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Review Article

How do tendons adapt? Going beyond tissue responses to understand positive adaptation and pathology development: A narrative review

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Abstract

Understanding how tendons adapt to load is crucial to understanding how training can improve performance, minimise the risk of injury and aid rehabilitation. Adaptation is the positive response of an organism or tissue to benefit its function. In tendons, numerous tissue responses to load have been identified *in vivo*. Changes in tendon dimensions, structure on imaging, mechanical properties, and blood flow have been reported in response to mechanical stimuli. However, research has focused on tissue level changes with little understanding of how changes at the tissue level affect the person, their athletic performance or injury risk. Tendons can have a paradoxical response to load, load can induce positive adaptation, however it is also a major factor in the development of tendon pathology and pain. Tendon pathology is a risk factor for developing symptoms, yet the high rate of asymptomatic pathology suggests that the pathological tendon must adapt to be able to tolerate load. Similarly, there is mounting evidence to suggest that tendon remodelling or repair is not necessary for a positive clinical outcome following rehabilitation, suggesting that the tendon must adapt via other mechanisms. This narrative review synthesises evidence of how normal and pathological tendons adapts to load, and how this relates to adaptation of load capacity and function of the individual.

Keywords: Adaptation, Injury, Tendon, Pathology, Rehabilitation

Introduction

Whatever your role within sports medicine and science, an understanding of mechanobiology (how the body senses and responds to mechanical stimuli[1]) is critical. Understanding how load can have a positive or negative effect on the tendon is critical. From a clinical perspective, negative consequences to load may result in tendon pathology and in turn pain and compromised function (the clinical presentation of tendinopathy). Positive responses include increasing the tendon's capacity to tolerate load, or rehabilitating a painful tendon. Similarly, sports/exercise scientists are interested in tendon adaptation to improve tissue or athletic performance.

Tendons were initially considered to be metabolically inert to mechanical stimuli[2]. However, numerous studies have shown that the tendon responds both *in vitro*[3,4] and *in vivo*[5,6] to mechanical stimuli. There are extensive narrative and systematic reviews that have collated the current evidence of how tendons respond to mechanical stimuli that should be referred to[7-10]. While these reviews establish that tendons are responsive to mechanical stimuli in a myriad of ways, they do not provide insight into how these complex biochemical/mechanical responses contribute to positive adaptation of the tendon or person. This paper will attempt to define the mechanoresponses potentially related to adaptation of the normal and pathological tendon, how they may relate to improved load capacity or function, and pose questions for future research to better understand tendon adaptation.

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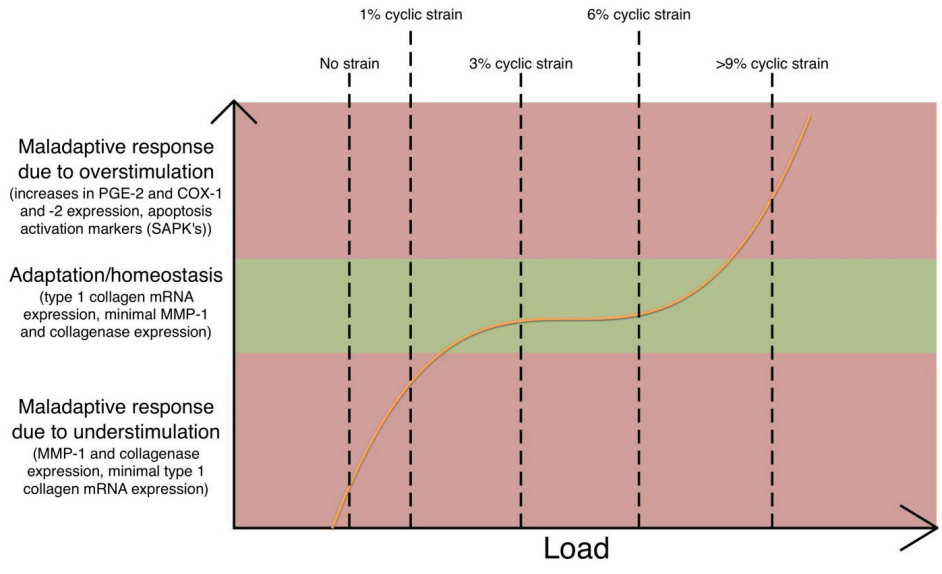

Figure 1. Schematic representation of the 'mechanostat point' for tendons. Mechanical stimulus within a certain level maintains homeostasis and potential adaptation of the tendon. Mechanical stimulus below this level (ie no strain, 1% cyclic strain) produces a maladaptive response due to increases in digestive enzymes. Conversely, large cyclic strains (ie 9% and over) produces increase in inflammatory cytokines and markers of apoptosis consistent with maladaptation. Figure adapted from[3,13,14,99].

What is adaptation?

Adaptation is how an organism, organ system, or tissue alters its structure or function to best suit its environment. Tendon adaptation is primarily driven by the application, or absence, of mechanical stimuli – either tensile strain, compression, or shear-stress solely or in combination. While adaptation is a commonly used term it has been poorly defined, with different meanings utilized depending on the authors view. The term adaptation can be separated into two broad categories; person-level changes or tissue-level changes. Person-level markers (ie athletic performance or load tolerance to activity or tendon loading activities) measure the capacity of a number of tissues and systems within the kinetic chain. While person-level changes are easy to quantify, it is not specific to any one tissue or structure. Tissue-level changes, such as changes in the structural, mechanical, or biochemical properties are quantifiable and specific to the tissue, yet their role in contributing to adaptation at a person-level is unclear.

