A Discussion on the Pathophysiology, Risk Factors and Management of Achilles Tendinopathy
Abstract

Achilles Tendinopathy is a chronic degenerative condition of the Achilles tendon, which results in pain, focal swelling and loss of tensile properties. Although largely a sporting injury, the condition is becoming increasingly common among the general population. For this reason, there has been a growing body of evidence surrounding the pathological processes of tendinopathy and who is most likely to develop the condition. This discussion examines the underlying pathophysiological mechanisms of tendinopathy, including disintegration of the collagenous structure, alterations in tendon metabolism with increased proteoglycan content, tenocyte proliferation and finally neoneurovascularisation.

Tendinopathy is a potentially career-limiting injury among competitive athletes, in whom it is most common. Prevention and effective management is therefore key. Traditional risk factors include gender, age, adiposity and training/extrinsic variables such as increased frequency of training, variable training patterns and inappropriate footwear. In line with more recent focus of research, this paper places particular emphasis on genetic and intrinsic medical factors underlying the condition. Management of tendinopathy is primarily conservative and consists of an eccentric exercise protocol as the best-evidence approach to alleviating pain and allowing a return-to-sport. Adjuncts include sclerosing injections, aprotinin and platelet-rich plasma therapy, however evidence for these is limited and based on small populations, despite the weak positive results some authors have yielded. Platelet-rich plasma has received much focus in both the literature and sporting media as the most recent “in-vogue” approach to treatment, however it has consistently failed to stand up to scrutiny beyond anecdotal reports of its efficacy. Clinicians are therefore at a crossroads- do they choose the most advocated, or the most ‘fashionable’ treatment? In the absence of any high-quality evidence supporting this treatment, “Exercise is medicine” is the approach all clinicians should take to management of this chronic degenerative condition.

KEYWORDS: Achilles, Tendinopathy, Pathophysiology, Risk, Management
**Achilles Tendinopathy (AT)** is defined as a degenerative condition of the achilles tendon, which is associated with a triad of symptoms including pain, focal swelling and loss of tensile properties of the tendon.

AT is traditionally considered to be a sporting injury. Thirty percent of high-level runners are thought to be affected by the condition, with a lifetime cumulative incidence as high as 52% among top level mid-long distance runners\(^1\)\(^2\). However even among the general population, this tendinopathy has a prevalence rate of 2.01 per 1000 and an incidence rate of 2.35 per 1000, thus reflecting the multi-factorial nature of the condition\(^3\).

The specific pathogenesis of degenerative tendinopathy remains largely unidentified, however it appears to be multi-factorial. Many aetiological factors have been implicated such as pes cavus, poor footwear & training technique, as well as variations in training pattern. However, the mechanical strain theory remains the most widely accepted\(^4\). This theory implicates repetitive loading within physiological limits, but of sufficient frequency to outpace the basal healing rate of the tendon; or low frequency overloading of the tendon such that otherwise physiologically normal recurrent loading does not promote the regeneration of healing tissue, resulting in tendinopathy. The exact pathophysiological effect that overloading seems to have is detailed by Selvanetti et al. in their 1997 study which suggests that the primary means by which the tendon fibres lose their tensile properties appears to result from continuous loss of lateral cohesion both between the collagen fibres, and within the fibrils themselves. This is a result of progressive destruction of inter- and intra-molecular crosslinks\(^5\). With this primary aetiological factor established, a discussion will follow on the pathophysiology of AT, the factors which may predispose to developing this tendon pathology, and finally evidence-based management of the condition and recent developments in this area.

**Pathophysiology**

A key process underlying the development and progression of AT is disruption to the collagen network, as collagen fibres become thinner than normal with the characteristic hierarchical structure being lost. This process is responsible for the loss of the tensile structure which is observed in AT.

One of the most cited studies is Jozsa and Kannus’ 1991 histological investigation which outlines multiple processes which have implications on collagen structure and tenocytes\(^6\). Collagen fibres were found to have disintegrated, with longitudinal splitting, abnormal variations in diameter, angulations of fibrils, and folding of the fibril surface. They suggested
decreased arterial blood flow as a cause for these hypoxic degenerative changes, but this is yet to be established. It could be speculated that with an increased load on a tendon, increased pressure within that tendon limits blood flow and ultimately induces this hypoxic degenerative tendinopathy. This pathological alteration is also associated with mucoid degeneration, where large vacuoles appear between the collagen fibres which contain proteoglycans and glycosaminoglycans. This disrupts continuity of the fibres, and is exacerbated by small groups of lipocytes forming cavities among the fibres.

These findings are corroborated by Astrom and Raising’s 1995 study which examined biopsies from 163 athletes with AT$. Tendon samples demonstrated a clear loss of normal crimped structure of the collagen fibers in all tendons, and individual bundles were seen to coalesce.

This histological finding of disruption to the tendon structure is accompanied by alterations in collagen destruction and production. Tendinopathic samples display an increased type 3 collagen:type 1 collagen ratio. Type 1 is normally the dominant fibre type within tendons and it is the primary contributory factor toward the tendon’s strength. Proportionally increased collagen type 3 levels weaken the tendon. Production of both type 1 and 3 collagen is induced as part of the physiological proliferative response of tenocytes to trauma, however greater quantities of type 3 collagen are produced in tendinopathic tendons. Maffulli (2000) suggests that this abnormal healing response may result from an increased propensity to produce type 3 collagen among some individuals$^8$. This is a hypothesis corroborated by Ireland D et al’s 2001 study which observed an increase in type 3 collagen mRNA levels in degenerative achilles tissue$^9$. More recent studies also implicate changes in proteoglycan content in affecting collagen fibre structure, suggesting that tendon structure is likely to be influenced by modified quantities of fibromodulin and biglycan, which are responsible for binding collagen fibrils at different sites$^{10}$. These pathological alterations to the collagen fibre network result in the achilles’ inability to withstand loads which were previously within physiological limits.

