser. Participants will receive treatment and measurements will be recorded of their level of pain and function before treatment 1 and after treatment 12, 3 months
after the first treatment and finally by a postal questionnaire 12 months after initial
treatment. Treatment will be carried out by a clinician who will have no knowledge as
to which group you belong to. Participants will receive a set of exercises and be advised
on how and when to perform the exercises. In addition you will be given laser
treatment to six points around the Achilles tendon 3 times per week for 4 weeks with
either a placebo or active laser probe. You will be required to keep a diary for the first 3
months to record your exercise activity on a daily basis while taking part in the study.

Exercise Routine:
Participants will be instructed on how to perform the exercise training by the same
therapist who will also instruct them on how to fill out the diary.
Participants are to perform the exercises two times daily 7 days a week for 12 weeks.
During the 12 week training regimen, running is allowed only if it can be performed with
mild discomfort and no pain.

Measures of Pain and Function:
You will be required to complete the VISA-A questionnaire, a questionnaire designed to
measure the impact of your injury on your daily activities, before treatment 1 and after
treatment 12, at the 3 month follow up and finally at the 12 month follow up. You will
also be asked at every visit and at the 3 and 12 month follow up periods, to indicate the
amount of pain you have experienced by marking on a scale your level of pain.

Follow up Procedure: Three months after the initial treatment participants will be
asked to return for a final assessment of their level of pain and function. Twelve months
after the initial treatment a postal questionnaire (containing a return stamped
addressed envelope) will be sent to participants to see if any benefits from the
treatment still remain.

Benefits, risks and safety:
Laser therapy uses specific wavelengths of light to stimulate damaged cells. The cells
receive energy from the light and increase their production of whatever substance they
would normally produce. In this case the cells we are targeting produce the fibres that
make up the tendon, thus enhancing the repair process.
Prior to commencing the study you will be asked questions regarding your health and
fitness to determine your suitability for the study. The risks associated with the laser
treatment and the exercise regime are; laser light may damage the eyes in some
instances and patients and therapists will wear protective glasses during treatment; also
muscle/tendon soreness during and after the exercise may be experienced. Please be
aware that every effort has been made to minimize these risks. Most patients benefit
from the exercises alone and this study is designed to see if laser therapy enhances the
effects of exercise.
If a situation arises where you feel uncomfortable you are encouraged to mention this
to the physiotherapist and your further participation in the project will be discussed
with you.
Data collection and use of information
Results of this project may be published but any data included will in no way be linked to any specific participant. You are most welcome to request a copy of the results of the project. The data collected will be securely stored in such a way that only the principal researchers will be able to gain access to it. At the end of the project any personal information will be destroyed immediately except that, as required by the University’s research policy. Any raw data on which the results of the project depend will be retained in secure storage for ten years, after which it will be destroyed.

Costs:
Participants will not be required to cover any of the costs of treatment during the study.

Cancellation Fee:
In accordance with the School of Physiotherapy Clinics’ policies and procedures, patients who have booked an appointment and then fail to cancel the appointment when they cannot attend will be charged a $25 cancellation fee.

COMPENSATION
In the unlikely event of a physical injury as a result of your participation in this study, you will be covered by the accident compensation legislation with its limitations. If you have any questions about ACC please feel free to ask the researcher for more information before you agree to take part in this trial.

Health & Disability Advocacy
If you have any questions or concerns about 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. Local (03) 479 0265; Telephone: (NZ wide) 0800 555 050; Free Fax (NZ wide): 0800 2787 7678 (0800 2 SUPPORT); Email (NZ wide): advocacy@hdc.org.nz If there is a specific Maori issue/concern please contact Linda Grennell at 0800 37 77 66.

If you have any questions about this project, either now or in the future, please feel free to contact:

Steve Tumilty
Principal Investigator
School of Physiotherapy
Tel: (03) 479 5757

This project has been approved by the Lower South Regional Ethics Committee.

