Exploring the role of intratendinous pressure in the pathogenesis of tendon pathology: a narrative review and conceptual framework

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ABSTRACT

Despite the high prevalence of tendon pathology in athletes, the underlying pathogenesis is still poorly understood. Various aetiological theories have been presented and rejected in the past, but the tendon cell response model still holds true. This model describes how the tendon cell is the key regulator of the extracellular matrix and how pathology is induced by a failed adaptation to a disturbance of tissue homeostasis. Such failure has been attributed to various kinds of stressors (eg, mechanical, thermal and ischaemic), but crucial elements seem to be missing to fully understand the pathogenesis. Importantly, a disturbance of tissue pressure homeostasis has not yet been considered a possible factor, despite it being associated with numerous pathologies. Therefore, we conducted an extensive narrative literature review on the possible role of intratendinous pressure in the pathogenesis of tendon pathology. This review explores the current understanding of pressure dynamics and the role of tissue pressure in the pathogenesis of other disorders with structural similarities to tendons. By bridging these insights with known structural changes that occur in tendon pathology, a conceptual model was constituted. This model provides an overview of the possible mechanism of how an increase in intratendinous pressure might be involved in the development and progression of tendon pathology and contribute to tendon pain. In addition, some therapies that could reduce intratendinous pressure and accelerate tendon healing are proposed. Further experimental research is encouraged to investigate our hypotheses and to initiate debate on the relevance of intratendinous pressure in tendon pathology.

WHAT IS ALREADY KNOWN ABOUT THIS TOPIC

⇒ Tendinopathy remains a major problem for athletes, accounting for 30% of all overuse injuries.
⇒ Despite advances in tendon research, the pathogenesis of tendon pathology is still poorly understood.
⇒ A disturbance of intratendinous pressure homeostatis has not yet been considered a possible factor.

WHAT THIS STUDY ADDS

⇒ Remodelling of tendon tissue into fibrocartilage-like tissue can result in an increase in intratendinous resting and dynamic pressure, mainly due to an excess of water-binding glycosaminoglycans and proteoglycans.
⇒ An increase in intratendinous resting pressure might explain the hypoxic state and the formation of leaky (neo)vessels in tendon pathology.
⇒ An increase in intratendinous dynamic pressure might make tendon pathology progressive and induce load-related tendon pain.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Treatments aimed at inhibiting maladaptive remodelling (eg, modified physiotherapy) or reducing intratendinous pressure (eg, human recombinant hyaluronidase) might be promising therapies that should be investigated.

INTRODUCTION

Tendinopathy, the clinical syndrome of tendon pain and dysfunction, remains a challenge of major concern for athletes and accounts for approximately 30% of all overuse injuries.[1–4] Despite strong advances in tendon research over recent decades, there is still a limited understanding of the underlying mechanisms involved in the development of tendon pathology that underpins tendinopathy. Consequently, management of this debilitating condition remains challenging, presumably because current treatment modalities do not directly address all aspects of the natural history of the disease. For example, 60% of patients still experience symptoms after completing an exercise-based rehabilitation programme.[5] These unsatisfactory treatment results, which might even lead to the premature end of a sporting career, continue to frustrate clinicians and athletes. The list of alternative treatment options, such as shockwave therapy, injections (platelet-rich plasma, prolotherapy, corticosteroids, high volume, sclerotherapy), nitric oxide patches, surgical debridement, etc is long and illustrates that despite meritorious attempts, a 'magic bullet' for tendinopathy will remain elusive when there are still significant gaps in knowledge of the pathogenesis of tendon pathology.[6 7] Should we simply acknowledge the difficult nature of tendinopathies or further invest in fundamental tendon research to create new hypotheses and insights? We propose the latter and therefore aimed to explore the potential role of intratendinous pressure in the development and progression of tendon pathology in both upper and lower limbs. This conceptual paper was developed on the basis that pressure dynamics in tendons have received little to no attention to date, yet may provide a coherent pathophysiological