Associated with this degeneration of collagen structure is an increase in ground substance. These areas of collagen degeneration and elevated interfibrillar ground substance are reported to contain high concentrations of hydrophilic glycosaminoglycans, which ultimately contributes considerably to destruction of the extra-cellular matrix (ECM)$^{11}$. Clinically, this corresponds to increased signal on MRI and hypoechoic regions on ultrasound, as well as focal swelling in the tendon. Tenocyte metabolism is regulated to maintain the ECM in
response to the mechanical forces acting on the tendon. Normal tendons are scarcely populated with cells, and the proteoglycan content is around one-percent of dry weight. Proteoglycans are crucial in ensuring the integrity of the ECM, as extremely negatively charged aggregating proteoglycans such as aggrecan and versican, draw water into the tendon. This acts to lubricate adjacent collagen fibres and provides resistance to compression. They are also involved in the regulation of cell activities.

Studies indicate that a transformed and disorganised ECM in chronic tendinopathy is a result of alterations in the metabolism of tendon matrix components, including collagens and proteoglycans. Proteoglycan levels are increased in tendinopathic tissues, as evidenced by Samiric et al. (2010) which found significantly increased levels of both large and small proteoglycans in clinical samples of patellar tendinopathy. Ireland D. et al mirrored these findings in AT in their 2001 study. These results included increased aggrecan and versican levels, increased biglycan levels in 3/5 patellar tendinopathy samples, and significant increases in fibromodulin. As there was no significant upregulation for any of these, it is suggested that accumulation of proteoglycans in the ECM of pathological tissue may reflect a decreased rate of turnover, resulting in water being drawn into the tissue and focal swelling occurring. As this leads to tendon thickening, rather than the normal healing response of stiffening, the tendon’s tensile properties are also diminished as a result.

Accumulation of proteoglycans in achilles tendinopathic tissue is associated with downregulation of MMP3, as observed in tendinopathic samples. Many publications on AT have demonstrated increased levels of matrix metalloproteases (MMPs) in tendinopathic tissue, particularly collagenases (MMP1, 8 and 13) and gelatinases (MMP2 and 9). MMPs are enzymes with a wide substrate range including proteoglycans and ECM. The tendon healing process and tendon homeostasis depends on a balance between MMPs and their inhibitors; tissue inhibitors of matrix metalloproteases (TIMPs). This balance determines the extent of ECM turnover.

MMP3 is one such enzyme which is downregulated in AT, and it counts collagen type 3 and proteoglycans among its substrates. Downregulation of MMP3 is evidenced by the significantly decreased levels of MMP3 mRNA in degenerative samples compared with varying levels in control samples, which are all still higher than tendinopathic tissue. Recent studies into why MMP3 is downregulated in some, but not others, are aimed at the genetic component of tendinopathy. Raleigh et al. (2008) have demonstrated a link between all three MMP polymorphisms and AT in a randomised control trial (RCT) of over 200
subjects. Specifically, MMP3 SNP rs679620 and COL5A1 polymorphism interaction was significantly associated with developing tendinopathy.12

However, development of tendon pathology may not only be associated with downregulation of MMP3. Paradoxically, elevated levels of this protein may also underlie a predisposition. Fluoroquinolones such as the antibiotic Ciprofloxacin, which is often associated with tendinopathic-like pain and rupture in some individuals, has also been demonstrated to produce significantly greater quantities of MMP3 mRNA in Interleukin-1β (IL-1β) treated human tendon cells in culture13 14.

While MMP3 is downregulated in AT, other MMPs which are involved in ECM breakdown, as mentioned above, are found to be increased. It is suggested that cytokines such as IL-1β and Tumor Necrosis Factor-α (TNF-α) enhance production of these MMPs, and that tenocytes express receptors and respond to these inflammatory proteins in an initial “molecular inflammation cascade”. This conforms to Cook and Purdam’s continuum of tendon pathology15. This continuum implicates an initial inflammatory response to acute tensile load. It is hypothesised that this would induce expression of MMPs, leading to matrix destruction. Tzuzaki et al. (2006) treated tendon cells from six human achilles tendons with IL-1β and found that this stimulated MMP1 production16. They suggest that following an injury to the tendon, release of exogenous IL-1β may be associated with local bleeding, or as leakage from local capillaries and may stimulate a pro-inflammatory response at cellular level. The resulting production of MMPs may then underlie the potential for further non-lymphocyte mediated cytokine induction of MMPs that causes ECM destruction and loss of the biomechanical attributes of the tendon. The role of cytokines is certainly well established in AT, with metabolically active central adiposity (which produces circulating adipocytokines) being a significant risk factor in developing the condition.

Tenocyte proliferation, as well as changes in tenocyte shape is a common pathological feature of AT, with tenocytes losing their typical fine spindle shape and their nuclei becoming more rounded. Furthermore, hypoxic degeneration induces changes in the shape and size of mitochondria. They become swollen, develop irregular membranes, and intermitochondrial cristae become fragmented or disappear entirely. Nuclei often become pyknotic and the nucleus:cytoplasm ratio is markedly reduced as the cytoplasm becomes filled with vacuoles. Jozsa and Kannus (1991) also occasionally observed necrosis of tenocytes. These changes occurred due to hypoxic degenerative tendinopathy6. These
findings have been supported by other histological studies, which also found focal areas of reduced cellularity and a rough correlation between the degree of collagen bundle loss and cellular abnormalities\textsuperscript{7}.

