Investigations on Tendinopathy: from Biomechanical Etiology to Novel Treatment Approaches

by

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ABSTRACT

Chronic tendinosis presents a considerable challenge for the health care professional treating either an athletic or sedentary population. Recent contributions from the literature assist in our understanding of the pathomechanics of overuse tendon injuries and provide greater understanding for potential new treatments. Nevertheless, our knowledge of the causative factors for tendinopathy remains incomplete and no standardized treatment protocol has been identified.

The research performed in this dissertation was intended to provide the clinician with an insight on two areas related to overuse tendinopathy: etiology and treatment. The specific objectives of the following studies include: understanding the contributions of movement patterns in tendinopathy at two sites in the lower-extremity, further our knowledge behind autologous blood injections as a treatment for tendinopathy, and provide preliminary evidence to the clinical efficacy for two experimental treatment approaches: a physiotherapy regimen incorporating dynamic stretches and balance exercises utilizing novel ultra-flexible footwear, and ultrasound guided hyperosmolar dextrose injections.

Our results indicate that there is may be an association between lower-extremity movement patterns and the occurrence of Achilles tendinopathy through differences in total eversion displacement of the sub-talar joint during the touchdown phase of running. While preliminary evidence from the literature of autologous blood injections appear promising, platinum-level evidence from well designed clinical trials must contend with the high degree of variability in the dose of the bioactive ingredients therein. An exercise-based treatment program incorporating multiple training elements appears to significantly improve the pain in a population with chronic plantar fasciitis, and performing these exercises wearing a soft, ultra-flexible shoe results in a faster improvement in pain. Lastly, sonographically guided injections of hyperosmolar dextrose emerge as a safe and effective treatment for recalcitrant tendinosis at the Achilles insertion, mid-portion, infrapatellar tendon and plantar fascia.

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LIST OF ABBREVIATIONS

- 2-D – Two-dimensional
- AEVmax – Maximum ankle eversion
- AFLmax – Maximum ankle plantarflexion
- AROMEV/IN – Frontal plane ankle range of motion (sub-talar joint)
- AROMFL/EX – Sagittal plane ankle range of motion (talocrural joint)
- AT – Achilles tendinopathy
- ATG – Achilles tendinopathy group
- AVELEV – Peak velocity of ankle eversion
- AVELEX – Peak velocity of ankle dorsiflexion
- AVELFL – Peak velocity of ankle plantarflexion
- AVELIN – Peak velocity of ankle inversion
- bFGF – Basic fibroblastic growth factor
- BMP – Bone morphogenic protein
- CON – Control group
- COX – Cyclooxygenase
- CS – Chondroitin sulfate
- CSA – Cross sectional area
- DS – Dermatan sulfate
- ECM – Extracellular matrix
- EGF – Endothelial growth factor
- EGF – Endothelial growth factor
- ERK – Extracellular signal-regulated kinase
- ESW – Extracorporeal shock waves
- ESWT – Extra-corporeal shock wave therapy
- GAG – Glycosaminoglycan
- HADmax – Maximum hip adduction
- HFLmax – Maximum hip flexion
- HROMAD/AB – Frontal plane hip range of motion
- HROMFL/EX – Sagital plane hip range of motion
- HVELAB – Peak velocity of hip abduction
- HVELAD – Peak velocity of hip adduction
- HVELEX – Peak velocity of hip extension
- HVELFL – Peak velocity of hip flexion
- IGF-1 – Insulin-like growth factor-1
- IL-1β – Interleukin-1β
- JNK – Jun N-terminal kinase
- KFLmax – Maximum knee flexion
- KROMFL/EX – Sagittal plane knee range of motion
- KS – Keratin sulfate

- KVELEX – Peak velocity of knee extension
- KVELFL – Peak velocity of knee flexion
- LLD – Leg length discrepancy
- MAPK – Mitogen-activated protein kinase
- MMP – Matrix metalloproteinase
- MRI – Magnetic resonance imaging
- NSAID – Non-steroidal anti-inflammatory drug
- PDGF – Platelet-derived growth factor (PDGF)
- PG – Proteoglycans
- PGE2 – Prostaglandin-E2
- PT – Patellar tendinosis
- Q-Angle – Quadriceps angle
- ROM – Range of Motion
- ROP – Roll over process
- RTK – Receptor tyrosine kinase
- SAPK – Stress activated protein kinases
- SLRP – Smaller leucine-rich proteoglycan
- SRS – Spatially resolved spectroscopy
- STJ – Subtalar joint
- tAEVmax – Timing of maximum ankle eversion
- tAFLmax – Timing of maximum ankle plantar flexion
- tAVELEV – Timing of peak velocity of ankle eversion
- tAVELEX – Timing of peak velocity of ankle dorsiflexion
- tAVELFL – Timing of peak velocity of ankle plantarflexion
- tAVELIN – Timing of peak velocity of ankle inversion
- TENS – Transcutaneous electrical nerve stimulation
- TGFb – Transforming growth factor b
- tHADmax – Timing of maximum hip adduction
- tHFLmax – Timing of maximum hip flexion
- tHVELAB – Timing of peak velocity of hip abduction
- tHVELAD – Timing of peak velocity of hip adduction
- tHVELEX – Timing of peak velocity of hip extension
- tHVELFL – Timing of peak velocity of hip flexion
- tKFLmax – Timing of maximum knee flexion
- tKVELEX – Timing of peak velocity of knee extension
- tKVELFL – Timing of peak velocity of knee flexion
- VAS – Visual analog scale
- VEGF – Vascular endothelial growth factor

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To Dorothy Jean Grimston

CO-AUTHORSHIP STATEMENT

Chapters 2 thru 9 include co-authors who have assisted Michael Ryan in carrying out of the respective research projects.

For chapters 2 and 3, Michael Ryan (MR) played a significant role within the team at the Department of Sports Medicine, Eberhard Karls University of Tübingen, Germany for the subject testing and research design. Data analysis and manuscript preparation was performed solely by MR.

For chapter 4, MR collaborated with the Centre of Blood Research at the University of British Columbia (UBC) in the design of the research. All research that was conducted and manuscript preparation, including data analysis, was performed solely by MR.

For chapter 5, MR collaborated with a physiotherapist at UBC for the design of the research study, and MR played a significant role in the subject testing. Data analysis and manuscript preparation was performed solely by MR.

For chapter 6, MR collaborated with the Department of Radiology at UBC, St. Paul's Hospital for the design of the research study and assisted in manuscript preparation. Data analysis was performed by MR.

For chapters 7 thru 9, MR continued collaboration with the Department of Radiology at UBC, St. Paul's Hospital for the design of the research. All data analyses and manuscript preparations were performed solely by MR.

Chapter 1 Introduction

1.1 TENDONS AND TENDINOPATHY

Tendons are connective tissue responsible for the transmission of the tensile forces of a muscular contraction to a bony attachment. Depending on their location, tendons can vary based on their specific function. For example: in the quadriceps, the tendon can be short and thick for efficient transmission of tensile load, whereas several of the tendons in the wrist and lower leg are long and thin making them better suited for the storage and release of elastic energy. The composition of tendons make them ideal structures for accommodating extraordinary tensile forces, sometimes as high as 10 times bodyweight. Accordingly, this form of connective tissue plays an important role in human locomotion.

Once thought of as relatively inert, avascular structures that occasionally become inflamed with too much exercise; a tremendous amount of information has been uncovered within the last 20 years concerning aspects related to tendon pathology. Yet there is still a tremendous amount left to be understood. Traditionally, individuals presenting to their family doctor complaining of long-standing pain at the Achilles, infra-patellar or supraspinatus tendons would be told they were suffering from tendinitis, would likely be given anti-inflammatory medication and be told to abstain or greatly reduce load to the affected joint. Not only do we understand now that the suffix “itis” is inappropriate for the majority of chronically painful cases of tendon pain due to a lack of inflammatory markers, but a lack of appropriate re-introduction and progression of mechanical loading may inadvertently lead to prolonged reduction of joint mobility, increased probability for rupture and pain. It is becoming understood that chronic tendinosis (the suffix “osis” reflecting the diseased or abnormal tissue condition) is a degenerative process that is characterized by a breakdown of the organization of the tendon at the tissue and cellular level.[1] At its full severity, tendinosis is extremely recalcitrant to treatment.[2] In certain cases where specific

evidence of tendon degeneration is not available (i.e. through surgical biopsy or imaging), the generalized term 'tendinopathy' is often used.[3]

Despite the increased neovascularity associated with pathology to tendon, one of the hallmarks of tendinosis is an abated or absent healing response.[4] [5] Subsequently, there are insufficiencies in the production of collagen, the maturation and cross-linking of collagen, or both. Coupled with a poorly organized and structurally compromised extracellular matrix (ECM), re-injury and increased chronicity are highly probable.[5]

Various treatments are currently available to address the symptoms of chronic tendon injuries, such as anti-inflammatory medication, activity modification, physical modalities (friction massage, Active Release Technique, transcutaneous electrical nerve stimulation (TENS)), extra-corporeal shock wave therapy, orthotic insoles, heel raises, stretching, strengthening, surgery and rest.[6,7] As our understanding of the pathomechanics of overuse tendinopathy has deepened there have been a series of next generation treatments documented within the past 10 years including extracorporeal shock wave therapy, nitric oxide, injections of stem cells or sclerosing agents, and modifications of training programs incorporating heavy load eccentric components. Some of these treatments hold tremendous promise in addressing the debilitating pain and loss of function associated with tendinosis while the practicality of others may challenge their clinical application.

Understandably, the best treatment for tendinopathy is prevention; however, our understanding of the etiology of overuse tendon injuries remains superficial. Much of the information available concerning the causative factors behind tendinopathies of the lower extremity is not pathology-specific (i.e. from studies of injuries to runners) and focuses on athletes, their training habits and movement patterns. In addition, there are challenges in isolating factors of interest within human subjects due to the presence of confounding variables that,

in some cases, are difficult to account for or we have only a limited understanding (i.e. genetic predisposition). With advancements in technology, such as three-dimensional motion capture and improved musculo-tendinous imaging capabilities, we can begin to understand other elements of an individual that were heretofore difficult to account for.

1.2 OBJECTIVES AND HYPOTHESES

The research outlined within this dissertation has attempted to capitalize on recent innovations within the fields of biomechanics and radiology in order to increase our understanding of the etiology and effectiveness of experimental treatments for chronic tendinopathy. The specific objectives of the following studies include: understanding the contributions of movement patterns in tendinopathy at two sites in the lower-extremity, further our knowledge behind autologous blood injections as a treatment for tendinopathy, and provide preliminary evidence for the clinical efficacy for two experimental treatment approaches: a physiotherapy regimen incorporating dynamic stretches and balance exercises using novel ultra-flexible footwear, and ultrasound guided hyperosmolar dextrose injections.

Based on data available from observational studies, it is hypothesized that specific movements of the foot and ankle (over-pronation) will be associated with the occurrence of Achilles tendinopathy in runners.[8]

A high degree of variability in the serum levels of three growth factors that feature prominently in the healing response for soft tissue (i.e. platelet-derived growth factor (PDGF), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF)) will be observed in a sample of healthy individuals providing implications on the dose of therapeutic agents in autologous blood injections.[9]

The physiotherapy regimen utilizing multiple training concepts will result in a reduction in the pain associated with chronic plantar fasciitis; however,

performing the exercises outlined in the regimen with the ultra-flexible footwear (Nike Free 5.0), versus conventional running shoes, will result in a greater reduction in pain.

For patients experiencing recalcitrant long-term tendinosis or degeneration of the plantar fascia, Achilles tendon insertion or mid-portion, and infra-patellar tendons, injections of ultrasound guided hyperosmolar dextrose are hypothesized to provide a significant clinical reduction in pain and positive structural improvement in sonographic tendon appearance.

1.3 LITERATURE REVIEW

1.3.1 Tendon Anatomy and Physiology

1.3.1.1 Tendon Structure

The structure, composition and organization of tendon are critically important for its physical properties. Formed from mesenchyme, this form of dense regular connective tissue is designed to withstand great tensile stress applied in one direction.[10] The smallest functional unit is the fibril, consisting largely of collagen molecules, which range in diameter from 10 to 500nm depending on the age, location and species from which the tendon was sampled.[11] Collagen fibrils aggregate together into fibers and bundles of fibers ('fascicles') are bound by a thin layer of loose connective tissue known as the endotenon. Blood vessels, lymphatics and nerves generally pass throughout the body of the tendon via the endotenon. Bundles of fascicles are further surrounded by the epitenon, a structure similar to the endotenon in its properties and supply of blood vessels, lymphatics and nerves.[12] Tensile strength of the tendon is assisted predominantly by aligning these bundle fibers with the long axis of the tendon. A small portion of the fibers run in alternate directions (i.e. transverse or spiral orientation) providing resistance against transverse, shear or rotational forces acting on the tendon.[13]

1.3.1.2 Cellular Composition

Tendons are comprised of primarily two distinct cell populations. Embedded within the proteoglycan-rich matrix of the epitenon, are synovial cells producing largely fibronectin, as well as collagens I and III, and positive and negative modulators of cell division (via IGF and its binding proteins 3 and 5).[14] Synovial epitenon cells have been demonstrated in playing a role in the reparative response to tendon by infiltrating the endotenon in the case of trauma. Fibroblasts (sometimes referred to as tenocytes) dominate the internal structure of tendons and are responsible for the primary physiologic function of tendons. The fibroblasts within tendon are arranged in longitudinal rows within the extracellular matrix (ECM) and have numerous sheet-like extensions providing a three-dimensional latticework for effective cell-cell signaling. These cells regulate and synthesize collagens, as well as proteoglycans and elastin fibers.

1.3.1.3 Collagen

Collagen forms the backbone of tendon tissue, assisting with its structure and providing tensile strength. Without collagen, tendons would not be able to perform one of their primary functions of transmitting muscle forces to bone. The collagen family is a group of triple-helix polypeptides formed from procollagen, a molecule transcribed from collagen genes inside of fibroblasts. While there are 27 different types of collagens encoded by 41 genes, tendons are comprised predominantly of type I collagen (around 60% dry mass of tendon tissue and approximately 95% of the total collagen content).[15] Type III collagen is the next most abundant, constituting around 3% of the total content and can also be interposed between type-I collagen fibers in aging or highly stressed tendons. In the healing equine tendon, the smaller and less organized type III collagen production is increased during the early phase of wound healing, however, is gradually replaced by type I as the tissue finishes remodeling.[16] The lesser biomechanical properties of type-III collagen are relevant in the pathomechanism of tendon injury, considering that return to pre-injury tensile loading may precede adequate transition back to the expression of type I collagen.[17]

Fibrillar collagen is synthesized from procollagen, a precursor molecule derived from preprocollagen, which is transcribed from collagen genes.[18] Actual collagen fibrils are formed after procollagen is secreted from the cell. Lysyl oxidase works at oxidizing specific lysine and hydroxylysine residues, allowing crosslinking to take place between individual collagen molecules. The stabilizing array secondary to this crosslinking is the characteristic component to collagen and is the major contributor to its tensile strength.

1.3.1.4 Proteoglycans

Proteoglycans (PG) are composed of a core protein to which one or more glycosaminoglycan (GAG) chains are covalently attached endowing the PG with its unique properties.[19] PG's within tendon can be divided into smaller leucine-rich proteoglycans (SLRPs) responsible to the facilitation and regulation of collagen synthesis, and larger modular PGs, whose negatively charged hydrophilic properties assist in resisting compressive forces (Table 1.1). The distribution of PG content varies with the site of the tendon and depends on whether the tendon experiences predominantly compressive or tensile loading forces.[20]

In recent years, the critical role that these non-collagenous matrix proteins play in the function of tendons has become increasingly clear.[21,22] Decorin is the most abundant tendon PG belonging to the SLRP family, and is considered a key regulator of matrix assembly due to its regulation of both collagen fibril formation and cell proliferation.[23,24] Electron microscope examination of the skin in decorin knockout mice show that, in the absence of decorin, collagen fibrils are coarse, irregular and unable to withstand sudden tensile strain. Biglycan also interacts with type I collagen though the nature of this interaction is not well understood.[19] It is known that the collagen fibrils are smaller in diameter with abnormal morphology in biglycan knockout mice.[25] Fibromodulin and lumican share the same collagen binding site and play a role in regulating collagen fiber diameter.[19] Certain flexor tendons that wrap around bony prominences (i.e. supraspinatus)

and areas in a tendon adjacent to the bone attachment site will have much higher concentrations of aggrecan owing to the compression adaptation inherent with this PG. Hyaluronan and versican are expressed largely in compressive tendons and increases in versican content leads to expansion of the ECM with increased compensatory viscoelasticity of neighboring cell shapes.

Tenascin-C is also believed to play an important role in the ECM, primarily at the osteotendinous junction, and is up-regulated when very strong attachments are needed.[26] The elastic properties of tenascin-C contribute to the ability of tendons to be stretched several times their resting length under tensile loading.

1.3.1.5 Tendon Vasculature

Compared with muscle, tendons have relatively limited vasculature, with the area occupied by vessels representing approximately 1-2% of the entire ECM.[27] The vessels mainly arise from the epitenon where longitudinal vessels run into the endotenon. While tendons are comparatively avascular, it is known that blood flow in both tendons and ligaments increase with exercise and during healing in animals. With the use of near-infrared spectroscopy and simultaneous infusion of contrast substance, it has been possible to demonstrate in humans that blood flow within and around tendon connective tissue increases up to sevenfold during exercise, both in young, middle-aged ad elderly individuals.[28 29,30]

With regard to the ECM, the main question is whether the increase in flow during intense exercise is sufficient to meet the oxidative needs of the tendon and its cells. Determination of oxygen saturation using spatially resolved spectroscopy (SRS) of the Achilles peritendinous region at rest and during increasing intensity levels demonstrated that a tight correlation exists between increasing blood flow and increasing oxygen uptake in tendon tissue.[30] The SRS-O_2 saturation represents the quantitative sum of venous and arterialized blood O_2 saturations in the specific tissue region; therefore, represents the net saturation of haemoglobin and indicates the balance of between O_2 delivery and O_2 uptake. Considering that even with intense exercise O_2 saturation levels did not drop

below 52% for the peritendinous tissue, there was no indication of tissue ischemia .[27]

1.3.1.6 Tendon Innervation

Tendon innervation originates from cutaneous, muscular, and peritendinous nerve trunks.[31] At the myotendinous junction, nerve fibers cross and enter the endotenon septa. Nerve fibers form rich plexuses in the paratenon, and branches will penetrate the epitenon. Most nerve fibers do not actually enter the main body of the tendon but terminate as nerve endings on its surface. Both sympathetic and parasympathetic fibers are present in tendon.[32]

1.3.2 Tendon Mechanobiology

1.3.2.1 Mechanical Properties

Tendons are able to tolerate tremendous tensile forces secondary to the elaborate interplay between their hierarchical and biochemical structure. In human tendons, it has been estimated that the peak force transmitted through the Achilles tendon during running was 9kN, equivalent to 12.5 times body weight.[33]

Mechanically, tendons behave a particular way when they encounter tensile stress.[34] The collagen in the tendon fiber is typically arranged in a wavy 'crimp' pattern will flatten when load is first applied. The flattening pattern is represented in the 'toe' region of the stress-strain curve and is tendon's first form of adaptation to strain.

The angle and length of the crimp pattern can influence the overall strength of the tendon, with larger angles reporting greater tensile strength than small.[35] Once tendons have been stretched beyond roughly 4% and the collagen fibers lose their crimp pattern, the slope of the stress-strain curve becomes linear and is referred to as the Young's module of the tendon.[35] At this point, microscopic tearing will occur. Beyond 8-10% strain, macroscopic tearing occurs, which precedes large scale rupture with continued strain.[36] These figures are given as

representing overall tendon tissue and may underestimate the biomechanical strength of specific tendons to a specific species.

Similar to other soft tissue, tendons are viscoelastic and sensitive to different strain rates. The viscoelasticity of tendon likely results from collagen, water and other non-collagenous proteins in the ECM (i.e. proteoglycans).[37] The important viscoelastic properties of tendon are its ability to deform and absorb more energy at low strain rates; but behave much stiffer with high strain rates allowing more efficient transfer of larger loads.[38]

1.3.2.2 Response to Training and Immobilization

It has been known for some time that the properties of tendon will change depending on the functional demands that are placed on them. Exercise has been shown in various animal models to increase the ultimate load and energy absorption at failure, increase the tendon strength at the insertion, and increase the number and size of collagen fibrils.[39,40,41,42] After prolonged training and repeated exposure to high tendon load (i.e. running mechanics on the Achilles tendon), it has been shown that runners who trained in excess of 80km/week had a larger Achilles tendon cross-sectional area (CSA) compared to age-matched controls.[43] The larger CSA of the trained tendon results in a lower stress on the tendon during maximal isometric force in trained compared with untrained individuals, and thus provides a potentially more injury-resistant tendon.

Biochemically, endurance training over 8 weeks has shown to increase collagen deposition by 46%; however, the collagen contained 50% fewer pyridinoline cross-links.[39] These results are suggestive to injury potential following intense exercise subsequent to the increased collagen turnover and reduced collagen maturation. Overall, the anabolic response and net synthesis of type I collagen will dominate in the regenerating tendon assuming an appropriate amount of time has elapsed between repeated intense bouts of tendon strain. Furthermore, when type I collagen synthesis and degradation in connective tissue of the

Achilles peritendinous space was studied before and after 4 and 11 weeks of intense physical training, a specific adaptive response of the collagen type I metabolism of the peritendinous tissue around the human Achilles tendon was found in response to physical training.[44]

The effect of disuse and immobilization on tendons is not as well investigated. Tendons will respond much slower than skeletal muscle to disuse due to their considerably slower metabolism and decreased vascularity.[34] Not surprisingly, the research that has been performed on tendon immobilization suggests that tendon responds much like other soft tissue when not used: decreased total weight, stiffness and tensile strength.[45]

1.3.2.3 Cellular Response to Mechanical Loading: Principles of Mechanotransduction

Tendons respond to altered mechanical loading conditions by changing their structure, composition and mechanical properties. Fibroblasts within the tendon respond to mechanical forces by altering gene expression, protein synthesis, and cell phenotype.

These early adaptive responses may proceed and initiate long-term tendon structure modifications and thus lead to changes in the tendon's mechanical properties. Mechanotransduction is the process involving several of the cellular components that transduce mechanical forces into a cellular and genetic response.[46] These cellular components include the extracellular matrix, cytoskeleton, integrins, G-proteins, receptor tyrosine kinases (RTKs), mitogen-activated protein kinases (MAPKs) and stretching-activated ion channels. These components are related in a cell either physically, functionally or both.

The extracellular matrix acts as a scaffold defining tissue shape and structure. Previous studies have shown that mechanical loading influences ECM protein production through both the release of growth factors (specifically TGF-β1, bFGF and PDGF) and the expression and activity of matrix metalloproteinases.[47,48]

Mechanically, the ECM transmits mechanical load, stores and dissipates loading-induced elastic energy.[34] Mechanical forces applied to the cell surface have been shown to transmit directly to the cytoskeleton via integrin proteins embedded within the cell membrane.[46] Changes to the cytoskeleton from applied mechanical forces then initiate complex signal transduction cascades within the cell through the activation of G protein receptors, RTKs, and MAPKs.[49,34]

MAPKs play particular importance in mechanotransduction pathways due to the fact they can travel into the nucleus and interact with transcription factors and promoters to alter gene expression as well as interact with the ribosomal S6 kinase (RSK) and initiate translation.[50] The MAPK cascade comprises three different pathways: the extracellular signal-regulated kinase (ERK) 1 and 2, and stress activated protein kinases (SAPK)/ c-Jun N-terminal kinase (JNK). A previous study has shown that mechanical forces, both *in vitro* and in vivo, activate MAPKs in vascular cells.[51] Cyclic stretching has also been shown to activate JNK in patellar tendon fibroblasts.[52]

1.3.2.4 Tendon Response to Injury

Studies of tendon healing predominantly have been performed on transected animal tendons or ruptured human tendons, and their relevance to healing of tendinopathic human tendons remains unclear.

Tendon healing can be largely divided into three overlapping phases: the inflammatory, repair, and remodeling phases.[31] In the initial inflammatory phase, which lasts about 24 hours erythrocytes, platelets, and inflammatory cells (e.g., neutrophils, monocytes, and macrophages) migrate to the wound site and clean the site of necrotic materials by phagocytosis. In the mean time, these cells release vasoactive and chemotactic factors, which recruit tendon fibroblasts to begin collagen synthesis and deposition.[18]

A few days after the injury, the repairing phase begins. In this phase, which lasts a few weeks, tendon fibroblasts synthesize abundant collagen and other ECM components such as proteoglycans and deposit them to the wound site. During the repairing phase, water content and glycosaminoglycan concentration remain high.

After approximately six weeks, the remodeling phase commences, with decreased cellularity and decreased collagen and glycosaminoglycan synthesis. The remodeling phase can be divided into a consolidation stage and a maturation stage. The consolidation stage begins at about six weeks and continues for up to ten weeks. In this period, the repair tissue changes from cellular to fibrous. Tenocyte metabolism remains high during this period, and tenocytes and collagen fibers become aligned in the direction of stress. A higher proportion of type-I collagen is synthesized during this stage. After ten weeks, the maturation stage occurs, with gradual change of the fibrous tissue to scar-like tendon tissue over the course of one year. During the latter half of this stage, tenocyte metabolism and tendon vascularity decline.

A large and growing body of evidence suggests that matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) play an important role in the remodeling of the extracellular matrix.[53] These enzymes constitute a family of zinc-dependent endopeptidases which are expressed at low levels in normal adult tissues but are up-regulated during normal and pathological remodeling processes such as embryonic development, tissue repair, inflammation, tumor invasion and metastasis.[54] As a family, MMPs degrade most components of the ECM. There are now >20 members of the MMP family. There are several distinct subgroups based on preferential substrates or similar structural domains: collagenases that are active against fibrillar collagen, gelatinases that have high activity against denatured collagens, stromelysins that degrade non-collagen components of the ECM, membrane type MMPs that are trans-membrane molecules, and other less characterized members.[55]

The levels of MMPs during tendon healing are known to be varied. In a rat flexor tendon laceration model, the expression of MMP-9 and MMP-13 (collagenase-3) peaked between the seventh and fourteenth days after the surgery.[56] MMP-2, MMP-3, and MMP-14 levels increased after the surgery and remained high until the twenty-eighth day. These findings suggest that MMP-9 and MMP-13 participate only in collagen degradation, whereas MMP-2, MMP-3, and MMP-14 participate both in collagen degradation and remodeling.

Wounding and inflammation of tendon tissue also provoke release of growth factors and cytokines from platelets, polymorphonuclear leukocytes, macrophages, and other inflammatory cells.[57] These growth factors induce neovascularization and chemotaxis of fibroblasts and tenocytes and stimulate fibroblast and tenocyte proliferation as well as synthesis of collagen.[58,59] Bone morphogenic proteins (BMPs) also play a positive role in the repair process in tendon, however, attempts at exogenous BMP interventions in healing rat Achilles models have failed to show conclusive results.

In cases of chronic injury to tendon, presumably after repeated injury/re-injury cycles, different physiological processes take place which are not completely understood. For instance, the presence of the neurotransmitter glutamate and substance-P has only recently been implicated in the hyperalgesia often accompanying chronic tendon injury.[4 60 61] The increased neovascularity seen clearly on Doppler ultrasound has also been associated with a neurogenic source of pain; however, results from other studies suggest this relationship may be more indirect.[62-64] A later section on the pathophysiology of tendinosis discusses in greater depth the changes occurring during the degeneration of tendon tissue during the chronic injury process.

1.3.3 Epidemiology, Etiology and Pathophysiology of Achilles and Infrapatellar Tendinopathy and Plantar Fasciitis

1.3.3.1 Epidemiology

The occurrence of Achilles tendinopathy is highest among individuals, predominantly men, who participate in middle and long-distance running, orienteering, track and field, tennis, badminton, volleyball and soccer.[7] It has been shown that Achilles tendinopathy has a particularly high incidence rate among former elite middle and long-distance runners.[65]

In a report on 698 patients with Achilles tendon injuries, 66% had injury to the mid-portion and 23% had Achilles tendon insertional problems.[66] In 8% of the patients, the injury was located at the myotendinous junction, and 3% of patients had a complete tendon rupture. Of the patients with Achilles tendon problems, 89% were men. Achilles tendinopathy is also known to affect individuals in an occupational setting, leading to pain and compromised function at the workplace.[67]

Patellar tendinosis, also referred to as 'jumper's knee', is associated with pain focusing directly on the patellar tendon, usually near its proximal insertion to the patellar.[68] As it's name suggests, it is particularly prevalent in athletic populations that require repetitive, explosive power from knee extensors such as basketball, volleyball, soccer and track and field such that upwards of 40-50% of participants are affected.[69,70] A prospective case control analysis of athletes with PT, more than half of the subjects had to stop their sports career because of the knee pain, although there was no difference in their workplace productivity or ability to enjoy leisure-time physical activity in the years following their injury.[71]

Plantar fasciitis, or its pseudonyms 'painful-heel syndrome' or 'chronic plantar heel pain', is a common injury among both athletes in running-based sports as well as professions requiring prolonged periods of weight bearing. It is reported to account for 15% of all adult foot complaints requiring profession consultation, and in a survey of 2002 running injuries, plantar fasciitis was the third most

prevalent injury.[72 73] Primarily affecting people over the age of 40 years, typical complaints involve morning pain, pain on standing after periods of inactivity, and pain with running subsiding after warm-up and returning later in the workout.[2]

1.3.3.2 Etiology

Overuse soft tissue injuries are considered to be multi-factorial in origin, culminating in the interplay between intrinsic and extrinsic factors. It is believed that intrinsic factors such as alignment and biomechanical faults play a causative role in two-thirds of Achilles tendon disorders in athletes.[66] This is still largely speculative, given the etiological strength of extrinsic variables such as weekly training volume, increases in training volume, and weekly frequency of training sessions in the cause of most sport-related overuse injuries.[74] Causation of tendinopathy, including in the Achilles tendon, in a sedentary population has not been well investigated. However, chronic painful mid-portion Achilles tendinopathy has been demonstrated in physically inactive individuals.[75,6] Furthermore, in a large study of patients with chronic Achilles tendinopathy, it was reported that physical activity was not correlated to histopathology suggesting that physical activity could be more important in provoking the symptoms than being the cause of the actual lesion.[76,77]

Over-pronation of the sub-talar joint has been suggested as etiologically important in the onset of mid-portion injury secondary to the “Whiplash effect”: a large degree of rear-foot eversion (i.e. leading to greater calcaneal valgus) at mid-stance may place disproportionate strain on medial fibers of the Achilles tendon.[8] Malalignment of the rear-foot during stance, together with high loads placed on the triceps surae muscle/tendon unit from eccentric contraction and release, was a proposed mechanism by Clement *et al.* (1984) that would ultimately result in injury. However, it was not specified which rear-foot or sub-talar joint position was clinically relevant with respect to the occurrence of Achilles tendinopathy.