CONSENT FORM FOR PARTICIPANT

REQUEST FOR INTERPRETER

<table>
<thead>
<tr>
<th>Language</th>
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<th>Translation (Maori)</th>
<th>Translation (Cook Island)</th>
<th>Translation (Fijian)</th>
<th>Translation (Niuean)</th>
<th>Translation (Samoan)</th>
<th>Translation (Tokelaun)</th>
<th>Translation (Tongan)</th>
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<td>Ka inangaro au I tetai tangata uri reo</td>
<td>Au gadreva me dua e vakadewa vosa vei au</td>
<td>Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu</td>
<td>Ou te mana’o ia I ai se fa’amatala upu</td>
<td>Ko au e fofou ki he tino ke fakaliliu te gagana Peletania kin a gagana o na motu o te Pahafika</td>
<td>Oku ou fiemaú ha fakatonulea</td>
</tr>
<tr>
<td>Maori</td>
<td>Yes</td>
<td>Ae</td>
<td>Ae</td>
<td>Io</td>
<td>E</td>
<td>loe</td>
<td>Io</td>
<td>Io</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Kao</td>
<td>Kare</td>
<td>Sega</td>
<td>Nakai</td>
<td>Leai</td>
<td>Leai</td>
<td>Ikai</td>
</tr>
</tbody>
</table>

I have read the information sheet dated July 2007 for volunteers taking part in the study designed to assess the effectiveness of lasers to treat Achilles tendon injury. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

- I have had the opportunity to use whanau support or a friend to help me ask questions and understand the study.
- I understand that taking part in the study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way effect my future health care/continuing health care.
- I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study.
- I understand that the treatment, or investigation, will be stopped if it should appear harmful to me.
- I understand the compensation provisions for this study.
- I have had time to consider whether to take part.
- I know who to contact if I have any side effects to the study.
I wish to receive a copy of the results.

YES/NO

Participants should be advised that a significant delay may occur between data collection and publication of results. Alternatively, I would like the researcher to discuss the outcomes of the study with me.

YES/NO

I agree to my G.P. or other current provider being informed of my participation in this study/the results of my participation in this study.

YES/NO

I …………………………………………….hereby consent to take part in this study.

…………………………………………………………….…………………………………….
(Signature of participant) ......................................................... (Date)

Project Explained by Steve Tumilty, principal researcher Tel: 03-479-5757

…………………………………………………………….…………………………………….
(Signature of researcher) ......................................................... (Date)
Summary of PROTOCOL for:
Low-Level Laser Therapy in the Management of Achilles Tendinopathy

16. Patient registers at the clinic.
17. Patient given information sheet and consent form. Researcher available to answer any questions.
18. Patient assessed by principal investigator against inclusion/exclusion criteria.
19. Clinic administrator randomizes the patient to a group.
20. Administration of VISA-A questionnaire and VAS of pain. Researcher available to answer any questions.
21. Start Investigator’s Diary
22. Refer patient to clinician for treatment.
23. Start Clinician’s Diary
25. Clinician explains eccentric exercises to the patient and monitors exercise progression (see eccentric exercise protocol).
26. Explanation/instruction on how to fill in the compliance log.
27. After 12 treatments principal investigator administers VAS, VISA-A and the exit questionnaire (LLLT 12).
28. Three months after initial visit principal investigator will once again administer VAS, VISA-A. Compliance log will be collected from the patients and an exit questionnaire (LLLT 3) will be completed.
29. At 12 months administer via the postal system, VISA-A, VAS of pain and follow-up questionnaire.
30. If a patient drops out of the study before the protocol is complete they will be asked to return and have the outcomes measured (VAS, VISA-A) and complete an exit questionnaire.

The therapy system used in this trial will be the Thor DD Laser Therapy Unit, a class 3B laser with an 810nm, 100mW infra red probe, spot size 0.0364cm² and power density of 2.75W/cm². The laser probe has been modified to provide a power density of 100mW/cm² (7mW over a spot size of 0.07 cm²). To produce a 3J dosage, irradiation will be allowed for 30s at each point.

1. Patient checked for contraindications.
2. Patient positioned prone on the plinth with the feet over the end of the plinth; ankle at a relaxed angle near plantargrade.
3. The skin around the treatment area is to be wiped with an alcohol swab.
4. The head of the laser probe is to be wiped with an alcohol swab.
5. Therapist and Patient to wear the protective glasses provided with the machine.
6. Switch on the laser device to be positioned at “1” or “2” as per allocation from the randomization process.
7. The timer is to be set for 30s and laser to be applied to 3 points each side of the tendon (6 X 30s). The sites are; at the site of the lesion, 2cm proximal and 2cm distal (see figure 1.).
8. Clinician to check the treated area for any abnormal signs.
9. Clinician to document the parameters (810nm, 100mW, spot size 0.07 cm², power density 100mW/cm², treatment time 30s, energy 3J per point) at each treatment session.
ROC Curve for Power Calculations.