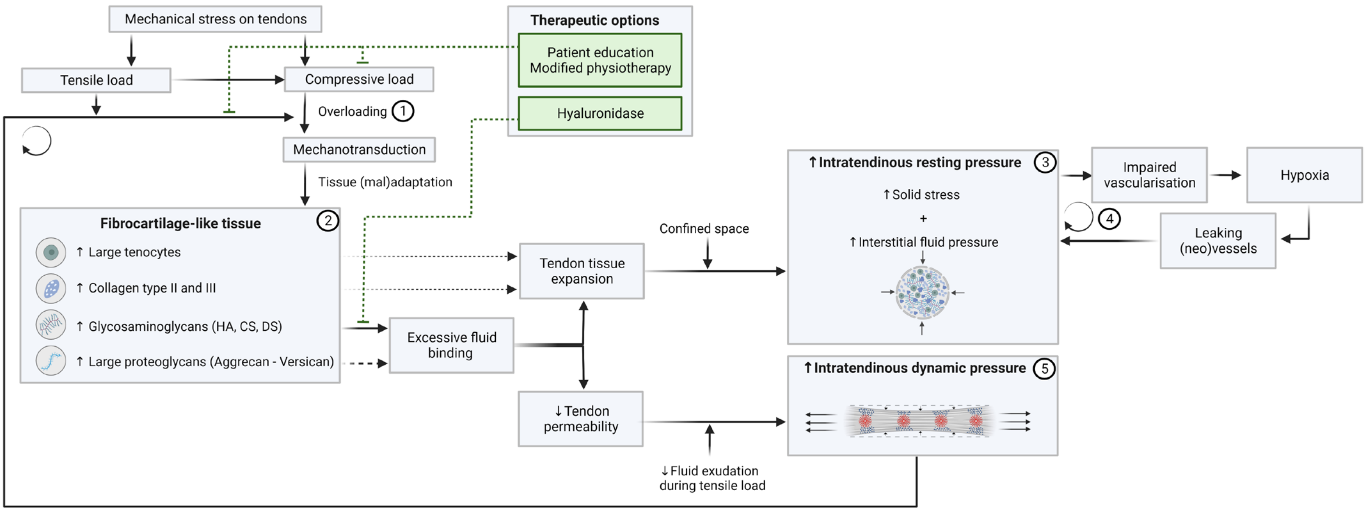

Figure 1 Conceptual framework describing the role of intratendinous pressure in the pathogenesis of tendon pathology. CS, chondroitin sulfate; DS, dermatan sulfate; HA, hyaluronan.

explanation for some of the mechanisms and structural manifestations involved in tendon pathology and pain. These reflections and the subsequent literature review led to several discussions among the authors that served as the basis for our integrative conceptual model summarised in figure 1. To facilitate the understanding of our model, each component will be discussed separately throughout the paper. We would like to point out that it is not our intention to claim that this model could lead us to the holy grail in tendon pathology, but rather to open a debate so that new experimental research can emerge and potentially serve as a stepping stone for the discovery of new targeted therapies to improve tendon healing.

METHODOLOGICAL CONSIDERATIONS

This narrative review article encompasses a literature search on four main aspects: (1) the relationship between compressive overload and tendon structure or pathology, (2) our current understanding of intratendinous pressure dynamics, (3) how structural changes in tendon pathology might disturb tissue pressure homeostasis and vice versa and (4) the recognised role of increased tissue pressure in the pathogenesis of other disorders that share structural similarities with tendons. By synthesising the scientific input gathered in the articles addressing these main areas, the authors attempted to answer the following research questions: (1) Can intratendinous pressure play a role in the development of tendon pathology? (2) Can a disturbance of intratendinous pressure be correlated with the clinical and paraclinical manifestations of tendon pathology? (3) Can novel therapies safely intervene in changing the intratendinous pressure to obtain better results in the future? We included previous review articles and consensus statements regarding the pathogenesis of tendon pathology, and the electronic database PubMed was searched from database inception to January 2022 using domain-specific terms (see online supplemental appendix). In addition, reference lists of articles obtained from this search were also examined for additional relevant articles. Only papers that made a significant contribution to the body of knowledge on this topic were included for review.

Proposed steps or mechanisms in the pathogenesis

Compressive overload as pathogenic stimulus

Excessive load or training volume is considered the main trigger for tendinopathy.[8] Traditionally, it was thought that the nature of this overload was purely tensile. However, evidence has emerged that tendons are also exposed to compressive loads, both in upper and lower limbs.[9–11] External compression or impingement occurs mainly at the insertion, where tendons wrap around bony protuberances or convex surfaces.[12–15] Two clear examples in the lower limbs are the Achilles tendon and the gluteus medius, where compression occurs at the posterosuperior border of the calcaneus[12 13] and the greater trochanter,[16 17] respectively. Some examples in the upper limbs include the long head of the proximal biceps tendon (at the level of the humeral head and bicipital groove)[18–21], the distal biceps tendon (at the level of the radial tuberosity),[14 22 23] the extensor carpi radialis brevis tendon (at the level of the lateral epicondyle and the capitellum)[24 25] and the supraspinatus tendon (at the level of the humeral head and greater tuberosity).[21 26–29] Internal compression, on the other hand, can also occur in the midsubstance because of the Poisson effect or torsion during tensile loading.[30–32] It should be noted that for both types of compression, the amount of compressive load will be higher when more tensile load is applied, demonstrating the close relationship between tensile and compressive loads in tendons.[13 31]