Previous research investigating the role that lower extremity movement patterns play in the occurrence of mid-portion Achilles tendinopathy is sparse and inconclusive. Kinematic analysis of runners with Achilles tendinopathy began with McCrory *et al.* (1999) using two-dimensional (2-D) video analysis to evaluate a series of variables associated with rear-foot motion.[78] They reported that, in comparison to their control group, the Achilles tendinopathy group displayed greater maximum pronation, time to maximum pronation and calcaneal to vertical touch-down angle. Despite the apparent differences reported in this study, significant sources of error (i.e. parallax) are well known to be associated with 2-D kinematic analysis and can significantly influence movement outcomes.[79,80] Recent 3-D kinematic investigations by Donoghue *et al.* (2008) have supported the concept of over-pronation playing a role in the onset of Achilles tendinopathy; however by limiting recruitment in their injury group to only those individuals with demonstrable over-pronation, the generalizability of the results are limited.[81]

It is also believed that certain genetic elements might, in part, be associated with tendinopathy. An idea which has recently been highlighted by the finding of a significantly higher involvement of bilateral Achilles tendon ruptures in subjects with a previous unilateral rupture.[82]

In an investigation of the genetic contributions to various musculoskeletal injuries, a gene on the tip of chromosome 9q, closely linked to the *ABO* blood gene, was shown to be related to both the occurrence of Achilles tendinopathy and Achilles tendon ruptures.[83] However, the strength of this particular association appears to be tenuous, as other authors have been unable to replicate these findings.[84] Interestingly, a separate investigation into the guanine-thymine dinucleotide repeat polymorphism on the gene coding for tenascin-C (ECM glycoprotein expressed in areas of tendon under high mechanical load and plays an important role in regulating cell-matrix interactions) was able to differentiate habitual runners with overuse Achilles tendon injuries from age and activity matched controls.[85] These authors further speculate that

because mechanical signals are able to regulate cell-matrix interactions, coupled with the knowledge that abnormal mechanical loading can initiate programmed cell death, tenascin-C may play an important role in the proposed apoptotic model of tendinopathy.[86] This is a promising future direction in our understanding of the etiology of chronic overuse tendinopathy.

1.3.3.3 Pathophysiology

From a histological perspective, degenerative tendinopathy is the most common histological finding in spontaneous tendon ruptures, which suggests a link between chronic painful overuse tendinopathy and tendon ruptures.[77] Whether symptomatic or not, In one study of seventy-four patients with an Achilles tendon rupture, degenerative changes were found in all tendons, and it was hypothesized that those changes were due to intrinsic abnormalities that had been present before the rupture.[76] These results have been confirmed in a further study of 891 tendons, where even 149 (33%) of the control tendons showed signs of degeneration.[87] It is believed that tendon degeneration secondary to repetitive overuse and cumulative micro-trauma leads to reduced tensile strength and a predisposition to rupture.[31]

Excessive loading of tendons during vigorous physical training is regarded as the main pathological stimulus for degeneration.[88] Tendons respond to repetitive overload beyond the physiological threshold with either inflammation of their sheath or degeneration of their body, or both.[89] Different stresses induce different responses. Unless fatigue damage is actively repaired, tendons will weaken and eventually rupture.[90] The repair mechanism is probably mediated by resident tenocytes, which maintain a fine balance between extracellular matrix network production and degradation. Tendon damage may even occur from stresses within the physiological limits, as frequent cumulative microtrauma may not allow enough time for repair.[89] Microtrauma can also result from nonuniform stress within tendons, producing abnormal load concentrations and frictional forces between the fibrils causing localized fiber damage.[91] Evidence of

degeneration can seen with MRI, but is also well observed with grey-scale and Power Doppler ultrasound modalities.[5] Failure of the surrounding tissue may explain the increase in cell number, angiogenesis, and neuronal sprouting observed in the area immediately adjacent to the hypoechoeic tendinosis lesion.

In chronic Achilles tendinopathy, the peritendinous tissue appears thickened on macroscopic examination, and fibrinous exudate, prominent and widespread proliferation of fibroblasts, and formation of new connective tissue and adhesions are evident on histological examination.[89] Two types of cells have been identified in the peritendinous tissue in the chronic phase of Achilles tendinopathy: fibroblasts and myofibroblasts.[92] The myofibroblasts have stress fibers that are composed of *α*- smooth muscle actin in their cytoplasm, and thus they are capable of creating forces required for wound contraction.[93] In Achilles tendinopathy, these cells are especially well established at the sites of scar formation, and it has been estimated that, in chronic tendinopathy, about 20% of the cells in the peritendinous tissue are myofibroblasts. The myofibroblasts synthesize abundant amounts of collagen and are believed to be responsible for the formation of permanent scarring and the shrinkage of peritendinous tissue around the tendon and most likely also play an important role in the clinical symptoms of this disorder.[92] They can induce and maintain a prolonged contracted state in the peritendinous adhesions around the tendon and thus influence the development of a contracture around the tendon. This, in turn, may lead to constriction of vascular channels and impaired circulation and may further contribute to the pathogenesis of Achilles tendinopathy.

Histologically, degenerative changes are found in 90% of the biopsy specimens taken from symptomatic parts of the degenerative tendon.[1] These changes can be classified as: (1) hypoxic degeneration, (2) hyaline degeneration, (3) mucoid or myxoid degeneration, (4) fibrinoid degeneration, (5) fatty degeneration, (6) calcification, or (7) fibrocartilaginous or osseous metaplasia.[94] Occasionally, these alterations can be found simultaneously, adjacent to each other in the

tendon affected by tendinopathy. Using a microdialysis technique, high levels of lactate were found intratendinously in patients with Achilles tendinosis and such hypoxic degenerative tendinopathy, alone or in combination with other forms of tendon degeneration, was shown to be associated with subcutaneous tendon rupture in >75% of 891 ruptured tendons.[87 95]

The exact mechanism of tendon pathophysiology remains unclear, however, there have been several proposed pathomechanisms including: free-radical release secondary to reperfusion of ischaemic tissue; hyperthermia subsequent to tendon overuse; excessive fibroblast apoptosis; and increased production of cytokines and inflammatory prostaglandins secondary to repetitive tensile stimulus.[96,97,98,99,100]

The latter mechanism involving increased cytokine and inflammatory prostaglandin expression has been well investigated. *In vitro* studies have shown that repetitive mechanical loading of human tendon fibroblasts increases the production of prostaglandin-E_2 (PGE_2) in human patellar fibroblasts, and it increases interleukin-6 (IL-6) secretion and interleukin-1β (IL-1β) gene expression in human flexor fibroblasts (Figure 1-4).[101,52] Coupled with the release of these cytokines is the release of MMP1 and MMP3 in rabbit Achilles tendon cells exposed to either IL-1β, stretch or both.[48]

IL-6 has been reported to stimulate the differentiation of lymphocytes and to contribute to inflammation, in addition to playing a pathogenic role in inflammatory arthropathies.[102] PGE_2 is synthesized from arachidonic acid via the action of cyclooxygenase (COX), and mechanical stretching of human tendon fibroblasts has been shown to lead to increased COX expression levels.[52] Further investigations show the degenerative response and inflammatory changes in tendon tissue by light and transmission electron microscopy after repeated exposure to various levels of PGE_2.[103] Therefore, the production of IL-6, PGE_2 by fibroblasts in tendon, paratendon, or surrounding connective tissue in

response to mechanical loading, as shown *in vitro* and in vivo studies, might represent an important step in the development of tendinopathy.

An alternative hypothesis has been postulated for tendinopathy occurring in tendons experiencing a differential compressive load.[104] As tendons undergo compressive forces certain morphological changes occur in the tendon ECM in order to adjust to that particular stress. In particular, it is known that introducing compressive load on a tendon results in changes in non-collagenous ECM proteins, such as an increased expression of high molecular weight proteoglycans (i.e. aggrecan) and decreased expression of low molecular weight proteoglycans (i.e. decorin).[105] As a consequence, specific tensile force placed on the remaining tendon tissue is higher resulting in pathological mechanisms.

Considerable research still must be undertaken to assist our understanding of all the elements of tendon pathology. With the complex interplay between inflammatory mediators, MMPs, TIMPs, as well as secondary proteins influencing their expression, orthopaedic researchers have begun to make considerable shifts in their approach to overuse soft issue injuries. The focus now is centered on the cellular mechanisms, rather than a general tissue response, and future directions will continue to explore cell-cell signaling pathways and mechanisms behind mechanotransduction. While our understanding of the pathomechanisms behind tendinopathy continues to improve, various experimental treatments are currently being explored.

1.3.4 Non-Operative Treatments for Tendinosis

Consistent with other soft tissue injuries, tendinopathy is often treatment initially by standard conservative measures. Rest, ice, non-steroidal anti-inflammatory drugs (i.e. Ibuprofen), calf stretching, heel raises and a gradual return to activity are considered the mainstay of most treatment methods when symptoms first appear.[31,8] The Cochrane Review of 2001 suggested that there was little evidence to support the use of any therapy for treatment of chronic Achilles

pain.[106] The challenge with treating any long-standing or recurrent tendon injury stems from our inability to completely understand its pathomechanisms. While biopsy samples and microdialysis techniques from chronic tendinosis patients demonstrate a clear absence of inflammatory markers, we are still unsure of the progression of pathology from an inflammatory response to a degenerative one.[1,5,4] Accordingly, it is increasingly important to ensure consistency in the pathology of patients participating in randomized control trials of treatments aimed at improving the outcomes of these patients. Despite our shortcomings in the understanding of its pathomechanics, several new treatment options for Achilles tendinosis have been proposed. Firstly, it may be important to clarify the efficacy of anti-inflammatory medications.

1.3.4.1 Steroids and Non-Steroidal Anti-inflammatory Interventions (NSAIDs)

NSAIDs inhibit tissue inflammation by repressing cyclooxygenase (COX) activity, with a reduction in the synthesis of proinflammatory prostaglandins.[107] Ironically, the analgesic effect of NSAIDs allows patients to ignore early symptoms, possibly imposing further damage on the affected tendon and delaying definitive healing.[108] Topical Naproxen gel produced a marginal advantage in relieving symptoms after 3 and 7 days in patients with acute tendinopathies who had symptoms for less than 48 hours.[109] Although NSAIDs may provide some pain relief in such patients, it is felt they do not result in a sustained improvement in the healing process.[110] In fact, it is still not known whether NSAIDs actually change the natural history of tendinopathy or whether they merely exert an analgesic action. A study using an acute tendon injury model with rats showed that NSAID administration does not prevent collagen degradation and loss of tensile force in tendons; therefore leaving it questionable whether NSAIDs should be used to alleviate pain in so-called acute tendinopathy.[111]

NSAIDs are have not shown favorable results in athletes with tendinopathy and most studies of NSAID treatment of tendinopathy have too a short follow-up

period to comment on the possibility of recurrence.[110,112] A double-blind, randomized, placebo-controlled clinical trial of NSAIDs used in the management of Achilles tendinopathy based on clinical signs and symptoms reported no beneficial effects.[113]

Ultrasound guidance in the delivery of a therapeutic agent directly to the injured plantar fascia has been documented in the case of corticosteroids. While a treatment effect of steroid injections for plantar fasciitis has been suggested, convincing evidence from well designed randomized control trials is still wanting.[114-116] Results from steroid injections must also be weighted against the risks of plantar fascial rupture.[117 118] Consequently, while the Cochrane group acknowledged the popularity of steroid injections, it concluded that its treatment efficacy is useful only in the short term and to a limited degree.[119]

Glucocorticoid injections intratendinously for Achilles tendinosis have shown a significant positive outcome in both symptoms and neovascularity up to 182 days.[120] These authors hypothesized that the presence of neovessels in chronically painful tendon lesions represented an inflammatory mechanism and attribute their positive effects of the steroid injection accordingly. The use of sclerosing agents for tendinopathy was born from this concept.

1.3.4.2 Sclerosing Injections

Reports on an in-growth of neovessels with colour Doppler ultrasound coupled with sprouting of substance P positive nerve fibers with high levels of the neurotransmitter glutamate in patients with chronic painful tendinosis has lead to new approaches of the treatment of tendinopathy.[4,60] After ultrasound-guided injection with the sclerosing agent Polidocanol, patients with tendinosis at the Achilles insertion and mid-substance and infrapatellar tendons report significant symptomatic improvements.[121,122,123] These improvements have been correlated with a decrease in neovascularity in the affected tendon region, raising the strong contention that neovascularity, as seen on ultrasound, is associated with a vasculo-neural source of pain in chronic tendinosis.[124]

1.3.4.3 Exercise

Tenocytes are known to up-regulate the production of collagen and improve the structural properties of tendon when exposed to moderate levels of tensile load.[125] However, moderate levels of concentric or eccentric training on Achilles tendon patients has produced equivocal results.[126] More recently, patients suffering long-standing painful Achilles mid-portion tendinopathy have shown tremendous improvements, including after one year follow-up, with a heavy-load eccentric only heel drop regimen.[127,128] The authors of this treatment regimen postulate that excessive tensile loading of tendon tissue, such as in a loaded heel drop, obliterates vascular and neural in-growth, thereby improving both symptomatic and functional outcomes.[129] However, the same regimen was much less clinically effective for cases of insertional Achilles tendinopathy, perhaps as a result of an alternate structural source of pain (such as from tendon, bursae, or bone).[130] A recent report on a variation of the heavy-load eccentric program whereby the ankle is restricted from entering a dorsiflexed position during the exercises resulted in improved patient satisfaction and pain reduction.[131] Other research centers have been unable to replicate the success of this heavy load exercise regimen in patients with mid-portion Achilles tendinopathy, perhaps as a result of extraneous variables accounting for the variation in patient outcomes, most notably female gender, pre-treatment tendon thickness and previous activity level.[132]

Eccentric-based exercise regimens have also been documented for patients suffering infrapatellar tendinopathy. Consistent with results from the Achilles patient population, eccentric-based programs have greater clinical efficacy than concentric-based.[133,134] Modification of such eccentric regimens at the knee has resulted in further improvements in pain reduction and functional recovery such that exercise-based programs are at least equivalent to surgical based interventions.[135,136]

For patients experiencing symptoms of plantar fasciitis, Achilles tendon or calf muscle stretching exercises are commonly incorporated into treatment regimens, with evidence that with a dedicated stretching regimen there can be both increases in ankle flexibility and decreases in pain.[137] Stretches that focus directly on the plantar fascia have also reported good improvement with respect to pain, function and patient satisfaction at both eight weeks and two years in a group with long-standing pain.[138],[139]

1.3.4.4 Extracorporeal Shock Wave Therapy

Extracorporeal shock waves (ESW) are generated by high voltage spark discharge under water, which causes an explosive evaporation of water, producing high-energy acoustic waves.[140] By focusing the acoustic waves with a semi-ellipsoid reflector, it is possible to focus the primary shock to a specific tissue site. Notably, ESW has been found to be an effective non-invasive treatment for resolving calcifying tendinitis of the shoulder and painful heel syndrome (plantar fasciitis).[141,142] Outcomes of ESW from recent randomized control trails and a systematic review conclude ESW has little benefit for chronic tendinopathy at the elbow.[143,144]

While the cellular and biochemical therapeutic mechanisms remain largely to be determined, recent research has shown improved tissue response, coupled with an increased expression of TGF-β1 and IGF-I in rat collagenase-induced Achilles tendinitis.[145]

ESW has recently been tested in randomized placebo-controlled trials on patients with chronic Achilles tendinopathy with mixed results. In one investigation on both mid-portion and insertional Achilles tendinopathy patients, there were no differences after one-year follow-up in rest and activity based pain scores, and only 13 of the 41 patients after one-year follow-up declared being pain-free.[146] In a later investigation on insertional Achilles tendinopathy patients only, significant clinical improvements who observed at 1 month, 3 months and 12 months post-ESW treatment.[147] An improvement in pain scores and vertical

jump height over controls post-treatment was observed in a blinded randomized controlled trial on jumping athletes with infrapatellar tendinopathy.[148]

1.3.4.5 Nitric Oxide

The role of nitric oxide during the healing process has been demonstrated through its inhibition in various circumstances. Inhibition of nitric oxide has been shown to reduce collagen content, contraction, and synthesis by wound fibroblasts *in vitro*.[149] In addition, animal studies have shown that nitric oxide synthase inhibition at a cellular level results in a significant reduction in the cross-sectional area and load to failure of healing tendons, suggesting that nitric oxide stimulates collagen synthesis by wound fibroblasts.[150] Nitric oxide has also been shown to modulate fracture-healing.[151]

In a prospective, randomized, double-blind, placebo-controlled trial of patients with noninsertional Achilles tendinopathy, continuous application of topical glyceryl trinitrate showed significant improvements in pain level, night pain, tenderness, hop test and ankle plantar flexor mean total work compared with controls.[152] The positive outcomes associated with topical nitric oxide application have been replicated by the same research group in tendinopathy at the elbow.[153] Despite the quality of the evidence from these studies, more research confirming the efficacy of nitric oxide application at alternate injury sites (such as infrapatellar tendon and plantar fascia) is needed.

1.3.4.6 Mesenchymal Stem Cells Implantation

It has been hypothesized that the best hope for engineering new tendon tissue that has compositional and functional similarities to non-degenerate weight bearing tendon will require a cell based approach with the delivery of mesenchymal stem cells, in far greater numbers than are present normally, into the damaged tendon.[154],[155]

Embryonic stem cells are truly pluripotential but have the disadvantages of being allogenic (although with immunological tolerance) and associated with a risk of

tumor formation. Postnatally derived stem cells are thought to be multipotential, having a restricted number of cell lineages into which they can differentiate.[154] They are subdivided into haemopoietic (blood cell lines) and mesenchymal stem cells which can give rise to osteoblasts (bone), chondrocytes (cartilage), tenocytes (tendon and ligament), fibroblasts (scar tissue), adipocytes (fat), and myofibroblasts (myotubes). Furthermore, these stem cells can be recovered from adult tissue, and hence there is the possibility of autologous re-implantation. While this treatment approach has not been tested in humans, more than 100 horses have undergone mesenchymal stem cell implantation from the harvesting of the bone marrow.[156] After 4 months follow-up there is an almost complete resolution of intra-tendinous lesions (confirmed by radiograph and ultrasound) and a return to full training after 48 weeks without any negative side-effects. The results from this stem cell treatment illustrate its potential in humans; however clinical trials have not yet been conducted on humans.

1.3.5 Prolotherapy for the Treatment of Chronic Tendinopathy: A Review of Basic Science

1.3.5.1 Introduction to Prolotherapy

Prolotherapy is defined as "the rehabilitation of an incompetent structure (as a ligament or tendon) by the induced proliferation of new cells".[157] Historically, the indications for prolotherapy have primarily centered on joint pain secondary to either hypermobility or instability of associated joints, namely the lumbar and thoracic spine.[158,159,160] Recently, solutions common to prolotherapy have shown success in addressing the pain associated with chronic tendinopathy.[161,162,163] The carry over of the clinical success of prolotherapy from the realm of ligament and joint pain to insertional based tendinopathies is plausible considering the similarities of the tissues involved. The mechanisms, however, by which these prolotherapy solutions are able to achieve these successful outcomes for any indication is still the product of considerable speculation.

Handicapping our efforts at understanding the therapeutic processes behind prolotherapy are the myriad of different drug combinations utilized. Most prolotherapy solutions use dextrose. It is common to combine dextrose with glycerin, phenol, and lidocaine, which collectively is known as Proliferol (P2G) and has been used as a proliferant and sclerosing solution since the 1940s.[164] The majority of solutions injected are not recognized by the FDA; however, the prevalence of reported adverse effects are low and those that do occur are often associated with either the needle stick injury or an increase in inflammation.[165,166,167] Dagenais *et al.* (2007) have demonstrated there is no evidence of systemic toxicity from intramuscular injection of P2G in rats at up to 10 times the dose currently used in humans.[168]

Despite the favorable clinical outcomes with prolotherapy solutions for tendon pain, it is worth examining what is known about the physiological properties of prolotherapy based solutions on connective tissue recovery. Therefore, the goal of this section is to provide a review of the basic science literature of prolotherapy as it applies to the treatment of overuse tendinopathy. The discussion is limited to solutions incorporating only dextrose, sodium morrhuate, or a combination of the two as those are the only solutions known to be used in the treatment of tendinopathy.

1.3.5.2 Current Scope of Prolotherapy Treatments for Tendinopathy

Injections of dextrose have been used individually for a variety of musculoskeletal indications: low back pain and sacroiliac joint dysfunction,[165,169,170,171] knee instability subsequent to ACL injury,[172] osteoarthritis, [173] anterior talofibular ligament sprain, and medial meniscus injury.[162] Specifically in the context of tendinopathy, dextrose prolotherapy has demonstrated clinical efficacy based on case series data at the following locations: adductor tendinopathy in elite soccer and rugby athletes,[161] patellar tendinopathy,[162] and Achilles insertional and non-insertional tendinopathy.[163]

Isolated applications of sodium morrhuate, on the other hand, have not been referenced for the treatment or management of any musculoskeletal condition. However, it's effectiveness as a sclerosing agent is documented in widespread clinical applications: vascular lesions and tumors,[174] benign lymphoepithelial cysts in HIV patients,[175] varicose veins,[176] and esophageal varices using US guided sclerotherapy.[177]

Only one paper has investigated an injection solution incorporating both dextrose and sodium morrhuate with lidocaine and sensorcaine anesthetics, that showed a greater reduction in pain and improvement in strength in patients with refractory lateral epicondylopathy than injections of a saline based control.[178]

1.3.5.3 Theoretical Mechanisms behind Clinical Outcomes of Prolotherapy

Both dextrose and sodium morrhuate, similar to other prolotherapy based agents, are understood to elicit a proliferant cellular response by inducing inflammation, subsequent growth factor production leading to increased fibroblast proliferation (either locally or systemic), and increased production of extracellular matrix materials.[160,164,179] Both substances however, achieve this cellular injury via reputedly different mechanisms. Dextrose is considered primarily an osmotic agent creating cellular dysfunction and loss of membrane integrity via increases in osmotic pressure from the introduction of the hypertonic solution.[164,180] Sodium morrhuate, on the other hand, is a mixture of the sodium salts of the saturated and unsaturated fatty acids of cod liver oil and is regarded as a chemotactic agent.

While sodium morrhuate is not as prevalent as dextrose in prolotherapy based treatments, there is more basic science on its effects on soft tissue, particularly from *in situ* based animal models. Liu *et al.* (1983) showed that repeated injections of 5% sodium morrhuate into the medial collateral ligament (MCL) and its bony attachments in a rabbit model significantly increased its bone-ligament-bone junction strength, ligament mass and thickness when compared to saline-

injected controls.[181] Morphometric analysis of electron micrographs in this study showed a highly significant corresponding increase of the collagen fibril diameters in the experimental ligament compared against the control MCL. However, the basis for these physiological changes remained unclear at the time. Two years later, research by Stroncek *et al.* (1985) helped to elucidate some of the mechanistic action of sodium morrhuate on cultured human endothelial and red blood cells.[182] Stroncek's group concluded that these drugs cause phlebosclerosis not primarily through induction of plasma coagulation, but by directly damaging endothelium and red cells, triggering platelets, and aggregating granulocytes at the venous wall endothelium; mechanisms that are similar to three other sclerosing agents in current use: ethanolamine oleate, sodium tetradecyl sulfate, and polidocanol. Parsi *et al.* (2007) has further reported the coagulating properties of different concentrations of 'detergent sclerosants'.[183] Maynard *et al.* (1985) studied the effects of 3 different concentrations of sodium morrhuate on the morphological and biochemical response in a rat patellar tendon.[184] In general, sodium morrhuate injected tendons were larger in diameter and contained more cells, smaller collagen fibrils, increased water and amino sugar content and reduced hydroxyproline content compared with their contralateral controls. Essentially, the sodium morrhuate treatment appeared to mimic the early stages of an injury-repair process. Aneja *et al.* (2005) supported the work of Maynard's group by reporting that rat patellar tendons treated with sodium morrhuate were stronger than their respective untreated control.[185]

Mechanistic background research on the effects of isolated dextrose prolotherapy is not as extensive and reports inconclusive results. Harrison (1995) investigated the effects of weekly injections of two different prolotherapy solutions: the Pomeroy (dextrose, sodium morrhuate, mepivacaine, cyanocobalamin) and Faber (calcium gluconate, lidocaine) from controls while a rat Achilles tendon was traumatized at 21-day intervals through a drop-weight mechanism.[186] There were no significant differences in the ultimate tensile

strength or elastic properties between the treatment groups. Jensen *et al.* (2008) compared 3 different prolotherapy solutions (dextrose, P2G and sodium morrhuate) on the effect of knee ligaments in a healthy rat model. The response from all of the prolotherapy solutions was varied and overall not significantly different from the needle stick injury or saline injection controls.[187] However, injections of dextrose prolotherapy, this time in a rat injury model, have resulted in an increase in the cross-sectional area of MCL ligament tissue compared with saline injected controls.[188]

While not as valid as *in situ* animal model research, the effects of dextrose-based soft-tissue intervention can be examined via *in vitro* diabetic research which provides observations of tissue response under high glucose environments. Dextrose is thought to illicit a proliferative response via osmotic shock. However, it is not well understood whether it is, in fact, the specific osmolarity change secondary to the dextrose injection, or whether the proliferative cellular response is more a result of the high glucose environment or direct stimulation of growth factor expression. Osmolarity has been shown to increase platelet-derived growth factor (PDGF) expression and up-regulate multiple mitogenic factors in two separate *in vitro* models.[189,190] Human mesangial cells exposed to high glucose environments are reported to produce elevated levels of PDGF, transforming growth factor-β1 (TGF-β1), and tissue-inhabiting metalloproteinases (TIMPs), combined with a decrease in matrix metalloproteinase-2 (MMP2) levels, ultimately resulting in ECM expansion and glomerulosclerosis in diabetic nephropathy.[191,192]

Based on the extent of basic science undertaken on the specific prolotherapy solutions for the indication of tendinopathy, there remain considerable gaps in knowledge of our basic understanding on how tissue responds with the injection of either dextrose or sodium morrhuate. Only one of the laboratory based studies on these drugs took place in tendons, most being conducted on ligaments or other connective tissue, and few to none using a single compound

solution of standard concentration whose results were repeated in another study. One could surmise that the basic building blocks of all connective tissue are similar, and the effects of a specific solution on fibroblast mitogenic activity, metabolism and subsequent ECM properties would carry over from one tissue type to another. However, there are obvious practical considerations halting this conjecture. The force and strain characteristics even among tendons in the body vary considerably, let alone comparisons between the cellular responses in the Achilles tendon to posterior sacroiliac ligaments, much less to glomerular or vascular endothelial cells.

There is a need to examine the effects of prolotherapy based solutions in an animal model that better approximates tendon pathology as seen in humans (i.e. reproducing a degenerative tendinosis rather than acute insult to tendon tissue), such as a previously validated rat supraspinatus injury model.[193,194] The challenges facing clinicians with patients with chronic tendinopathy is the very absence of inflammatory agents; therefore conventional anti-inflammatory based treatments are met with limited success. A new treatment paradigm following a best practices approach from evidence based medicine requires these processes to be established and proven on a tissue and cellular level. Improved standardization of solution preparation and the quality of investigations undertaken is a necessity, and more randomized control trials are needed with both injectable and non-injectable control groups to improve credibility of solution specific treatments in the clinical arena.

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Chapter 2 : A Biomechanical and Clinical Examination of Runners with Insertional Achilles Tendinopathy[1]

2.1 INTRODUCTION

Achilles tendinopathy is one of the most common running injuries that are seen in the sports medicine clinic, although it is a condition not limited to athletic populations.[3] Individuals who are obese and who must stand for prolonged periods of time are also susceptible. Some authors have suggested that the discrimination of pathology in the Achilles tendon between the two most common sites of injury – tendon mid-substance or insertion – may depend on factors such as, training status, running caliber, sedentary lifestyle and body-weight.[4,5]

The majority of tendinopathies at the Achilles tendon appear in the tendon mid-portion, approximately 2-6cm proximal to its insertion to the calcaneus. Histological biopsy samples on patients presenting with Achilles tendinopathy report only 24% presenting with pathology at the insertion site of the Achilles tendon, typically presenting as either fibrocartilaginous or calcifying degeneration in combination with hyaline, myxoid, fibrinoid or mixed lesions close to the area of tendinopathy.[6,7]

Often the presence of pathology at the Achilles enthesis is associated with Haglund's deformity or retrocalcaneal bursitis, and local conditions, such as os trigonum, posterior impingement, posterior talar process fracture, flexor hallucis longus tendinopathy, peroneal tendinopathy, deltoid ligament sprain and osteochondral lesions of the talus should be ruled out.[8,5] For the purpose of this paper, we will focus only on the occurrence of injury to the tendon enthesis itself.

Inflexibility of the triceps surae, inadequate footwear, sudden increases in training volume, excessive hill running and occupations requiring long periods of standing have been implicated in the etiology of Achilles tendinopathy.[4,9] Excessive

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pronation, or more specifically, rear-foot valgus during mid-stance has been observed clinically in connection with patients with mid-portion pathology; however, conclusive evidence supporting this claim is still wanting.[10,11] Furthermore, there have been no studies which have specifically investigated insertional Achilles tendinopathy patients in both a biomechanical and clinical setting. The majority of work on understanding the causes of Achilles tendinopathy has focused on patients presenting with mid-portion pain, with the remainder relying on expert opinion or anecdotal observations.

The objective of the present study is to observe the clinical, training and 3-D kinematic aspects of healthy runners and runners with insertional Achilles tendinopathy. In light of the recent literature findings centered on stress-shielding secondary to compressive forces at the Achilles enthesis, we are specifically interested in whether the insertional Achilles group would exhibit variables associated with greater dorsiflexion during stance creating greater contact and subsequent compression on the anterior fibers of the Achilles enthesis against the posterior border of the calcaneus.

2.2 METHODS

2.2.1 Subject Population

Ten runners with Achilles insertional tendinopathy, along with 10 control subjects, volunteered to participate in this study. All subjects were recruited from one of the following four sources near Tübingen, Germany: patient archives at the University of Tübingen's Sports Medicine clinic, new patients attending the same clinic, through advertisement in local newspapers, and through flyers distributed at local running events. Runners were recruited based on the presentation of pain localised to the insertion of the Achilles tendon (average symptom duration was 27 months), or the absence of any injury for the preceding 6 months. Subjects signed and agreed to a subject consent form approved by the Ethical Review Board at the University of Tübingen prior to data collection.

Achilles tendinopathy patients included individuals who had been diagnosed by the same orthopaedic surgeon based on localization of pain directly on the posterior calcaneal tubercle. Patients presenting with medial or lateral posterior palpable pain suggestive of bursitis were excluded. An ultrasound investigation confirmed the presence of tendon pathology at the enthesis with the presence of one or more of the following: region(s) of hypoechogenicity, anechoic clefts/tears, neovascularization, and/or calcification

Patients must have had symptoms for a period of 3 months prior to enrolment. Any person having pain or symptoms elsewhere in the lower extremities, having previous surgery to the Achilles tendon, or undergoing a new treatment regimen in the last 4 weeks was excluded. All subjects were required to have had maintained a minimum of 30km of running per week for the past 6 months and be between 18-50 years of age. Despite the occurrence of insertional Achilles pathology in the injured group there were no visible signs of compensation owing to running on the injured side.

2.2.2 Clinical Evaluation

Basic descriptive and anthropometrical data were documented at the entrance to the study, as well as symptom duration and previous treatments administered. Training variables recorded included: running mileage per week; weekly running frequency; estimated training speed; best 10km, half-marathon and marathon completion times; total number of running events completed; years spent running and running surface. A summary description of the clinical variables of each subject can be found in Table 2-1.

Clinical Variable	Description	Unit/Categorization
Ankle Range of Motion (ROM)(Straight knee)	Active plantarflexion / dorsiflexion range	Angle (˚)
Ankle ROM (knee at 30˚ flexion)	Active plantarflexion / dorsiflexion range	Angle (˚)
Ankle dorsiflexion ROM (straight knee)	Maximum active dorsiflexion angle	Angle (˚)
Ankle dorsiflexion ROM (knee at 30˚ flexion)	Maximum active dorsiflexion angle	Angle (˚)
Knee ROM	Passive maximum flexion angle	Angle (˚)
Hip ROM	Passive maximum flexion angle	Angle (˚)
Hallux dorsiflexion ROM	Categorical assessment of global joint range	Hypomobile (<45˚), Within Normal Limits (45˚-60˚) Hypermobile (>60˚),
Ankle laxity	Subjective assessment of subtalar joint and midtarsus mobility	Hypomobile, Hypermobile, Within Normal Limits
Functional leg length difference	Anterior superior iliac spine (ASIS) to medial malleolus	Length difference between right and left legs (mm)
Knee Alignment	Width in centimetres between either medial malleoli or medial femoral epicondyles	Genu varum (≥2cm at medial femoral epicondyles), rectus, or genu valgum (≥2cm at medial malleoli)
Q-Angle	Angle of the lines bisecting centre of patella with ASIS, and centre of patella with tibial tubercle	Angle (˚)
Foot Arch Profile	Subjective standing arch profile	Low, Neutral, High

Table 2-1 Qualification of clinical variables

2.2.3 Biomechanical Measurements

Subjects ran barefoot along a 13m padded runway 5 times at a self-selected running pace. Running speed was recorded for each trial with two light emitting stands spaced 1m apart. After calculating an average running speed from the 5 preliminary trials with a ± 5% border, measurements began as subjects performed 10 trials at their averaged self-selected pace.