A more recent 2011 study by Anderson et al. studied 24 female rabbits split into four groups in a RCT\textsuperscript{17}. Three groups were subject to an exercise programme of varying length in one leg, while the fourth group did not exercise. The exercise groups displayed a significant increase in tenocyte number, and this elevation was proportional to the length of the exercise programme. The one-week group showed little change, and even a slight decrease, while the three-week group showed significant increase compared with the control. Finally, the six week group showed the greatest increase. In any specific area of 283x213µm, 145 tenocytes on average were found in the tendinopathic tissue of the six week group, compared with just 99 in the control group. The small decrease in the week one group is possibly due to the increase in water bound content, but it also supports earlier studies on cellularity in tendinopathy which suggested that early stages of tendinopathy are characterised by a reduction in cell number initially, which is then followed by a marked elevation in later stages.

A key finding of this study, and supported by several other studies in the area, is that the increase in tenocyte number was mirrored in the opposite leg. It is not uncommon for those presenting with unilateral tendinopathy to later develop bilateral tendon degeneration at a later stage. In one eight-year longitudinal study, 41% of those who initially presented with tendinopathy in just one achilles tendon, later went on to develop the condition in the other tendon also\textsuperscript{18}. This highlights that tendinopathic changes not only occur locally, but that there is a neurogenic aspect to the pathology also, helping to explain the phenomenon of unilateral tendinopathy often spreading bilaterally.

Neoneurovascularisation is the final keystone of the tendinopathic pathological process, and accounts for the clinically pertinent pain in AT. The achilles tendon is primarily supplied from the anterior paratenon, and normal tissue is perfused by a scarce system of small arteries running alongside the collagen fibres in thin fibrous septa between collagen bundles. Jozsa and Kannus\textsuperscript{6} observed vascular changes in 62% of the 891 tendons they studied, which had ruptured and previously displayed degenerative changes. This included narrowing or obliteration of the lumen of arteries, usually due to hypertrophy of the intima and media of the vessel walls. In addition to these findings, vessels have also been found running
perpendicular to collagen fibres. The 2011 study by Andersson et al. found vascular proliferation occurred after three weeks of exercise and also occurred bilaterally. Neovascularisation is thought to occur along a hypoxic gradient, which would support the mechanical strain theory. One theory is that calcifying tendinopathy observed in some tendon samples is not simply a degenerative process, but is a phase in the healing process which facilitates neovascularisation. It is suggested that the necrotic tissue of the tendon in poorly vascularised areas is transformed into granulation tissue in which chondrocytes mediate calcium deposition. These are then phagocytised and vascularised, restoring normal perfusion and $O_2$ tension in the tissue so that matrix and function will be restored. However this theory has yet to be pursued in further high quality trials. It is certainly supported by Schubert et al. (2008) who demonstrated granulation tissue in 8/10 achilles tendinosis samples, comprising capillaries which contained macrophages, B and T lymphocytes, and hemosiderophages. The presence of hemosiderophages lends credence to mechanical strain inducing microtrauma in the tendon, as these digest red blood cells which would have leaked into the tendon tissue due to this repetitive tissue damage.

Recent studies have demonstrated that neovascularisation in the degenerative areas of the tendon on ultrasonography and MRI correlates with pain. This supports the notion that neovascularisation is accompanied by nerve structures. Substance P (SP) and calcitonin gene-related (CGRP) positive fibres are nociceptive nerve fibres which are substantially increased in tendinopathic portions of the tendon. Schubert et al. reported an average of 1.06 SP Positive nerve fibers/mm$^2$ among the tendinopathy group studied, compared with just 0.35 in the rupture group, which was used as a control in the absence of valid healthy data. In addition to their nociceptive functions, these neuropeptides are shown to exercise trophic effects in different tissues, as they are both involved in the proliferation of cultured fibroblasts and are known to stimulate the release of cytokines, growth factors, and inflammatory mediators such as COX2 and IL-1β. With COX2 being an enzyme involved in pain and inflammation, and IL-1β being discussed earlier as promoting the initial “molecular inflammation cascade”, SP and CGRP positive nerve fibers could be implicated in this neurogenic inflammation, leading to degenerative changes within the tendon. However, studies examining this stimulatory effect on COX2 and IL-1β by SP and CGRP positive nerve fibres used non-physiologic strain patterns or additional mechanisms to elicit these results. Therefore, more in-vivo studies using natural mechanical loading patterns without any interference would be needed before these could be considered truly clinically relevant.
The observation of free-spouting nerve fibres around neovessels in AT demonstrates that healing during the inflammatory and early proliferation phase (up to two weeks following injury) correlates with growth of intra-tendinous nerve fibres and a distinct time pattern of neuropeptide occurrence. Nerve fibre withdrawal from the tendon tissue occurs between six and twelve weeks post-injury, but pain continues during these weeks due to the level of excitatory glutamate being elevated centrally, and the number of SP and CGRP positive fibres remaining significantly increased within the tendon in chronic degenerative tendinopathy.

**Risk Factors**

A plethora of factors relating to the individual human form itself have been implicated in increasing the risk of AT. These most often examine the role of age, gender, weight and foot abnormalities.