(Mal)adaptive tendon matrix remodelling

Mechanotransduction describes the ability of a cell to detect and convert mechanical stimuli into biochemical signals, resulting in intracellular changes and remodelling of the extracellular matrix (ECM) to adapt to the external loading environment.[9] In mechanically active tissues, such as tendons, this mechanotransduction process plays a crucial role in tissue protection. It has been shown that the tendon micro-architecture continuously adapts to the applied or removed loads, and that this adaptive process is driven by the tenocyte. Fibrocartilage metaplasia, which is characterised by an increase in (1) glycosaminoglycans (GAGs), ie, hyaluronan (HA), chondroitin (CS) and dermatan sulfate (DS), (2) large proteoglycans (PGs), ie, aggrecan and versican, (3) rounded and enlarged tenocytes and (4) collagen type II, can therefore be considered a physiological adaptation to compressive loads, as it increases the resistance of tendon tissue to compressive loads.[33 34] A typical example is the fibrocartilage at entheses, which are characterised by a four-zone gradient, transitioning from tendon to bone (figure 2). In this deep tendon area, compressive loads are extremely high and tensile loads are rather limited.[13 35–37] However, when compressive loads are

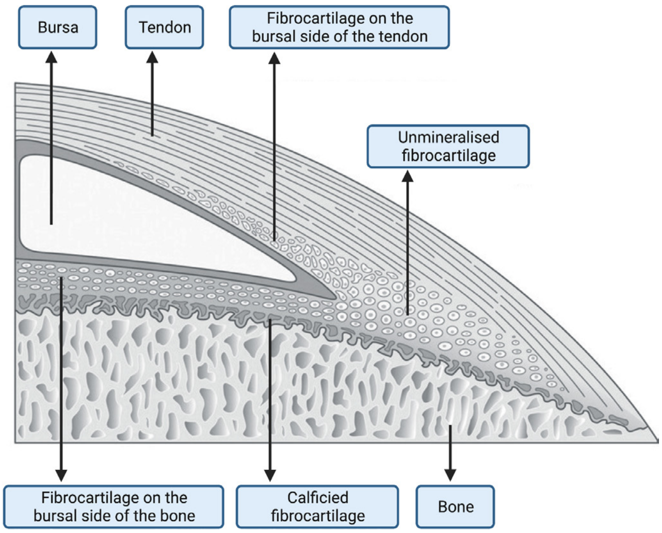

Figure 2 Illustration of the enthesis showing the presence of fibrocartilage in areas where tendon and bone are adjacent. Picture adapted with permission from Elsevier.[156]

suddenly increased in magnitude, metaplasia from a tensile to a fibrocartilaginous morphology can become excessive and occur beyond the 'classical' zone.[9 21 38] This change in phenotype can have a number of negative consequences for tendons, especially for areas that are also exposed to a significant amount of tensile loads. First, it may gradually reduce the tendon's tensile stiffness, which explains why the combination of tensile and compressive overloads is most damaging to tendons.[26 33 39–41] Second, due to the strong water-binding properties of negatively charged GAGs and PGs, it also induces fluid accumulation, increasing susceptibility to external compression as tendon thickness increases and making the compressive overload progressive.[10 42 43] Third, it may also disrupt intratendinous pressure dynamics, which will be clarified in the following sections.[9 44] These arguments indicate that excessive remodelling of tendon tissue into fibrocartilage-like tissue due to compressive overload may result in failure to achieve optimal tendon matrix homeostasis and is therefore considered potentially maladaptive in our model.[43–46] In addition, if overload persists, the change of tissue phenotype may alter the tendon cell response and result in loss of the organised structure of the fibrocartilage matrix, and thus also be the first stage of tendon pathology.

Volume expansion induces an increase in intratendinous resting pressure

Although somewhat ignored in tendons, every structure in our body (eg, nerves, muscles, joints, brain) has a total tissue pressure (TTP), which is the sum of the interstitial fluid pressure (IFP) and the solid stress (SS).[47] While IFP correlates only with the amount of free fluid, SS is the pressure exerted by the cells, collagen and GAGs or PGs, including their bound fluid.[48] The TTP can vary slightly but usually remains below 10 mm Hg in normal conditions.[49] However, in various pathologies, such as muscular compartment syndromes, compression induced neuropathies, osteoarthritis and tumours, TTP may increase significantly.[48 50–54] In these disorders, the TTP increase is attributed to either a solitary increase in IFP or SS or the combination, with the associated volume expansion being resisted by an enclosed sheath. For example, intraneural pressure increases fourfold in compressive neuropathies due to fluid accumulation beneath the impermeable perineurium.[54] In tendon pathology, this phenomenon also seems plausible, as the cellular proliferation and upregulation of several components of the ECM, especially GAGs and PGs with its bounded fluid, may induce a strong swelling pressure (figure 3).[55–58] It is unclear which sheath would primarily resist the volume expansion, but both the endotenon (interfascicular matrix (IFM)) and epitenon seem possible as they have a fairly low permeability and closely surround the fascicles and the whole tendon, respectively.[59 60] The increase of TTP in these confined spaces, namely intrafascicular or interfascicular, respectively, can therefore lead to a 'miniature compartment syndrome' in tendons, whereby continuous pressure is exerted on the associated tenocytes and ECM.[54 61] This term was coined by Lundborg *et al*, who described that the swollen nerve fascicles in neuropathies exhibit a behaviour similar to that of a muscle compartment in chronic compartment syndrome.[54] For convenience, TTP is further discussed as intratendinous pressure.