During each trial, subjects were instructed to strike a platform placed in the centre of the capture volume of a 6-camera motion analysis system (250 Hz, Vicon Motion Systems Ltd., Oxford, UK). Anatomical tracking markers were placed on 21 positions on the Hallux, foot, ankle, lower leg, thigh, hip and back in order to create a 5 segment model for the lower extremity. Subtalar and talocrural joint axes were established according to Close *et al.* (1969) and hip joint center estimation was done according to Bell and colleagues.[12,13] A one-piece running suit with holes at the anterior superior iliac spine (ASIS), greater trochanter and lower back allowed exposure of markers placed at these locations. Static calibration was performed with the subject standing in a neutral position prior to commencement of the trials.

Joint position, displacement, and angular velocity were calculated relative to the neutral position of a prior conducted static trial for entire stance phase and apportioned into phases within stance representing significant kinematic events: maximum hip adduction, subtalar eversion, and knee flexion after heel strike. Model calculation and analysis was conducted using BodyBuilder software package (Vicon Motion Systems Ltd., Oxford, UK). The Foot Progression Angle is the angle formed from the long axis of the foot and the direction of running. Relevant slope and mean data were included. See Table 2-2 for a complete listing of all dependent variables.

Data from the kinematic were normalized to 100% stance phase for each of the 10 trials of each subject and averaged for further analysis.

Training Dependent Variables	Count
Training Experience	1
Weekly Running Volume	1
Weekly Running Frequency	1
Weekly Running Time	1
Kinematic Dependent Variables	
Hip: range (transverse)	1
Hip: rate of max internal rotation	1
Hip: max internal rotation	1
Hip: max flexion	1
Hip: max adduction	1
Hip: rate of adduction	1
Knee: range (sagittal)	1
Knee: max flexion	1
Knee: time at max flexion	1
STJ: range	1
STJ: max inversion	1
STJ: max eversion	1
STJ: time at max eversion	1
STJ: time at max inversion	1
STJ: rate of eversion	1
STJ: time at max rate of eversion	1
STJ: rate of inversion	1
STJ: time at max rate of inversion	1
Talocrural: range	1
Talocrural: max plantarflexion	1
Talocrural: max dorsiflexion	1
Foot Progression Angle	1
Clinical Dependent Variables	
Ankle laxity	1
Hallux ROM	1
Passive Hip Flexion ROM	1
Passive Knee Flexion ROM	1
Ankle Dorsiflexion (Straight Knee)	1
Ankle Dorsiflexion (Knee 30deg Flexion)	1
Functional LLD Difference	1
Q-Angle	1
Leg Alignment	1
Total Variable Count	35

Table 2-2 Dependent variable list. Abbreviations: STJ = Subtalar joint; ROM=Range of Motion; LLD = Leg length discrepancy; Q-Angle = Quadriceps angle

2.2.4 Data Analysis

Data between the Achilles tendinopathy group and healthy controls were compared between the injured leg in the tendinopathy group, and matched side from the control group. All clinical, kinetic and kinematic data were entered into a personal computer and analyzed using JMP (SAS Institute Inc. Version 4.0.0). Student's t-tests for continuous variables were used to determine significant differences when comparing the tendinopathy group with controls. After accounting for a Bonferroni correction for the 35 separate comparisons, the new alpha for this study was set at 0.0014.

Personal Variable	Achilles Insertional Group (n=10)	Controls (n=10)
Age	39.9 +/- 10.4 yrs	38.75 +/- 9.4 yrs
Height	179.3 +/- 5.8 cm	177.6 +/- 3.0 cm
Weight	71.9 +/- 8.0 kg	72.3+/- 4.7 kg
BMI	22.4 +/- 2.9 kg/m^2	22.9 +/- 1.2 kg/m^2

Table 2-3 Baseline variables

2.3 RESULTS

There were no significant differences between the injured and control groups in terms of age, height, weight, and body mass index (BMI) (Table 2-3). A summarization of the clinical and training data can be found in tables 2-4, 2-5 and 2-6. There were no differences between the injured and non-injured groups for any of the clinical or training variables measured. Interestingly, the runners with insertional Achilles tendinopathy ran, on average, 16.7km/week more and had 5½ years more running experience than the non-injured controls; however, these differences were not significant. The injured and non-injured runners in our study did not differ in their 3-dimensional motion analysis, with movement at the hip, knee and ankle joints being similar between the two groups (Table 2-7).

Clinical Variable	Categorization	Achilles Insertional Group (n/%)	Control Group (n/%)
Ankle laxity	Limited	0/0	0/0
	Within normal limits	10/100	9/90
	Hypermobile	0/0	1/10
Hallux ROM	Limited	4/40	1/10
	Within normal limits	6/60	9/90
Knee alignment	Varus	6/60	4/40
	Rectus (neutral)	3/30	6/60
	Valgus	1/10	0/0

Table 2-4 Summary of categorical clinical data between groups. No significant differences are reported

Clinical Variable	Achilles Insertional Group (mean, ± std dev)	Control Group (mean, ± std dev)
Ankle Range of Motion (ROM)(Straight knee)	61.4 ± 8.5°	61.1 ± 6.1°
Ankle ROM (knee at 30˚ flexion)	62.2 ± 5.6°	62.7 ± 8.0°
Ankle dorsiflexion ROM (straight knee)	8.5 ± 2.7°	8.5 ± 3.6°
Ankle dorsiflexion ROM (knee at 30˚ flexion)	12.5 ± 3.2°	11.2 ± 4.4°
Knee ROM	152.0 ± 3.7°	152.5 ± 2.6°
Hip ROM	135.3 ± 6.0°	136.2 ± 3.7°
Functional leg length difference	0.15 ± .47cm	0.1 ± 0.57cm
Q-Angle	9.2 ± 2.0°	11.6 ± 2.9°

Table 2-5 Summary of continuous clinical variables between groups. No significant differences are reported.

Training Variable	Achilles Insertional Group (mean, ± std dev)	Control Group (mean, ± std dev)
Running experience (years)	14.6 ± 11.1	9.1 ± 7.4
Running volume (km/wk)	47.5 ± 23.2	30.8 ± 14.4
Average running speed (km/hr)	11.0 ± 1.5	11.4 ± 1.7
Weekly running frequency (# running sessions/wk)	4.3 ± 1.8	2.9 ± 0.74
Weekly running time (hours)	5.1 ± 2.5	3.5 ± 1.3
10km best time (min)	37:39 ± 3:45 (n=6)	41:53 ± 4:37 (n=8)

Table 2-6 Summary of training variables between groups. No Significant differences reported.

Kinematic Variables	Achilles Insertional Group (mean, ± std dev)	Control Group (mean, ± std dev)
Hip: range (transverse)	14.5 ± 4.0°	14.7 ± 5.3°
Hip: rate of max internal rotation	0.2 ± 0.4°/% ROP	0.4 ± 0.4°/% ROP
Hip: max internal rotation	0.4 ± 5.5°	0.6 ± 6.1°
Hip: max flexion	30.7 ± 7.0°	30.1 ± 3.6°
Hip: adduction max	11.5 ± 4.0°	13.0 ± 4.4°
Hip: rate of adduction	0.6 ± 0.2°/s	0.6 ± 0.3°/s
Knee: range (sagittal)	24.8 ± 4.1°/s	26.8 ± 3.4°
Knee: flexion max	38.0 ± 5.3°	32.0 ± 6.0°
Knee: time at max flexion	31.9 ± 4.5°	32.2 ± 5.7°
STJ: range	30.7 ± 5.8°	28.4 ± 3.3°
STJ: max inversion	11.3 ± 1.9°	10.6 ± 3.1°
STJ: max eversion	6.1 ± 2.6°	5.23 ± 3.1°
STJ: time at max eversion	41.8 ± 4.2% ROP	39.3 ± 3.7% ROP
STJ: time at max inversion	97.5 ± 2.7% ROP	99.1 ± 1.2% ROP
STJ: rate of eversion	0.03 ± 0.2°/% ROP	0.03 ± 0.3°/% ROP
STJ: time at max rate of eversion	12.9 ± 7.4% ROP	12.0 ± 6.7% ROP
STJ: rate of inversion	0.06 ± 0.2°/% ROP	0.05 ± 0.1°/% ROP
STJ: time at max rate of inversion	88.5 ± 17.73% ROP	87.3 ± 10.6% ROP
Talocrural: range	48.4 ± 7.8°	49.0 ± 5.9°
Talocrural: max plantarflexion	28.6 ± 6.9°	31.2 ± 4.9°
Talocrural: max dorsiflexion	19.8 ± 3.2°	17.9 ± 3.8°
Foot Progression Angle	1.7 ± 3.2°	5.0 ± 4.5°

Table 2-7 Summary of kinematic comparison between groups (ROP = Roll over process). No significant differences reported.

2.4 DISCUSSION

The present study has observed the 3-dimensional motion analysis of hip, knee, talocrural and subtalar joint movement in patients with insertional Achilles tendinopathy and compares them to healthy runners. There were no differences between the groups in their training status which eliminates one of the strongest confounding factors in our comparison of the kinematics; training factors are routinely cited as the strongest predictor for injury in runners. Similarly, there were no differences in injured and non-injured runners in this study in age, height, and weight; all of which may individually predispose individuals to a higher incidence of soft tissue injury.

Our results from the kinematic motion analysis showed no differences between any of the movement parameters studied (Table 2-7). Of particular interest was the lack of significant differences at either the subtalar joint or talocrural joint. Although relying on expert opinion, it has been suggested that pronation (specifically sub-talar joint eversion) is associated with the occurrence of Achilles tendinopathy in athletes; however, Clement *et al.* (1984) did not differentiate insertional and non-insertional pathology and McCrory *et al* (1998) investigated only runners with non-insertional tendinopathy.[10,14]

Clinical factors were non-significantly associated with insertional tendinopathy is this study. Considering there were no differences with respect to kinematics in this study, it was not surprising to find no significant differences between the groups in terms of lower-leg alignment and range-of-motion values from the hip to the Hallux. There is, however, a possibility for error in measuring the clinical variables in this study. Previous authors have assessed the reliability of goniometric range of motion assessment. While Gogia *et al.*(1987) and Watkins *et al.* (1991) found it to be a valid and reliable tool for measurement at the knee, Rome and Cowieson (1996) suggested that angular changes of less than 10 degrees at the talocrural joint should be interpreted with caution, and Youdas *et al.* (1993) reported relatively low intra-tester reliability for active dorsiflexion/plantarflexion at the ankle.[15,16,17,18] Hopson *et al.* (1995) evaluated

the intra-tester reliability of both visual evaluation and goniometric measurements of static motion of the first MTPJ and reported both methods to be reliable.[19]

There are several limitations in this study which are worth noting. The sample size in this study, while homogeneous, is relatively small. We did not calculate an *a-priori* power analysis before setting the limits to our subject recruitment. In addition, the large number of individual comparisons used in this study has likely reduced the statistical power. However, this study was intended as an introductory approach to observing movement patterns in patients with insertional Achilles tendinopathy and comparing them with the movement of healthy runners. The dependent variable list was compiled to provide a comprehensive listing of all relevant factors, and it should be mentioned that many variables were discarded in our consideration for the statistical approach. Considering that the absolute differences between the groups in any of the kinematic variables did not exceed two degrees, we are unsure whether adding more subjects would necessarily produce a clinically relevant significance. Furthermore, in interpreting the kinematic results specifically, it should be considered that there can be a minimum of a 2 degree error when making comparisons between populations secondary to marker movement.[20,21] Differences may also exist between the reliability of flexion/extension movements versus abduction/adduction and internal/external rotation.

The kinematics were measured barefoot in this study and there have been reported differences between shoe/shod running versus barefoot. In comparison to shod running, individuals running barefoot will adopt a flatter foot placement after touchdown combined with a neural-mechanical adaptation with pre-activation of triceps surae and extensor musculature as a strategy to reduce impact pressure at the heel.[22,23] The present study is the first of its kind of measure 3-dimensional motion of multi-joint segments of the lower extremity in an effort to understand the kinematic differences between runners with insertional Achilles tendinopathy and runners without injury. It was our intention to measure lower-extremity kinematics without the confounding effect of footwear between

subjects; however, in so doing we could expect our kinematic data to vary from other studies incorporating a shod running condition.

2.5 CONCLUSION

The objective of this study was to observe whether any clinical or kinematic differences could be seen in a group of runners with insertional Achilles tendinopathy and healthy runners. There were no clinical or kinematic differences between the injured and non-inured runners in this study.

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Chapter 3 : A Kinematic Analysis of Runners with Achilles Mid-Portion Tendinopathy: Are There Movement Differences in the Lower Extremity between Injured and Non-Injured Runners?[2]

3.1 INTRODUCTION

Achilles tendinopathy (AT) is commonly found in both sedentary and athletic populations causing pain, disability and compromised sport performance. The majority of overuse injuries to the Achilles tendon occur in middle aged recreationally active males, with injury rates to runners and those in running based sport particularly high.[4] Injury to the mid-portion of the Achilles tendon, typically 2–6 cm proximal to its insertion, is more prevalent than tendon pathology found at the insertion and accounts for approximating 66% of all injuries to the Achilles tendon.[18] Pain is considered to be the primary symptom of AT, such that it is suggested that a patient's symptoms can reflect the severity of the condition.[6] Often patients describe a period of tendon pain that is at least partially resolved through either time or a treatment intervention.[1] Unfortunately, symptoms often return with increased and repeated tensile strain as the athlete returns to their pre-injury training regimen. This pattern of injury, healing, and re-injury with return to sport is understood to contribute to biochemical changes in the extracellular matrix and degradation in the collagen composition eventually resulting in microtearing within the tissue.[16,14]

Over-pronation of the sub-talar joint has been suggested as etiologically important in the onset of mid-portion injury secondary to the "Whiplash effect": a large degree of rear-foot eversion (i.e. leading to greater calcaneal valgus) at mid-stance may place disproportionate strain on medial fibers of the Achilles tendon.[4] Malalignment of the rear-foot during stance, together with high loads placed on the triceps surae muscle/tendon unit from eccentric contraction and

[2] A version of this chapter has been submitted for publication. Ryan, M., Grau, S., Krauss, I., Maiwald, C., Taunton, J., and Horstmann, T. A Kinematic Analysis of Runners with Achilles Mid-Portion Tendinopathy: Are There Movement Differences in the Lower Extremity between Injured and Non-Injured Runners?

release, was a proposed mechanism by Clement et al. (1984) that would ultimately result in injury. However, it was not specified which rear-foot or sub-talar joint position was clinically relevant with respect to the occurrence of AT.

Previous research investigating the role that lower extremity movement patterns play in the occurrence of mid-portion Achilles tendinopathy is sparse and inconclusive. Kinematic analysis of runners with AT began with McCrory et al. (1999) using two-dimensional (2-D) video analysis to evaluate a series of variables associated with rear-foot motion.[15] They reported that, in comparison to their control group, the AT group displayed greater maximum pronation, time to maximum pronation and calcaneal to vertical touch-down angle. Despite the apparent differences reported in this study, significant sources of error (i.e. parallax) are well known to be associated with 2-D kinematic analysis and can significantly influence movement outcomes.[17,22] Recent 3-D kinematic investigations by Donoghue et al. (2008) have supported the concept of over-pronation playing a role in the onset of AT; however by limiting recruitment in their injury group to only those individuals with demonstrable over-pronation, the generalizability of the results are limited.[9]

Despite the lack of direct evidence, the use the custom made foot orthoses and motion controlled footwear are often prescribed to individuals experiencing AT in an effort to correct pronation on the basis that an excessive amount of this movement is associated with injury in all subjects with AT. The objective of this study; therefore, is to examine the 3D multi joint lower-extremity kinematics in a population of healthy runners and runners with mid-portion Achilles tendinopathy. Our goal is to observe differences in 3-D movement patterns between these two subject groups in order to examine the global potential of any injury prevention and treatment strategy focused on motion control of the ankle and foot.

3.2 MATERIALS AND METHODS

3.2.1 Subject Population

Forty eight subjects (sample of convenience) volunteered to participate in this study: 27 with Achilles tendinopathy (ATG)(age 40 $\pm$ 7 years; height 181 $\pm$ 7 cm;

weight 78 ± 11 kg) and 21 control subjects (CON)(age 40 ± 9 years; height 177 ± 7 cm; weight 71 ± 9 kg). All subjects were recruited from one of the following four sources near Tübingen, Germany: patient archives at the University of Tübingen's Sports Medicine clinic, new patients attending the same clinic, through advertisement in local newspapers, and through flyers distributed at local running events. Runners were recruited based on the presentation of mid-portion Achilles symptomology, or the absence of any injury for the preceding 6 months. An ultrasound evaluation confirmed the presence of pathology through observation of one or more of the following sonographic features: region of hypoechogenicity, tendon thickness greater than 6mm, neovessel in-growth, and/or intra-tendinous microtearing. Subjects signed and agreed to a subject consent form approved by the Ethical Review Board at the University of Tübingen prior to data collection.

Subjects in the ATG included individuals who had been diagnosed by the same orthopaedic surgeon based on localization of pain approximately 2-6cm proximal to insertion (i.e. mid-portion injury), and structural changes seen on ultrasound investigation. Subjects in the ATG must have had symptoms for a period of 3 months prior to enrollment (average symptom duration was 27 months, range 3 months to 20 years), while CON subjects had to have an absence of injury over the preceding 6 months. Any person having pain or symptoms elsewhere in the lower extremities, having previous surgery to the Achilles tendon, or undergoing a new treatment regimen in the last 4 weeks was excluded. All subjects were required to have had maintained a minimum of 30km of running per week for the past 6 months and be between 18-50 years of age.

3.2.2 Experimental Procedure

Subjects ran barefoot along a 13m padded runway 5 times at a self-selected running pace. Running speed was recorded for each trial with two light emitting stands spaced 1m apart. After calculating an individual average running speed per subject from 5 preliminary trials, measurements began as subjects performed 10 trials at their averaged self-selected pace with a ± 5% border. The average of these 10 trials was taken for further analysis. There were no visible signs of

compensation (i.e. favouring healthy limb) in the injury group and all subjects remarked there was negligible pain throughout the running exercise. An independent samples t-test confirmed there were no significant differences in the self-selected running speeds between the ATG and CON.

3.2.3 Kinematic Measurements

All trials were recorded using a 6-camera 3D infrared system (ViconPeak, MCam M1, 250 Hz, Oxford, UK). The marker set used in this study comprises a total of 18 spherical reflective markers, marking the pelvis (4th lumbar vertebra, 2_ ASIS), the thigh (greater trochanter, lateral and medial femoral condyle), the shank (tibial tuberosity, tibial crest, lateral and medial malleolus), and the foot (posterior calcaneus, medial and lateral calcaneus, navicular and cuneiform bones, metatarsals 1, 2/3 and 5), constituting a four segment model. Three-dimensional joint motions were quantified by calculating Cardan angles using the program Bodybuilder 3.6 (ViconPeak, Oxford, UK).[3] Locating joint centers and joint axes was accomplished according to Isman and Inman (1969) for the talocrural and subtalar joints, and Bell et al. (1990) for the hip joint.[12,2] Measurements were recorded one-sidedly; the affected leg in ATG and a randomly selected leg in CON. The stance phase of the measured leg was normalized to 100 frames.

In summary, range of motion values (°), maximum velocity values (°/s) and timing of maximum velocity values (percent roll-over-process or % ROP) of transverse plane tibial motion ($TROM_{IR/ER}$, $TVEL_{IR,}$ $tTVEL_{IR}$, $TVEL_{ER,}$ $tTVEL_{ER}$), sagittal plane ankle motion with isolated ranges for dorsiflexion and plantarflexion ($AROM_{DF}$, $AROM_{PF}$, $AROM_{PF/DF}$, $AVEL_{PF}$, $tAVEL_{PF}$, $AVEL_{DF}$, $tAVEL_{DF}$) and frontal plane ankle motion with isolated ranges for eversion and inversion ($AROM_{EV}$, $AROM_{IN}$, $AROM_{EV/IN}$, $AVEL_{EV}$, $tAVEL_{EV}$, $AVEL_{IN}$, $tHVEL_{IN}$) in controls and Achilles tendinopathy subjects (Table 1).

The following dependent variables were also recorded: Maximum values (°) and timing of maximum values (% ROP) of internal tibial rotation (TIRmax, tTIRmax),

ankle dorsiflexion (ADFmax, tADFmax) and ankle eversion (AEVmax, tAEVmax) in CON and ATG (Table 2).

3.2.4 Data Analysis

All clinical and kinematic data were entered into a personal computer and analyzed using JMP Version 4.0.0 (SAS Institute Inc., Cary, NC). An independent t-test was performed to test for differences between ATG and CON. The significance level for this study was set at a p-value of 0.05 and trends were suggested at p-values of 0.10. An estimate of the effect size (Cohen's *d*) was calculated for all comparisons, whereby small, medium and large effect sizes roughly correspond with values of 0.3, 0.5 and 0.8, respectively.[5] An *a*-priori power analysis was not performed.

3.3 RESULTS

The ATG reported significantly ($p<0.05$) greater ankle eversion than CON with a moderate effect size of the difference (Cohen's $d = 0.67$), but no difference was seen for ankle inversion between the groups. A trend was observed for ATG reporting lower peak ankle dorsiflexion velocity than CON ($p=0.08$, Cohen's $d = 0.61$), as well as a trend that ATG had greater overall frontal plane ankle joint range of motion ($p=0.09$, Cohen's $d = 0.57$).

Most of the effect size values for the remaining comparisons made in this study were relatively small; however, for timing of the peak velocity of both external tibial rotation and ankle inversion had reported medium effect sizes of 0.56 and 0.55, respectively. All means, standard deviations and effect size estimates may be seen in Tables 1 and 2.

Group	$TROM_{IR/ER}$ (°)	$TVEL_{IR}$ (°/s)	$tTVEL_{IR}$ (%ROP)	$TVEL_{ER}$ (°/s)	$tTVEL_{ER}$ (%ROP)
ATG	5 ± 2	118 ± 50	11 ± 4	180 ± 51	83 ± 7
CON	4 ± 3	119 ± 45	13 ± 6	176 ± 76	78 ± 10
ES	0.03	0.02	0.32	0.07	0.56
P-Value	0.80	0.97	0.36	0.85	0.11

Group	$AROM_{DF}$ (°)	$AROM_{PF}$ (°)	$AROM_{PF/DF}$ (°)	$AVEL_{DF}$† (°/s)	$tAVEL_{DF}$ (%ROP)	$AVEL_{PF}$ (°/s)	$tAVEL_{PF}$ (%ROP)
ATG	21 ± 2	50 ± 6	70 ± 7	300 ± 39	14 ± 4	677 ± 118	81 ± 3
CON	21 ± 4	50 ± 6	72 ± 9	330 ± 59	13 ± 4	641 ± 108	80 ± 3
ES	0.00	0.00	0.24	0.61	0.12	0.32	0.29
P-Value	0.49	0.77	0.62	0.08	0.73	0.35	0.41

Group	$AROM_{EV}$* (°)	$AROM_{IN}$ (°)	$AROM_{EV/IN}$† (°)	$AVEL_{EV}$ (°/s)	$tAVEL_{EV}$ (%ROP)	$AVEL_{IN}$ (°/s)	$tAVEL_{IN}$ (%ROP)
ATG	13 ± 3	32 ± 6	45 ± 7	325 ± 176	11 ± 7	471 ± 105	81 ± 2
CON	11 ± 3	30 ± 5	41 ± 7	276 ± 104	10 ± 7	414 ± 108	80 ± 3
ES	0.67	0.36	0.57	0.35	0.22	0.55	0.33
P-Value	0.04	0.20	0.09	0.31	0.53	0.12	0.34

Table 3-1 Mean values, with standard deviations for range of motion values (°), maximum velocity values (°/s) and timing of maximum velocity values (% ROP) of transverse tibial motion ($TROM_{IR/ER}$, $TVEL_{IR}$, $tTVEL_{IR}$, $TVEL_{ER}$, $tTVEL_{ER}$), sagittal plane ankle motion ($AROM_{DF}$, $AROM_{PF}$, $AROM_{PF/DF}$, $AVEL_{PF}$, $tAVEL_{PF}$, $AVEL_{DF}$, $tAVEL_{DF}$) and frontal plane ankle motion ($AROM_{EV}$, $AROM_{IN}$, $AROM_{EV/IN}$, $AVEL_{EV}$, $tAVEL_{EV}$, $AVEL_{IN}$, $tHVEL_{IN}$) in control group (CON) and Achilles tendinopathy group (ATG). An estimate of effect size (ES), or Cohen's *d*, for the comparison is also listed.

*** p< .05, ** p< .01, † p< .10.**

Group	TIRmax (°)	tTIRmax (%ROP)	ADFmax (°)	tADFmax (%ROP)	AEVmax (°)	tAEVmax (%ROP)
ATG	4 ± 2	38 ± 8	20 ± 3	46 ± 3	11 ± 3	39 ± 5
CON	5 ± 2	36 ± 10	20 ± 4	45 ± 2	12 ± 3	38 ± 4
ES	0.04	0.29	0.25	0.49	0.27	0.26
P-Value	0.90	0.41	0.48	0.16	0.44	0.45

Table 3-2 Mean values, with standard deviations, for maximum values (°) and timing of maximum values (% ROP) of internal tibial rotation (TIRmax, tTIRmax), ankle dorsiflexion (ADFmax, tADFmax) and ankle eversion (AEVmax, tAEVmax) in control group (CON) and Achilles tendinopathy group (ATG). An estimate of effect size (ES), or Cohen's *d*, for the comparison is also listed.

*** p< .05, ** p< .01, † p< .10.**

3.4 DISCUSSION

The objective of this study was to investigate the movement patterns in runners with and without AT, paying particular interest to the kinematics of the talocrural and sub-talar joints. Data from this study suggest a greater overall amount of frontal plane ankle movement as a result of significantly greater eversion displacement after touchdown in the runners with Achilles mid-portion tendinopathy. There were no differences in either the peak eversion angle or the peak eversion velocity between the groups reported in this study. The increase in the eversion displacement of the ankle after heel strike in the ATG may be a consequence of the ankle being in a more inverted position at touchdown; therefore undergoing a greater movement excursion in the frontal plane throughout the deceleration phase of running without increasing the overall eversion displacement. Ankle position at touchdown, unfortunately, was not investigated in this study.

The significant movement differences of the sub-talar joint found in the present study appear to support the common clinical concept of the "whip-lash" effect postulated by Clement et al. (1984).[4] Two studies by Donoghue et al. (2008, 2008) provide quantitative support for results in this study. They also performed a 3D kinematic analysis on subjects with and without AT and reported significantly increased sub-talar joint eversion, ankle dorsiflexion and knee flexion in the AT group.[9,10] However, in the interest of comparing homogeneous kinematic groups, the authors had pre-selected for the injury group "subjects displaying levels of pronation during running which were likely to be related to the clinical presentation of AT injury", while the control subjects were randomly selected from the standpoint of gait characteristics. Presumably, the levels of pronation indicated by the above mentioned criteria suggest obvious signs of rear-foot eversion (or high degrees of calcaneal valgus) accompanying medial longitudinal arch collapse during mid-stance. Previous research using 2D

kinematic analysis has reported that runners with AT display greater maximum pronation and time to maximum pronation.[15]

There is not complete agreement with our results and those from the literature. The results from the present study only report a difference in the amount of eversion displacement, and not an increase in peak eversion nor an increase in eversion velocity in the ATG. Some investigations on runners with AT have even reported no significant increase in pronation movements.[15,9] Assuming there is general agreement in what defines over-pronation (from a clinical standpoint only, a biomechanical standard has yet to be identified), there are three keys findings that are relevant to the discussion of the role that rear-foot mechanics play in the onset of AT: 1) it has been identified that a significant proportion of runners experiencing AT over-pronate[15,9]; 2) a significant proportion (~40%) of runners who present with AT do not significantly over-pronate[4,20]; and 3) there are many runners who over-pronate that do not experience injury.[19] One can hypothesize two different scenarios relating strictly to the biomechanical causes of AT based on this information: 1) over-pronation is relevant only to a sub-group of individuals experiencing AT; or 2) pronation, and it's associated lower-extremity movements, are themselves unrelated to the onset of AT.

A separate, although possibly not mutually exclusive, mechanical hypothesis for the onset of AT relates to the high forces experienced by the triceps surae/Achilles muscle-tendon unit during the ground contact phase of running.[4,15] Specifically, there has been a positive association between AT and runners with triceps surae tightness with corresponding reduction in talocrural joint range of motion.[13] The connection is intuitive considering a corresponding force throughout the gastrocnemius/soleus muscle and Achilles tendon in a runner with reduced ankle ROM is applied over a shorter time frame generating a larger impulse throughout the muscle-tendon unit. Evidence of biomechanical indicators (such as ground contact time, peak dorsiflexion, time of peak

dorsiflexion) secondary to tightness within the triceps surae in a population with AT, however, was not identified in the present study or reported elsewhere.

The focus on over-pronation as an outcome in this study deserves comment considering the attention this potential causative factor receives in the literature.[4 5 11 15 26 28 15] Furthermore, the lack of random sampling and 3-D modeling in many previous studies limits the extent that conclusions relating foot and ankle mechanics to the onset of Achilles tendinopathy can be made. The goal of this study was to examine strictly biomechanical differences between these two groups in order to comment on the potential efficacy of biomechanical interventions (i.e. motion controlling shoes or foot orthoses) in the treatment of Achilles tendon overuse injury. Based on our results, it appears over-pronation may differentiate a runner with or without Achilles tendinopathy. However, to truly understand and differentiate injured from non-injured runners a multi-factorial study design and statistical analysis package (i.e. regression modeling) should be utilized whereby risk ratios for specific independent factors may be determined in the presence of all other training, anthropometric and biomechanical variables.[23]

With respect to the interpretation of the results from this study, there are some limitations to consider. When interpreting the kinematic results, previous authors have reported that there can be a minimum of a 2 degree error when making comparisons between populations secondary to marker movement.[21,24] Differences may also exist between the reliability of flexion/extension movements versus abduction/adduction and internal/external rotation. The subjects in this study commented that they experienced little to no pain while performing the running trials for our kinematic assessment, and they could still perform a minimum of 30km per week of running despite the complaints and pathology associated with Achilles mid-portion tendinopathy. It should be noted that these subjects may not be representative of all patients suffering Achilles tendinopathy, particularly patients whose injury etiology is less a function of prolonged running

but a result of long periods of standing at work, postural/alignment factors and/or increased body mass.

The case-control and cross-sectional design of this study limits the inferential power of these results as only associations between certain variables and the occurrence of injury were discussed. Cause-effect relationships could not be determined. A study incorporating a larger sample size in a cohort design with all participants following the same run-training protocol would be an appropriate follow-up to the present study.

The kinematics were measured barefoot in this study and there have been reported differences between shoe/shod running versus barefoot. In comparison to shod running, individuals running barefoot will adopt a flatter foot placement after touchdown combined with a neural-mechanical adaptation with pre-activation of triceps surae and extensor musculature as a strategy to reduce impact pressure at the heel.[7,8] The intention was to measure lower-extremity kinematics without the confounding effect of footwear between subjects; however, in so doing we could expect our kinematic data to vary from other studies incorporating a shod running condition. Considering that it is accepted that most runners wear shoes when running and this was presumably the condition in which the runner experienced their injury, measuring barefoot kinematics may not be entirely valid.