Receiver operating characteristic (ROC) curve MCID was determined to be the magnitude of change associated with the uppermost left-hand corner of the curve, where both sensitivity and 1-specificity are maximized resulting in 16 points on the VISA-A scale with a sensitivity of 92.3% and a specificity of 85.7%.

ROC Curve

Diagonal segments are produced by ties.
Coordinates of the Curve

Test Result Variable(s): VISA Change score

<table>
<thead>
<tr>
<th>Positive if Greater Than or Equal To ( ^{a} )</th>
<th>Sensitivity</th>
<th>1 - Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>-18.00</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>-13.50</td>
<td>1.000</td>
<td>.857</td>
</tr>
<tr>
<td>-2.00</td>
<td>1.000</td>
<td>.714</td>
</tr>
<tr>
<td>6.50</td>
<td>1.000</td>
<td>.571</td>
</tr>
<tr>
<td>9.50</td>
<td>1.000</td>
<td>.429</td>
</tr>
<tr>
<td>13.50</td>
<td>.923</td>
<td>.286</td>
</tr>
<tr>
<td><strong>16.00</strong></td>
<td><strong>.923</strong></td>
<td><strong>.143</strong></td>
</tr>
<tr>
<td>17.50</td>
<td>.846</td>
<td>.143</td>
</tr>
<tr>
<td>19.50</td>
<td>.769</td>
<td>.143</td>
</tr>
<tr>
<td>21.50</td>
<td>.692</td>
<td>.143</td>
</tr>
<tr>
<td>22.50</td>
<td>.615</td>
<td>.143</td>
</tr>
<tr>
<td>23.50</td>
<td>.538</td>
<td>.143</td>
</tr>
<tr>
<td>25.00</td>
<td>.462</td>
<td>.143</td>
</tr>
<tr>
<td>29.50</td>
<td>.385</td>
<td>.143</td>
</tr>
<tr>
<td>34.00</td>
<td>.385</td>
<td>.000</td>
</tr>
<tr>
<td>36.50</td>
<td>.308</td>
<td>.000</td>
</tr>
<tr>
<td>41.00</td>
<td>.231</td>
<td>.000</td>
</tr>
<tr>
<td>54.50</td>
<td>.154</td>
<td>.000</td>
</tr>
<tr>
<td>69.00</td>
<td>.077</td>
<td>.000</td>
</tr>
<tr>
<td>74.00</td>
<td>.000</td>
<td>.000</td>
</tr>
</tbody>
</table>

The test result variable(s): VISA Change score has at least one tie between the positive actual state group and the negative actual state group.

a. The smallest cut-off value is the minimum observed test value minus 1, and the largest cut-off value is the maximum observed test value plus 1. All the other cut-off values are the averages of two consecutive ordered observed test values.
Power Calculations:

From Melanie Bell (Statistician):

Plotting a ROC curve using SPSS (from VISA-A data and exit questionnaire) gives MCID of 16, therefore sample size calculations are;

sampsi 50 34, sd1(20.25) sd2(20.25) method(ancova) pre(1) post(2) r1(.3) power(0.80)

Estimated sample size for two samples with repeated measures

Assumptions:
  - alpha = 0.0500 (two-sided)
  - power = 0.8000
  - m1 = 50
  - m2 = 34
  - sd1 = 20.25
  - sd2 = 20.25
  - n2/n1 = 1.00

  number of follow-up measurements = 2
  correlation between follow-up measurements = 0.300
  number of baseline measurements = 1
  correlation between baseline & follow-up = 0.300

Method: ANCOVA
  - relative efficiency = 1.786
  - adjustment to sd = 0.748
  - adjusted sd1 = 15.154
  - adjusted sd2 = 15.154

Estimated required sample sizes:
  - n1 = 15
  - n2 = 15

Allowing for dropouts, 20 per group
Appendix VII: Alfredson’s Heavy Load Eccentric Exercise Protocol

EXERCISE PROTOCOL (Alfredson et al 1998)

The subjects will be instructed on how to perform the eccentric training by the same therapist who will also instruct them on how to fill out the activity/compliance log. Subjects to perform the exercises two times daily 7 days a week for 12 weeks. During the 12 week training regimen, **running is allowed only if it can be performed with mild discomfort and no pain.**

Two types of exercise to be used; eccentric loading of the calf muscles with knee straight, and to maximize the activation of the deep calf muscle with the knee bent. Each of the exercises to include 15 repetitions done in 3 sets (3 X 15 twice per day with knee bent and knee straight).