Increased intratendinous resting pressure impairs vascularisation

Although controversial, biopsy and in vivo model studies suggest that hypoperfusion and subsequent hypoxia are features of tendon failure.[62] Indeed, histopathological changes in chronic tendinopathies consist of necrotic tenocytes and an excess of blood vessels with narrowed lumen.[63–68] In addition, microdialysis studies have shown high levels of lactate within tendinosis, even in tendons at rest, suggesting that hypoxia may persist.[69] However, the exact mechanism of how hypoxia develops and can persist in tendinopathy has not yet been defined. We speculate that an increased intratendinous resting pressure (IRP) might be a crucial contributor, as it impairs vascularisation in two ways (figure 4). First, the elevated pressure is transmitted to the postcapillary venules, increasing venous pressure and decreasing the arteriovenous pressure gradient.[70] Indeed, an increase in venous pressure, indicating venous congestion, has already been found in midportion tendinopathy.[71 72] Second, further increase of the IRP could also cause the capillaries to deform or collapse, reducing their radius and decreasing capillary blood inflow. A similar phenomenon has already been described in oedematous neuropathies[53 54 73–75] and it may explain why narrowed vascular lumens are also found in degenerative tendinopathies. The IRP thresholds that can impede blood flow are based on the mean capillary and venous intravascular pressures, ie, 30 mm Hg and 15 mm Hg, respectively.[76] For example, pressure thresholds for chronic exertional compartment syndrome are intramuscular resting pressure >15 mm Hg, a one-minute postexercise pressure of >30 mm Hg or a 5 min postexercise pressure >20 mm Hg.[77] It should be mentioned that there is also a reciprocal relationship between tissue pressure and hypoxia. First, hypoxia can lead to arteriolar vasodilation and an increase in vascular permeability, allowing more fluid to enter the affected compartment.[70] Second, it has already been shown in retinopathies and tumours that neovessels, which are formed during prolonged hypoxia, typically have a chaotic, leaky architecture.[78] Järvinen recently noted that leakage can also occur in the neovessels typically found in chronic tendinopathies.[63] As described in muscles, nerves and tumours, blood vessel leakage increases IFP, creating a vicious cycle, which theoretically could also occur in tendinopathies.[70 73 77 79]

Reduced permeability induces an increase in intratendinous dynamic pressure

Approximately 70% of the weight of tendons consists of water, which is either free or bound to the ECM.[80–82] However, the