In conclusion, we report an increase in eversion displacement of the sub-talar joint in runners with Achilles mid-portion tendinopathy. Based on the findings from this study, there is evidence that devices used to control sub-talar eversion may be warranted in patients with Achilles mid-portion tendinopathy who demonstrate over-pronation during mid-stance of the running gait. From an injury prevention and treatment perspective, activity modification and proper adherence to sound training principles may be the most effective strategy for

injury prevention, and treatment approaches should be considered on an individual basis depending on presenting causative factors.

Ethical approval for this study was obtained by the ethical review board of the Karl-Eberhard University of Tübingen.

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Chapter 4 : Variation in Serum PDGF, VEGF and IGF-I Levels: Implications for Autologous Blood Injections for Overuse Tendinopathy[3]

4.1 INTRODUCTION

Overuse tendon injuries, or tendinopathy, represent some of the most common reasons for a visit to the sports medicine practitioner's office. Tendinopathy, at either the infra-patellar or Achilles tendons, were one of the top-10 diagnoses among 2002 running injuries seen at a local sports medicine centre.[1] The precise pathomechanism is still largely misunderstood with several theories postulated: cumulative micro-trauma, excessive release of free-radicals, hyperthermia subsequent to overuse, excessive fibroblast apoptosis, and adaptive proteoglycan changes to compressive loading.[2,3,4] Histologically, there is general agreement as to the degenerative nature of chronic tendinosis, such that irregular collagen formation, increased expression of collagen type III, cyst formation, neovascularity and a lack of inflammatory cytokines are representative of tendon tissue in patients with long-standing tendon pain.[5]

Ultrasound guided autologous blood injections have recently been administered to patients suffering chronic painful common extensor tendinopathy at the elbow with promising results.[6,7,8] Data from these three papers show significant reductions in the Nirschl stage and visual analog scale pain ratings from 6 to 10 months after last injection.

What is currently unclear by this treatment approach is whether the active levels of growth factors that are believed to play a role in the healing response vary considerably between subjects. Injection of autologous blood is a relatively new

[3] A version of this chapter has been submitted for publication. Ryan, M., Devine, D., Rupert, J., and Taunton, J. Variation in Serum PDGF, VEGF and IGF-I Levels: Implications for Autologous Blood Injections for Overuse Tendinopathy

approach to treating tendon injuries, and it would be helpful to understand the variation in the level of certain growth factors being administered between patients. In addition, we are also currently unaware whether time of day would influence the serum levels of these substances. Therefore, the objectives of this study are to compare the within subject differences in the serum levels of platelet-derived growth factor (PDGF), insulin-like growth factor 1 (IGF-I), and vascular endothelial growth factor (VEGF) at three separate times in the day, as well as compare the between-subject variation.

4.2 METHODS

Four healthy male subjects (28, ± 1.5 yrs old) with no currently known musculoskeletal or systemic pathology volunteered for participation. Subjects must have been injury free for minimum of 6 months prior to start of study. In order to control for general fitness profile, we searched for subjects who currently participate between 3-5 hours of exercise a week. All tests were preformed at the Centre for Blood Research, University of British Columbia. Subjects signed and agreed to a subject consent form approved by the Clinical Review of Ethics Board at the University of British Columbia prior to data collection (Appendix II). Subjects were requested to limit strenuous activity two days prior to enrolment to reduce the influence of delayed-onset muscle soreness on serum growth factor levels, and were matched for activity level (in hours participated per week) and age.

Venous blood samples were collected at 6 hour increments: 8am, 2pm and 8pm into a serum-separator tube and stored at room temperature for 30 minutes to allow samples to clot. After a 36 hour period, we repeated the collection procedure at 8am, 2pm and 8pm. Before centrifugation, a complete blood cell count, including platelet number and volume, was analysed using an Advia 120 Hematology System (Bayer Diagnostics, Tarrytown, NY, USA). All samples were centrifuged for 15 minutes at approximately 1000 x g. The serum portion was isolated and underwent enzyme-linked immunosorbant assay (ELISA) for PDGF-

AB, IGF-I, and VEGF (R&D Systems Inc., Minneapolis, MN, USA) as per manufacturer's instructions.

Comparison tests were performed using analysis of variance test (ANOVA) to determine whether there was a significant time or subject effect with respect the variance in serum levels of PDGF, IGF-I and VEGF. Within subject differences for both testing days were averaged and compared using an independent samples t-test. All statistical comparisons had an alpha set to 0.05.

4.3 RESULTS

For all three growth factors investigated in this study, there were significant between subject differences found. For PDGF, subject 1 (34.79 ± 2.6ng/mL) and subject 4 (26.14 ± 3.5ng/mL) were significantly different ($p < 0.001$) from each other and subjects 2 and 3 (29.01 ± 3.1ng/mL and 28.49 ± 2.4ng/mL respectively)(figure 4-1). For IGF-I, subject 3 (211.44 ± 27.8ng/mL) and subject 4 (104.04 ± 9.3ng/mL) were significantly different ($p < 0.001$) from each other and subjects 1 and 2 (134.13 ± 10.4ng/mL and 150. 27 ± 9.3ng/mL respectively). VEGF showed a similar trend with 2 of the subjects (subjects 1 (665.80 ± 44.4pg/mL) and 2 (393.65 ± 62.8pg/mL)) showing significantly different ($p < 0.001$) mean levels of VEGF from each other and subjects 3 and 4 (211.27 ± 29.4pg/mL and 222.37 ± 9.2pg/mL respectively).

There was no significant effect for time of day between the three different time periods measured in this study. Mean PDGF levels were 29.21 ± 4.0ng/mL, 30.62 ± 4.5ng/mL, and 29.00 ± 4.6ng/mL for the samples collected at 8am, 2pm and 8pm respectively; mean IGF-I levels were 146.33 ± 43.2ng/mL, 161.71 ± 55.5ng/mL and 146.33 ± 43.20ng/mL for all the time periods respectively; and the mean VEGF levels were 385.18 ± 213.7pg/mL, 350.97 ± 184.4pg/mL and 383.66 ± 200.3pg/mL for all three collection times respectively.

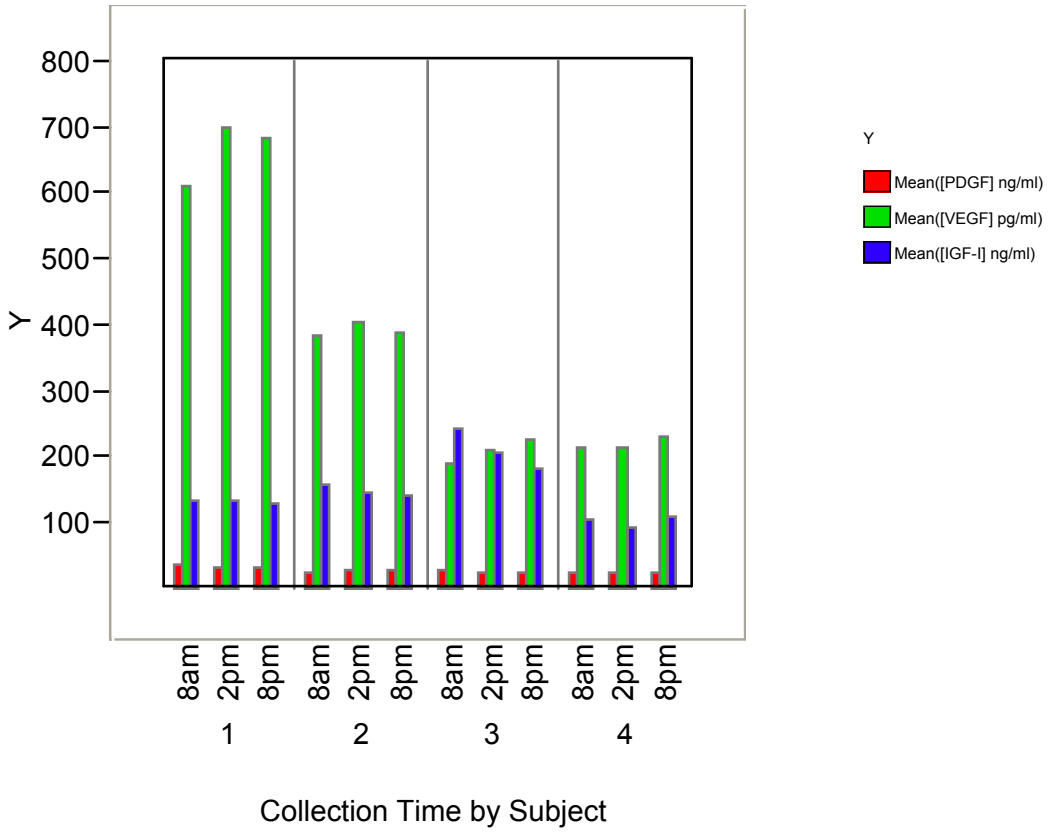

Figure 4-1 Mean serum growth factor levels across subjects and collection time

There was no difference between the collection days for any of the three growth factors measured. Mean PDGF levels for days 1 and 2 were 28.87 ± 5.1 ng/mL and 30.35 ± 3.2ng/mL respectively; for IGF-I were 147.63 ± 42.5ng/mL and 152.31 ± 44.8 respectively; and for VEGF were 355.14 ± 201.4pg/mL and 391.40 ± 188.3 respectively.

4.4 DISCUSSION

The purpose of this investigation was to determine whether there are differences between subjects, and within subjects across different testing points in a day for three growth factors associated with soft tissue repair. Our results indicate there were no significant differences in the serum levels of PDGF, IGF-1 and VEGF at our collection times of 8am, 2pm and 8pm; nor were there any differences with a repeat collection at the same times 36 hours later. There were, however,

significant between-subject differences in the levels of all three growth factors examined in this study.

One of the shortcomings of autologous blood injections as a treatment for soft tissue injuries is the uncertainty of what substance(s) are actively involved in the therapeutic response. The large between-subject variation in growth factor levels seen in this study has been demonstrated by other authors and presents a challenge in terms of not only isolating the therapeutic substance(s), but also being able to standardize its effective dose.[9] In the design of potential clinical trials of autologous blood injection, the inability to effectively standardize the 'intervention/treatment effect' creates the possibility of false negatives in interpreting outcomes. Should the autologous blood injections produce no treatment effect in certain individuals, it would be uncertain whether this was a true negative response from the treatment, or a result of this subgroup of 'non-responders' receiving a significantly lower dose than the 'responders'.

The lack of temporal differences found in this study does suggest that time of day may not significantly influence the serum levels of PDGF, IGF-1 and VEGF. The results from this pilot investigation need to be expanded to include a larger sample size, and should this result be confirmed, it would suggest the time of blood collection for autologous blood injection treatment does not influence the serum levels of PDGF, IGF-1 and VEGF.

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Chapter 5 : Examining the Treatment Effect of a Static and Dynamic Stretching and Balance Exercise Regimen Using a Novel Soft, Ultra-Flexible Shoe: The Nike Free 5.0[4]

5.1 INTRODUCTION

Plantar fasciitis, or its pseudonyms 'painful-heel syndrome' or 'chronic plantar heel pain', is a common injury among both athletes in running-based sports as well as professions requiring prolonged periods of weight bearing. It is reported to account for 15% of all adult foot complaints requiring profession consultation, and in a survey of 2002 running injuries, plantar fasciitis was the third most prevalent injury.[1,2] Primarily affecting people over the age of 40 years, typical complaints involve morning pain, pain on standing after periods of inactivity, and pain with running subsiding after warm-up and returning later in the workout.[3]

In the interests of supporting the medial longitudinal arch, lessening stress on the plantar fascia and addressing any exacerbating foot alignments, foot orthoses are often one of the first treatment options for patients experiencing plantar fasciitis. Evaluating the effectiveness of foot orthotic therapy; however, is not without considerable challenge in light of the large degree of variance between orthotic materials, provider specifications and impression methods, notwithstanding differences between study methodologies. Not surprisingly then, the evidence for the effectiveness of foot orthoses against plantar fasciitis is equivocal. Roos et al (2006) reports significant improvement with pain scores in plantar fasciitis patients over and above the benefits of wearing a night splint.[4] In a randomized, single-blinded control trial testing a custom orthosis, pre-fabricated insole and sham insole, there was no difference between any of the groups in pain scores after 12 month follow-up.[5] A Cochrane systematic review

[4] A version of this manuscript will be submitted for publication. Ryan, M., Fraser, S., McDonald, K., and Taunton, J. Examining the Treatment Effect of a Static and Dynamic Stretching and Balance Regimen Using a Novel Soft, Ultra-Flexible Shoe: The Nike Free 5.0.

reports that it is unclear whether custom foot orthoses are effective at reducing the pain associated with plantar fasciitis.[6]

Depending on the initial efficacy of insole or orthotic support, injections of a corticosteroid may follow as a treatment alternative. Several authors report the success of steroid injections, however there is limited evidence for this treatment without consistent results from well designed randomized control trials.[7-9] Results from steroid injections must also be weighted against the risks of plantar fascial rupture.[10, 11]

While orthotic insoles help to lessen stress on the plantar fascia and cortisone injections limit pain and degeneration caused by inflammation, neither of these treatments contributes to the strength and flexibility of the intrinsic structures of foot, a treatment element identified as important in the non-operative management of plantar fasciitis.[12]

Physiotherapy treatments, specifically involving exercises, stretching, and ultrasound analgesia can be an excellent method to provide targeted and progressive levels of strain to injured soft-tissue stimulating appropriate re-modeling.[13] A physiotherapy regimen will often also incorporate balance training or dynamic stretches to improve overall posture and increase flexibility and activation of lower-limb muscle groups; however, the effects of these physiotherapy interventions have not been formally investigated for a patient group with plantar fasciitis.

Figure 5-1 The Nike Free 5.0. Originally designed to assist track and field runners perform barefoot training exercises with the cushion and protection of a shoe, the Free 5.0 achieves its high degree of flexibility from a series of clefts made to the mid-sole/out-sole of the sole.

The objective of the present study is to investigate the effectiveness of a physiotherapy regimen encompassing static, dynamic and tissue-specific stretches, as well as balance exercises, directed at improving the pain levels in individuals experiencing plantar fasciitis. Furthermore, this study will examine whether individuals performing the exercises in shoes with a soft, ultra-flexible mid-sole (Figure 5-1) will have a greater improvement in pain than individuals wearing conventional running shoes.

5.2 METHODS

5.2.1 Subjects

All subjects signed informed consent before participating in this study in accordance with the Clinical Ethics Research Board of the University of British Columbia (Appendix III). Individuals aged 18-60 experiencing tenderness to pressure at the origin of the plantar fascia on the medial tubercle of the calcaneus coupled with sharp, shooting inferior foot pain made worse with

activity and/or upon arising in the morning were invited to participate in this study. Subjects must have been symptomatic for a minimum of six months and were excluded if there was a history of systemic inflammatory disease, connective tissue disease or previous local trauma to the legs or feet. After baseline interview, all subjects were randomized into either one of two groups: one wearing a novel ultra-flexible shoe (Nike Free 5.0, Beaverton, USA) (FREE), or the second wearing the subjects' own conventional running shoes (CON). The Nike Free 5.0 achieves its high degree of flexibility from a series of eight cross-sectional and three longitudinal clefts that run the width and length of the mid/out-sole of the shoe, respectively and the fact that it lacks a heel counter.

After randomization, subjects underwent a brief injury and treatment history followed by a physical exam by a physiotherapist (SF) documenting resting calcaneal standing position, frontal and sagittal plane midfoot alignment on the rearfoot, passive Hallux range of motion, and a functional assessment of talocrural joint range of motion.

5.2.2. Exercise Regimen

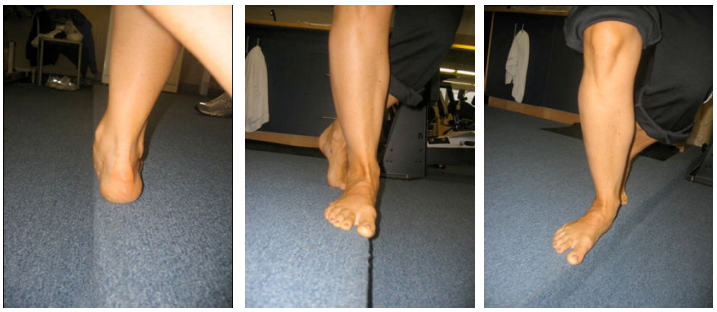
Subjects were then instructed on the exercises of the rehabilitation protocol. These exercises for static and dynamic stretching, as well as balance improvement, were performed four times per week over a 12-week period and included (Figures 5-2 and 5-3):

- Karaoke: lateral side step movement involving crossing one foot over the next for 5 sets of 15 cross-overs in each direction;
- Balance walking, or walking along a straight line on the ground, for 5 sets of 30 strides;
- Forefoot extension exercise: subject stands feet shoulder width apart with one foot ahead of the other and then contracting only calf muscles of the back leg, lifts the heel of the back leg until the metatarsophalangeal joint of that foot is maximally extended. The subject is instructed to concentrate on maintaining balance on the back leg over the first and

second metatarsophalangeal joints throughout movement for 5 sets of 15 repetitions.

- Standing one-legged balance exercise: performed initially with eyes open, then with mastery exhibited by being able to hold balance and not touch the ground with contralateral leg performed with eyes closed, then on an unstable surface with and without eyes open for 1 minute.
- Ankle inversion/eversion exercise: foot is placed sideways at the edge of a step. After stabilizing the remainder of the foot and leg, the ankle is inverted and everted to the limits of the range for 3 sets of 15 repetitions.
- Gastrocnemius and soleus stretching: while standing in a neutral position and the knee extended the foot is placed on top of a ramp or phone-book elevating the forefoot on the rearfoot (talocrural dorsiflexion) and held for 3 sets of 30 seconds each. Next the foot is again placed on top of a phone-book with the knee flexed approximately 15-20 degrees and held for 3 sets of 30 seconds each.
- Tissue-specific plantar fascia stretch: in a sitting position the right foot is crossed over the left while one hand passively extends the right forefoot. The left hand then applies light to moderate pressure in 3-5 second intervals along the length of the medial longitudinal arch. Same procedure is then repeated for the left foot.

A



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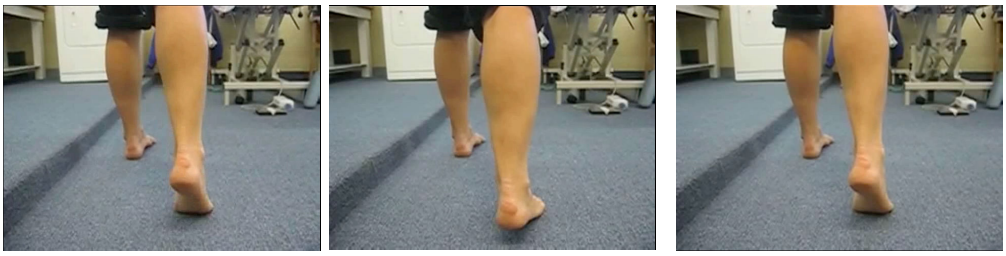


C

D

Figure 5-2 Overview of ankle inversion/eversion (A), forefoot extension (B), balance walking (C) and standing one-legged balance exercises (D) incorporated in physiotherapy regimen for the treatment of plantar fasciitis. Note: All exercises were performed with footwear despite exercises A and B above being shown in a barefoot condition.

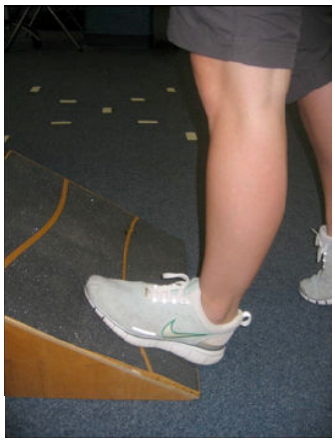
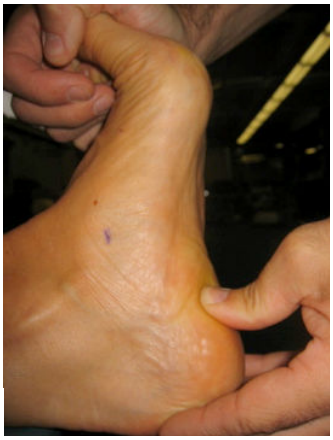
A  B  C 

Figure 5-3 Overview of the static stretching for the gastrocnemius (A) and soleus (B) muscles, and a tissue-specific stretch for the plantar fascia (C).

Subjects performed all of the above exercises, except for the tissue-specific plantar fascia stretch, wearing their footwear. Compliance with the physiotherapy regimen was confirmed with a training log that subjects were required to submit on a weekly basis.

A visual analogue scale (VAS) (100mm) questionnaire was used as the outcome measure for pain assessment (Appendix V).[14] Measurements were taken during the baseline testing, mid-program, at the conclusion of the 12-week treatment protocol, and at a 6-month follow-up. Items for pain after palpation and peak pain experienced in the previous 24 hours were recorded.

All data were entered into a personal computer and analyzed using JMP Version 4.0.0 (SAS Institute Inc., Cary, NC). Independent samples t-tests tested whether a significant difference existed between footwear groups at specific time intervals. The significance level for this study was set at a p-value of 0.05.

5.3 RESULTS

A total of 25 subjects were recruited. Over the course of the study, 3 subjects dropped out. Two subjects experienced an increase in foot pain and one had a family emergency which did not allow the time to continue completing the rehabilitation program. All three of these subjects were part of the FREE Group.

Twenty-two subjects completed the 12 week program, with a total of 33 feet being analyzed (due to 11 subjects experiencing bilateral foot pain). There were 10 subjects in the FREE Group, with 4 males and 6 females. The average age was 40 years, average weight was 80.1kg and average height was 169.3 cm. Forty percent of the subjects reported prolonged standing at work averaging 9 hours per day. There were 12 subjects in the CON Group, with 4 males and 8 females. The average age was 41.8 years, average weight was 85.4kg and average height was 169.1 cm. Sixty seven percent of subjects reported prolonged standing at work averaging 7.9 hours per day. The average symptom duration was 30.3 months (range 6 – 132 months).

On average, each study participant had attempted two previous treatments. The most frequently attempted previous treatment was orthotics at 34%, followed by exercises at 14%, massage at 10%, and a variety of other treatments such as acupuncture, laser therapy and fascial release.

	VAS Palpation mm (± SD)		**VAS Previous 24 Hours mm (± SD)**	
	FREE	**CONTROL**	**FREE**	**CONTROL**
Pre-Test	46.6 ± 20.8	50.1 ± 25.5	52.8 ± 32.7	56.7 ± 32.9
Mid-Point	19.2 ± 16.9	46.9 ± 21.9***	25.9 ± 21.0	47.2 ± 27.1*
Post-Test	18.5 ± 20.1	42.6 ± 26.7**	16.7 ± 13.9	37.1 ± 28.6*
Follow-Up	18.6 ± 30.8	21.0 ± 12.5	18.6 ± 30.7	20.5 ± 19.2

Table 5-1 Visual analog scale scores for both footwear groups across all four testing times. *, **, * represents significant group differences in VAS scores at that time point at a p-value equal to 0.001, 0.01, and 0.05 levels, respectively.**

There were significant differences in the pain scores between the footwear groups throughout the 12-week physiotherapy regimen (Table 5-1). VAS scores

for pain on palpation in the CON group and FREE group showed a 15% and 60% reduction in pain between the two groups over the 12-week program, respectively. Significant group differences appeared at the mid-point and post-test of the program between the two shoe groups (Figure 5-4). There was also a significant difference in VAS scores for the peak pain recorded in the previous 24 hours; the CON group showed a 30% reduction in peak pain while the FREE group had a 63% reduction over the 12 week time period. Differences between the FREE and CON group over the program duration were seen as early as the mid-point (6-week) testing and the reductions in pain scores at these time points between the groups were statistically significant (Figure 5-5).

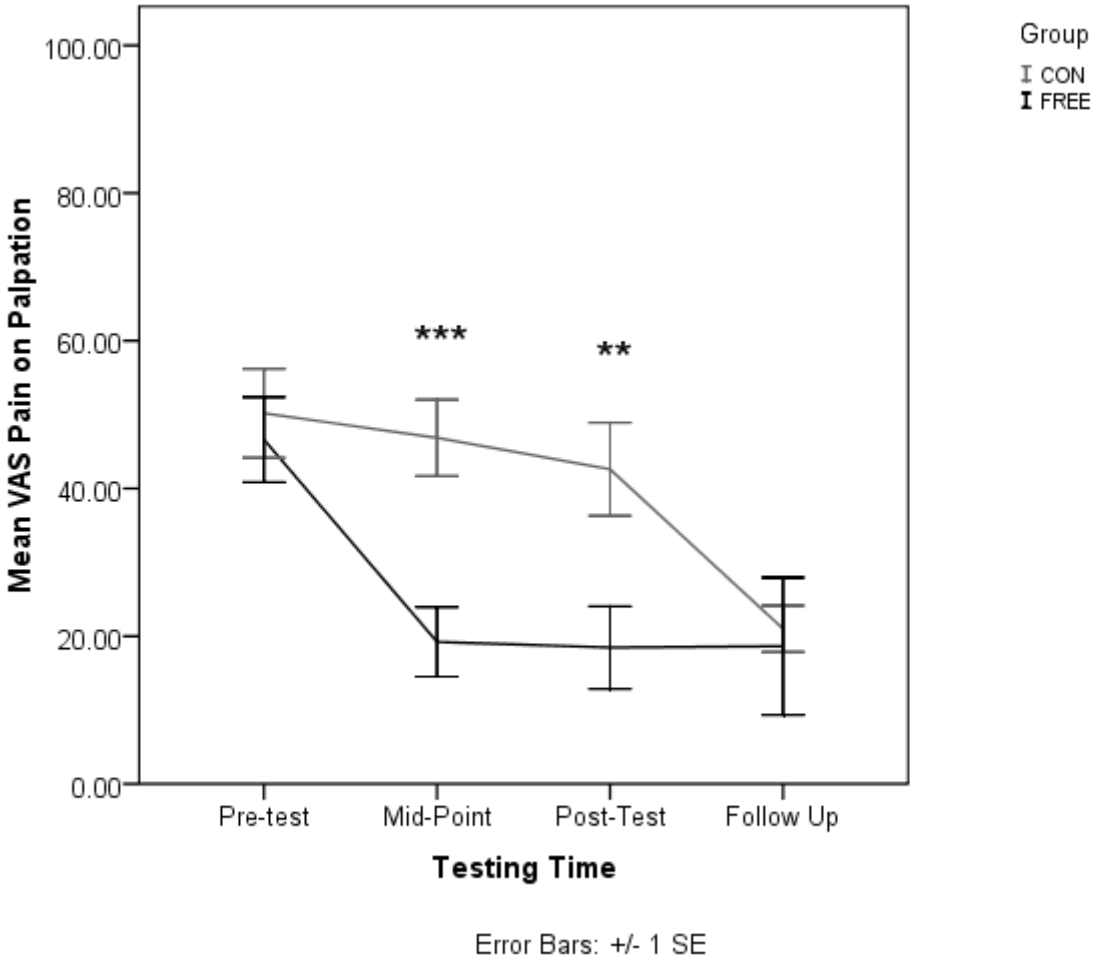


Figure 5-4 Graph representing change in visual analog scores for pain on palpation between the footwear groups across all testing times. *, ** represents significant group differences in VAS scores at that time point at a p-value equal to 0.001 and 0.01 levels, respect**

Long term follow-ups were conducted 6 months after the training program completion on 27 cases (8 FREE subjects and 10 CON, with 9 cases having bilateral symptoms). There were no significant differences between the post-test pain levels and follow-up values for any of VAS items and there were no differences between the footwear condition groups at follow-up.

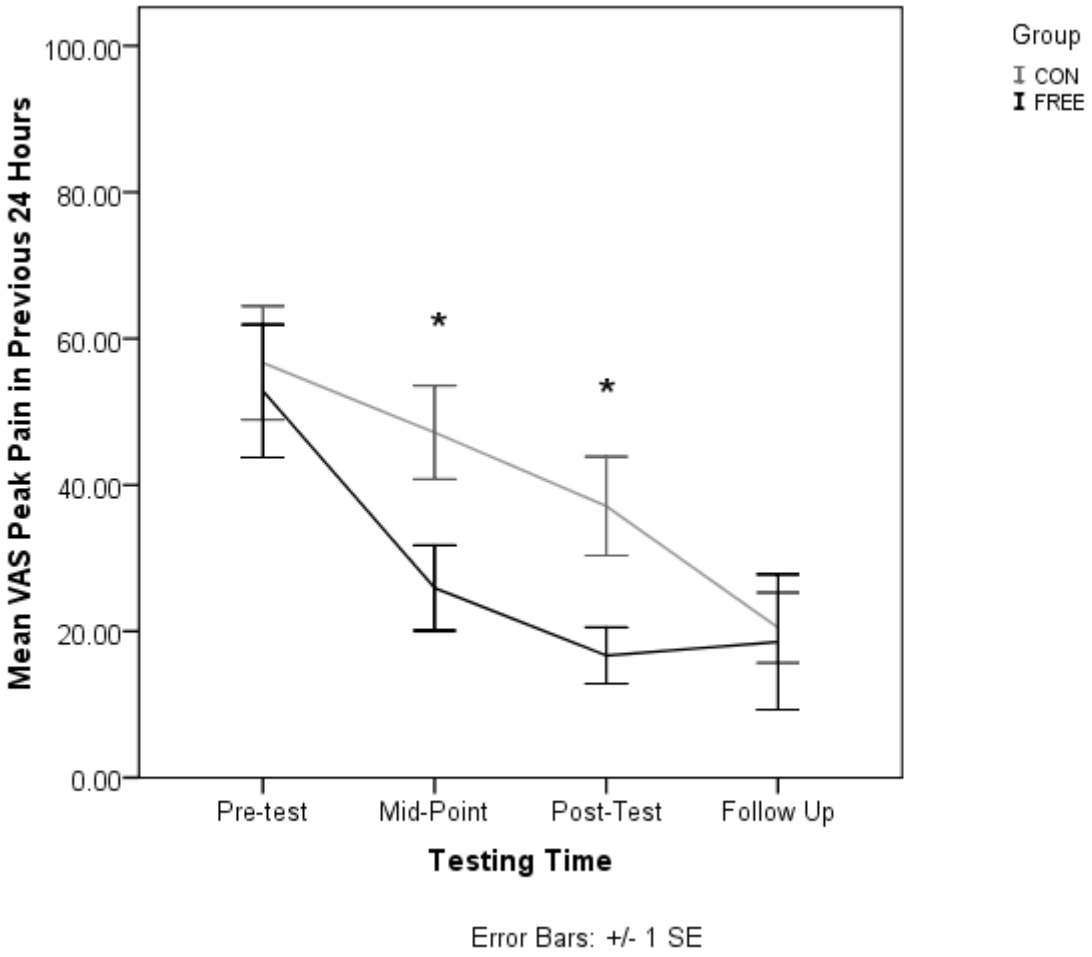


Figure 5-5 Graph representing change in visual analog scores for peak pain in the previous 24 hours between the footwear groups across all testing times. * represents significant group differences in VAS scores at that time point at a p-value equal to 0.05 level.

5.4 DISCUSSION

The physiotherapy regimen employed in this investigation appeared to reduce the pain associated with long standing plantar fasciitis. The group performing the exercises in this regimen wearing the Nike 5.0 shoe reported a reduction in pain significantly sooner than the group wearing their own conventional running shoes. The implications of pain relief in this population are sizeable considering half of our study population is required by work to stand for greater than 7 hours a day, a risk factor often impeding the success of conservative treatments or resulting in a higher degree of injury recurrence.