In the beginning the loading consists of body weight, subjects stand on their toes with all their body weight on the injured leg. The calf muscles are loaded by having the subject lower the heel beneath the forefoot. **No following push up onto the toes is allowed;** the non-injured leg is used to get back to the start position.

Subjects are told to **go ahead even if they experience pain and are only allowed to stop if the pain becomes disabling.**

**When subjects can complete the exercise without pain they must increase the loading by adding extra weight.** This can be done by filling a backpack with successively more weight or by using a weight machine.
Appendix VIII: VISA_A Questionnaire

The VISA-A questionnaire: An index of the severity of Achilles tendinopathy

IN THIS QUESTIONNAIRE, THE TERM PAIN REFERS SPECIFICALLY TO PAIN IN THE ACHILLES TENDON REGION

1. For how many minutes do you have stiffness in the Achilles region on first getting up?

<table>
<thead>
<tr>
<th>100 mins</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

2. Once you are warmed up for the day, do you have pain when stretching the Achilles tendon fully over the edge of a step? (keeping knee straight)

<table>
<thead>
<tr>
<th>Strong</th>
<th>Severe</th>
<th>Pain</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

3. After walking on flat ground for 30 minutes, do you have pain within the next 2 hours? (If unable to walk on flat ground for 30 minutes because of pain, score 0 for this question).

<table>
<thead>
<tr>
<th>Strong</th>
<th>Severe</th>
<th>Pain</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
4. Do you have pain walking downstairs with a normal gait cycle?

<table>
<thead>
<tr>
<th>strong</th>
<th>severe</th>
<th>pain</th>
<th>no pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

5. Do you have pain during or immediately after doing 10 (single leg) heel raises from a flat surface?

<table>
<thead>
<tr>
<th>strong</th>
<th>severe</th>
<th>pain</th>
<th>no pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

6. How many single leg hops can you do without pain?

<table>
<thead>
<tr>
<th>strong</th>
<th>severe</th>
<th>pain/usable</th>
<th>no pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

7. Are you currently undertaking sport or other physical activity?

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>x</td>
<td>Not at all</td>
</tr>
<tr>
<td>4</td>
<td>x</td>
<td>Modified training £ modified competition</td>
</tr>
<tr>
<td>7</td>
<td>x</td>
<td>Full training £ competition but not at same level as when symptoms began</td>
</tr>
<tr>
<td>10</td>
<td>x</td>
<td>Competing at the same or higher level as when symptoms began</td>
</tr>
</tbody>
</table>
8. Please complete EITHER A, B or C in this question.
   • If you have **no pain** while undertaking Achilles tendon loading sports please complete Q8a only.
   • If you have **pain** while undertaking Achilles tendon loading sports but it does not stop you from completing the activity, please complete Q8b only.
   • If you have **pain which stops you from completing Achilles tendon loading sports**, please complete Q8c only.

A. If you have **no pain** while undertaking Achilles tendon loading sports, for how long can you train/practise?

<table>
<thead>
<tr>
<th></th>
<th>1-10 mins</th>
<th>11-20 mins</th>
<th>21-30 mins</th>
<th>&gt;30 mins</th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIL</td>
<td>r</td>
<td>r</td>
<td>r</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>14</td>
<td>21</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

OR

B. If you have some pain while undertaking **Achilles tendon loading sport**, but it does not stop you from completing your training/practice for how long can you train/practise?

<table>
<thead>
<tr>
<th></th>
<th>1-10 mins</th>
<th>11-20 mins</th>
<th>21-30 mins</th>
<th>&gt;30 mins</th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIL</td>
<td>r</td>
<td>r</td>
<td>r</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>10</td>
<td>14</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

OR

C. If you have **pain that stops you** from completing your training/practice in **Achilles tendon loading sport**, for how long can you train/practise?