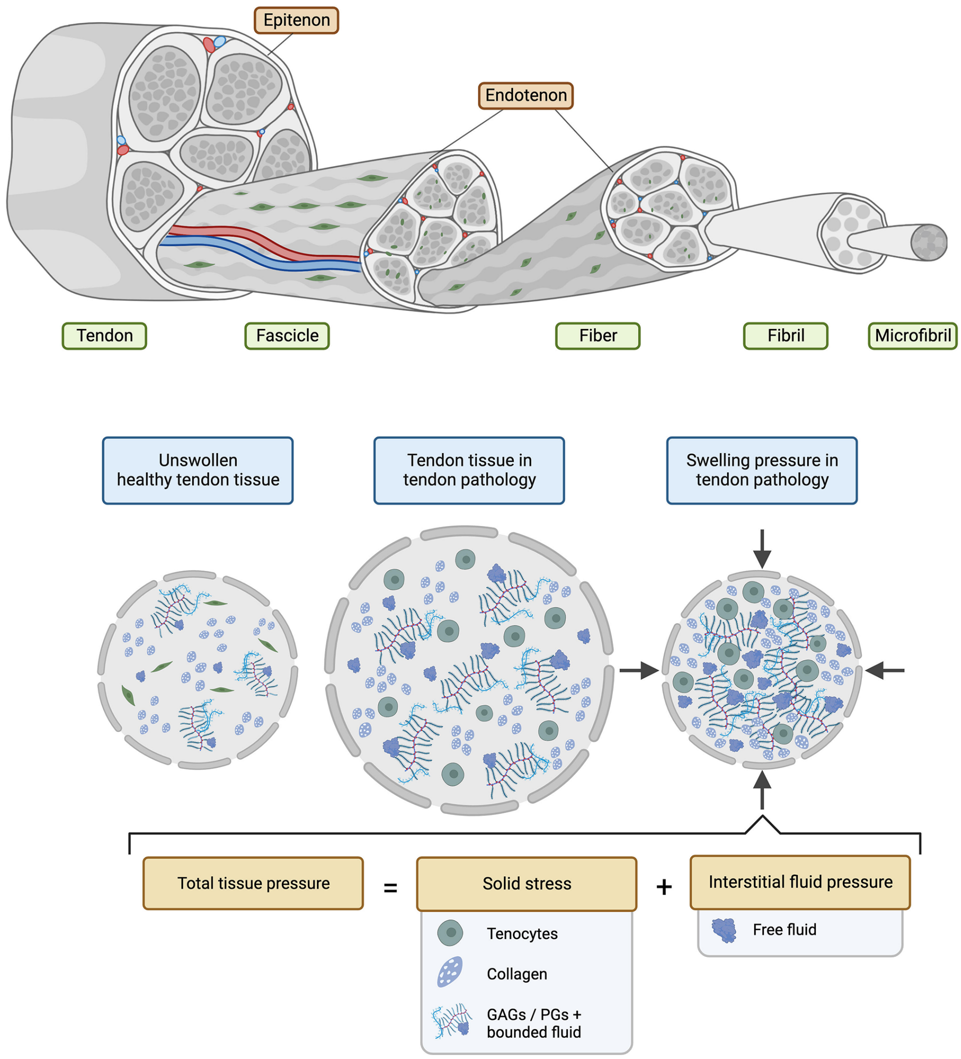

Figure 3 Illustration of how swelling pressure in tendon pathology may occur, resulting in an increased intratendinous resting pressure.

amount of water may vary due to fluid movement inwards and outwards of the tendon. Tendons undergo lateral contraction during tensile loading (Poisson's ratio >0.5), which generates a positive fluid pressure and leads to radial fluid exudation and consequently volume shrinkage (figure 5A).[83] This phenomenon, in part, explains the acute reduction in tendon thickness in response to exercise, equating to a cumulative transverse strain of approximately 6%.[84–87] Moreover, fluid and SS pressurisation is also thought to be responsible for the observed decrease in microvascular blood flow during passive stretching in tendons, muscles and nerves, and the poststretch hyperaemia reaction that follows when tension is released.[88–92] For convenience, we will further use the term intratendinous dynamic pressure (IDP) to refer to the amount of internal pressure generated during tensile loading in tendons. Although a direct analysis of IDP has not yet been carried out, a positive correlation between fluid pressure and passive strain has already been demonstrated in nerves and muscles.[93–96] For example, intraneural pressure in the sciatic nerve increases from 8 mm Hg to 56 mm Hg during a straight leg raise.[95] Theoretical and experimental studies have also shown that fluid pressure increases strongly when hydraulic permeability of the ECM decreases, as this is associated with a higher resistance to fluid flow.[31 60 80 83 97–101] Such a decrease in transverse permeability typically occurs in tendon pathology due to the increase of water-retaining GAGs and PGs. Fluid can therefore be trapped inside the tendon matrix during tensile loading, resulting in significantly higher IDP (figure 5B). In addition, since free fluid volume is also increased in tendon pathology, allowing more fluid to be trapped, the pressurisation effect can be even more pronounced.[81 102] These assumptions are consistent with clinical findings that tendon thickness decreases less after exercise in patients with tendinopathy.[103 104] Moreover, it also implies that for the same amount of tensile load, tendon cells will experience more IDP in tendon pathology than in healthy tendons, which again creates a vicious cycle, and represent a plausible mechanism for the progression of tendon pathology.

How does this model fit into the continuum model?

The continuum model by Cook *et al* classifies tendinopathy based on the changes and distribution of disorganisation within the tendon. Three different phases were distinguished, namely reactive tendinopathy, tendon disrepair and degenerative tendinopathy.[105 106] Each of these phases might also be related to changes in intratendinous pressure. Reactive tendinopathy, due to (compressive) overload, is essentially accompanied by an accumulation of hydrophilic GAGs, PGs and associated fluid.[107] These GAGs (eg, HA) and PGs (eg, aggrecan and versican) can be produced rapidly, within a few hours to days, and are responsible

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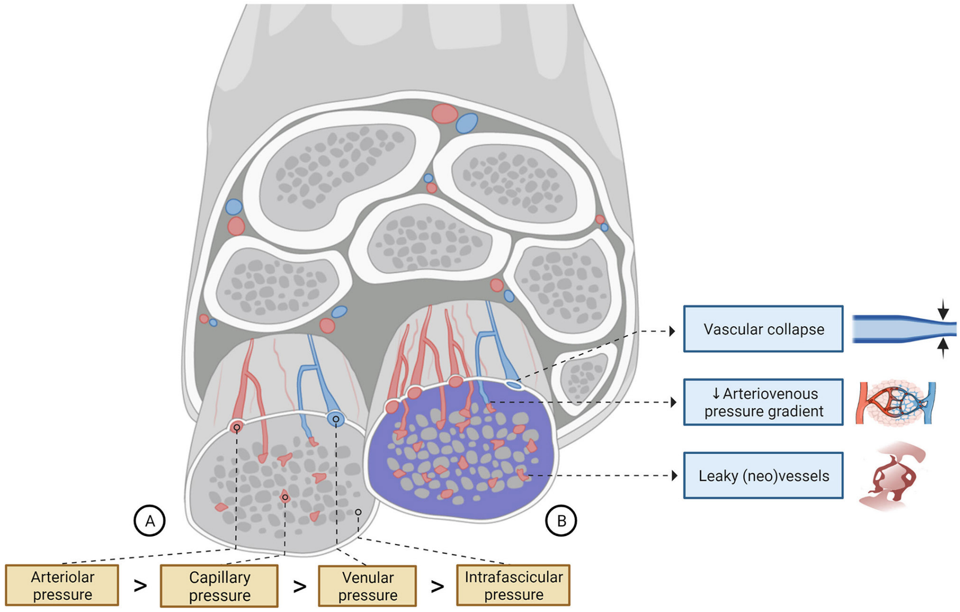