Brüggemann (’04) conducted a physiological investigation comparing the use of the Nike Free 5.0 shoe compared to a conventional training shoe for a series of 30 minute warm-up exercises, three to four times per week over a 6 month period. At the conclusion of the post-test, the group wearing the Free shoe reported having significantly greater Hallux flexion and extension, and ankle plantarflexion strength; greater active range of motion of their first metatarsophalangeal joint; and a greater improvement in finishing time for an agility running course or shuttle run (unpublished). One of our objectives with the present study was to capitalize on the potential physiological changes that may occur when wearing the Nike Free 5.0 for the benefit of a population who are experiencing foot pain.

While the Nike Free 5.0 is not considered a strict replica for a barefoot condition, the increased flexibility of the sole might contribute to similar stresses being applied to the foot, particularly from the standpoint of allowing increased forefoot extension compared to conventional running footwear. As a result of the increase in sole flexibility, the foot could better engage its windlass mechanism during toe-off resulting in greater stress on the intrinsic soft-tissue structures due to an increase in the mechanical work of the foot, coupled with greater storage and release of elastic components.[15,16] Increasing load in a controlled setting has been well documented as a successful treatment option for chronic soft-

tissue injuries of the Achilles insertion and mid-portion, infrapatellar and common elbow extensor tendons.[17,18,19,20,21]

Similar exercise-based protocols have been implemented for patients with plantar fasciitis. Achilles tendon or calf muscle stretching exercises are commonly incorporated into treatment regimens when patients complain of heel pain, with evidence that with a dedicated stretching regimen there can be both increases in ankle flexibility and decreases in pain.[22] Stretches that focus directly on the plantar fascia have also reported good improvement with respect to pain, function and patient satisfaction at both eight weeks and two years in a group with long-standing pain.[23,24]

One of the primary limitations to the present study is the lack of more extensive control groups, namely a group performing the same exercise regimen barefoot (to validate the mechanism of the shoe effect) and a group not receiving any intervention (to validate the presence of a treatment effect). An ultrasound assessment was not conducted prior to subject enrollment, therefore, we can not be certain of the standardization of disease pathology across our population. While the absence of any notable recurrence in pain throughout the population at the 6-month follow-up is promising, ultimately a 12 or 24 month follow-up period is needed to confirm the positive long-term treatment benefit.

The mechanism(s) behind the treatment effect in this study remains speculative. The results of this investigation would be strengthened by including measures to understand the nature of the treatment effect, such as by documenting isokinetic strength of talocrural, sub-talar and first metatarsophalangeal joints. Balance or agility testing would determine whether there were reported improvements in standing or dynamic posture. Electromyography of such foot and lower-leg muscles as gastrocnemius, soleus, flexor hallucis longus and brevis, peroneus longus/brevis, flexor digitorum longus/brevis to determine whether the increased forefoot extension range of motion, either alone or in combination with the soft

durometer mid-sole, translates into greater strength and/or activation of relevant muscle groups.

In conclusion, the outcomes of the present study report that a 12-week physiotherapy regimen that incorporates static and dynamic stretching and balance exercises significant improves the pain in patients experiencing chronic plantar fasciitis. Furthermore, it appears that carrying out this exercise regimen wearing the Nike Free 5.0 shoe results in significantly faster pain improvement than conventional running shoes.

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Chapter 6 : Sonographically Guided Intratendinous Injections of Hyperosmolar Dextrose/Lidocaine: A Pilot Study for the Treatment of Chronic Plantar Fasciitis[5]

6.1 INTRODUCTION

Plantar fasciitis, or its pseudonyms 'painful-heel syndrome' or 'chronic plantar heel pain', is a common injury among both athletes in running-based sports as well as professions requiring prolonged periods of weight bearing. It is reported to account for 15% of all adult foot complaints requiring profession consultation, and in a survey of 2002 running injuries, plantar fasciitis was the third most prevalent injury.[1 2] Primarily affecting people over the age of 40 years, typical complaints involve morning pain, pain on standing after periods of inactivity, and pain with running subsiding after warm-up and returning later in the workout.[3]

There is limited evidence for the effectiveness of any one treatment for plantar fasciitis. In many cases, patients are recommended or prescribed a multitude of treatments of varying degrees of conservatism, usually starting with exercises to stretch and strengthen both the plantar intrinsic musculature of the foot and calf, ice, supportive footwear, and activity modification.[1 4] Depending on outcomes, physicians may try prescription non-steroidal anti-inflammatory medication, night-splints, off-the-shelf or custom made in-shoe orthotic devices, and/or corticosteroid injections (which are either delivered blindly or through ultrasound guidance).[5 6] Extra-corporeal shock wave therapy (ESWT) may be indicated for some patients.[7 8] Surgery may be considered, however, like most soft-tissue overuse injuries, is not considered until all other measures have failed.[9 10]

The Cochrane Review Group concluded after reviewing 19 randomized trials involving 1626 patients that there is only limited evidence for the effectiveness of

[5] A version of this manuscript was accepted for publication. Ryan, M., Wong, A., Gillies, G., Wong, J., and Taunton, J. Sonographically guided intratendinous injections of hyperosmolar dextrose/lidocaine: a pilot study for the treatment of chronic plantar fasciitis Br J Sports Med 2009;43 303-306.

local corticosteroid injections, and the efficacy of all other apparent treatments has not been sufficiently proven in randomized control trials.[4] Some authors have suggested that plantar fasciitis represents a self-limiting condition without explicit proof of a treatment benefit over a wait-and-see approach.[1] In general, the clinical course of plantar fasciitis is reported as favorable, with resolution of symptoms in more than 80 percent of patients within 12 months.[1] The concern for the practitioner lies with the roughly 20 percent of patients who are non-responders to conservative treatment.

Prolotherapy is a technique in which a small volume of an irritant solution (proliferant) is injected at multiple sites around a ligament or tendon insertion.[11] This solution initiates a localized inflammatory response at the site of injection, which induces fibroblast proliferation and subsequent collagen synthesis from the resultant up-regulation and migration of various growth factors responsible for tissue repair.[12,13] In the case of dextrose, the proliferative response is speculated to result from the higher osmolarity of the injected solution relative to the interstitial tissue, and correspondingly, the treatment solution is often referred to as 'hyperosmolar dextrose'. Evidence exists for the stimulation of transforming growth factor-beta 1, platelet-derived growth factor, connective tissue growth factor, epithelial growth factor and basic fibroblastic growth factor from mesangial cells, smooth muscle cells and gingival fibroblasts respectively upon exposure to various levels of glucose.[14-18] Topo et al (2005) report that 12.5% dextrose/0.5% Lidocaine injections administered blindly at 1-month intervals are highly effective in their population of elite soccer and rugby players with chronic groin pain.[19]

We report on a modification of this therapeutic injection technique for the treatment of chronic plantar fasciitis. Instead of injecting peripheral to the ligament, or performing the procedure blindly, we administered intraligamentous injections of hyperosmolar dextrose/Lidocaine under ultrasound guidance targeting the abnormally thickened and hypoechoic areas in the ligament in order to stimulate healing. The present study describes the effectiveness of

ultrasound-guided dextrose/Lidocaine injections on pain removal in a population suffering chronic plantar fasciitis. Previous research from our group report good results from sonographically guided intratendinous dextrose/Lidocaine injections for patients with chronic painful Achilles tendinosis.[20]

6.2 MATERIALS AND METHODS

6.2.1 Subject Profile

Twenty consecutive patients, 3 men and 17 women (mean age 51.2 ± 12.6 years) with chronic plantar fasciitis with symptoms for more than 6 months (median 21 months; range 7-228 months) participated in this prospective study. Diagnosis of plantar fasciitis was made on the basis of pain at, or around, the plantar surface of the heel or the medial longitudinal arch. All patients in the study group were referred from board-certified sport medicine specialists within the local Vancouver area and must have failed the previous conservative treatments prescribed. Treatments included home-based physiotherapy prescribed exercises (n=10), custom foot orthotics (n=7)(two included heel lifts), therapeutic ultrasound (physiotherapist) (n=4), ESWT (n=4), massage (registered massage therapist) (n=3), prescribed medication (in all cases non-steroidal anti-inflammatory) (n=3), cortisone injections (n=3). The majority of subjects were runners (n=13) and six individuals reported spending prolonged periods of time with weight-bearing activities (i.e. standing and walking) at work.

Exclusion criteria included patients with acute plantar foot pain or symptoms associated with acute trauma. Patients who had surgery or interventional procedures within the preceding 6 months were also excluded. All patients were fully informed and provided written consent. The study was approved by the local institutional ethics review board (Appendix IV).

6.2.2 Ultrasound Examination

The ultrasound examination and the injection procedure were performed by a radiologist (AW) with extensive experience in musculoskeletal ultrasound. The

plantar fascia and surrounding tissue was examined with the patient in a prone position. The ultrasound examination was performed on a Philips HDL 5000 using both a 5-12MHz and a 7-15MHz linear array high resolution transducer. The ligament in its entirety was examined in the longitudinal and transverse planes. Care was taken to image the plantar fascia parallel with the fibres in the longitudinal plane and perpendicular to the fibres in the transverse plane to avoid artefact such as anisotrophy (Figure 6-1). Colour flow Doppler was used to diagnose neovascularity.

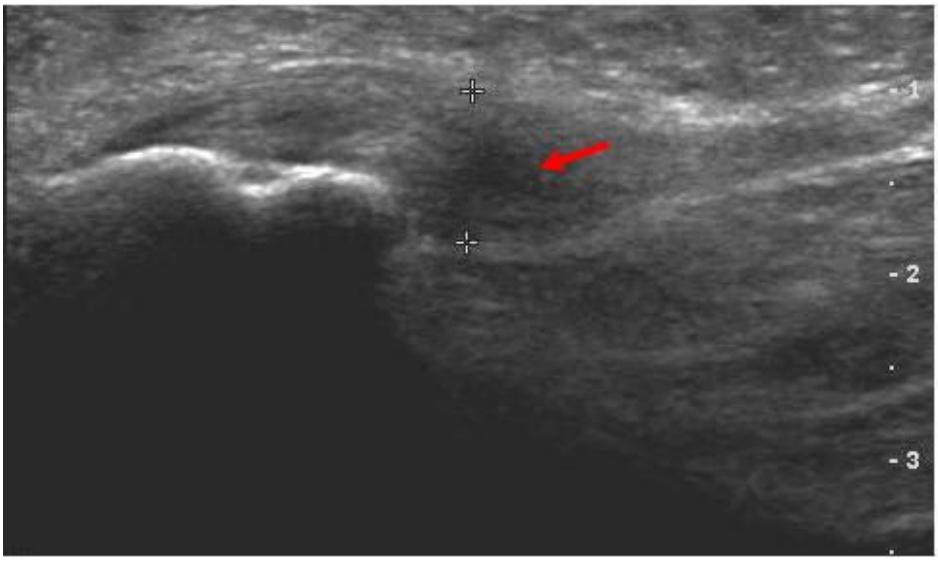

Figure 6-1 Ultrasound image of calcaneal insertion of plantar fascia with cursor markers indicating exaggerated tendon thickness and hypoechoic region.

6.2.3 Hyperosmolar Dextrose Injection

A 2.5mL syringe was filled with 1mL of 2% lignocaine (20mg/ml) and 1mL of 50% dextrose (25g/50ml) (dextrose monohydrate 500mg) giving a 25% dextrose solution. Care was taken to expel all the air from the syringe and needle prior to the injection. The injection procedure was performed under aseptic conditions using a 27G needle. Abnormal hypoechoic areas and anechoic clefts/foci in the thickened portion of the plantar fascia were targeted under ultrasound guidance using the 7-15MHz Hockey Stick linear array transducer. The volume of solution injected varied slightly from ligament to ligament and depended on the degree of resistance, spread of solution within the ligament and extent of the abnormality. Generally less than 0.5 mL was injected at any one site. Between 1 and 3 sites were injected during a treatment session. The ligament was re-imaged following

the injection procedure to assess for spread of the dextrose solution and identify any intrasubstance or partial tears which became more conspicuous following the injection.

The patient was instructed to refrain from any heavy loading activity during the week following the procedure. Patients were cautioned against taking aspirin or other anti-inflammatory agents to relieve any discomfort. Acetaminophen based analgesia was allowed.

The patient was asked to return for repeat ultrasound and injection approximately every 6 weeks depending on scheduling. This continued until either the patient's symptoms resolved or no improvement was evident, at which time the treatment was discontinued.

6.2.4 Data Collection

At the initial consultation all patients were asked to fill out an information questionnaire containing brief questions regarding their condition including participation in sporting activity, length of symptomatic period, previous and current treatments and level of disability (Appendix VI).

Visual analogue scale (VAS) scores (100mm) were recorded for assessment of pain at the baseline consultation (pre-test), and at the final treatment consultation (post-test) (Appendix VII). VAS scales have been shown to be reliable, valid and responsive tools in assessing pain levels in patients rehabilitating from a musculoskeletal condition.[21] A follow-up telephone interview conducted a mean of 11.8 months (range 6 – 20 months) following the patient's final treatment session (follow-up) assessed long-term outcomes by asking the patients to rate their current levels of pain at rest, during activities of daily living, and during or after sport or activity on a scale from '0' to '100'. Patients were asked to complete a Visual Analogue Scale item for pain at rest (VAS1), pain during normal daily activity (VAS2), and pain during or after sporting or other physical activity (VAS3).

6.2.5 Data Analysis

Descriptive and mean comparisons of the study data were analyzed using SPSS statistical software (copyright 2006, version 15.0.1.). Paired samples t-test compared the change in scores from baseline (pre-test) to post-test for the three visual analog scale items. While the follow-up telephone interview did serve as a quantitative measure of pain, its results were not formally analysed due to the unequal distribution of sample sizes in response numbers from post-test to follow-up. Consequently, data from the follow-up will be listed in a descriptive format. Statistical significance for this study was set at a *p*-value of 0.05.

6.3 RESULTS

There were no reported complications from the injection of hyperosmolar dextrose/lidocaine into the plantar fascia in our subject population. A median number of 3 injection sessions (range 1 to 12) were necessary for either a satisfactory treatment outcome or determining that the patient was not responding. The majority of treatment sessions required only one injection site per treatment session (74.7%) with a mean volume of 0.7cc (± 0.45cc). Patients returned for follow-up consultations 5.6 weeks (± 2.0 weeks) after each treatment session. The average time period required to administer all treatment injections was 22 ± 15 weeks.

Most of our patients responded well to the ultrasound guided dextrose/Lidocaine injections as reflected in the significant difference between the pre-test and post-test VAS values (Table 6-1). The effect sizes, or Cohen's *d* value, for the difference in pre and post-test VAS1, VAS2 and VAS3 values were 1.3, 1.9, and 2.0, respectively. After the 11.8 month follow-up period, twelve patients reported being asymptomatic, four reported good outcomes (70-80% reduction in pain with return to activity), and four reported not responding to the treatment at all.

	Pre-Test VAS (mm) (mean ± SD)	Post-Test VAS (mm) (mean ± SD)	Follow-Up (mean ± SD)
Pain at rest	36.8 ± 25.6	10.3 ± 10.9†	12.1 ± 21.0
Pain with daily living	74.7 ± 20.8	25.0 ± 27.7†	21.6 ± 29.5
Pain with sport/activity Sport	91.6 ± 9.2	38.7 ± 35.1†	35.1 ± 41.4

Table 6-1. A summary of baseline and outcome scores for visual analog scales (VAS) and follow-up telephone interview at rest, with activities of daily living and during sport/activity. † Indicates significant difference ($p < 0.001$)

6.4 DISCUSSION

Chronic overuse injury to tendon follows a degenerative pathway that results in breakdown of extracellular constituents, namely type I collagen and proteoglycans, leading to tissue disorganization.[22 23] The tensile strength of the tendon unit is reduced, and re-injury of the structure is increasingly likely when high load is re-applied.

The present study indicates that injections of dextrose/Lidocaine under ultrasound guidance appear to reduce the pain in a majority of patients with chronic plantar fasciitis. All patients were referred from board-certified sports medicine physicians, and all patients had previously failed their prescribed conservative treatment regimen. Eighty percent of patients undergoing this treatment reported good to excellent outcomes in pain reduction at the cessation of their treatment.

Similar findings have recently been published using sonographically guided intratendinous injections of dextrose to treat chronic insertional and non-insertional Achilles tendinosis.[20] A mean reduction of 88%, 84% and 78% to pain levels while at rest, performing activities of daily living, and during or after physical activity, respectively was reported. Structurally, there was a mean reduction in tendon thickness, number of tendons with anechoic clefts or foci, and degree of neovascularity. Ninety six percent of patients contacted at 12

month follow-up reported either being asymptomatic or having a treatment satisfaction level of between 70-90%.

The concept of using ultrasound guidance in the delivery of a therapeutic agent directly to the injured plantar fascia has been documented in the case of corticosteroids. Several authors report the success of steroid injections, however there is limited evidence for this treatment without consistent results from well designed randomized control trials.[24-26] Results from steroid injections must also be weighted against the risks of plantar fascial rupture.[27 28] Consequently, while the Cochrane group acknowledged the popularity of steroid injections, it concluded that its treatment efficacy is useful only in the short term and to a limited degree.[4]

In the administration of cortisone to the plantar fascia, there is some discussion as to the necessity of using ultrasound guidance for optimal clinical efficacy. Tsai *et al.* (2005) recommend using ultrasound guidance for improved injection accuracy which could result in patients tolerating greater direct pressure on the plantar fascia and having a lower recurrence rate than patients receiving palpation guided injections.[29] However, these results were not in agreement with Kane *et al.* (2001), who reported no significant difference in pain levels between their ultrasound guidance and palpation control groups.[30] Sonography is implemented in our study as much to provide a comment of changing tissue structure with treatment progression, as it is useful in refining the clinical protocol of injecting dextrose into the plantar fascia.

There are some limitations to consider with the present pilot study. The case-series design and the lack of control group limit the evidence of the treatment effect. Neither the physician administering the dextrose nor the patient was blinded to the treatment. While there was a significant improvement in pain scores from the baseline consultation to the final consultation that remained until follow-up, we can not comment on the exact treatment mechanism whether from

the needle stick injury, the dextrose, or the average of 6-months needed to conduct the treatment.

Despite the absence of a control group and a formal randomization scheme, the results of this study introduce a potential treatment indicating long-term efficacy in pain relief for a patient group experiencing chronic plantar fasciitis. A multi-arm clinical trial implementing proper blinding of the practitioner and participant and randomization into a treatment group, anesthetic only group, or a wait-and-see group would provide greater insight to the specific role that dextrose plays in the effectiveness of this treatment regimen.

In conclusion, sonographically guided intraligamentous injections of hyperosmolar dextrose/Lidocaine showed good clinical response in patients with long-standing plantar fasciitis with significant reduction in plantar fasciitis pain at rest and during weight-bearing activities.

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Chapter 7 : Sonographically Guided Intratendinous Injections of Hyperosmolar Dextrose to Treat Chronic Tendinosis of the Achilles Tendon: A Pilot Study[6]

7.1 INTRODUCTION

Chronic tendinosis of the Achilles tendon is a common overuse injury that is seen not only in athletes but also in the general population.[1] This condition is painful and a cause of considerable distress and disability. Previous research has shown that histologically tendinosis is a non inflammatory process resulting from a failed wound-healing cascade with evidence of disordered, haphazard healing; intratendinous collagen degeneration; fiber disorientation and thinning; hypercellularity; scattered vascular in-growth; and increased interfibrillar glycosaminoglycans.[2,3] Studies have also shown that these areas of collagen degeneration correspond to the hypoechoic areas seen on sonography.[4] Hyperosmolar dextrose has been used for years by medical practitioners as part of prolotherapy regimens for the treatment of chronic musculoskeletal pain with varying degrees of success reported in the literature.[5] Prolotherapy is a technique in which a small volume of an irritant solution (proliferant) is injected at multiple sites around a ligament or tendon insertion.[6] This solution is purported to initiate a local inflammatory response at the site of injection, which induces fibroblast proliferation and subsequent collagen synthesis resulting in a tighter and stronger ligament or tendon.[7] We report on a modification of this therapeutic injection technique for the treatment of chronic Achilles tendinosis. Instead of injecting a proliferant around the tendon insertion and performing the procedure blindly, we performed intratendinous injections of hyperosmolar dextrose under sonographic guidance, targeting the abnormal anechoic and hypoechoic areas in the tendon, to induce an inflammatory reaction and initiate a wound-healing cascade and subsequent collagen synthesis.

[6] A version of this manuscript will be submitted for publication. Maxwell, N., Ryan, M., Taunton, J., Gillies, J., and Wong, A. Sonographically Guided Intratendinous Injections of Hyperosmolar Dextrose to Treat Chronic Tendinosis of the Achilles Tendon: A Pilot Study.

7.2 SUBJECTS AND METHODS

7.2.1 Subjects

Thirty-six consecutive patients, 25 men and 11 women (mean age, 52.6 years; range, 23–82 years), with chronic tendinosis of the Achilles tendon—that is, those with symptoms for more than 3 months (mean, 28.6 months; range, 3–120 months)—participated in this prospective study. In all the patients in the study group, multiple previous conservative treatments had failed. Some of the treatments included physiotherapy (*n* = 19), acupuncture (*n* = 5), shockwave therapy (*n* = 2), sonography (*n* = 8), intramuscular stimulation (*n* = 3), steroid injections (*n* = 4), orthotics (*n* = 4), massage (*n* = 3) water running (*n* = 1), and laser treatment (*n* = 1). In 22 patients, there was minimal improvement after completion of a heel-drop program, which is the current standard conservative treatment for Achilles tendinosis. Exclusion criteria included patients with acute tendinitis or symptoms associated with acute trauma. Patients who had surgery or interventional procedures within the preceding 3 months were also excluded. All patients were fully informed about the study and provided written consent. The study was approved by the local institutional ethics review board(Appendix IV).

7.2.2 Sonography Examinations

The sonography examinations and injection procedures were performed by a radiologist with extensive experience in musculoskeletal sonography. The Achilles tendon was examined with the patient in a prone position with both feet hanging over the end of an examination table. The sonography examinations were performed on a unit (HDL 5000, Philips Medical Systems) using both a 5-12–MHz and a 7-15–MHz linear array high-resolution transducer. The tendon in its entirety was examined in the longitudinal and transverse planes. Care was taken to image the tendon parallel with the fibers in the longitudinal plane and perpendicular to the fibers in the transverse plane to avoid artifact such as anisotropy. Color flow Doppler imaging was used to diagnose neovascularity. Tendon thickness, the presence of anechoic clefts or foci, echogenicity,

neovascularity, the presence of intratendinous calcification, and the presence of cortical irregularity at the tendon insertion were all recorded for each tendon at baseline and before each injection procedure.

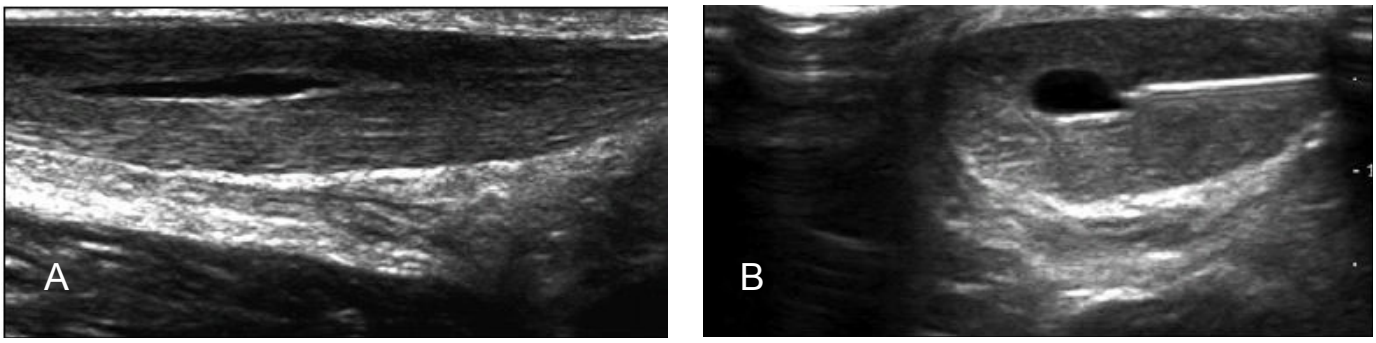

Figure 7-1 58-year-old woman with midportion Achilles tendinosis. A, Longitudinal sonographic image obtained using 5-12–MHz linear array transducer shows large anechoic cleft in midportion of Achilles tendon. B, Transverse sonographic image of same anechoic cleft after insertion of 27-gauge needle shows tip of needle is located at edge of cleft.

Tendon thickness was recorded as the maximum anteroposterior diameter (in millimeters) of the tendon measured on the transverse images. A distinction was made between anechoic clefts or foci (intrasubstance tears) and abnormal hypoechoic areas (collagen degeneration). A grading system for tendon echogenicity was devised as follows: grade 0 represented normal fibrillar echotexture; grade I, mild focal inhomogeneous echotexture; grade II, moderate focal inhomogeneous echotexture; and grade III, severe diffuse inhomogeneous echotexture. A grading system for neovascularity was also devised as follows: grade 0 represented no neovascularity (no detectable vessels); grade I, mild neovascularity (one or two vessels identified extending into the tendon); grade II, moderate neovascularity (three or four vessels identified extending into the tendon); and grade III, severe neovascularity (more than four vessels identified extending into the tendon). If the sonographic changes of tendinosis were seen in the midportion of the tendon, the patient was diagnosed as having midportion tendinosis; however, if the sonographic changes were seen in only the distal portion of the tendon, the patient was diagnosed as having insertional tendinosis. The study population was therefore divided into subjects with midportion

tendinosis and those with insertional tendinosis. The final sonographic evaluations were performed 6 weeks after treatment.

7.2.3 Hyperosmolar Dextrose Injection

A 3-mL syringe was filled with 1 mL of 2% lignocaine (20 mg/mL) and 1 mL of 50% dextrose (25 g/50 mL) (dextrose monohydrate, 500 mg), giving a 25% dextrose solution. Care was taken to expel all air from the syringe and needle before the injection. Each injection procedure was performed under aseptic conditions using a 27-gauge needle. Abnormal hypoechoic areas and anechoic clefts or foci (Fig. 7-1) in the thickened portion of the tendon were targeted under sonographic guidance using the 7-15–MHz hockeystick linear array transducer. The volume of solution injected varied slightly from tendon to tendon and depended on the degree of resistance during the injection and on spread of the solution within the tendon. In general, less than 0.5 mL was injected at any one site. One, two, or three sites were injected during a treatment session. The tendon was re-imaged after the injection procedure to assess for spread of the dextrose solution (Fig. 7-2) and to identify any intrasubstance or partial tears that may have become more conspicuous after the injection.

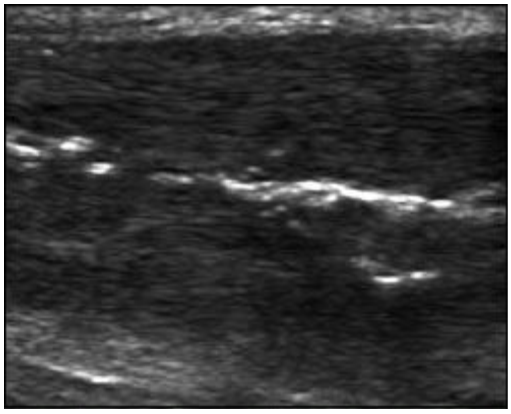

Figure 7-2 Sonographic image obtained after injection in 82-year-old man with midportion Achilles tendinosis shows hyperechoic dextrose solution dispersing within abnormal tendon

Patients were instructed to refrain from any heavy tendon-loading activity during the first 2 weeks after the procedure. They were also cautioned against taking

aspirin or other anti-inflammatory agents to relieve any discomfort. Acetaminophen-based analgesia was allowed.

Each patient was asked to return for repeat sonography and injection approximately every 6-weeks depending on scheduling. This continued until either the patient's symptoms resolved or no improvement was evident, at which time the treatment was discontinued. In general, if there was no improvement after four injection procedures, the treatment was discontinued.

7.2.4 Data Collection

At the initial consultations, all patients were asked to complete a questionnaire regarding their condition including participation in sporting activity, length of symptomatic period, previous and current treatments, and level of disability. Visual analogue scale (VAS) scores were recorded for assessment of tendon pain. This scale is a 100-mm-long line marked with anchors at each end. One anchor was labeled "No pain" and corresponded to 0, whereas the second anchor was labeled "Severe pain" and corresponded to 100. Patients were asked to mark with an X on the line the point that corresponded to their level of tendon pain. They were asked to complete a VAS for tendon pain at rest, tendon pain during normal daily activity, and tendon pain during or after sporting or other physical activity. VAS scores were recorded at baseline and before each injection. Final VAS scores were recorded 6 weeks after treatment.

A telephone interview with each study group participant was performed a mean of 12 months (range, 4.5–28 months) after the last treatment to assess the medium- to long-term efficacy of dextrose injection therapy.

7.2.5 Data Analysis

Descriptive and mean comparisons of the study data were analyzed using statistical software (JMP version 4.0.0 [2000], SAS Institute). A paired samples Student's *t* test compared the change in scores before and after treatment for

VAS1, VAS2, and VAS3 and for tendon thickness, which was recorded in millimeters. Data for comparisons were divided as follows: subjects with midportion Achilles tendinosis, those with insertional Achilles tendinosis, and both groups combined (i.e., all Achilles tendinosis subjects). A second paired Student's *t* test was performed using the location of tendinosis as an additional level for comparison of VAS scores before and after treatment. Statistical significance relating in the clinical context for this study was set at a *p* value of 0.10.

7.3 RESULTS

7.3.1 Patient Profile

After receiving multiple injections, three patients with insertional tendinosis showed only minimal response to the injection therapy and the treatment was therefore discontinued. A fourth patient was referred for surgical consultation after the initial intratendinous injection revealed a large tear in the distal insertional fibers of the Achilles tendon. This large irregular bursal surface partial-thickness tear became apparent on sonography only after injection of the dextrose solution (Fig. 7-3). Thirty-three tendons in 32 patients were successfully treated. The location of the tendinosis was midportion in 23 tendons and insertional in 10 tendons. The mean number of treatment sessions for the study group was 4.0 (range, 2–11). The mean volume of solution injected into the tendon during each treatment session was 1.35 mL.