It is suggested in the literature that an age greater than 34-35 years may predispose to AT. This may be due to the age-related degeneration of collagen, accompanied by decreases in the elastin and proteoglycan matrix which results in reduced elasticity of the tendon, and a lower water content. The lower water content results in the tendon becoming stiff, so it is less likely to withstand an increase in load. This is supported by evidence demonstrating that the water content in tendons declines to 30% in old age, from a peak of 80% at birth. Other age-related declines in tenoblastic activity and collagen turnover act to retard the reparative ability of the tendon, and metabolic pathways utilised for energy production shift from aerobic to more anaerobic mechanisms. This shuts down some avenues of energy production such as the krebs cycle. Jozsa and Kannus’ extensive 1991 study found that of the young control subjects who had a mean age of 38 years, 30% had pathological changes in the achilles tendon, while almost half of the older 110 control subjects, with a mean age of 66 years, had such changes. They suggested that these findings demonstrate that degenerative changes in tendons may be more frequent in those older than 35 years. Other studies have identified a similar starting age for an increased risk of developing tendinopathy. Taunton et al.’s 2002 retrospective study of over 2000 runners, ranging from recreational to international athletes, identified men who are older than 34 years as being at a greater risk of AT than their younger counterparts. In further support of the negative impact age has on tendinopathy, Klein et al. reported that when comparing 500 AT subjects against 500 control
subjects, there was a significant association between increased age at presentation and failure of conservative treatment.

Another demographic factor suggested to predispose to AT is gender. The literature seems to be mixed, with studies leaning towards males being at a greater risk of AT\textsuperscript{20}, while others demonstrate significant factors in females which also predispose to developing the condition. Maffulli et al. (2003) reports that 89\% of those with achilles tendon problems are male\textsuperscript{22}, and other studies have found a significant difference between the prevalence of the condition between men and women. Taunton et al. reported 58\% of their 96 AT cases were male, concluding that gender was a risk factor\textsuperscript{20}

Research on predisposing factors within females seems to be quite undecided. Cook et al. (2007) suggest that oestrogen is a protective factor for women, which explains the lower incidence of midportion AT in females\textsuperscript{23}. Their study looked at 85 post-menopausal female golfers and compared them with a similar control group for the effect of hormone replacement therapy (HRT) on tendinopathy. They found that the treatment group improved significantly on VISA-A scores and ultrasound, while the control group who received no HRT had worse pathology and a more thickened tendon at the end of the trial. They concluded that this was due to the presence of elevated oestrogen, and to a lesser extent progesterone, associated with HRT. Conversely, the literature also implicates the attenuated response to acute tendon load in women as a factor which places this population at greater risk of developing tendinopathy. Magnusson et al. (2007) found that 72 hours after an acute bout of exercise, female subjects had a collagen functional sedimentation rate just 47\% that of the men in the study\textsuperscript{24}. This may also be the reason why females show an inferior response to eccentric exercise protocols\textsuperscript{25}. The results of these studies underline a gender-based difference, supporting the theory that oestrogen, and possibly progesterone, may influence the exercise-induced increase in collagen synthesis following an acute bout of activity.

Adiposity is one of the most significant risk factors for developing tendinopathy. A 2009 systematic review by Gaida et al. showed a significant positive association between elevated adiposity and tendinopathy\textsuperscript{26}. There are two broad hypotheses regarding the mechanism linking adiposity and tendinopathy, and there are studies to support both. The mechanical hypothesis suggests that elevated weight levels place higher loads on weightbearing tendons, and this leads to tendinopathy. Body mass index (BMI) is an adequate measure of overall obesity, and has been repeatedly shown to be a risk factor in the development of AT. The
investigation by Fahlström et al. (2003) on eccentric exercise showed that there was a substantially greater number of subjects with a higher BMI (greater than 28) in those who had poor results. Klein et al. (2013) recently demonstrated some of the strongest support for a causal relationship between weight and tendinopathy. They found that those with AT had an average BMI of 30.2, compared with 25.9 in the matched control group, concluding this difference was statistically significant.

The systemic hypothesis on the other hand suggests that production of bioactive peptides by adipose tissue may alter the structure of the tendon directly or indirectly. The literature is increasingly showing that elevated adiposity supports chronic low-grade microvascular inflammation, which underpins well-known relationships with cardiovascular disease and type-2 diabetes mellitus. It is thought that this systemic pathway contributes to musculoskeletal symptoms and pathologies such as tendinopathy, which become increasingly common in those who are overweight. A distinction must be made between a central distribution of fat and a peripheral distribution. It is the former that is implicated in the systemic hypothesis, as it is this central adiposity which is metabolically active and produces adipocytokines such as IL-1β and TNF-α whose role in the initial molecular inflammation cascade in the early stages of tendinopathy has been discussed. Central adiposity also promotes tendolipomatosis in the achilles tendon, where lipids are deposited in the tendon and interrupt the continuity of the collagen fibres, reducing the level of load they can tolerate. Gaida et al. (2010) also show that unique patterns of fat distribution between men and women are responsible for predisposing to tendinopathy. Men with AT tend to have a central distribution of fat, with an increased waist circumference (greater than 83cm) and waist:hip ratio. Women with tendinopathy tend to have a peripheral distribution of fat, with a lower waist:hip ratio due to the presence of oestrogen, which prevents central accumulation of adipose tissue.

Muscular insufficiency in the leg is cited as a significant factor in AT. It is suggested that during the onset of the support phase of running, the gastrosoleus complex in some individuals is deficient in eccentrically controlling dorsiflexion. This results in repetitive microtrauma, and thus tendinopathy develops. In supporting this, McCrory et al. (1999) demonstrated that their control group exhibited greater strength in all dorsiflexion variables, which were significant discriminators at 60°/S¹ and 180°/S⁻¹. In the AT group, strength and endurance values of the injured leg were not significantly different than the non-injured leg.
This suggests that muscle insufficiency was likely present before development of the injury, and not simply a result of it.