Figure 4 Illustration of how ischaemia may occur in tendons due to an increased IRP. (A) Normal fascicle in which pressure gradient is necessary for adequate intrafascicular circulation. (B) IRP in tendon pathology may be increased, inducing vascular collapse and a reduced arteriovenous pressure gradient. The resulting hypoxia stimulates vascular permeability and the formation of leaky neovessels, which further contribute to an increase in IFP. It should be noted that the IRP can also increase interfascicularly with the same phenomena, but with the epitenon as the main barrier sheath. IFP, interstitial fluid pressure; IRP, intratendinous resting pressure.

for the rapid tendon swelling.[105] As already described in detail for tumours, it is precisely these GAGs that increase the SS and consequently cause the IRP to rise sharply.[108–111] Moreover, the increase in GAGs is also responsible for the reduced matrix permeability, which further leads to an increase in IDP.[44 60 112 113] Fortunately, GAGs and PGs have a fast turnover rate, which means they can also be degraded just as quickly.[105] Therefore, by removing the compressive stimulus on the tenocyte, GAGs, PGs and associated fluids might decrease, and a normalisation of the IRP and IDP could occur. This explains why rest is so successful in the reactive phase.[105] However, if the athlete continues to train with a swollen, less permeable tendon, the tenocyte will gradually experience more pressure for the same amount of load, further stimulating the production of GAGs, PGs and associated fluid, resulting in persistently high IRP and IDP. As a result, the tendon matrix may enter the disrepair phase, on the one hand, due to hypoxia and, on the other hand, due to physical disruption because of high IRP and IDP, respectively. It has recently been highlighted that degradation of the IFM precedes damage to the intrafascicular matrix and is therefore an important feature of the progression of tendon pathology.[107] Our theory may also fit these findings. Since the IFM cell population is more metabolically active than the fascicular tenocytes, it is also more oxygen-dependent.[114–116] Ischaemia will, therefore,

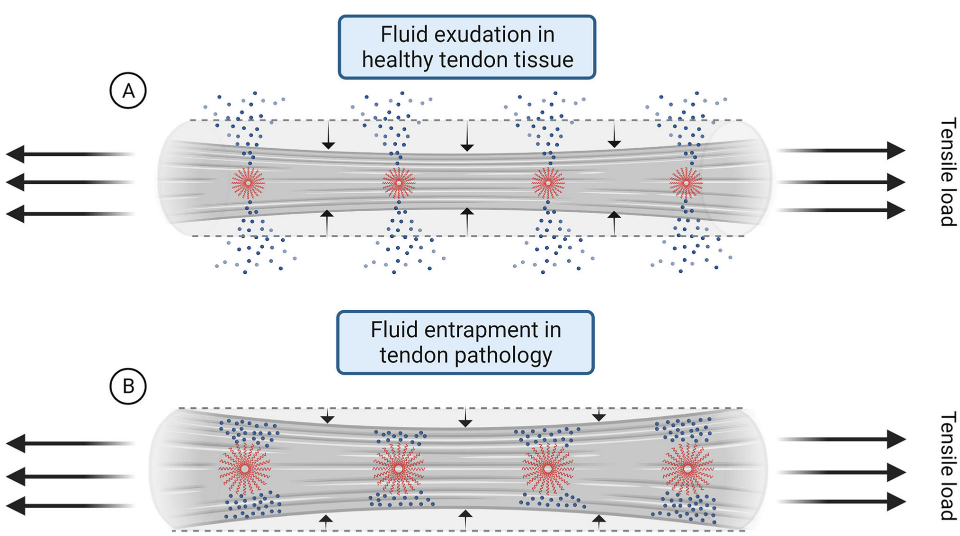

Figure 5 Illustration of how IDP occurs in tendons, resulting in fluid exudation. (A) During tensile loading, tendon fluid moves radially from the tendon core to the outside, due to lateral contraction and the associated increase in pressure. (B) In tendon pathology, hydraulic permeability decreases due to the accumulation of GAGs and PGs, resulting in fluid entrapment and higher IDP. GAGs, glycosaminoglycans; IDP, intratendinous dynamic pressure; PGs, proteoglycans.