<table>
<thead>
<tr>
<th></th>
<th>1-10 mins</th>
<th>11-20 mins</th>
<th>21-30 mins</th>
<th>&gt;30 mins</th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIL</td>
<td>r</td>
<td>r</td>
<td>r</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5</td>
<td>7</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TOTAL SCORE</th>
<th>/100</th>
</tr>
</thead>
</table>

%
Appendix IX: Numeric Pain Rating Scale NPRS

Numeric Pain Rating Scale (NPRS)

**NPRS** scoring scheme (Point to one number):

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worst Possible Pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Assessment</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td></td>
</tr>
<tr>
<td>Worst in last 24 Hrs</td>
<td></td>
</tr>
<tr>
<td>Best in last 24hrs</td>
<td></td>
</tr>
<tr>
<td>Total xx/30</td>
<td></td>
</tr>
</tbody>
</table>

Rate your pain using the scale above; enter a score in each of the three boxes current; worst in last 24 hrs; best in last 24hrs. Then add them together and enter the total in the bottom box, giving you a score out of 30 points.
Appendix X: Questionnaires

Low Level Laser Therapy Questionnaire (at 4 & 12 Weeks)

1. Have you received Low Level Laser therapy as a form of treatment before?
   Yes □ No □
   If yes, please state for which condition you received treatment ……………………
   …………………………………………………………………………………
   …………………………………………………………………………………

2. What type of treatment do you believe you received in our study?
   LLLT□ Sham LLLT □ Don’t Know □

3. Would you recommend your treatment to a friend or colleague?
   Yes □ No □

4. Were you satisfied with the treatment given?
   Not satisfied □ satisfied □ very satisfied □

5. Did you find the treatment received benefited your condition?
   No benefit □ Some benefit □ A great deal □ Do not know □

6. Would you be happy to receive this form of treatment again
   Yes □ No □
   If no, please state why ………………………………………………………
   …………………………………………………………………………………
   …………………………………………………………………………………

7. Please add any other comments in the space below…………………………
   …………………………………………………………………………………
   …………………………………………………………………………………
   …………………………………………………………………………………
   Thank you for taking the time to complete this questionnaire.
1. How has your level of function changed compared to that at the 3 month point of the study?
   Much better □  Slightly better □  Same □  Slightly worse □  Much worse □

2. How has your level of participation in sports changed compared to that at the 3 month point of the study?
   Much better □  Slightly better □  Same □  Slightly worse □  Much worse □

3. If you are not back to full function or participation in sports, is this because of your Achilles tendon problem?
   Yes □  No □

4. Have you had a re-occurrence or re-injury of your Achilles tendon problem?
   Yes □  No □

5. Have you continued to do the eccentric exercises after the first 3 month period?
   1 per week □  2 per week □  3 per week □  not at all □  sporadically □

6. Would you be happy to self manage your Achilles problem for a period of time if the symptoms returned in the future?
   Yes □  No □

7. Please add any other comments in the space below..........................
   …………………………………………………………………………………..
   …………………………………………………………………………………..
   …………………………………………………………………………………..

Thank you for taking the time to complete this questionnaire.
Appendix XI: Compliance Data

Apart from the data presented in Chapter 7 (Tables 7-2 and 7-3), below is the results of a regression analysis on the compliance data from the main RCT, which was performed to explore any relationship between the number of exercise sessions completed at 12 weeks and the change in VISA-A scores over the first 3 months. Twenty eight completed logs were returned and due to the lack of statistically significant difference between the groups (reported in Chapter 6); analysis has been performed as per group allocation and as a single cohort.

Table A: Regression analysis with VISA-A Change Scores as the Dependant Variable.

<table>
<thead>
<tr>
<th>Model</th>
<th>Beta</th>
<th>Sig</th>
<th>95% CI</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Group (n=28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>26.275</td>
<td>0.001</td>
<td>12.589 to 39.962</td>
<td>0.045</td>
</tr>
<tr>
<td>Compliance at 12 weeks</td>
<td>0.072</td>
<td>0.281</td>
<td>-0.062 to 0.207</td>
<td></td>
</tr>
<tr>
<td>Placebo (n=12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>28.428</td>
<td>0.009</td>
<td>8.916 to 47.940</td>
<td>0.031</td>
</tr>
<tr>
<td>Compliance at 12 weeks</td>
<td>0.043</td>
<td>0.586</td>
<td>-0.127 to 0.213</td>
<td></td>
</tr>
<tr>
<td>Laser (n=16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>24.225</td>
<td>0.030</td>
<td>2.760 to 45.690</td>
<td>0.062</td>
</tr>
<tr>
<td>Compliance at 12 weeks</td>
<td>0.106</td>
<td>0.352</td>
<td>-0.130 to 0.342</td>
<td></td>
</tr>
</tbody>
</table>