Foot instability is the final risk factor relating to human form implicated in developing the condition. Kvist’s 1991 study shows malalignments and faulty biomechanics as having a role in the development of achilles tendon disorders in 58% of athletes\(^3\). The most widely accepted factor is restricted subtalar joint mobility, and a rigid ankle joint accompanied by a pes cavus\(^3\). It is proposed that the stiffness of the cavus foot causes compensatory overpronation, and this is a forerunner to AT. In terms of the rearfoot motion, the heel moves from supination at heel strike, to pronation during midstance and finally re-supinates prior to toe-off. This results in the achilles tendon undergoing a bowstringing action.

**Training/Extrinsic factors**

AT is frequently associated with the physically active athlete, and is especially common in running athletes. For this reason, there has been much research into the effect that training variables and associated extrinsic factors have on tendinopathy.

Research shows that increased frequency of training is associated with increased prevalence of the condition, with one such study showing a tendinopathy rate of 6.7% among 449 subjects\(^3\). Eight-eight percent of these reported running at least three times per week for a minimum of three months prior to the study. Injured runners also run for more years than their control counterparts. By definition, an overuse injury is the result of accumulated impact loading of the lower extremity. Therefore, logic would dictate that the higher the frequency of running, and the greater number of years a person has run, the greater the role training abnormalities may have in overuse injuries. Abate et al. (2012) found that all of their subjects on one futsal team, who had demonstrated degenerative changes in the achilles tendon, had played for several years (14.3 years on average)\(^3\). Footwear is an extrinsic factor associated with developing AT, as poor footwear is reported to increase risk. In the study already mentioned by Abate and colleagues, futsal players were prospectively observed from beginning of the playing season to the end. At the beginning of the season, 39% of players on one team had signs of degeneration on ultrasound, while at the end of the season this increased to over 55%. Low heel footwear, characteristically used in futsal, was suggested to be a causative factor. This footwear can expose the achilles tendon to higher straining and stretching. It also fails to cushion the impact of the foot against the hard and adherent playing surface, further stressing the tendon. Likewise, changes in footwear can predispose to AT among the general population. Women who regularly wear high-heeled
footwear for work and recreation, but then switch to runners for exercise are at risk of developing AT, as the achilles tendon and gastro-soleus complex progressively shorten as the heel is restricted from reaching to the ground. When the individual then changes to trainers, the achilles tendon is forced to stretch further than it has adapted to, resulting in inflammation and a reduced ability to adequately absorb load.

**Genetic and Medical Factors**

The role of genetic and medical factors in tendinopathy is being increasingly elucidated in recent studies. Research into these intrinsic factors is important, because AT is not just seen in physically active people. In fact, it is regularly observed among overweight individuals who are receiving treatment for aspects of metabolic syndrome. Even in athletes, a marginally increased waist circumference above 83cm carries a significantly greater risk of tendon abnormality. Therefore it is improbable that this relationship can solely be explained by increased forces associated with greater body weight acting on the tendon. Relationships with other systemic factors that are linked with obesity are therefore thought to increase disposition to achilles tendon degeneration. These include dyslipidaemia, hypertension, insulin resistance and genetic factors.

Dyslipidaemia refers to abnormal amounts of lipids/cholesterol in the blood. As discussed, lipid deposition (tendolipomatosis) is a feature of AT. It is not surprising then that high cholesterol levels are reported in those with injury of the achilles tendon, and the esterified fraction of cholesterol is increased in biopsies from those with AT. A 2009 study by Gaida et al. found evidence of underlying dyslipidaemia in AT subjects compared with the control. The AT group displayed significantly higher triglyceride levels, apolipoprotein B concentration (responsible for carrying cholesterol to the tendon) and an elevated triglyceride:HDL-C ratio. This dyslipidaemic profile displays a remarkable conformity with insulin resistance, which has also been reported to predispose to tendinopathy. In those with insulin resistance, elevated concentrations of insulin fail to increase glucose uptake by the muscle. It is remarkably frequent amongst the general population, and a dyslipidaemic profile is associated with even a mild insulin resistance. The elevated circulating triglyceride level conforms to histological findings of lipid accumulation in biopsies from tendinopathic subjects, resulting in tendolipomatosis which accounts for the loss of tensile properties of the tendon. An increased waist circumference is a criteria for diagnosis of insulin resistance syndrome, and so the link between insulin resistance and achilles tendinopathy is supported in the research by Gaida, Alfredson and others into the association between the two adiposity measures and tendinopathy.
Holmes et al. (2006) report that hypertension is only a significant risk factor in women. Hypertension causes a diminution of local microvascularity in the tendon, which is its main influence in AT. It affects all three limbs of Virchow’s triad, including endothelial damage, stasis or turbulence of flow, and hypercoagulability. This promotes a pro-thrombotic state whereby small thrombi, arterial occlusion and reduced blood flow modify blood perfusion to the tendon. This impairs the tendons ability to heal itself and so is a risk factor for developing AT.

Fluoroquinolones such as Ciprofloxacin are broad-spectrum antibiotics that are used in the management of bacterial infections, especially those acquired in hospital and resistant to other forms of treatment. As discussed, the mechanism by which they increase risk of tendinopathy is through enhancing IL-1β mediated induction of MMP3, thus inhibiting proliferation of tenocytes and decreasing matrix and collagen synthesis. Fluoroquinolone-induced tendon injury is a significant source of tendinopathy. In a review of the evidence surrounding fluoroquinolone-induced tendinopathy, tendon injury occurred as early as eight days following fluoroquinolone treatment. Some subjects reported symptoms just two hours after the first dose and symptoms continued to be reported as late as six months after treatment had ceased.