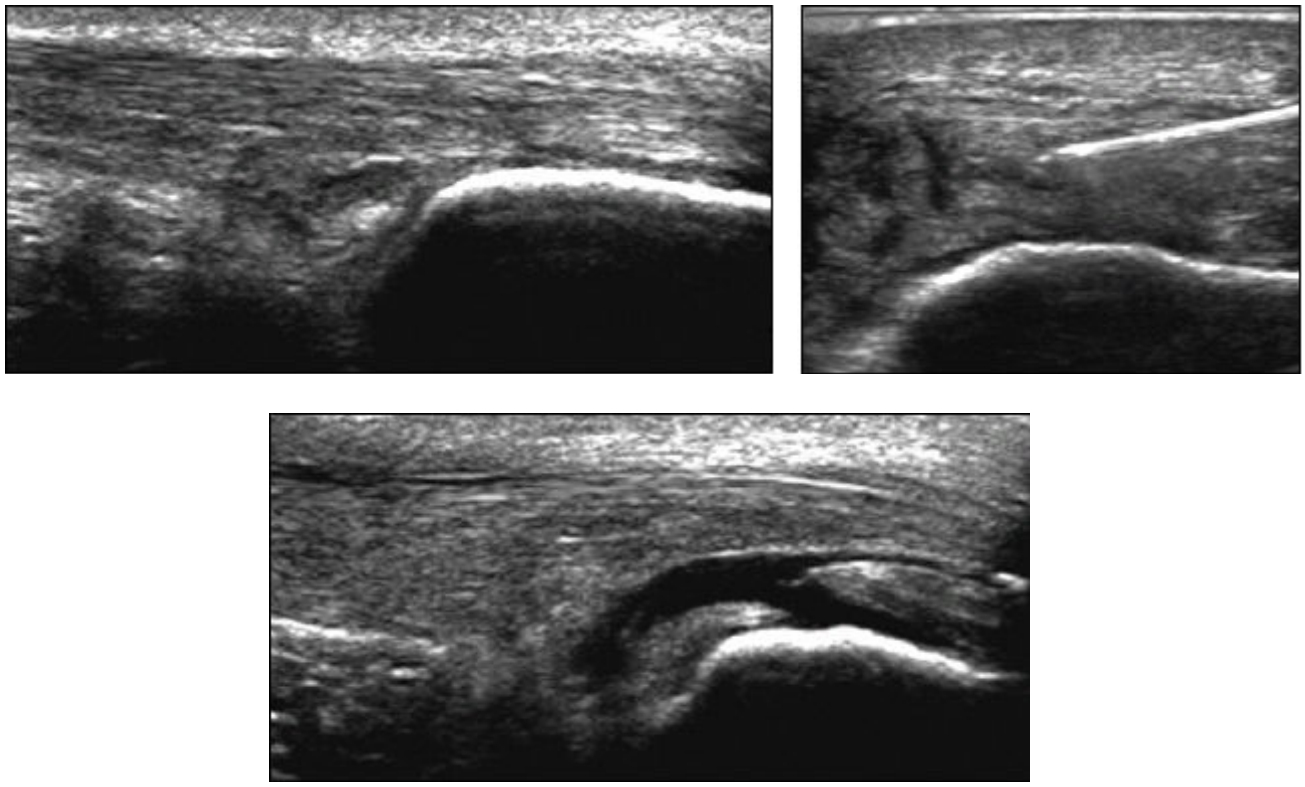

Figure 7-3 49-year-old man with insertional Achilles tendinosis. A, **Sonographic image shows typical appearance of insertional tendinosis.** B **and** C, **Sonographic images obtained after single hyperosmolar dextrose injection into distal thickened portion of tendon show large bursal-surface partial thickness tear that has opened up. This patient was withdrawn from study and referred for surgical consultation.**

7.3.2 VAS Scores

Table 7-1 illustrates the mean VAS scores before and after treatment for tendon pain at rest (VAS1), tendon pain during normal daily activity (VAS2), and tendon pain during or after sporting or other physical activity (VAS3) for the study population. There was a significant improvement in the VAS scores for the study group (midportion and insertional), with a mean percentage reduction in pain for VAS1 of 88.2% ($p < 0.0001$), for VAS2 of 84.0% ($p < 0.0001$), and for VAS3 of 78.1% ($p < 0.0001$). There was no significant difference between the midportion and insertional groups for VAS1 or VAS2; however, there was a significant difference between groups for VAS3 ($p = 0.06$).

Score	Mean VAS Score						Mean % Change in VAS Score[a]		
	Before Therapy			After Therapy					
	Midportion	Insertional	Combined	Midportion	Insertional	Combined	Midportion	Insertional	Combined
VAS1	41.7	30.3	38.2	4.7	4.1	4.5	88.7	86.5	88.2
VAS2	55.5	45.3	52.4	7.8	9.6	8.4	85.9	78.8	84.0
VAS3	73.9	66.4	71.6	12.4	23.4	15.7	83.2	64.7	78.1

Table 7-1 Visual Analog Scale (VAS) scores for study group before and after dextrose injection therapy for treatment of chronic Achilles tendinosis. Note: Combined = both groups combined (all subjects), VAS1 = pain at rest, VAS2 = pain during normal daily activity, VAS3 = pain during or after sporting or other physical activity. [a] $p < 0.001$

7.3.3 Sonographic Evaluation

Table 7-2 outlines the results of sonographic evaluations before and after treatment for the study population. The mean tendon thickness decreased from 11.7 mm before treatment to 11.1 mm after treatment ($p = 0.007$). Anechoic clefts or foci were seen in 18 tendons (55%) before treatment; however, only four of these tendons had evidence of clefts or foci after treatment. In 27 tendons (82%), echogenicity was unchanged after treatment. Six tendons (18%) were downgraded from grade II to grade I. There was no neovascularity present in four tendons (12%) before or after treatment. In 11 tendons (33%), neovascularity was unchanged after treatment. In 18 tendons (55%) there was decreased neovascularity after treatment: Six tendons decreased from grade III to grade I, three tendons decreased from grade III to grade II, and nine tendons decreased from grade II to grade I. Insertional cortical irregularity was seen in six tendons (18%) before and after treatment. Insertional intratendinous calcifications were seen in seven tendons (21%) before treatment. These calcifications were unchanged after treatment.

7.3.4 Follow-Up Telephone Interview

Thirty of the 32 patients were successfully contacted by telephone a mean of 12 months after treatment (Table 7-3). Twenty of the 32 patients were still asymptomatic, with 19 patients giving a satisfaction level of 95–100%. Nine

patients described only mild symptoms and had a satisfaction level of 70–90%. One patient had moderate symptoms and described only 50% satisfaction level.

Characteristics of Tendons on Sonography	Before Treatment	After Treatment
Mean tendon thickness (mm)	11.7	11.1
Anechoic clefts or foci present	18	4
Echogenicity[a]		
Grade 0	0	0
Grade I	15	21
Grade II	17	11
Grade III	1	1
Neovascularity[b]		
Grade 0	4	4
Grade I	10	25
Grade II	10	4
Grade III	9	0
Cortical irregularity at tendon insertion present	6	6
Intratendinous calcifications present	7	7

Table 7-2 Sonographic evaluation of study group before and after dextrose injection therapy for treatment of chronic Achilles tendinosis. Note: All data except mean tendon thickness are the number of tendons.
[a]Grade 0 = normal fibrillar echotexture, Grade I= mild focal inhomogeneous echotexture, Grade II= moderate focal inhomogeneous echotexture, Grade III= severe diffuse inhomogeneous echotexture.
[b]Grade 0= no neovascularity (no detectable vessels), Grade I= mild neovascularity (one or two vessels identified extending into the tendon), Grade II= moderate neovascularity (three or four vessels identified extending into the tendon), Grade III= severe neovascularity (more than four vessels identified extending into the tendon).

No. of Patients	Symptoms None	Mild	Moderate	Severe	Satisfaction Level (%)
19	19				95-100
7	1	6			80-90
2		2			70
2		1	1		50
Total: 30	20	9	1		

Table 7-3 Results of telephone interview performed a mean of 12 months after last dextrose injection therapy

7.4 DISCUSSION

Banks (1991) proposed that hyperosmolar dextrose induces an inflammatory reaction at the site of injection by dehydrating cells (osmotic proliferant) causing localized tissue trauma.[8] Local tissue damage causes an influx of inflammatory cells and initiates the wound-healing process. Granulocytes, which are attracted to the injection site by cellular debris and chemotactic agents, begin to chemically débride the injection site and during the process secrete humoral factors that attract macrophages. The macrophages phagocytize cellular debris and secrete polypeptide growth factors that attract and activate fibroblasts. The fibroblasts infiltrate the injection site and begin new collagen synthesis. This new collagen undergoes contraction due to a process of cross linking and dehydration of the newly formed fibers, resulting in stronger and tighter connective tissue at the injection site. In a human biopsy study by Klein *et al.* (1989), a 60% increase in collagen fibril diameter measured at 3 months was shown with high statistical significance ($p < 0.001$) after 6 weekly proliferant injections into the lumbar and sacroiliac ligaments in three patients with lower back pain.[9]

In most of the previously published research on prolotherapy, investigators report its efficacy in treating ligament instability. Several studies have looked at its role in musculoskeletal lower back pain and osteoarthritis, particularly of the

knee.[10,11,12,13] Very few published studies have reported on its role in treating chronic tendinosis. Topol *et al.* (2005) injected 24 elite rugby and soccer players who had chronic groin pain.[14] Those investigators performed monthly injections of 12.5% dextrose and 0.5% lidocaine into the thigh adductor origins, suprapubic abdominal insertions, and symphysis pubis. At final data collection a mean of 17 months after treatment, 20 of the 24 patients had no pain and 22 of 24 patients were unrestricted with sports activity. In our study, the dextrose injections were intratendinous as opposed to injections around the tendon insertion, and the injections were performed under sonographic guidance so that the hypoechoic and anechoic areas could be precisely targeted. To our knowledge, there is no mention in the published prolotherapy literature of sonographic guidance being used in the injection procedure.

In our study, we make a distinction between hypoechoic areas and anechoic clefts or foci. We believe both are part of the spectrum of tendon degeneration with anechoic clefts or foci representing intrasubstance microtears and hypoechoic areas representing abnormal areas of collagen degeneration.[4,15,16] In 18 tendons (55%), there were small anechoic clefts or foci present on the pretreatment sonography examination. In one patient with insertional tendinosis, a large partial-thickness tear became apparent only after the initial injection of the dextrose solution (Fig. 7-3). This preinjection sonographically occult tear was so large that the patient was withdrawn from the study and referred for surgical consultation due to fear of tendon rupture. This observation emphasizes the fact that intrasubstance and partial-thickness tears in chronic tendinosis may be sonographically occult. In 27 tendons (82%), the hypoechoic areas in the thickened portion of the tendon were unchanged after treatment. We expected that more tendons would have shown improvement or resolution of the abnormal hypoechoic areas.

There was no evidence of echogenic scar tissue formation on the final sonography examination. This may be related to the fact that a longer period of time than the treatment period is required for the tendon to remodel itself.

Öhberg and Alfredson (2002) proposed in their study that neovascularity is associated with chronic tendon pain; however, whether its presence indicates an unfavorable outcome is still unclear.[17] Zanetti *et al.* (2003) proposed that tendon inhomogeneity seems to be more relevant to outcome than neovascularity.[18] In our study, injections were not targeted at the neovessels but rather at the hypoechoic and anechoic areas in the tendon. Despite this, 18 tendons (55%) had decreased neovascularity after treatment. We postulate that neovascularity may represent an attempt by the body to reverse the intratendinous changes of tendinosis by improving the blood supply to the areas of collagen degeneration.

The results of our study show a significant reduction in tendon pain at rest and during tendon-loading activities. Unfortunately, we cannot fully explain the exact cause for the reduction in tendon pain. We do not believe that the reduction in tendon pain can be attributed totally to a reduction in neovascularity because 11 tendons (33%) in this study had unchanged neovascularity after treatment despite these patients having a significant reduction in tendon pain. The results and observations in our study are similar to those recently reported by Connell *et al.*(2006).[19] In contrast to our study, they performed autologous blood injections under sonographic guidance on 35 patients for the treatment of refractory lateral epicondylitis. They hypothesized that fibroblast growth factor, which is carried in blood, acts as a humoral mediator and induces the wound-healing cascade when injected into an abnormal tendon. The end result of fibroblast proliferation and initiation of the wound-healing cascade is common to both treatments.

There were three unsuccessful outcomes in our study. All three patients had insertional tendinosis with evidence of cortical irregularity at the insertion of the tendon and intratendinous calcification. It is our experience that some patients

with insertional tendinosis are more difficult to treat and have less favorable outcomes than patients with midportion tendinosis. This is emphasized by less marked reduction in tendon pain for VAS3 in the insertional group when compared with the midportion group (65.1% vs. 82.7%, respectively) (p = 0.06).

We realize there are certain limitations to our study. First, there was no control group and the patients were not blinded to what they perceived was a new treatment. The mean symptomatic period of our study population was 28.6 months, which is consistent with long-standing refractory Achilles tendinosis. The results of our follow-up telephone interview performed a mean of 12 months after treatment showed that 20 patients were still asymptomatic, nine patients had only mild symptoms, and only one patient had moderate symptoms (Table 7-3). There was a satisfaction level of 80–100% in 26 of the 30 patients contacted.

Despite the absence of a control group, the results of this pilot study are very promising and indicate satisfactory medium- to long-term efficacy of the dextrose injection therapy. We recognize that further clinical studies comparing hyperosmolar dextrose injections with other therapies and with no therapy are required.

There were no adverse effects or complications of the dextrose injection therapy identified in this study. Hyperosmolar dextrose has an excellent safety profile and is cost-effective.

In conclusion, sonography-guided intratendinous injections of hyperosmolar dextrose showed good clinical response in patients with long-standing refractory Achilles tendinosis with significant reduction in tendon pain at rest and during tendon-loading activities.

7.5 REFERENCES

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Chapter 8 : Favorable Outcomes with Ultrasound Guided Hyperosmolar Dextrose Injections for Chronic Achilles Tendinosis: Expanded Case Series with Two Year Follow-up[7]

8.1 INTRODUCTION

Achilles tendinosis is a chronic, degenerative condition affecting both sedentary individuals and athletes of all abilities, with prevalence in running based sports particularly high.[1] In a survey of 2002 running injuries seen over a 10 year period at the referral sports medicine clinic, Achilles tendon injury was the 6th most common injury.

Injury to the mid-portion of the Achilles tendon, typically 2–6 cm proximal to its insertion, is more prevalent than tendon pathology found at the insertion and accounts for approximating 66% of all injuries to the Achilles tendon.[2] Pain is considered to be the primary symptom of AT, such that it is suggested that a patient's symptoms can reflect the severity of the condition.[3] Often patients describe a period of tendon pain that is at least partially resolved through either time or a treatment intervention.[4] Unfortunately, symptoms often return with increased and repeated tensile strain as the athlete returns to their pre-injury training regimen. This pattern of injury, healing, and re-injury with return to sport is understood to contribute to biochemical changes in the extracellular matrix and degradation in the collagen composition eventually resulting tissue degeneration and compromised biomechanical properties.[5,6] Signs of tissue degeneration are observable sonographically with the use of modern high resolution ultrasound transducers and may include: intra-tendinous tearing, changes in tendon echotexture (structural degeneration), neovessel infiltration, intra-tendinous calcification, and irregularities to bone cortex at tendon insertion.[7,8,9,10,11]

[7] A version of this manuscript will be submitted for publication. Ryan, M., Wong, A., and Taunton, J. Favorable Outcomes with Ultrasound Guided Hyperosmolar Dextrose Injections for Chronic Achilles Tendinosis: Expanded Case Series with Two Year Follow-up.

A previous pilot investigation of injections of hyperosmolar dextrose administered under ultrasound guidance report favorable outcomes in a population with chronic Achilles tendinosis.[12] Significant improvements in pain at rest, with activities of daily living, as well as during or immediately following sport were documented coupled with improvements in the ultra-structure of the tendon throughout the treatment process. We have recently published a similar injection procedure to address pain associated with long-standing plantar fasciitis, with 16 of the 20 patients investigated reporting being either asymptomatic, or at a minimum of 70% pain reduction, at one year follow-up.[13]

The present study reports the outcomes of pain and sonographically observable structure changes of ultrasound guided injections of hyperosmolar dextrose on an expanded patient population experiencing pain at both the Achilles tendon insertion and mid-portion. Our outcomes will include our standard assessment of pain at baseline, after final consultation, as well as a follow-up duration encompassing one to four years post-treatment.

8.2 METHODS

8.2.1 Patient Profile

Diagnosis of Achilles tendinosis was made on the basis of pain directly at the posterior border of the calcaneus, or along the mid-portion of the tendon 2-6cm proximal to its insertion. All patients in the study group were referred from board-certified sport medicine specialists within the local Vancouver area and must have failed the previous conservative treatments prescribed. Treatments included home-based physiotherapy prescribed exercises (n=38), exercise regimen including eccentric heel drops (n=22), extra corporeal shock wave therapy (n=7), custom foot orthotics (n=5), massage (registered massage therapist) (n=4), prescribed medication (in all cases non-steroidal anti-inflammatory) (n=7), cortisone injections (n=6). The majority of subjects were runners (n=25), with cycling (n=13), tennis (n=10) and hiking (n=10) also listed as

activities undertaken on a regular basis. All patients gave informed consent prior to enrollment and all study protocols received ethical approval from the local university clinical review board (Appendix IV).

8.2.2 Ultrasound Examination

The ultrasound examination and the injection procedure were performed by a radiologist (AW) with extensive experience in musculoskeletal ultrasound. The Achilles tendon and surrounding tissue was examined with the patient in a prone position. The ultrasound examination was performed on a Philips HDL 5000 using both a 5-12MHz and a 7-15MHz linear array high resolution transducer. The tendon in its entirety was examined in the longitudinal and transverse planes with tendon thickness recorded as the greatest distance spanning the tendon in the anterior-posterior plane. Care was taken to image the Achilles tendon parallel with the fibres in the longitudinal plane and perpendicular to the fibres in the transverse plane to avoid artefact such as anisotrophy. Colour flow Doppler was used to diagnose neovascularity with the severity of neovessel in-growth evaluated on a 0-3 ordinal scale, whereby a ‘0’, ‘1’, ‘2’ and ‘3’ represented ‘no’, ‘mild’, ‘moderate’ and ‘marked’ neovascularity, respectively (Figure 8-1).

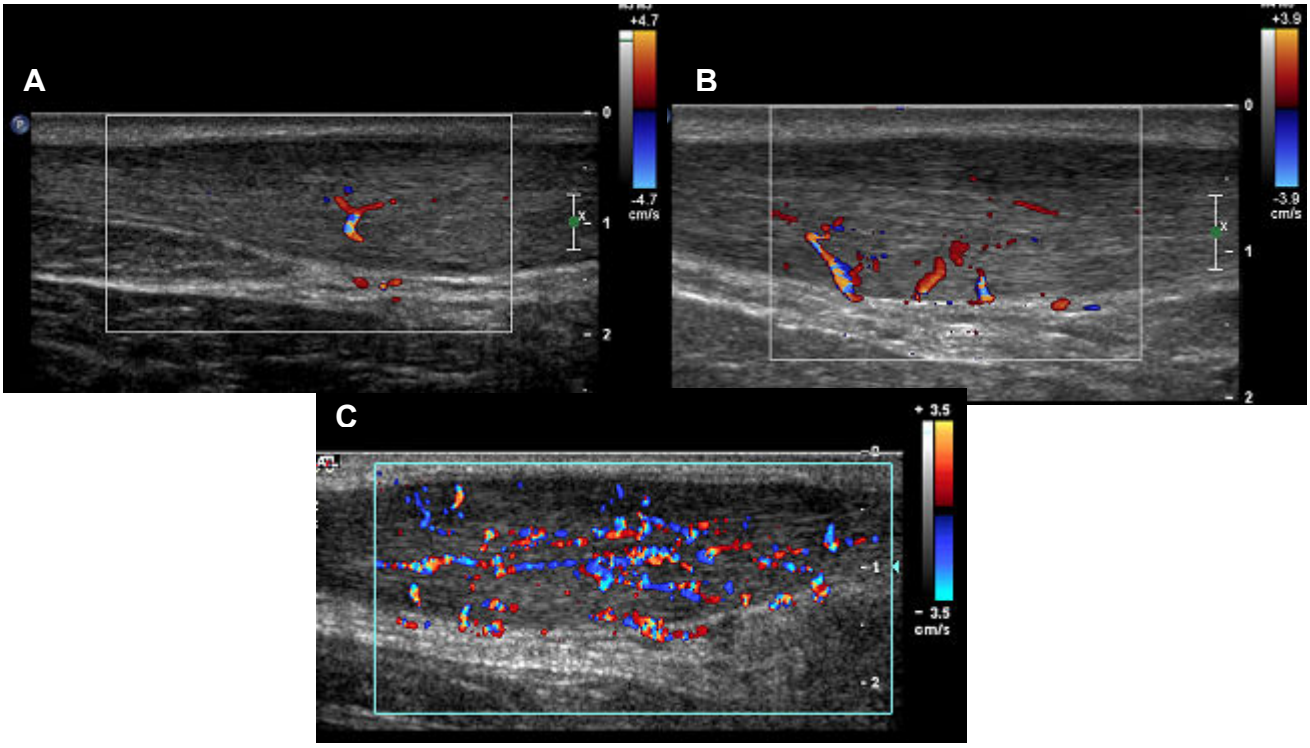

Figure 8-1 Example ultrasound images illustrating the different degrees of neovascularity: A) grade 1, B) grade 2, and C) grade 3

Hypoechoic regions were documented in two ways. The first measured the cross-sectional area of the hypoechoic region in square millimetres using the free-hand measurement tool in Inteleviewer radiological software (Intelerad Medical Systems Inc, 2002, Montreal, CAN Version 3.5.1.P98). The second evaluation of hypoechoic areas used a 0-3 ordinal scale to document the severity of any given hypoechoic area, whereby a '0' represented normal echogenicity and fibular pattern, '1' represented predominately signs of irregular collagen fibre pattern coupled with a slightly weakened echo signal, '2' represented significant hypoechoic regions and fibre irregularity, and '3' represented marked hypoechogenicity with periodic anechoic regions (Figure 8-2). All observable tears were measured in the longitudinal plane in millimetres.

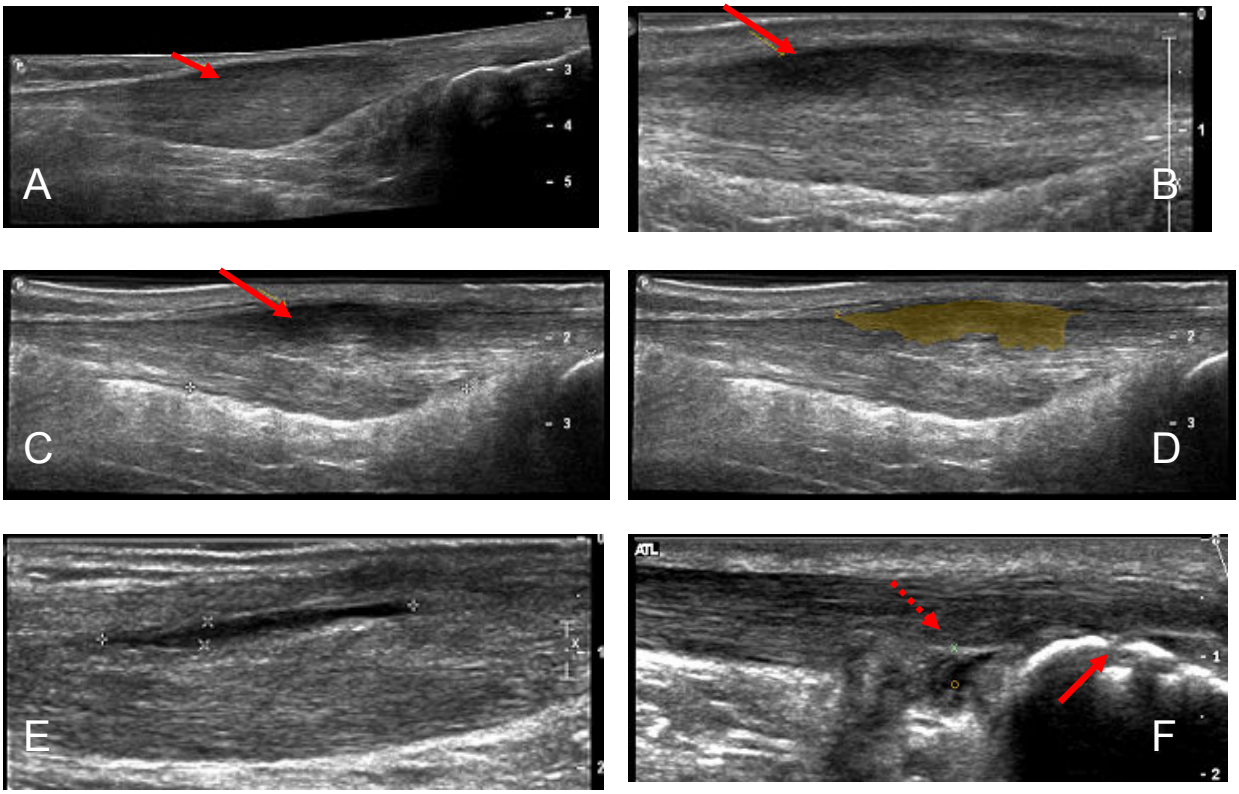

Figure 8-2 Overview of structural changes at the Achilles tendon. Slides A thru C illustrate grades 1 thru 3, respectively, with arrow indicating hypoechoic region. Slide D illustrates the free-hand measurement tool used to measure the area of hypoechogenicity. An intra-tendinous tear in slide E is seen between the marks within the tendon mid-substance. An irregularity to the cortex of the calcaneus (solid arrow) and intra-tendinous calcification (dotted arrow) are seen in the slide F.

The presence or absence of intra-tendinous calcification was documented, as was irregularity of the cortical bone of the calcaneus and inflammation of the periosteum.

8.2.3 Hyperosmolar Dextrose Injection

A 2.5mL syringe was filled with 1mL of 2% lignocaine (20mg/ml) and 1mL of 50% dextrose (25g/50ml) (dextrose monohydrate 500mg) giving a 25% dextrose solution. Care was taken to expel all the air from the syringe and needle prior to the injection. The injection procedure was performed under aseptic conditions using a 27G needle (Figure 8-3). Abnormal hypoechoic areas and anechoic clefts/foci in the thickened portion of the Achilles tendon were targeted under

ultrasound guidance using the 7-15MHz Hockey Stick linear array transducer. The volume of solution injected varied slightly from tendon to tendon and depended on the degree of resistance, spread of solution within the tendon and extent of the abnormality. Generally less than 0.5 mL was injected at any one site. Between 1 and 3 sites were injected during a treatment session. The tendon was re-imaged following the injection procedure to assess for spread of the dextrose solution and identify any intrasubstance or partial tears which became more conspicuous following the injection.

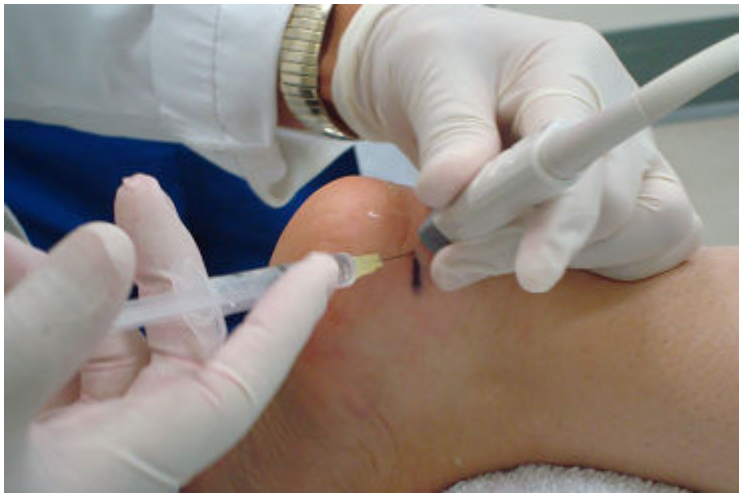

Figure 8-3 The ultrasound guided dextrose injection procedure, demonstrating simultaneous use of ultrasound probe and 27-guage needle to target significant sonographic features.

The patient was instructed to refrain from any heavy loading activity during the week following the procedure. Patients were cautioned against taking aspirin or other anti-inflammatory agents to relieve any discomfort. Acetaminophen based analgesia was allowed.

The patient was asked to return for repeat ultrasound and injection approximately every 6 weeks depending on scheduling. This continued until either the patient's symptoms resolved or no improvement was evident, at which time the treatment was discontinued.

8.2.4 Data Collection

At the initial consultation all patients were asked to fill out an information questionnaire containing brief questions regarding their condition including participation in sporting activity, length of symptomatic period, previous and current treatments and level of disability (Appendix VI).

Visual analogue scale (VAS) scores (100mm) were recorded for assessment of pain at the baseline consultation (pre-test), and at the final treatment consultation (post-test) (Appendix VII). VAS scales have been shown to be reliable, valid and responsive tools in assessing pain levels in patients rehabilitating from a musculoskeletal condition.[12] Patients were asked to complete a visual analogue scale item for pain at rest (VAS1), pain during normal daily activity (VAS2), and pain during or after sporting or other physical activity (VAS3). A follow-up telephone interview conducted a mean of 28.6 months (range 12 – 48 months) following the patient's final treatment session (follow-up) assessed long-term outcomes by asking the patients to rate their current levels of pain at rest, during activities of daily living, and during or after sport or activity on a scale from '0' to '100'.

8.2.5 Data Analysis

Descriptive and mean comparisons of the study data were analyzed using SPSS statistical software (copyright 2007, version 16.0.0.). Following a test of the homogeneity of variances, and one-way analysis of variance (ANOVA) determined whether a significant difference in the pain score outcomes was reported for the patients across all three testing times. Post-hoc analysis using Tukey's LSD for homogeneous variance or a Dunnet T3 correction if the variance is not homogeneous across groups will be applied if there is a significant difference in an outcome measure of pain between the levels for the independent variable of time. Statistical significance for this study was set at a *p*-value of 0.05. Trends are suggested at p-values less than 0.10.

8.3 RESULTS

One hundred and eight consecutive tendons from 99 patients, 58 men and 41 women (mean age 54.0 ± 10.8 years) with chronic Achilles tendinosis with symptoms for a minimum of 6 months (median 21 months; range 7-228 months) participated in this prospective case-series. Eighty-six of the cases were at the Achilles mid-portion and 22 with documented pain and pathology at the insertion. A median number of five (range 1 to 13) injection consultations were recorded for each patient, spaced an average of 5.6 (± 3.1) weeks apart.

Follow-up data was obtained from 75 patients. Two patients (each with unilateral symptoms) informed us at follow-up that they had subsequently gone on to have successful surgery on their Achilles tendon as a result of the dextrose injection protocol being ineffective against their tendon pain, and their data was not included in the follow-up analysis. Consequently, data from 73 tendons (68%) was included in the final follow-up analysis.

There was a significant improvement in the pain scores for both the mid-portion and insertional groups from baseline to the final consultation (post-test) for all of the pain scores, except for VAS1 for the group with insertional Achilles tendinosis (Tables 8-1 and 8-2). The mean differences in all of the pain scores continued to improve as recorded at the 28 month follow-up time, whereby all pain scores for both Achilles tendon injury sites where significantly lower at the follow-up time compared to baseline.

	Pre-test (mean ± SD)	Post-test (mean ± SD)	Follow-up (mean ± SD)	Mean Δ (ES) Pre-test to Post-test	Mean Δ (ES) Pre-test to Follow-up
VAS1 (Rest)	34.1 ± 27.7	12.6 ± 16.5	3.3 ± 7.4	21.3*** (0.93)	30.8*** (1.4)
VAS2 (ADL)	50.2 ± 25.6	21.8 ± 21.8	9.5 ± 16.2	28.2*** (1.2)	40.7*** (1.9)
VAS3 (Sport)	70.7 ± 23.3	36.7 ± 28.0	16.7 ± 22.0	34.0*** (1.3)	54.0*** (2.4)

Table 8-1 Summary of visual analog scale items for pain at rest (VAS1), pain with activities of daily living (VAS2), and pain during or immediately following sport participation (VAS3) for patients experiencing mid-portion Achilles tendinosis. * Indicates a significant difference between time interval to a p-value of 0.001. ES is a measure of the effect size of the difference represented as Cohen's *d*.**

	Pre-test (mean ± SD)	Post-test (mean ± SD)	Follow-up (mean ± SD)	Mean Δ (ES) Pre-test to Post-test	Mean Δ (ES) Pre-test to Follow-up
VAS1 (Rest)	33.0 ± 26.5	18.0 ± 25.8	2.7 ± 6.0	14.9 (0.58)	30.2*** (1.5)
VAS2 (ADL)	51.3 ± 25.4	29.6 ± 29.4	10.0 ± 16.3	21.7* (0.80)	41.3*** (1.6)
VAS3 (Sport)	69.6 ± 24.5	39.8 ± 29.6	17.7 ± 29.1	29.9** (1.1)	51.9*** (2.0)

Table 8-2 Summary of visual analog scale items for pain at rest (VAS1), pain with activities of daily living (VAS2), and pain during or immediately following sport participation (VAS3) for patients experiencing insertional Achilles tendinosis. *, **, * Indicates a significant difference between time interval to a p-value of 0.05, 0.01 and 0.001, respectively.**

Improvements in pain appeared to correspond with improvements in some aspects of the sonographic appearance of the Achilles tendon. A significant reduction in the size of intra-tendinous tearing was observed for the mid-portion group, with a trend for a reduction in the tear size for the insertional patients suggested (Table 8-3). The size of the hypoechoic region appeared reduced only in the patients with mid-portion tendinosis. There were no differences in the recorded thickness of the Achilles tendon at either injury site.