It can be seen that no statistically significant relationship was established regardless of group allocation, or even when forming a single cohort. According to this data, the number of exercise sessions performed over the 12 week period can only explain 4.5% to 6.2% of the change in VISA-A score, depending on the grouping used above.
Considering that in both the pilot study and the main RCT, there were no statistically significant differences between groups with regards to change scores, it could be justified to amalgamate this compliance log data and form a single cohort to explore any relationships between compliance and change scores on the VISA-A at 12 weeks. This resulted in 43 sets of data being available; this data is presented below in the following two tables. Pain was measured differently across the two trials; therefore amalgamation of these scores was not attempted.

Table B: Change Scores and Compliance (number of exercise session completed) at 12 Weeks.

<table>
<thead>
<tr>
<th></th>
<th>VISA-A Mean (SD)</th>
<th># Exercise Sessions Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Group (n=43)</td>
<td>29.9 (17.0)</td>
<td>101.4 (43.2)</td>
</tr>
<tr>
<td>Placebo (n=20)</td>
<td>30.3 (12.1)</td>
<td>116.4 (43.8)</td>
</tr>
<tr>
<td>Laser (n=23)</td>
<td>29.5 (20.6)</td>
<td>88.5 (39.1)</td>
</tr>
</tbody>
</table>

Considering the larger numbers in this data set, compared to the main RCT alone, once again regression analysis was performed (Table C). Following the style reported in Chapter 7, sub-groupings were formed depending on the number of exercise sessions completed (Table D).
Table C: Regression Analysis with VISA-A Change Scores as the Dependant Variable (Pilot & Main RCT Data).

<table>
<thead>
<tr>
<th>Model</th>
<th>Beta</th>
<th>Sig</th>
<th>95% CI</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Group (n=43)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>32.159</td>
<td>0.000</td>
<td>18.546 to 45.771</td>
<td>0.003</td>
</tr>
<tr>
<td>Compliance at 12 weeks</td>
<td>-0.022</td>
<td>0.716</td>
<td>-0.146 to 0.101</td>
<td></td>
</tr>
<tr>
<td>Placebo (n=20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>35.289</td>
<td>0.000</td>
<td>18.495 to 52.082</td>
<td>0.024</td>
</tr>
<tr>
<td>Compliance at 12 weeks</td>
<td>-0.043</td>
<td>0.515</td>
<td>-0.178 to 0.093</td>
<td></td>
</tr>
<tr>
<td>Laser (n=23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>30.645</td>
<td>0.011</td>
<td>7.664 to 53.626</td>
<td>0.001</td>
</tr>
<tr>
<td>Compliance at 12 weeks</td>
<td>-0.013</td>
<td>0.913</td>
<td>-0.251 to 0.226</td>
<td></td>
</tr>
</tbody>
</table>

As in the previous analysis above, no statistically significant relationship was established regardless of group allocation, or even when forming a single cohort. The number of exercise sessions performed over the 12 week period can only explain at best 2.4% of the change in VISA-A score for the placebo group. In fact increasing the size of the data set has if anything weakened the relationship. Forming subgroups depending on the number of exercise sessions performed over the 12 week period (Table D), also failed to identify any relationship between the number of exercise sessions and the change in VISA-A scores.

The discussion in Chapter 7 highlighted the problem around patient adherence to a prescribed regime of treatment and the reporting of compliance in published studies. This data analysis presented here has also been unsuccessful in establishing any relationship between devotion to the exercise protocol and outcome (as measured on the VISA-A). It is evident that further work investigating this relationship, with a well designed adequately powered study is needed.
Table D: Change Scores and Compliance at 12 Weeks by Sub-grouping (Pilot & Main RCT Data).