In recent years evidence has emerged that AT has a genetic component. A GT repeat variant within the gene that codes the Tenascin C protein; a key constituent of the tendon which is regulated by mechanical loading, is associated with AT. Polymorphisms within the COL5A1 gene and in genes responsible for encoding regulatory proteins that are involved in maintenance of ECM homeostasis have also been associated with AT.

MMP3 is one such protein which has a role in tendinopathy, with a substrate range including collagen, fibronectin and proteoglycans such as decorin and aggrecan. It is also known to activate several other MMPs. Reduced expression of MMP3 has been demonstrated in studies by diminished MMP3 mRNA and MMP3 protein levels on immunochemical investigation of resected AT tissue compared with control tissue. Raleigh et al. (2009) found significant differences in their RCT between subjects with AT and the control, in terms of the genotype and allele frequencies of the MMP3 rs679620 SNP (Single Nucleotide Polymorphism), with the GG genotype being significantly overrepresented in the AT group (present in 37.3% of this group) compared with the control (present in 19.4% of this group). Similar overrepresentation was found in the CC and AA genotypes of rs591058 and rs650108. Furthermore, they found significant association between MMP3 and COL5A1 allele.
combinations in those with AT; specifically the G and T allele combination. This would explain the decreased MMP3 expression, resulting in tendon pathology.

However genetic abnormalities are not only implicated in altering MMP expression, but in the regenerative mechanism of controlled apoptosis also. The normal tendon cell healing response involves cytokine-mediated apoptosis of damaged tenocytes. Excessive apoptosis has been seen in tendinopathy, and this may compromise the tendon’s ability to regulate repair processes. Genes involved in this pathway of inflammatory apoptosis are associated with elevated risk of developing AT. Significant associations have been found between two CASP8 polymorphisms- rs3834129 genotype and rs1045485 genotype. Specific allele distributions have also been implicated. Those with the D/D genotype of the former polymorphism have an eight-percent higher risk of AT than other genotypes, and each C allele in the latter reduces the odds of developing AT by 41%. Nell et al. (2012) suggest that the two CASP8 polymorphisms, in addition to gender, are sufficient to predict risk of AT. They estimate that females who are homozygous C/C and heterozygous D/I for CASP8 rs3834129 and rs1045485, respectively, are at the least risk of developing AT. In contrast to this, males with G/G and D/D genotypes at the two CASP8 polymorphisms have the greatest predilection for the condition.

Studies have demonstrated a positive family history of chronic achilles tendon pathology in relatives, with Kraemer et al. (2012) reporting a five-fold increase in risk for those with such disorders in first and second degree relatives. It is clear that there is a hereditary factor at play in explaining the variation among the general population in susceptibility to chronic achilles tendon degeneration.

Management

AT is well known to be difficult to treat due to the relative paucity of knowledge on the pathogenesis of the condition. Researchers have been unable, as yet, to devise a “one size fits all” treatment approach, where one form of treatment is successful in all patient groups. Conservative management is employed first, and is primarily aimed at symptom-relief, with surgical management considered when avenues of conservative treatment have been exhausted. There are a plethora of conservative options available, with eccentric exercise being the most widely accepted. In the absence of a definitive treatment option with known success across all patient groups, the clinician may employ various combinations of these
treatments in order to alleviate the condition, before surgery being considered if conservative treatment has not been successful.

**Eccentric Exercise**

Eccentric exercise is the standard treatment option for AT and has produced some great results, especially among competitive athletes. Knobloch et al. (2008) reported that out of 291 competitive runners with AT, 190 knew about eccentric training and 135 had been performing it on a weekly basis for an average of 38 months. The protocol, designed by Alfredson et al., consists of two types of heel-drop exercise. The patient stands on the edge of a step, with heel raised and knee fully extended, and lowers the heel so that the foot is parallel with the ground. This is repeated with the knee flexed to 45° so that Soleus is engaged. The uninjured leg is used to raise the affected leg back up to starting position, so no concentric exercise is taking place with the injured tendon. This protocol consists of 15 repetitions of each exercise performed three times, twice a day, daily for 12 weeks. Pain in the first two weeks is normal, however if it is disabling the patient should stop. When the patient can perform the exercise without pain, the load is increased by using a backpack successively loaded with weight up to maximum of 60kg until mild pain is felt again. While variations of this protocol may also be effective, none of them have been as rigorously tested as Alfredson’s heel drop programme.

Clinical results for this eccentric protocol have been very positive. Fahlström’s 2003 large-scale study showed that it was effective in 89% of chronic midportion AT cases, with patients being able to return to their level of activity prior to the injury following the 12 week programme. Pain as recorded on the VAS reduced from 66.8 on average to 10.2, which was highly significant regardless of gender. Furthermore, 83% of subjects were satisfied with their outcome. These results were mirrored to a lesser extent in a 2007 RCT by Mayer et al. where 73% of patients in the eccentric exercise group reported a pain decrease of greater than 25%, and 55% reported a pain reduction in excess of 50%. These slightly smaller improvements could be accounted for by the way in which Alfredson’s protocol was adapted, as it consisted of just a four week intervention rather than a 12 week intervention.