Sonographic Feature (Mid-Portion)	Test time	
	Pre-test	Post-test
Tendon Thickness (mm ± SD)	10.1 ± 2.9	10.4 ± 2.4
Size of Hypoechoic Region (mm^2 ± SD)	81.60 ± 108.7	52.1 ± 87.1†
Intratendinous Tear Size (mm ± SD)	7.1 ± 6.4	3.1 ± 4.7**
Sonographic Feature (Insertional)	**Test time**	
	Pre-test	**Post-test**
Tendon Thickness (mm ± SD)	10.5 ± 3.4	10.1 ± 2.6
Size of Hypoechoic Region (mm^2 ± SD)	178.6 ± 119.8	176.5 ± 112.6
Intratendinous Tear Size (mm ± SD)	5.3 ± 4.5	1.6 ± 2.8†

Table 8-3 Overview of continuous sonographic variables across time sub-divided for patients with pain at either the Achilles mid-portion or insertion. **,† indicate either a significant difference or suggested trend between post-test and pre-test at a p-value equal to 0.01 and 0.10, respectively

The number of patients with both grade 3 or 2 hypoechogenicity and neovascularization in the mid-portion group were considerably lower at post-test compared to pre-test findings; a difference that was much less remarkable in the insertional group (Tables 8-4 and 8-5). The insertional group had more observable cases of intratendinous calcification and cortical irregularities than the mid-portion group; however, there were no appreciable differences in either of these features from baseline to post-test.

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Sonographic Feature (Mid-Portion)	Test time	
	Pre-test	Post-test
Echotexture Severity (#)		
Grade 0	35	50
Grade 1	13	21
Grade 2	31	14
Grade 3	7	1
Degree of Neovascularity (#)		
Grade 0	22	38
Grade 1	20	28
Grade 2	36	20
Grade 3	8	0
Intratendinous Calcification (#)	1	1
Cortical Irregularity (#)	2	2
Periostitis (#)	0	0

Table 8-4 Overview of ordinal or dichotomous sonographic variables across time sub-divided for patients with pain at the Achilles mid-portion.

Sonographic Feature (Insertional)	Test time	
	Pre-test	Post-test
Echotexture Severity (#)		
Grade 0	2	3
Grade 1	3	10
Grade 2	12	9
Grade 3	5	5
Degree of Neovascularity (#)		
Grade 0	1	10
Grade 1	6	5
Grade 2	12	7
Grade 3	3	0
Intratendinous Calcification (#)	11	10
Cortical Irregularity (#)	5	6
Periostitis (#)	1	2

Table 8-5 Overview of ordinal or dichotomous sonographic variables across time sub-divided for patients with pain at the Achilles insertion.

8.4 DISCUSSION

Achilles tendinosis with pain and degeneration at either the tendon mid-portion or at the insertional (enthesis) is a common soft-tissue injury predominantly affecting individuals who must weightbear for prolonged periods of time in the day, and athletes involved in running-based sports. In severe and chronic cases, it presents a considerable challenge for the health care professional due to our limited knowledge of the source of pain, and lack of consensus on appropriate management strategies. For patients where conservative treatment measures

for tendinosis, such as ice, rest, activity modification, footwear changes and in-shoe orthoses have failed there are other more aggressive, or experimental, treatment options reported in the literature. These include: heavy-load eccentric only heel drops, extra-corporeal shock wave therapy (ESWT), or injections of either autologous blood, sclerosing agents (polidocanol), platelet-rich plasma preparations (PRP) or stem cells.[13,14,15,16,17,18] Some of these treatment options such as a heavy-load heel drop program may not be appropriate or may pose challenges on patient compliance for certain populations. Other options, at least in Canada, are coupled with a significant financial cost (ESWT), or include agents which are not readily available (polidocanol injections). Autologous blood or PRP injections require addition steps of blood withdrawal (and centrifugation with PRP and haematopoietic stem cells) before re-administering treatment injection. Injections of bone marrow stromal stem cells are still too invasive and experimental in nature to be considered as a conventional treatment.

The present study reports significant short-term and long-term improvements in the pain scores after patients with Achilles tendinosis at both the insertion and tendon mid-portion had received ultrasound-guided injections of dextrose. The positive outcomes from this study confirm the findings from our earlier pilot study on a patient population with the same condition and expand on those findings with, on average, a follow-up duration that is over two times longer than previously reported in our pilot investigation. Both Achilles tendon pathology sites also reported corresponding improvements in the sonographic appearance of the tendon, in particular, a reduction in the size and severity of hypoechoic regions, intra-tendinous tears, and neovascularization. There was an improvement in the echotexture of the tendon in the patients with mid-portion tendinosis at post-test; however, the size of the hypoechoic regions and the overall severity of the hypoechogenicity remained relatively unchanged in the insertional group. In addition, the insertional group registered more patients with calcific changes within the tendon and irregularities of the cortical bone of the calcaneus.

The patient group in this study represented a population with chronic long-standing symptoms (median 21 months symptom duration; range 7-228 months) who had already sought treatment from their primary care physician or sports medicine specialist and were then further referred for the ultrasound-guided dextrose injection treatment. Due to the resources involved in carry out the dextrose injections (i.e. ultrasound machine and radiologist trained in musculoskeletal pathology) and the needle stick injury involved it is suggested this treatment be administered only after conservative measures have been deemed ineffective.

Some of the sonographic features of insertional tendinosis observed in this study appeared resistant to change (hypoechogenicity, intratendinous calcification and cortical irregularities). The remaining presence of these features at post-test may account for the decreased effect size of the difference in pain scores, particularly for VAS1 and VAS2, reported from the insertional Achilles tendinosis group. Fahlström *et al.* (2003) reported differences in the response to treatments between a population with mid-portion and insertional Achilles tendinosis, namely with the use of eccentric exercise; the insertional group reported less improvement over time.[19]

A similar treatment protocol by Öhberg and Alfredson (2002, 2003, 2005) involving injections of a sclerosing agent, Polidocanol, into the peritendinous space ventral to the Achilles tendon reported successful pain and satisfaction outcomes for patients experiencing either mid-portion or insertional Achilles tendinosis.[7,17,20] The primary difference between the procedure described in the present study versus that of Öhberg and Alfredson is a change in the injection target from infiltrating blood vessels to intra-tendinous structural defects, such as tears or hypoechoic regions. In contrast to their findings, the present study reported the presence of neovascularization remaining at either a mild to moderate level in 60 cases at the post-test suggests an alternate, or

complimentary, source of pain apart from that suggested by Alfredson *et al.* (2003) for this patient group.[21] The results from the present study appear in agreement with Zanetti *et al.* (2003) who reported similar trends in their association with tendon echotexture, presence of neo-vessels and pain.[22]

The present study's strength of evidence for the treatment effect of the ultrasound-guided dextrose injections is compromised by the fact there is no control group included and therefore, no randomization protocol. The available data from the sonographic changes reported would also be improved with the addition of an ultrasound evaluation of the patients at the 28 month follow-up point. Such a sonographic evaluation would help to provide an insight onto the improvements in pain reported in both Achilles tendon pathology groups at follow-up over their post-test values. In other words, would we continue to see improvements in the sonographic appearance of the tendons 28 months after post-test, and would these changes be correlated with improvements in pain?

In conclusion, the present study expands upon the positive outcomes reported previously by our group for the use of ultrasound guided dextrose injections for mid-portion and insertional Achilles tendinosis by including results from now 108 tendons in 99 patients with an average follow-up duration of over two-years. Future research is underway to conduct a clinical trial including an injection and non-injection control groups to strengthen the evidence for this promising treatment alternative.

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Chapter 9 : A Pilot Study Investigating a New Treatment for Overuse Patellar Tendinosis: Ultrasound Guided Intratendinous Injections of Hyperosmolar Dextrose[8]

9.1 INTRODUCTION

Prolotherapy is defined as "the rehabilitation of an incompetent structure (as a ligament or tendon) by the induced proliferation of new cells".[1] Historically, the indications for prolotherapy have primarily centered on joint pain secondary to either hypermobility or instability of associated joints, namely the lumbar and thoracic spine.[2,3,4] Recently, solutions common to prolotherapy have shown success in addressing the pain associated with chronic tendinopathy.[5,6,7] The carry over of the clinical success of prolotherapy from the realm of ligament and joint pain to insertional based tendinopathies is plausible considering the similarities of the tissues involved.

Patellar tendinosis (PT), also referred to as 'jumper's knee', is associated with pain focusing directly on the patellar tendon, usually near its proximal insertion to the patellar.[8]

As it's name suggests, it is particularly prevalent in athletic populations that require repetitive, explosive power from knee extensors such as basketball, volleyball, soccer and track and field such that upwards of 40-50% of participants are affected.[9,10] A prospective case control analysis of athletes with PT, more than half of the subjects had to stop their sports career because of the knee pain, although there was no difference in their workplace productivity or ability to enjoy leisure-time physical activity in the years following their injury.[11]

[8] A version of this manuscript will be submitted for publication. Ryan, M., Wong, A., and Taunton, J. A Pilot Study Investigating a New Treatment for Overuse Patellar Tendinosis: Ultrasound Guided Intratendinous Injections of Hyperosmolar Dextrose

The pathology of PT is understood to not involve significant inflammatory processes. The source of pain in this patient group remains speculative; however, there is evidence behind pain stemming from a 'neurogenic' process, in association with new blood vessel infiltration, within the tendon.[12,13] Immunohistochemical and microdialysis technique studies provide insights to the source of pain in patients with chronic tendinopathy. Elevated amounts of substance P nerve fibers were found in patients with Achilles tendinosis and patients with long-standing jumper's knee report significantly higher levels of free glutamate, along with the NMDAR1 receptors.[14,15]

Ultrasound has been demonstrated as an effective diagnostic tool for identifying pathology associated with tendinosis or overuse tendinopathy, in particular through observation of areas of tendon degeneration, thickening, tearing, calcific changes, and neovascularization.[16,17] In addition, sonography has been used to assist in real-time guidance of injectable treatments to the peritendinous space or directly into the tendon itself.[18,19]

Previously, we have reported successful outcomes with injections of hyperosmolar dextrose administered under ultrasound guidance in patients experiencing chronic injury to the Achilles tendon and plantar fascia.[7,20] The objective of the present study is to report on findings using the same technique on individuals experiencing chronic infrapatellar tendinopathy.

9.2 METHODS

9.2.1 Patient Population

Diagnosis of infrapatellar tendinopathy was made on the basis of pain centered along the length of the patellar tendon, often at its proximal insertion directly at the inferior pole of the patella. All patients in the study group were referred from board-certified sport medicine specialists within the local Vancouver area and must have failed the previous conservative treatments prescribed. Exercise-

based treatments were the most frequently cited treatments previously undertaken, with 16 patients attending physiotherapy sessions. Drop-squat programs were used unsuccessfully by 22 subjects. Other prior treatments include: non-steroidal anti-inflammatory medication (n=9), general exercises for knee extension and for the lower extremity (n=8), lithotripsy or extra-corporeal shock wave therapy (n=4), foot orthoses (n=4), knee braces (n=4), acupuncture (n=2), chiropractic (n=1), and cortisone injections (n=1). Running (n=9) and basketball (n=8) were the most common activities undertaken by this patient population, with two of the runners elite caliber involved in international competition. One patient was on the Canadian National Alpine Ski Team, another was a professional ballet dancer and one patient was on the Canadian Developmental Team for spring-board diving. Nine patients were active with racquet-sports, including badminton, racquetball, tennis and squash. All patients gave informed consent prior to enrollment and all study protocols received ethical approval from the local university clinical review board (Appendix IV).

9.2.2 Ultrasound Examination

The ultrasound examination and the injection procedure were performed by the same radiologist (AW) with experience in musculoskeletal radiology. The patellar tendon and surrounding tissue was examined with the patient lying supine and the knee in a straight position. The ultrasound examination was performed on a Philips HDL 5000 ultrasound machine using both 5-12 MHz and 7-15 MHz linear array high resolution transducer/receiver. The tendon in its entirety was examined in the longitudinal and transverse planes with tendon thickness recorded as the greatest distance spanning the tendon in the anterior-posterior plane. Care was taken to image the patellar tendon parallel with the fibres in the longitudinal plane and perpendicular to the fibres in the transverse plane to avoid anisotropic artifacts. Colour flow Doppler was used to diagnose neovascularity with the severity of neovessel in-growth grade on a 0-3 ordinal scale, whereby a ‘0’, ‘1’, ‘2’ and ‘3’ represent ‘no’, ‘mild’, ‘moderate’ and ‘marked’ neovascularity, respectively (Figure 9-1).

Hypoechoic regions were documented in two ways. The first measured the cross-sectional area of the hypoechoic region in square millimetres using the free-hand measurement tool in Inteleviewer radiological software (Intelerad Medical Systems Inc, 2002, Montreal, CAN Version 3.5.1.P98). The second evaluation of hypoechoic areas used a 0-3 ordinal scale to document the severity of any given hypoechoic area, whereby a '0' represented normal echogenicity and fibular pattern, '1' represented predominately signs of irregular collagen fibre pattern coupled with a slightly weakened echo signal, '2' represented significant hypoechoic regions and fibre irregularity, and '3' represented marked hypoechogenicity with periodic anechoic regions. All observable tears were measured in the longitudinal plane in millimetres (Figure 9-2).

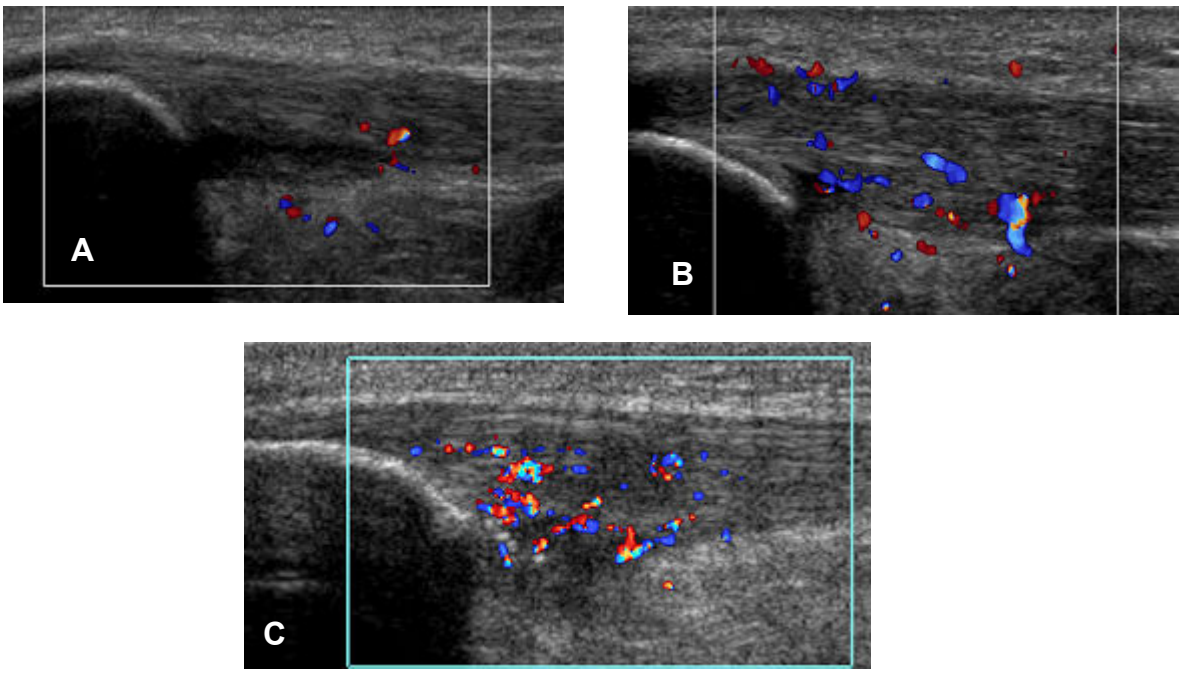

Figure 9-1 Example ultrasound images illustrating the different degrees of neovascularity: A) grade 1, B) grade 2, and C) grade 3

The presence or absence of intra-tendinous calcification was documented, as was irregularity of the cortical bone of the inferior pole of the patella and inflammation of the periosteum.

9.2.3 Hyperosmolar Dextrose Injection

A 2.5mL syringe was filled with 1mL of 2% lignocaine (20mg/ml) and 1mL of 50% dextrose (25g/50ml) (dextrose monohydrate 500mg) giving a 25% dextrose solution. Care was taken to expel all the air from the syringe and needle prior to the injection. The injection procedure was performed under aseptic conditions using a 27G needle. Abnormal hypoechoic areas and anechoic clefts/foci in the thickened portion of the patellar tendon were targeted under ultrasound guidance using the 7-15MHz Hockey Stick linear array transducer. The volume of solution injected varied slightly from tendon to tendon and depended on the degree of resistance, spread of solution within the tendon and extent of the abnormality. Generally less than 0.5 mL was injected at any one site. Between 1 and 3 sites were injected during a treatment session. The tendon was re-imaged following the injection procedure to assess for spread of the dextrose solution and identify any intrasubstance or partial tears which became more conspicuous following the injection.

The patient was instructed to refrain from any heavy loading activity during the week following the procedure. Patients were cautioned against taking aspirin or other anti-inflammatory agents to relieve any discomfort. Acetaminophen based analgesia was allowed.

The patient was asked to return for repeat ultrasound and injection approximately every 6 weeks depending on scheduling. This continued until either the patient's symptoms resolved or no improvement was evident, at which time the treatment was discontinued.

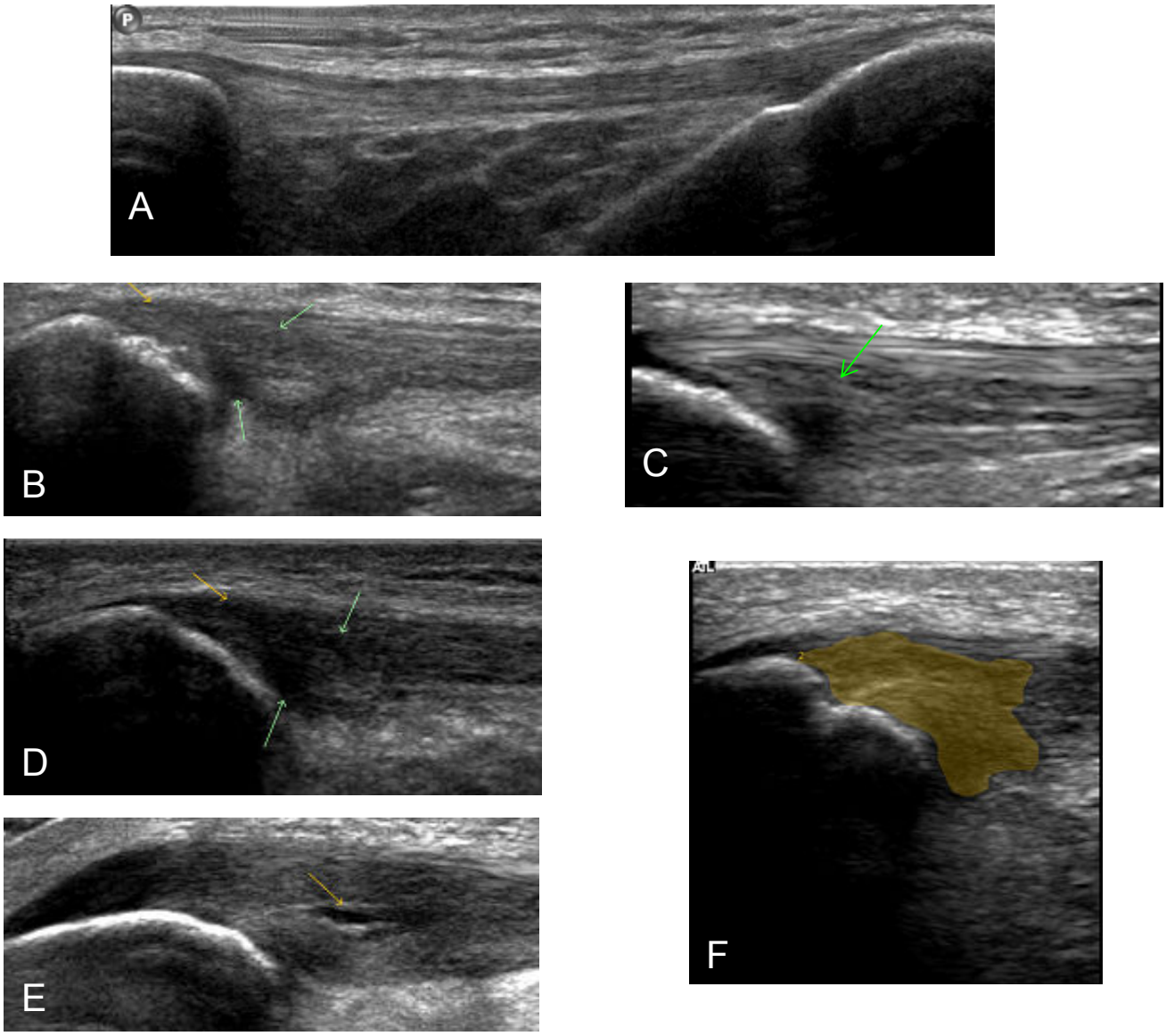

Figure 9-2 Overview of structural changes at the patellar tendon. Slide A shows a normal patellar tendon without marked thickening or hypoechoic changes. Slides B thru D illustrate grades 1 thru 3 hypoechogenicity, respectively, with arrow indicating hypoechoic regions. Slide E illustrates an intratendinous tear. The free-hand measurement tool used to measure the area of hypoechogenicity is shown in slide F highlighting an area of irregular echo texture.

9.2.4 Data Collection

At the initial consultation all patients were asked to fill out an information questionnaire containing brief questions regarding their condition including participation in sporting activity, length of symptomatic period, previous and current treatments and level of disability (Appendix VI).

Visual analogue scale (VAS) scores (100mm) were recorded for assessment of pain at the baseline consultation (pre-test), and at the final treatment consultation (post-test) (Appendix VII). VAS scales have been shown to be reliable, valid and responsive tools in assessing pain levels in patients rehabilitating from a musculoskeletal condition.[21] Patients were asked to complete a visual analogue scale item for pain at rest (VAS1), pain during normal daily activity (VAS2), and pain during or after sporting or other physical activity (VAS3). A follow-up telephone interview conducted a mean of 22 months (range 8 – 45 months) following the patient's final treatment session (follow-up) assessed long-term outcomes by asking the patients to rate their current levels of pain at rest, during activities of daily living, and during or after sport or activity on a scale from '0' to '100'.

9.2.5 Data Analysis

Descriptive and mean comparisons of the study data were analyzed using SPSS statistical software (copyright 2006, version 15.0.1.). Paired samples t-test compared the change in scores from baseline (pre-test) to post-test for the three visual analog scale items. While the follow-up telephone interview did serve as a quantitative measure of pain that is similar in format to the VAS items, its results were not formally analysed due to the unequal distribution of sample sizes in response numbers from post-test to follow-up. Consequently, data from the follow-up will be listed in a descriptive format. Statistical significance for this study was set at a *p*-value of 0.05.

9.3 RESULTS

Forty eight patellar tendons from 41 male and 6 female patients (one patient had bilateral symptoms) aged 38 (± 14.1) years participated in this prospective case-series. The median reported symptom duration was 16 (range 5 - 72) months. The mean number of injections needed to treat was four (± 3.4) spaced an average of seven (± 6) weeks apart.

Follow-up data was available from 21 of the 47 patients (45%). Of the phone numbers of the 26 patients who could not provide follow-up information, 12 had apparently changed, 9 were listed as not in service, two had no listing on file, one person had moved, one was for fax and one person could not be reached after repeated tries.

All tendons at the baseline appointment had documented structural hypoechoic changes with only one tendon improving to normal sonographic appearance at post-test. Twelve tendons (25%) showed no evidence of positive neovascularization at baseline, and at post-test 19 tendons were documented as having no neovascularity. There were no changes in any other observed sonographic feature.

	Pre-Test VAS (mm) (mean ± SD)	**Post-Test VAS (mm) (mean ± SD)**	**Follow-Up (mean ± SD)**
Pain at rest	38.4 ± 25.0	18.7 ± 18.4***	4.5 ± 8.1
Pain with daily living	51.1 ± 22.9	25.8 ± 20.1***	18.9 ± 22.6
Pain with sport/activity Sport	78.1 ± 15.7	38.8 ± 26.1***	34.1 ± 28.6

Table 9-1 A summary of baseline and outcome scores for visual analog scales (VAS) and follow-up telephone interview at rest, with activities of daily living and during sport/activity. * Indicates significant difference in outcome measure from pre-test to post-test at p < .001.**

There was a significant improvement in pain scores from baseline to the final consultation (Table 9-1). The effect sizes, or Cohen's d value, for the difference in pre and post-test VAS1, VAS2 and VAS3 values were 0.68, 0.92, and 21.3, respectively. Nine of the 47 patients were non-responsive to the hyperosmolar dextrose injection, twelve patients reported good outcomes yet were satisfied with treatment (50-70% pain relief) and the remainder were asymptomatic.

Improvements in the pain scores appear to coincide with structure changes to the patellar tendon. Specifically, there were 12 fewer documented cases of

intratendinous tearing at post-test and 8 fewer cases of marked hypoechogenicity (Table 9-2). Modest improvements in the degree of neovascularization appeared at post-test. Changes in the severity of the observed hypoechogenicity appeared be better than neovascularity at associating reported VAS changes across testing time (Figure 9-3, 9-4).

Sonographic Feature	Test time	
	Pre-test	Post-test
Tendon Thickness (mm ± SD)	8.1 ± 2.3	8.1 ± 2.2
Size of Hypoechoic Region (mm^2 ± SD)	185.4 ± 86.5	178.3 ± 80.4
Tendons with intratendinous tear and mean size (n, mm ± SD)	22, 6.1 ± 5.2	10, 6.8 ± 7.1
Echotexture Severity		
Grade 0	0	1
Grade 1	7	17
Grade 2	28	25
Grade 3	13	5
Degree of Neovascularity (#)		
Grade 0	12	19
Grade 1	13	14
Grade 2	20	13
Grade 3	3	2
Intratendinous Calcification (#)	21	21
Cortical Irregularity (#)	1	1
Periostitis (#)	5	4

Table 9-2 Overview of continuous, ordinal and dichotomous sonographic variables across time.

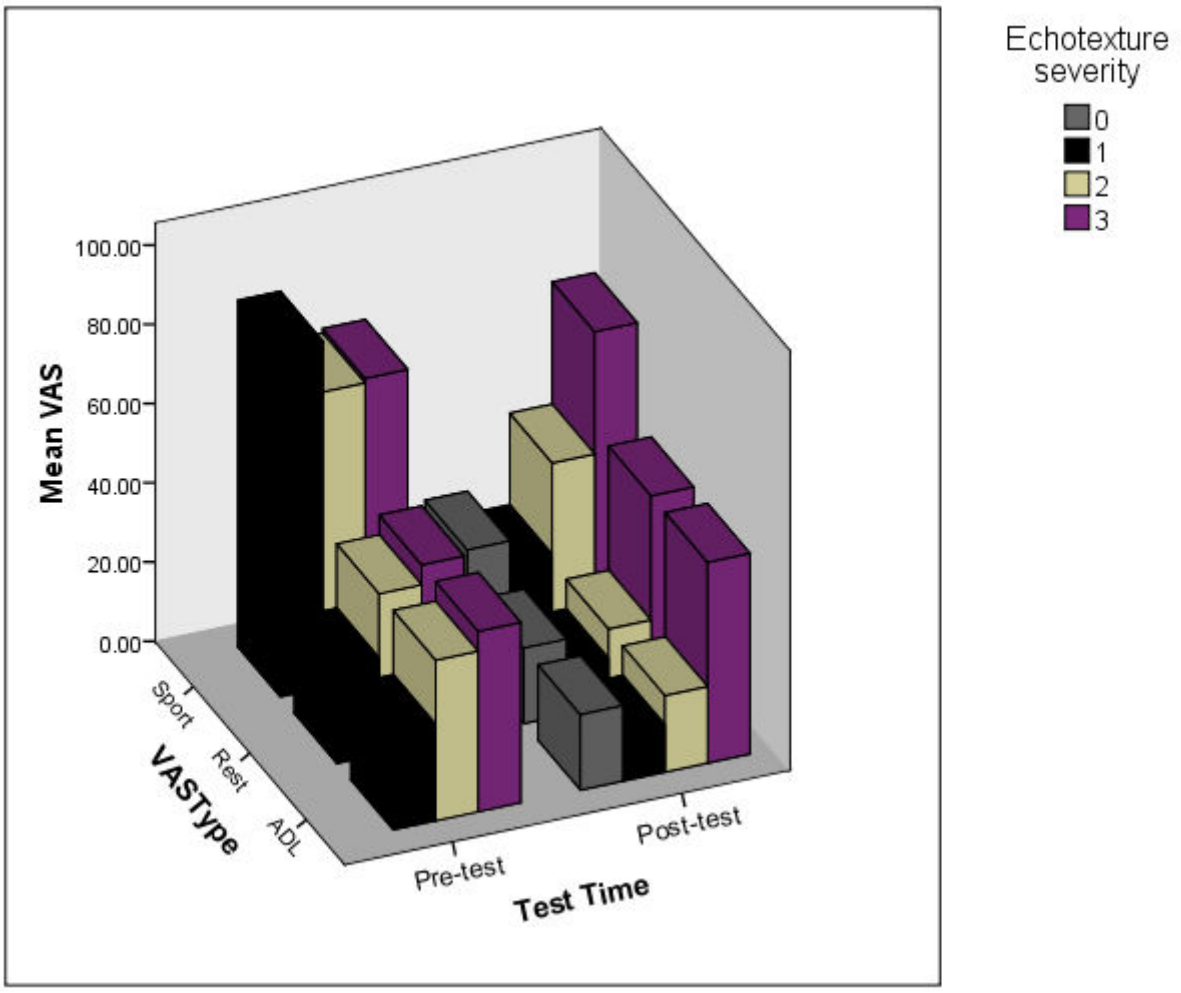

Figure 9-3 Three dimensional bar graph illustrating how corresponding changes in the severity of the hypoechoic regions were associated with changes in pain scores for each visual analog scale (VAS) item from baseline to final consultation. Note: none of the patients had normal echotexture (severity '0') at pre-test.