<table>
<thead>
<tr>
<th>Subgroup (n)</th>
<th>VISA-A Mean (SD)</th>
<th># Exercise Sessions Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole group (n=43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; once per day (n=29)</td>
<td>30.6 (16.5)</td>
<td>124.7 (27.0)</td>
</tr>
<tr>
<td>&lt; once per day (n=14)</td>
<td>28.4 (18.5)</td>
<td>53.4 (27.9)</td>
</tr>
<tr>
<td>&lt; once every 2 days (n=6)</td>
<td>30.8 (9.8)</td>
<td>23.5 (9.7)</td>
</tr>
<tr>
<td>Placebo group (n=20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; once per day (n=17)</td>
<td>29.6 (12.7)</td>
<td>130.5 (27.6)</td>
</tr>
<tr>
<td>&lt; once per day (n=3)</td>
<td>34.3 (8.4)</td>
<td>36.3 (29.0)</td>
</tr>
<tr>
<td>&lt; once every 2 days (n=2)</td>
<td>29.5 (0.7)</td>
<td>20.5 (13.4)</td>
</tr>
<tr>
<td>Laser group (n=23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; once per day (n=12)</td>
<td>32.0 (21.2)</td>
<td>116.4 (24.8)</td>
</tr>
<tr>
<td>&lt; once per day (n=11)</td>
<td>26.8 (20.5)</td>
<td>58.0 (27.1)</td>
</tr>
<tr>
<td>&lt; once every 2 days (n=4)</td>
<td>31.5 (12.6)</td>
<td>25.0 (9.4)</td>
</tr>
</tbody>
</table>
### Main RCT Week 4 & 12 Questionnaire Results

<table>
<thead>
<tr>
<th>Question 1</th>
<th>Question 3</th>
<th>Question 6</th>
<th>Question 2</th>
<th>Question 4</th>
<th>Question 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>Week 12</td>
<td>Week 4</td>
<td>Week 12</td>
<td>Week 4</td>
<td>Week 12</td>
</tr>
<tr>
<td>Laser</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>18</td>
<td>18</td>
<td>2</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>1</td>
<td>15</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Placebo</td>
<td>18</td>
<td>18</td>
<td>4</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>1</td>
<td>15</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Whole Group</td>
<td>35</td>
<td>35</td>
<td>6</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>No</td>
<td>35</td>
<td>35</td>
<td>6</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>1</td>
<td>30</td>
<td>28</td>
<td>34</td>
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<tr>
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<td>2</td>
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<td>24</td>
<td>25</td>
<td>13</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>1</td>
<td>15</td>
<td>13</td>
<td>11</td>
</tr>
</tbody>
</table>
| Question 1: Have you received Low Level Laser Therapy as a form of treatment before?  
Question 2: What type of treatment do you believe you received in our study?  
Question 3: Would you recommend your treatment to a friend or colleague?  
Question 4: Were you satisfied with the treatment given?  
Question 5: Did you find the treatment received benefited your condition?  
Question 6: Would you be happy to receive this form of treatment again?
## Main RCT 52 Week Questionnaire Results

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Much better</th>
<th>Slightly better</th>
<th>Same</th>
<th>Slightly worse</th>
<th>Much worse</th>
<th>Not at All</th>
<th>Sporadically</th>
<th>1 per week</th>
<th>2 per week</th>
<th>3 per week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Group n=33</td>
<td>5</td>
<td>28</td>
<td>21</td>
<td>5</td>
<td>7</td>
<td>0</td>
<td>7</td>
<td>32</td>
<td>14</td>
<td>22</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Placebo n=16</td>
<td>2</td>
<td>14</td>
<td>11</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>16</td>
<td>6</td>
<td>13</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Laser n=17</td>
<td>3</td>
<td>14</td>
<td>10</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>16</td>
<td>8</td>
<td>9</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Question 1: How has your level of function changed compared to that at the 3 month point of the study?
Question 2: How has your level of participation in sports changed compared to that at the 3 month point of the study?
Question 3: If you are not back to full function or participation in sports, is this because of your Achilles tendon problem?
Question 4: Have you had a re-occurrence or re-injury of your Achilles tendon problem?
Question 5: Have you continued to do the eccentric exercises after the 3 month period?
Question 6: Would you be happy to self manage your Achilles problem for a period of time if the symptoms returned in the future?
9 References


Saygun, I., Karacay, S., Serdar, M., Ural, A. U., Sencimen, M., & Kurtis, B. (2008). Effects of laser irradiation on the release of basic fibroblast growth factor (bFGF), insulin like growth factor-1 (IGF-1), and receptor of IGF-1 (IGFBP3) from gingival fibroblasts. Lasers in Medical Science, 23(2), 211-215.