Long-term studies on this heel-drop protocol have also shown very positive results. A 2012 five year follow-up on a previous RCT by the same authors showed that a significant improvement in VISA-A score can be predicted. Median VISA-A score of the intervention group rose from 49.2 at baseline to 83.6 after five years, while just under 52% of the subjects required no other form of treatment in the five year period.
The exact mechanisms by which eccentric exercise works are not fully known. Eccentric exercise alters production of type 1 collagen, and without further injury or strain, may strengthen the tendon in the medium-long term. Recurrent loading and elongation of the musculo-tendinous unit is thought to enhance the unit’s ability to absorb load. Finally, in its role in alleviating pain, it is proposed that Substance P nerve endings which have infiltrated the tendon tissue during neoneurovascularisation are mechanically destroyed. Importantly, there seems to be a consistent pattern in the literature for greater results in men than women. This is more than likely due to gender differences in tendon structure and its mechanical properties. Fahlström’s 2003 study found that there was a substantially greater frequency of women with poorer results in response to the protocol. In a 2010 non-randomised prospective trial by Knobloch et al., results showed that eccentric training as per Alfredson’s protocol with straight leg only, resulted in pain reduction of 44% in males, but only 27% in females. Furthermore, while VISA-A score increased by 27% in males, they only increased by 20% in females. Studies implicate gender differences in collagen synthesis as the reason for the inferior response to eccentric exercise. A recent study has suggested that both oestrogen and progesterone may attenuate the response of the achilles tendon to loading such as running. It found that at rest, and 72 hours after exercise, the tendons of women displayed lower collagen fractional sedimentation rate (FSR) values than in males, demonstrating a difference between genders compatible with the idea that these female sex hormones could abate any increases in collagen synthesis following an acute bout of exercise. After 72 hours of exercise, the FSR of female participants was only 47% that of their male counterparts, increasing slightly to 55% at rest. For this reason, eccentric exercise alone may not be suitable for all populations, and so clinicians may wish to combine it with adjunct treatments such as injection therapy.

**Injection Therapy**

There are a range of substances that have been used both in around the achilles tendon. The basis for injection is often failure to respond to an exercise programme, or as a passive adjunct to a structured exercise regimen. The use of injections in treating tendinopathy is contentious, as none have been shown to be as effective as eccentric exercise, and many patients believe that exercise is somehow less effective than medical therapies such as injection. Indeed, it has been shown that simply the act of injecting a patient may stimulate recovery due to the enhanced placebo effect associated with more invasive treatments.
One such injection therapy is the use of Polidocanol; a sclerosing agent normally used in treating varicose veins. With ultrasound guidance, it is injected into the area of neovascularisation anterior to the tendon, acting on the intima of local blood vessels to cause thrombosis, while also working extravascularly to destroy nerves adjacent to neovessels. Polidocanol injected at multiple sites around the tendon and areas of neovascularisation induces a local inflammatory response, which initiates proliferation of fibroblasts and collagen synthesis. This is intended to produce a stronger, more organised tendon. One double-blind RCT found improved results after injections with polidocanol compared to injections with lidocain or adrenaline in patients with AT. The majority of patients were satisfied after therapy and the mean pain score was decreased. The same patients were evaluated two years later and were found to have kept their subjective improvements in satisfaction, participation in sport, and reduction in pain. Ultrasound imaging also demonstrated thinner, more normal appearing tendons, thus suggesting a remodelling effect in the tendons after prolotherapy. In contrast to this, the placebo group found no patients were satisfied after two placebo injections, while 9/10 of those patients were satisfied after crossing over to the polidocanol injections. However another RCT comparing prolotherapy with polidocanol found all ten patients in the intervention group were satisfied with their results at six months, and returned to sport sooner than the prolotherapy group. An important consideration in interpreting these results is the small population studied. Authors such as van Sterkenburg et al. (2010), therefore, question any true clinical value of sclerosing injections. In their study of 53 tendinopathic tendons, 42% of subjects reported no change and 14% reported a worsening in their condition following a six-week regimen of ethoxysclerol. At up to five year follow-up, over half of the subjects required further intervention. Sclerosing injections therefore may have a role in patients who have extensive vascularity and who have failed to respond to exercise.

Another injection treatment available is Aprotonin, which is a collagenase inhibitor derived from bovine lung. It is particularly effective at inhibiting plasmin, an activator of collagenases (MMP1, 8 and 13). Increased levels of MMP collagenases in tendinopathy have been implicated in the degenerative process, as they count type 1 collagen and the ECM as their substrates. A prospective double-blind RCT by Brown et al. in 2006 looked at 33 tendons split between one group receiving aprotinin injections and eccentric exercise, and another group receiving placebo injections and eccentric exercise. It found that while there was a consistent tendency for greater increases on VISA-A and some other secondary outcome measures in the intervention group, the difference was not statistically significant.
from the placebo group, possibly owing to the small sample sizes. In fact, at 12 months 85% of the placebo group had returned to exercise compared with 77% of the aprotinin group. Other lower quality studies have reported benefits associated with the treatment, such as an 84% improvement rate with aprotinin, and 64% satisfaction rate among participants\textsuperscript{40}. There were no age, or gender differences in those treated by aprotinin. While the results in the literature are somewhat promising, aprotinin carries a much higher risk of allergic reaction than other injection therapies due to its bovine origin which imparts antigenic properties in humans, including anaphylaxis. Orchard et al. (2008) reported 13 subjects out of a total of 343 patients had probable systemic allergic reactions, seven of which had to be treated within 30 minutes with adrenaline\textsuperscript{50}. Other reports suggest it is the repeated exposure to aprotinin in such a short time frame that increases risk. A systemic allergy rate of less than 0.1% has been identified among those with no prior exposure, compared with 2.7% upon re-exposure\textsuperscript{51}. This raises many questions regarding aprotinin’s use clinically. If the justification for its use is simply as a form of prolotherapy, alternative prolotherapy treatment options that carry less of a systemic risk would be more appropriate. However, if aprotinin does have therapeutic effects itself, it would be advantageous over other injection therapies such as dry needling or sclerosing agents which necessitate penetrating the tendon and theoretically increase risk of damage. Aprotinin can be injected around the tendon, reducing the risk of iatrogenic damage. Despite this, authors seem to be in agreement that aprotinin should only be considered where more basic measures have failed, and that patients should be observed for 30-60 minutes after injection for signs of allergy. It is recommended ahead of cortisone treatments as it has proven more successful in studies comparing the two.