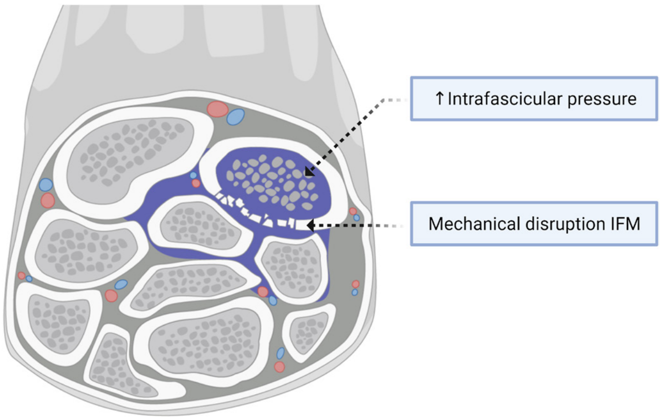

Figure 6 Illustration of how disruption of the interfascicular matrix may occur in tendons due to high intratendinous dynamic pressure.

have a greater detrimental effect on IFM cells, which will more quickly alter phenotype or succumb to apoptosis. Furthermore, we believe that mechanical disruption will also start in the IFM due to high IDP, as pressurisation begins within the packed microstructure of tendon fascicles (figure 6).[60 97 117 118] Eventually, if the patient continues their activities during this phase of disrepair, prolonged oedema and hypoxia will also lead to cell apoptosis and irreversible matrix breakdown products within the fascicles.[119] This theory is already accepted to explain tissue changes that occur in chronic compressive neuropathies due to increased intraneural pressure.[52 75] In turn, the damaged collagen network may also further fail to oppose the swelling pressure, resulting in loss of parallel alignment with large deposits of GAGs and PGs in between.[17 119–122] The degenerative phase has then reached the affected tendon region. Finally, it should not be ignored that proinflammatory cytokines are also observed in tendinopathies. It is suggested that these should be attributed mainly to the mechanosensitive tenocytes in response to overload or disruption of homeostasis.[106] Since local chronic inflammation also occurs in compressive neuropathies because of increased intraneural pressure, this could theoretically also be the case for tendons.[52 123]

How does this model relate to (para)clinical features of tendinopathy?

Pain

In general, the term 'tendinopathy' refers to a pathological condition of a tendon with a complaint of pain and decreased function.[124] At present, there are still many questions about the identity of the nociceptive driver in tendinopathy as the relation between tendon pain and tissue disruption is not straightforward.[125 126] We speculate that a disturbance of the intratendinous pressure homeostasis might be involved in pain perception. First, an increase in intratendinous pressure can activate the mechanonociceptors located in the peritendinous connective tissue (both endo- and epitenon), subsequently firing the fast, myelinated Aδ fibres and the slow, non-myelinated C fibres. These fibres are responsible for the first, sharp pain and the later, dull pain, respectively. Both nociceptors have a noxious pressure threshold around 100 mm Hg tissue pressure, but their firing frequency, and thus the sensation of pain, increases significantly as pressure rises.[127–129] We suggest that such high pressures in tendons can only be achieved during loading (IDP) and if the matrix permeability is sufficiently reduced. This is consistent with the observation that tendon pain correlates well with load intensity and GAG or PG content.[106 130] Moreover, since IDP also correlates with strain rate, this elucidates why fast loading exercises (eg, plyometrics) are more provocative than slow exercises (eg, isometrics).[131–133] Furthermore, it also clarifies the warming-up effect in tendinopathy, since tendon preconditioning leads to controlled fluid exudation, which will reduce the IDP.[134] Conversely, it may also explain morning stiffness, as fluid reabsorption and accumulation typically occur at night, as already described in carpal tunnel syndrome.[135] As a result, presumably higher IDP pressures will occur in a stiff, overhydrated tendon during the first steps in the morning. Finally, two other noxious stimuli that are highly elevated in tendon pathology, namely glutamate and lactate, can also be associated with our pressure model.[69 119 136] Glutamate is typically released by activation of C fibres, while lactate is a consequence of prolonged hypoxia.