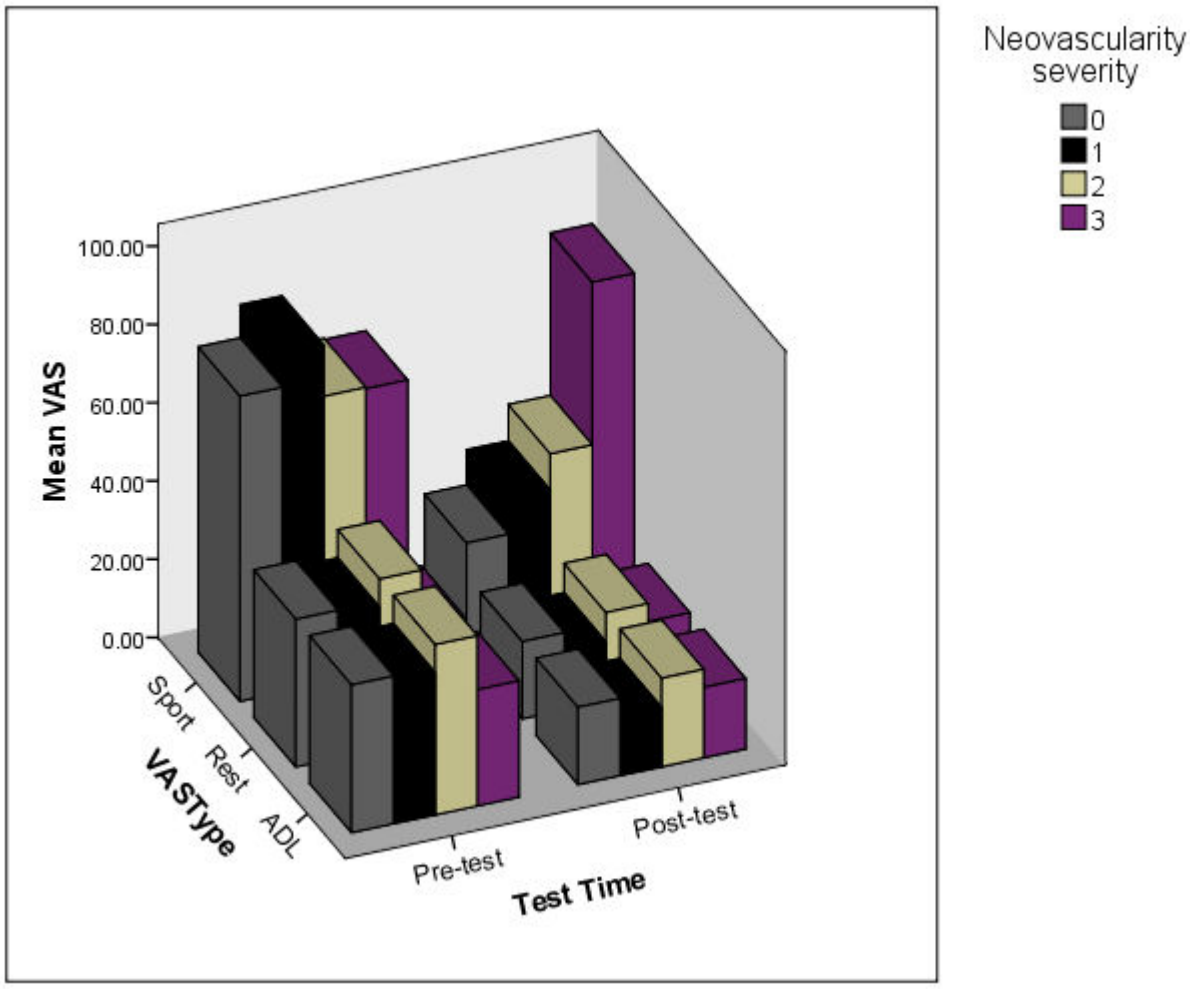

Figure 9-4 Three dimensional bar graph illustrating how corresponding changes in the severity of neovessel infiltration or neovascularity were associated with changes in pain scores for each visual analog scale (VAS) item from baseline to final consultation.

9.4 DISCUSSION

Infrapatellar tendinosis is characterised by persistent pain along length of the patellar tendon, often with a focal point directly at the inferior pole of the patellar. Occasionally, symptoms and the appearance of tendon degeneration take place at the distal insertion on the tibial tubercle. The challenge in treating this condition lies with the high physical demands that the athlete or individual often

places in performing movements of repetitive power through the knee extensors in sports such as basketball, running and volleyball.

The present case series investigated the efficacy of ultrasound guided injections of dextrose in relieving the pain associated with painful infrapatellar tendinosis. Overall, there were significant mean reductions in pain scores in all three categories of daily activities (rest, activities of daily living, and during or immediately following sport) from baseline to post-test. The responses from the 21 patients at approximately 2 year follow-up provide a preliminary evaluation of the treatment effectiveness on a long-term basis; however, the relatively low percentage of follow-up data recorded from this population weakens the study design. Similarly, the lack of any injection or non-injection based control group limits our understanding of the underlying therapeutic mechanism and the validity of the treatment intervention.

Injections of dextrose have been used individually for a variety of musculoskeletal indications: low back pain and sacroiliac joint dysfunction,[22,23,24,25] knee instability subsequent to ACL injury,[26] osteoarthritis, [27] anterior talofibular ligament sprain, and medial meniscus injury.[6] Specifically in the context of tendinopathy, dextrose prolotherapy has demonstrated clinical efficacy based on case series data at the following locations: adductor tendinopathy in elite soccer and rugby athletes,[5] patellar tendinopathy,[6] and Achilles insertional and non-insertional tendinopathy.[7]

The mechanism for the underlying treatment effect of the dextrose injections is believed to stem from an osmotic reaction within the interstitial tissue following the introduction of the dextrose. As water vacates the fibroblasts at the injection site down the osmotic gradient, cell membrane disruption may take place releasing inflammatory cytokines and stimulating a wound healing response.[28,29] However, mechanistic background research on the effect of isolated dextrose injections is not extensive and currently yields inconclusive results.[30,31]

Figure 3 illustrates the general trend that increasing severity of the hypoechoic regions appears to correspond with increasing pain scores. The apparent reduction in both the number of tendons with intratendinous tearing and marked hypoechoic regions subsequent to the dextrose injection therapy is, therefore, a promising indication of likely both positive tissue remodelling and an improvement in the structural integrity of the tensile unit. Unfortunately, ultrasound investigations were not performed at the 22 month follow-up point which would have allowed us to expand our comment on structural changes within the tendon in the months following this treatment.

The presence of neovessels, or angiogenesis, within a tendon is accepted as an indication of tendon pathology.[18,17] Neovascularity was modestly improved following treatment with ultrasound guided dextrose injections such that there was a mild reduction in the number of patients documented as having moderate to marked neovessel infiltration. The association between the pain scores and the severity of neovascularization was less apparent than for hypoechogenicity, in fact, was only apparent with pain scores recorded during sport participation (Figure 4). In fact, seven patients reported being asymptomatic post-treatment despite also having either moderate to marked neovascularity. Zanetti *et al.* (2003) reports that the presence of hypoechoic changes, rather than the presence of neovascularity, appear to have a greater association with treatment outcome.[32] However, Hoksrud et al (2008) concluded that regardless of the presence of neovascularity or structural hypoechoic changes there is no significant relationship to these sonographic features and sclerosing treatment outcome.[33]

Twenty-one patients (45%) had documented intratendinous calcification that remained unchanged following treatment. The number of patients in the present study with reported calcific changes is markedly higher than in previous studies on mid-portion Achilles tendinosis, but consistent with other insertional soft-tissue

enthesopathies of the Achilles tendon, patellar tendon and plantar fascia.[34,35,36,37] Intratendinous calcification has also been well documented within the supraspinatus tendon whereby it is reported to be associated with the appearance of symptoms.[38,39]

In conclusion, results from the present study report that there is a clinical benefit in reducing pain in patients with patellar tendinosis with ultrasound guided dextrose injections. The reduction in pain appeared closer associated with structural changes to tendon echotexture than the presence of neovascularization.

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Chapter 10 : Conclusion

10.1 DISSERTATION THEME AND OVERVIEW

Tendinopathy presents a considerable challenge for the health care professional treating either an athletic or sedentary population. While the scientific community has made tremendous strides in the understanding of potential causative factors, classification of the pathology and mechanisms of tissue degeneration, we have ultimately benefited from the knowledge of knowing how much is yet to be understood. No longer are there assumptions regarding the disease process in chronically injured tendons, and no longer is there a carry forward in falsely applying treatment, as with repeated cycles of anti-inflammatory medication.[1] No longer do we assume only athletes experience overuse tendon pain, and furthermore assume only abstinence of activity will be enough for a cure.[2] [3] Many elements of chronic tendon degeneration remain still speculative or unknown. Where is the source of pain? Does the neurogenic model proposed initially by Alfredson *et al.* (2003) hold the answer?[4] What type of exercise-based therapy is the most effective for returning athletes to sport? Should the exercise program conservatively incorporate concentric exercises or can we with confidence prescribe pain-inducing heavy-load eccentrics? For those athletes in running based sports, are there predisposing factors for developing tendinopathy that are within their scope of control?

While the challenges facing clinicians who face the patient with long-standing tendinopathy are becoming increasingly understood, there is an emerging trend of a new generation of treatments ready to be included in the clinician's arsenal.[5] Many of these treatments are being developed and documented in the interests of sharing their success with this difficult condition with others in the health care field who might share their treatment burden. Advances in sports or musculoskeletal medicine often are clinically generated, in that observational or anecdotal experience drives research to support and strengthen evidence for the treatment effect. Only after such a treatment is established do mechanistic

investigations proceed to uncover why. Our collective motivation is a drive to search out solutions as quickly as possible for individuals experiencing chronic pain from tendinopathy.

The research performed in this dissertation was intended to provide the clinician with an insight on two areas related to overuse tendinopathy: etiology and treatment. The analysis of kinematic variables associated with the occurrence of Achilles tendinopathy in runners was undertaken to validate the provision of movement altering treatments of the foot and ankle, such as motion controlling footwear and foot orthoses. While preliminary evidence of autologous blood injections appear promising, platinum-level evidence from well designed clinical trials must contend with the high degree of variability in the dose of the bioactive ingredients therein. Two treatment approaches are introduced for chronic plantar fasciitis, one exercise-based and the other using ultrasound guided injections of a solution that traces its history back to treating patients with jaw and low-back pain in the 1950s.[6 7] The same ultrasound guided injection therapy was further documented at the infrapatellar tendon and with an expanded population suffering either insertional or mid-portion Achilles tendinosis.

10.2 DISCUSSION OF CHAPTER CONTRIBUTIONS

10.2.1 Biomechanics and the Etiology of Achilles Tendinopathy

Biomechanical investigations attempting to understand whether movement patterns of the lower-extremity can differentiate runners with and without Achilles tendinopathy are not common, and conspicuously absent when addressing cases at the Achilles insertion. Early observations of runners seen at a sports medicine clinic first established the concept of specific movements of the foot and ankle, namely excessive pronation, may be a causative factor.[8 9] As quantitative techniques of the leg and foot were introduced through 2-dimensional video-based analysis, overpronation was further implicated as having a strong association with Achilles mid-portion injuries.[10] Our analysis of

runners with and without Achilles mid-portion pain in Chapters 2 and 3; however, provide only partial support for this concept is supplied with the results in this dissertation as only differences in total eversion excursion, and not peak eversion angle nor velocity, were observed. Azevedo *et al.* (2009) in a similar investigation using 3-D kinematics only found differences in total knee range of motion between injured and non-injured runners, with no differences appearing in the ankle.

The limitations of the 3-dimensional analysis techniques used in Chapters 2 and 3 are worth reiterating, especially due to the relatively high reported error of measurements in both the frontal and transverse planes associated with skin marker movement.[11] Intuitively, it remains plausible that the Achilles tendon becomes degenerative in habitual runners through some degree of either excessively high or low amounts of mechanical stress that is a result of morphological tissue characteristics, biomechanical movement patterns, or both.[12] It further stands that such predisposing intrinsic factors would then result in some degree of observable movement pattern.

Attempting to understand the nature of predisposing factors without regard for other potential and highly confounding factors may ultimately render our investigations much less effective. As our understanding of genetic contributions of overuse tendinopathy deepen, it is now conceivable that the same stress applied to two tendons of different phenotypic expression of cellular and extra-cellular materials may result in very different circumstances. Results from the analysis of repeat polymorphisms of collagen I, V, XII and XIIII have produced outcomes that are difficult to interpret in the clinical setting, as only collagen V with tenascin *C* were significantly associated with tendon pain or rupture; however, are quantitatively small as a constituent of the tissue.[13-15] A rare variant of the COL1A1 polymorphism was under-represented in a population of athletes experiencing anterior cruciate ligament injury; however, the impact this has specifically on tendinopathy is uncertain.[16] In the future, the studies of genomics

and proteomics will provide us deeper insights on the underpinnings of soft-tissue, and how differences in structural composition can influence the incidence of overuse tendinopathy.

10.2.2 New Insights on the Role of Eccentric Exercise

The role of exercise as a treatment for even long-standing tendinosis has become increasingly well documented due to the reported success of regimens using eccentric-based exercises. Programs utilizing particularly high levels of eccentric load have been demonstrated at the Achilles insertion and mid-portion and infrapatellar tendons with good clinical success.[18-20] Other exercise programs involving eccentric movements and/or stretching have had good reported outcomes for the plantar fascia and common elbow extensor, with anecdotal evidence of a similar effect for the supraspinatus tendon.[21-23] Results from the static and dynamic exercise regimen in Chapter 5, particularly from the group wearing the ultra-flexible footwear, further strengthen the concept of exercise-based therapy for plantar fasciitis. In the absence of alternate treatment arms within our study, we can only speculate to the significantly faster clinical response from the group wearing the Nike Free 5.0. The increased flexibility allowed from the Free shoe condition in comparison to conventional training shoes, particularly in the forefoot region, allows the foot to undergo a greater activation of the windlass mechanism resulting in greater stress on plantar intrinsic muscle and soft-tissues of the foot.[24 25] In addition, the longitudinal clefts within the sole of the Free shoe may result in greater instability for frontal plane movement of the foot and ankle providing a further somatosensory training stimulus for postural balance improvement.[26] Recent publications discussed below offer further insights into the potential treatment mechanisms of eccentric stretch training for tendinopathy.

While there is speculation as to the specific treatment mechanism behind eccentric movements, it is becoming clear that incorporating eccentric exercise

into treatment regimens results in superior outcomes than concentric-based programs.[27] Allison and Purdam (2009) suggest that the role eccentric exercise plays in the treatment of chronic tendon injury is likely not through optimizing strengthening elements, but postulate that there may be a unique stretching stimulus that results in one, or a combination, of the following: an improved homogeneity of passive structures, modulation of the neurological stretch responses back to normal, and increasing shear forces between the tendon and peritendinous structures that may interfere with vascular infiltration associated with neurogenic pain.[28] Eccentric-based programs have also been shown to result in a greater decrease in tendon thickness than concentrically-based exercises for the calf and Achilles tendon, presumably as a result of greater extravascation of water attributed to an increase in tendon crimp strengthening, combined with greater collagen stretch and realignment.[29] However, it remains to be determined whether this process is specifically related to positive remodeling.

As neurological aspects are becoming incorporated into pathology models of tendinopathy, there is an increasing attention focused on the role of secondary hyperalgesia stemming from the original tendon pathology which further disrupts motor function of the muscle-tendon unit.[30] Compromised mechanical function, in addition to exaggerated pain sensations, could result in a significant negative motivation, either voluntarily or subconsciously, for persistent movement of the affected limb. Consequently, lower levels of stress would be applied through the tendon which would further contribute to the degenerative process, either on a whole-tissue level or at specific focal points.[12 31 32] Exercise-based therapy may intervene in this apparent vicious cycle by minimizing motor function detriments that are secondary to hyperalgesia and tissue degeneration.[28]

Unfortunately, there is a significant shortfall of research reporting on exercise-only treatments for plantar fasciitis, especially considering how commonplace it is for patients undergoing physiotherapy for heel pain to be administered exercises

of varying descriptions.[33 34] There is documented validation of physiological changes after a heavy-load eccentric protocol was performed in a population with Achilles tendinopathy, specifically a more normalized sonographic appearance and an increase in type I collagen turnover.[35 36] Similar series of investigations have not been conducted for exercise regimens targeting the plantar fascia, in fact, there is still no consensus on a standardized exercise approach for this condition.

10.2.3 Introducing Sonographically Guided Dextrose to the Family of Injection Therapies for Tendinosis

Injection-based treatments for chronic tendinosis are quickly becoming a popular trend for addressing the pain associated with this challenging clinical entity. No less than seven separate solution-based treatments, delivered either blindly or with sonographic guidance, for chronic tendon pain have been documented in the literature within the past 10 years: corticosteroid (betamethasone), polidocanol, prolotherapy solution (sodium morrhuate 14.7% and dextrose 10.7%), dextrose (25%), the MMP-inhibitor aprotinin, whole autologous blood and platelet-rich preparations (PRP).[37-43] Interestingly, a procedure involving only dry-needling and no injectable solution resulted in clinically significant improvements in pain in patients with calcific shoulder tendinosis and there was no significant difference between a steroid treatment group versus placebo in the case of rotator cuff tendinopathy.[37 44] Based on the circumstantial evidence herein, it is reasonable to speculate there is a common underlying treatment effect across these injectable treatments that is likely stemming, at least partially, from the needle stick injury.

To counteract the degenerative process, external stimuli delivered via the injectant may be necessary to assist in the healing response of tendon. Intratendinous injections of either irritant materials – such as dextrose alone or in combination with sodium morrhuate – or whole blood or blood-borne bioactive solutions (i.e. PRP) are understood to deliver directly to the injury site pro-wound

healing cytokines and platelet-born growth factors, such as PDGF, VEGF, IGF-I and bFGF, as well as creating significant fibril disruption allowing greater blood permeation and healing stimulus.[45-47] The vascular sclerosing effect of peritendinous polidocanol injections has been well documented by Alfredson and Öhberg interfering with an apparent neurogenic source of pain in patients with chronic Achilles and infrapatellar tendinopathies.[4 43 48-51] As previous research has uncovered the role of MMPs in the pathogenesis of tendinosis, selective use of MMP inhibitors, such as aprotinin, has become documented.

The positive outcomes reported in Chapters 6 - 9 from injections of sonographically guided dextrose are a promising introduction of a treatment that has an excellent safety record in musculosketal applications, is inexpensive and relatively easy to work with.[46 52] Furthermore, our long-term follow-up outcomes at the Achilles and infrapatellar tendons present good evidence against a reoccurrence of injury. Sonographic evidence of degeneration is reported to precede injury in populations with chronic tendinosis; therefore our finding of improved sonographic appearance of the tendons post-treatment is an encouraging sign.[53]

Interpretation of our results should also consider the limitations of the methodology. Functional testing of the affected limb in our tendinopathy populations was not carried out. Silbernagel *et al.* (2007) report a significant disparity between reported improvements in pain and a corresponding improvement in lower-leg muscle-tendon function in patients with Achilles tendinopathy. Therefore, while we report significant improvements in pain with corresponding improvements in the tendon's sonographic appearance, care should always be exercised when return to activity programs are prescribed. The absence of an injection or non-injection control arm within our investigations in Chapters 6 - 9 limits our understanding, and weakens the validity of, the treatment effect observed in our reports on the plantar fascia, infrapatellar and Achilles tendons. A histopathological analysis was also not conducted to

correlate improvements seen on ultrasound, pain scores and biopsy samples. Previously, a comparison between MRI, ultrasound and biopsy samples revealed that multiple areas demonstrating sonographic hypoechogenicity were associated with similar histopathological findings: loss of collagen organization, a gradual increase in mucoid ground substance, hypercellularity and capillary proliferation.[54] All sonographic observations in this dissertation were made by the same radiologist; hence we have no measure of either intra- or inter-observer variability. A recent study does report good to excellent inter-observer reliability in documenting neovascularization in injured tendons.[55] Future research on the use of dextrose for overuse tendinopathy should endeavor to address these limitations and expand the application of injection-based treatments.

10.3 FUTURE DIRECTIONS

To further our biomechanical understanding of the etiology of Achilles tendinopathy, future research in this area should be focused on addressing the limitations currently existing in tri-planar kinematic assessment of the lower-extremity. Being able to accurately and reliably document both frontal and transverse plane movement of both the hip and sub-talar joint are crucial to our understanding of lower-leg function. Current skin-mounted marker placement schemes present challenges to the researcher attempting to discriminate relatively small movement differences across subjects, as in the case of otherwise healthy runners compared to individuals with more obvious movement disorders, such as Parkinson's disease or multiple sclerosis.[11] Improving our quantification and analysis of the movement of proximal joints in the lower-extremity will provide a more holistic biomechanical approach and allow entry of prevalent clinical entities such as hip-abductor weakness into the etiology of this condition.[17] Ultimately, multivariate statistical strategies must also be employed to truly understand the impact of any one factor in the presence of all other likely candidate variables.

Based on the outcomes reported with the physiotherapy regimen outlined in Chapter 5, future research should be undertaken to further validate the treatment effect. Such a study should include with a larger sample size for two additional treatment arms: a group performing the same exercise regimen in a barefoot condition and a group performing only a standard calf stretching regimen. The inclusion of the barefoot group will provide an insight on the treatment mechanism behind the superior results observed with the Free group, while a typical calf-stretching routine would be utilized as a group undergoing "standard care".

From a clinical perspective, a goal for future research projects based on the outcomes in Chapters 6 - 9 should be to expand the practice of dextrose applications to the primary care sports medicine setting. The use of sonographic guidance in the delivery of a therapeutic agent has obvious advantages when reporting in a research setting, particularly from the standpoint of standardized injection targeting and quantification of structural outcomes. The clinical advantages of ultrasound guidance are less clear, nevertheless, use of sonography may be a useful tool in assisting with a tissue or pathology centered injection protocol.[56 57] After appropriate instruction and training, a feasibility study investigating the inter-clinician variability in administering intratendinous injections should be conducted to ensure a similar degree to treatment efficacy and greatly expand the accessibility to this effective treatment option. Further integration into the primary care clinic might include functional assessments of the affected limb and satisfaction scores pertaining to return to activity.

Well designed randomized control trials, implementing both an injection and non-injection control groups, are a necessary step in the validation of intratendinous dextrose injections. Use of a sham injection of likely a lidocaine/saline solution will assist in uncovering the extent of the therapeutic response from the placebo effect, and overcome a subject bias when there is only one intervention offered. A wait-and-see group (true control) would validate the overall treatment effect

from any injection approach; however, given the extensive chronicity (minimum symptom duration report was 22 months) of the subject population in all of the studies contained in this dissertation, it is unlikely the patients would recover to same extent without treatment. Ultimately, the wide-spread adoption of regenerative injection techniques, such as injections of hyperosmolar dextrose for chronic tendinosis, depends on policy decisions determined in the face of the evidence provided by such clinical trials.

10.4 SUMMARY

In conclusion, the results from this dissertation firstly provide greater insight into the role of lower-extremity movement patterns and the occurrence of Achilles tendinopathy by suggesting that the greater eversion displacement of the sub-talar joint during the touchdown phase of running may be associated with injury. Secondly, an exercise-based treatment program incorporating multiple training elements (such as stretching and balance training) appears to significantly improve the pain in a population with chronic plantar fasciitis, especially when wearing a soft, ultra-flexible shoe. Lastly, sonographically guided injections of hyperosmolar dextrose emerge as a safe and effective treatment for recalcitrant tendinosis at the Achilles insertion, mid-portion, infrapatellar tendon and plantar fascia.

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Appendices

APPENDIX I

Ethics Certificate for Chapters 2 and 3

Eberhard-Karls-Universität
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Universitätsklinikum Tübingen

Universitätsklinikum Tübingen
Ethik-Kommission der
Medizinischen Fakultät

Ethik-Kommission der Medizinischen Fakultät der Eberhard-Karls-Universität un
am Universitätsklinikum Tübingen, Schleichstrasse 8, D-72076 Tübingen

Herrn
Dr. rer.soc. Stefan Grau

Abt.Sportmedizin, Medizinische Klinik und
Poliklinik
Abteilung Sportmedizin

Silcherstraße 5
72076 TÜBINGEN

Vorsitzender
Prof. Dr. med. D. Luft

☎ 07071-29 77661
Fax 07071-29 5965
ethik.kommission@med.uni-tuebingen.de

nachrichtlich:
Herrn Prof.Dr.med. Thomas Horstmann

138/2005V
Projekt-Nummer
Bitte stets angeben

19. April 2005
eingegangen am

1. Juni 2005
Datum

Vergleich klinischer, kinematischer und isokinetischer Messgrößen bei Patienten mit Achillessehnenbeschwerden am Ansatz und Patienten mit Beschwerden im mittleren Bereich der Sehne. Version 1, 7.April 2005

Sehr geehrter Herr Kollege,

die Unterlagen zu der von Ihnen geplanten Studie haben der Ethik-Kommission zur Beratung vorgelegen.
Danach bestehen gegen die Durchführung dieser Studie seitens der Kommission keine Bedenken.

Für die Durchführung Ihres Studienvorhabens wünschen wir viel Erfolg.

Mit freundlichen Grüßen

Prof.Dr.med. Dieter Luft
Vorsitzender der Ethik-Kommission

APPENDIX II

Ethics Certificate for Chapter 4

The University of British Columbia
Office of Research Services
Clinical Research Ethics Board –
Room 210, 828 West 10th Avenue,
Vancouver, BC V5Z 1L8

ACKNOWLEDGEMENT LETTER

PRINCIPAL INVESTIGATOR:	INSTITUTION / DEPARTMENT:	UBC CREB NUMBER:
Jack E. Taunton	UBC/Medicine, Faculty of/Family Practice/Sports Medicine	H06-70002

SPONSORING AGENCIES:
Unfunded Research - "Temporal Changes of In-Vivo Human Platelet Derived Growth Factor (PDGF), Insulin-Like Growth Factor (IGF-I) and Vascular Endothelial Growth Factor (VEGF)"
PROJECT TITLE:
Temporal Changes of In-Vivo Human Platelet Derived Growth Factor (PDGF), Insulin-Like Growth Factor (IGF-I) and Vascular Endothelial Growth Factor (VEGF)

This letter will acknowledge receipt of the following document(s) regarding the abovementioned study:
Notification of study closure

DATE OF ACKNOWLEDGEMENT:

Acknowledged on behalf of the Clinical Research Ethics Board by:

July 23, 2007

Ms. Erin Skrapek, Manager

APPENDIX III

Ethics Certificate for Chapter 5

The University of British Columbia
Office of Research Services
Clinical Research Ethics Board –
Room 210, 828 West 10th Avenue,
Vancouver, BC V5Z 1L8

ETHICS CERTIFICATE OF EXPEDITED APPROVAL: RENEWAL

PRINCIPAL INVESTIGATOR:	DEPARTMENT:	UBC CREB NUMBER:
Jack E. Taunton	UBC/Medicine, Faculty of/Family Practice	H07-01122

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

Institution	Site
Vancouver Coastal Health (VCHRI/VCHA)	UBC Hospital

Other locations where the research will be conducted:
Allan McGavin Physiotherapy Clinic, War Memorial Gym, UBC Subject's Home

CO-INVESTIGATOR(S):
Scott Fraser
Ashley Baker
Michael B. Ryan

SPONSORING AGENCIES:
N/A

PROJECT TITLE:
The effectiveness of the Nike Free shoe in the alleviation of pain symptoms in participants with cavus feet who present with plantar fasciitis – Pilot Project

EXPIRY DATE OF THIS APPROVAL: August 28, 2009

APPROVAL DATE: August 28, 2008

CERTIFICATION:
In respect of clinical trials:
1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.
2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.
3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

The Chair of the UBC Clinical Research Ethics Board has reviewed the documentation for the above named project. The research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was

approved for renewal by the UBC Clinical Research Ethics Board.

Approval of the Clinical Research Ethics Board by:

Dr. James McCormack,
Associate Chair

APPENDIX IV

Ethics Certificate for Chapters 6-9

UBC-Providence Health Care Research Institute
Office of Research Services
11th Floor Hornby Site - SPH
c/o 1081 Burrard St.
Vancouver, BC V6Z 1Y6
Tel: (604) 806-8567
Fax: (604) 806-8568

ETHICS CERTIFICATE OF EXPEDITED APPROVAL: ANNUAL RENEWAL

PRINCIPAL INVESTIGATOR:	DEPARTMENT:	UBC-PHC REB NUMBER:
Anthony Wong	UBC/Medicine, Faculty of Radiology	H05-50063

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

Institution	Site
Providence Health Care	St. Paul's Hospital

Other locations where the research will be conducted:
N/A

CO-INVESTIGATOR(S):
Jack E. Taunton
Michael B. Ryan

SPONSORING AGENCIES:
Workers' Compensation Board of British Columbia - "Optimization of Ultrasound Guided Hyperosmolar Dextrose Injection Therapy for Chronic Tendinopathy"

PROJECT TITLE:
Ultrasound Guided Intratendinous Injection of Hyperosmolar Dextrose in the Treatment of Chronic Tendinosis of the Infrapatellar and Achilles Tendons

EXPIRY DATE OF THIS APPROVAL: June 9, 2009

APPROVAL DATE: June 9, 2008

CERTIFICATION:

1. The membership of the UBC-PHC REB complies with the membership requirements for research ethics boards defined in Part C Division 5 of the Food and Drug Regulations of Canada.
2. The UBC-PHC REB carries out its functions in a manner fully consistent with Good Clinical Practices.
3. The UBC-PHC REB has reviewed and approved the research project named on this Certificate of Approval including any associated consent form and taken the action noted above. This research project is to be conducted by the principal investigator named above at the specified research site(s). This review of the UBC-PHC REB have been documented in writing.

The UBC-PHC Research Ethics Board Chair or Associate Chair, has reviewed the documentation for the above named project. The research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved for renewal.

Approval of the UBC-PHC Research Ethics Board or Associate Chair, verified by the signature of one of the following:

Dr. I. Fedoroff,	Dr. J. Kernahan,	Dr. Kuo-Hsing Kuo,
Chair	Associate Chair	Associate Chair

APPENDIX V

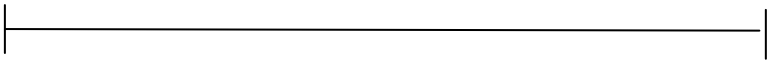
Visual Analog Scales for Plantar Fasciitis (Chapter 5)

Today's date:

Visual Analog Scales

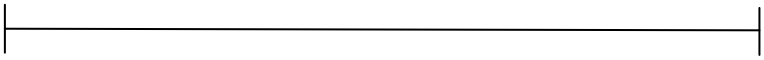
Please place a vertical mark on the horizontal line that corresponds with your response for each question.

1. **<u>Palpation</u>: Following identification of the most painful part of the plantar fascia of your foot, indicate the level of pain you are feeling in this specific part.**



No pain — Worst pain imaginable

2. **<u>Last 24 hours</u>: Indicate the worst level of pain you experienced in the plantar fascia of your foot over the past 24 hours.**



No pain — Worst pain imaginable

APPENDIX VI

Preliminary Questionnaire: Dextrose Injection Study (Chapters 6 – 9)

1. Name:

2. Date:

3. Date of Birth:

4. Do you play sport or participate in sporting activities?
   If yes, what sport or activities do you perform?

5. How long are you symptomatic?

6. What previous treatments did you receive for your tendinosis (include exercise program, surgery, injections, shock wave therapy etc)?

7. Are you currently on a specific exercise program as part of your treatment?
   If yes, please give details including length of time on exercise program.

8. Did your previous treatments (including exercise program) relieve your symptoms or help in any way?

9. Does your symptoms prevent you from training/ participating in your sport?

10. Does your symptoms affect you during your daily activities?

11. If you have had previous dextrose injections, have the injections helped you in any way? If so, are you satisfied with your treatment to date?

APPENDIX VII

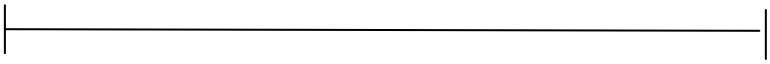
Visual Analogue Scale for Tendon Pain with Dextrose Injections (Chapters 6 – 9)

Today's date:

Visual Analog Scales

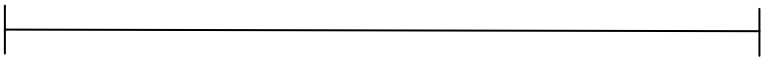
Please place a vertical mark on the horizontal line that corresponds with your response for each question.

1. **<u>Rest</u>: Presently, indicate the level of pain you are feeling [at affected site].**



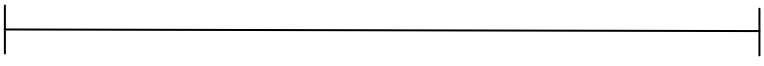
No pain — Worst pain imaginable

2. **<u>Activities of Daily Living</u>: Indicate the level of tendon pain [at affected site] during normal daily activity?**



No pain — Worst pain Imaginable

3. **<u>Sporting Activity</u>: Indicate the level of tendon pain [at affected site] during or after sporting or other physical activity.**



No pain — Worst pain imaginable