More recent studies have looked at Platelet-rich Plasma Injections (PRP) in treating tendinopathy. Recent insights into the role platelets may have in tendon regeneration have led to the development of various therapeutic strategies based on high concentrations of these platelets. Platelets are key to thrombus formation, and aid in regeneration through removal of necrotic tissues and stimulating re-growth and healing of tendon tissue. PRP has been used in various types of surgery, but more recently has been used in the treatment of muscle, tendon and cartilage injury. Advocates of PRP suggest that platelets derived from whole blood deliver high concentrations of various growth factors like VEGF, PDGF and TGF-β, which they propose aid in tendon regeneration through proliferation of tenocytes, collagen synthesis and enhanced neovascularisation. Two small clinical studies on PRP in tendinopathy have found positive effects on patient satisfaction and self-reported pain. Ferrero et al.’s 2012
study examined the effects of PRP under ultrasound-guidance in achilles and patellar tendinopathy in 24 physically active individuals52. Following two PRP treatments, they demonstrated significant improvements in VISA-A and ultrasound imaging after six months, and a patient satisfaction rate of 70%. Filardo et al. (2013) had similar results in their medium-term study of 54 subjects with patellar tendinopathy, exhibiting improvements in VISA-P and EQ-VAS at two, six and 48 months follow-up. A satisfaction rate of 79.1% was reported, and PRP was said to result in a reduction in tendon thickness and hypoechoic regions on ultrasound53. These studies seem to indicate clinical efficacy of PRP in management of tendinopathy, however they had many limitations. Both studies lacked control groups, and subjects in Ferrero’s study were advised to receive physiotherapy, however no information was given on the uptake of physiotherapy treatment or what such treatment consisted of. Meanwhile the study by Filardo and colleagues also included an eccentric exercise component in addition to PRP. It may very well be that the positive results yielded in this study could be entirely due to this 12 week eccentric exercise component which already has proven efficacy. Therefore without a control group, no definitive conclusions on the benefits of PRP can truly be drawn from this study.

In addressing the significant limitations underlying studies promoting PRP, de Vos et al. (2010) carried out a stratified, double-blind, block-randomised, placebo-controlled trial in 99 patients with chronic mid-portion AT. The aim was to compare the impact of PRP on functional outcome and pain scores against placebo injection, when both are combined with eccentric exercise 54. They found that improvements in VISA-A score were non-significant between the groups, or in any secondary outcome measures, thus demonstrating no benefit on pain or function up to 24 weeks after injection. It is likely that the improvements obtained were mostly due to the eccentric exercise programme. This high quality study was succeeded by two follow-up investigations55 56, which showed no significant difference against eccentric exercise in ultrasound imaging, VISA-A, return to play or patient satisfaction up to one year after treatment. High quality studies such as de Vos’ and its follow-ups in which PRP brings about a significantly positive outcome are not forthcoming.

It is clear that there are a wide range of therapies and treatments at the clinician’s disposal in treating tendinopathy, however eccentric exercise is the only one which has stood up to scrutiny. Recent treatment research focuses on more medical interventions such as PRP despite the complete inability of the proponents of such treatments to back up their assertions with any objective, quality evidence.
Only five studies have examined the efficacy of its application in AT to date, and only one has directly compared PRP as a standalone treatment against the already established gold standard eccentric exercise protocol. Furthermore, while the prospective nature of these studies provides a higher quality of evidence than a retrospective study, by minimizing sources of bias and confounding factors such as previous physical activity levels in de Vos’s 2010 study, the literature investigated in this discussion is restricted by the relatively small population sizes. Definitive conclusions about a medical intervention cannot be drawn from studies of just 20-60 tendons each.

As K.M Khan recently put it at the 2012 IFOMPT symposium on tendinopathy; “My 84 year old mum would be able to see that PRP is not effective”. And yet high-level athletes will still be seen foregoing the tried-and-tested eccentric exercise protocol in search of such injection treatments simply because they are new and in-vogue. In other cases, these are coupled with the eccentric exercise protocol, and upon completion of the treatment, the success of the intervention is placed on the PRP injections, leading to such headlines as “PRP Therapy; Reason Behind Rafael Nadal’s Comeback”. It is easy and understandable for athletes and the general population not involved in the research and implementation of interventions in tendinopathy and other musculoskeletal injuries to believe the hype surrounding PRP. However it is the job of the evidence-based practitioner to not simply select a treatment based on how new or popular it is, but to make an informed decision based on best clinical practice and the evidence available. While other injection treatments have a more logical grounding in their proposed mechanisms, such as aprotinin and polidocanol, they too lack the evidence required to make a definitive assertion on their efficacy in tendinopathy.

Further clarity around the pathophysiological mechanisms involved in tendinopathy is required so that new treatments can be formulated, or existing ones modified, in order to treat this condition effectively in all patient groups. Until then, “Exercise is Medicine” is the philosophy which all practitioners should be applying to the management of achilles tendinopathy.
Bibliography