Swelling

Another clinical feature of tendon pathology is swelling, usually fusiform in shape,[137] which is mainly attributed to the strong increase in highly negatively charged GAGs and PGs that induce water absorption.[8] For example, in patellar tendinopathy, the GAG content increases fivefold, accompanied by a fluid increase of more than 16%.[34] Yet, the amount of free fluid also appears to increase in tendinopathy.[138] Within our conceptual model, tendon swelling also occupies a central position, as it is necessary to obtain swelling stress and consequently an increase in IRP. However, there are two important factors to consider. First, based on tumour studies, an increase in GAG-bound fluid (SS) will have a significantly greater impact on IRP than an increase in free fluid (IFP).[108–110 139 140] Second, the amount of swelling pressure will be highly dependent on the location of the fluid accumulation within the tendon matrix (figure 7). Indeed, the intrinsic compartment, the fascicle, has a much smaller diffusion space than the large extrinsic compartment of the IFM.[65] By analogy, it has already been described in nerves that a small fascicular fluid increase is associated with an intense pressure increase (up to 750 mm Hg), whereas the same fluid increase in the IFM resulted in a significantly lower pressure (up to 60 mm Hg).[141] Although PGs and GAGs occur both inter- and intrafascicularly, fluid accumulation appears to occur primarily interfascicularly and, consequently, extremely high resting pressures (> 100 mm Hg) are unlikely to occur in tendon pathology.[55–58]

Structural findings

Tendon pathology is rarely homogeneous in terms of severity of tendon damage—some fascicles are more affected than others.[142 143] Recently, it was described that the degree of permeability of the fascicles differs and that this might play a role in the development of tendon pathology.[144] These observations fit perfectly in our conceptual model. We believe that the IRP and IDP will also be heterogeneous, as it is related to the amount of fluid in the fascicles and the permeability of the IFM in the affected tendon region. Consequently, disrepair of the IFM is expected to occur mainly in the regions where the intratendinous pressures are highest.

Therapeutic implications

The quest for novel therapies in sports medicine must be based on discoveries through basic science. This conceptual model proposes a central role of increased intratendinous pressure in the pathogenesis of tendon pathology. Therefore, strategies that can restore intratendinous pressure might be relevant to consider as an (additional) treatment strategy. We speculate that

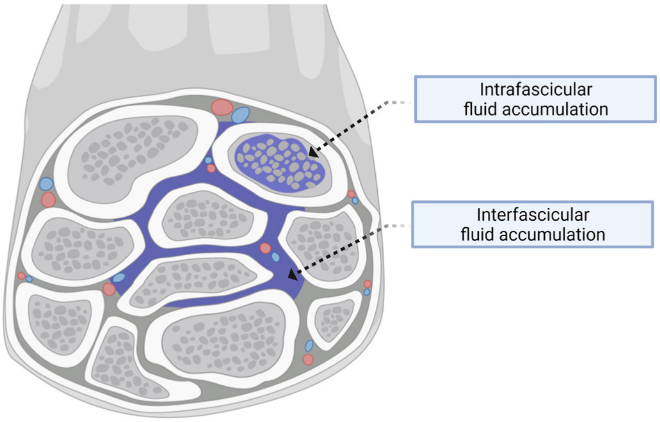

Figure 7 Illustration demonstrating the importance of the location of fluid accumulation.

this can be achieved in two ways. On the one hand, maladaptive mechanotransduction must be addressed. This can be done by reducing the amount of compressive load, but still exerting sufficient tensile forces on the tenocyte during rehabilitation to restore its normal phenotype and promote proper ECM synthesis. For example, in insertional Achilles tendinopathy, this can be relatively easily achieved by reducing the amount of dorsiflexion.[10 145 146] In addition, heavy-slow resistance exercises would also give better results than high-speed exercises, as these are associated with a lower IDP.[132] On the other hand, drug treatment that directly targets the elevated GAG content might also be a very powerful tool. A potential treatment that has been mentioned recently for tendinopathies is human recombinant hyaluronidase, as it degrades HA, CS and DS from the ECM to preinjury levels.[147 148] The removal of these excess GAGs can liberate the bound fluid and significantly reduce the fluid content, resulting in a lower IRP, thus enabling vascular re-expansion.[101 140 149] This novel agent is already used for tumours as it successfully reduces interstitial pressure to enhance the delivery of cytotoxic agents.[150] Furthermore, since enzymatic degradation of GAGs also increases matrix permeability, allowing the fluid to exude more easily during loading, this will also result in a lower IDP.[80] The use of human recombinant hyaluronidase may therefore be particularly useful in the reactive or early disrepair phase, before irreparable structural damage has occurred. Fortunately, previous experimental studies have shown that depletion of GAGs from tendon fascicles does not decrease tensile stiffness.[40 147 151 152] We, therefore, speculate that this treatment, which has been used in different medical applications for over 60 years, could be safe for tendons as well.[153–155]

Future research

Further research into the relationship between intratendinous pressure dysregulation and tendon pathology is a promising domain. A better understanding of intratendinous pressure dynamics could provide invaluable information about the aetiology and progression of tendon pathology. This would allow researchers and clinicians to translate this information into the identification of potential risk factors and effective treatment strategies, leading to better outcomes for all tendinopathy patients. More specifically, we propose to first focus on identifying the suspected elevated IRP and IDP in tendon pathology, using minimal or non-invasive techniques. In addition, the effects of the mentioned treatment strategies that could reduce these intratendinous pressures should also be investigated.

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