From the perspective of the individual, adaptation results in improved load capacity. In tendons, most simply this results in improved athletic performance. Adequate load capacity also theoretically reduces the susceptibility of developing tendon pathology and/or clinical symptoms; though a number of other factors are also involved in this. Load capacity has been defined as being "able to perform functional movements at the volume and frequency required without exacerbating injury or causing tissue injury"[11], which is potentially mediated through changes in tendon properties and/or kinetic chain function. Load capacity was proposed to be a dynamic phenomena, where load capacity can be increased with the appropriate application of load or decreased in the absence of any load.

The concept of load capacity is analogous to the 'mechanostat point' proposed for bone[12]. While load capacity is a person-level change and 'mechanostat point' is a tissue-level change, both suggest that there is a tissue-based threshold that determines whether the applied load induces an adaptive or maladaptive response. Using tendon cell cultures, the application of 6% tensile strain produced a potential adaptive response from the tendon (increase in collagen I mRNA and an inhibition of degradation enzymes), where an absence of load induced markers of degradation (increase in matrix metalloproteinases and collagenase enzymes) (Figure 1)[3,13,14]. Critically, the 'mechanostat point', or level at which load induces a positive or negative response, is fluid and influenced by long-term load. Lavagnino & Arnoczky[13] showed that long-term stress deprivation induced a maladaptive response; where the same load produces different responses due to the change in 'mechanostat point'. It is proposed that while long-term under-stimulation can result in maladaptation, appropriate loading results in an adaptive response and a positive change in the 'mechanostat point (Figure 2).

It is important to note that adaptation in one tissue or system may not explain adaptation of the individual. Changes within the tendon may contribute to, but not fully explain, improved athletic performance. The musculature, nervous system and other connective tissues contribute to person-

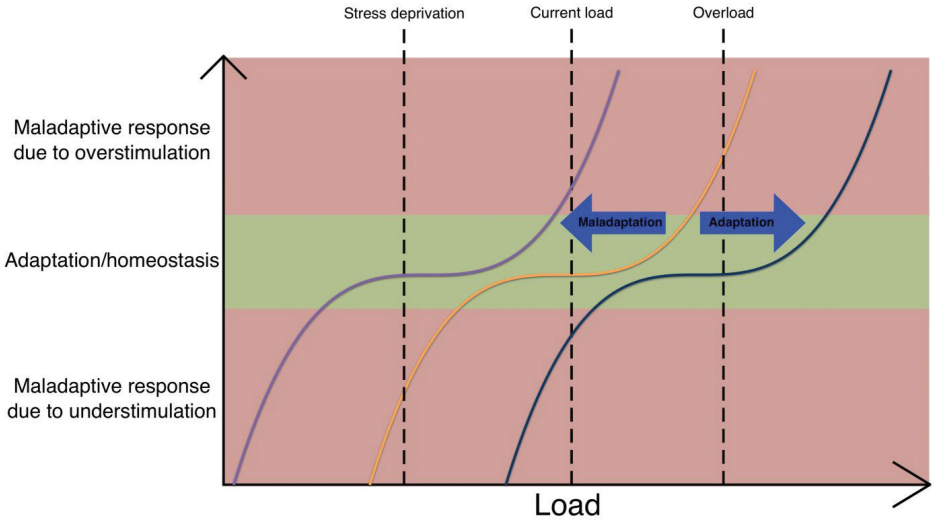

Figure 2. Schematic representation of re-calibration of the 'mechanostat point' following stress deprivation or overload. Maladaptation results in a shift of the 'mechanostat point', where stress deprivation now results in an adaptive/homeostatic process. Adaptation results an increase in load capacity and the 'mechanostat point'. Where overload once triggered a maladaptive response, the change in 'mechanostat point' now results in an adaptive process.

level adaptation[15,16]. While it needs to be acknowledged that these systems contribute to adaptation, this paper will primarily focus on tendon tissue properties and how they relate to adaptation.

How do tendons adapt?

Tendon size

Changes in tendon dimensions in response to load have been extensively investigated to explain tendon adaptation. With collagen being the principal load-bearing component of tendon, its mRNA and protein expression has been a focus of considerable investigation. *In vivo* studies have shown increases in collagen synthesis markers 24-hours post-exercise, both in the tendon and in the space between the tendon and peritendinous sheath[6,17,18]. While it was suggested this increase in collagen synthesis may lead to an increase in tendon dimensions, a concomitant increase in collagen degradation markers and digestive enzymes have been detected within the same 24-72 hours post-exercise period[18,19]. Increases in collagen mRNA or protein may not necessarily result in the synthesised collagen being integrated into the tendon matrix, as collagen degradation can occur both intra- or extra-cellular prior to integration[20].

Collagen turnover, or the integration of new collagen, in the tendon appears to be limited after skeletal development. Thorpe et al[21] observed that 0.25% of collagen was turned-over each year in skeletally mature horses, equating to a collagen half-life of ~200 years. Heinemeier et al[22] utilised the carbon-14 (^{14}C) bomb-pulse technique to show that ^{14}C levels within the tendon reflected the atmospheric ^{14}C during the first 17 years of life, suggesting that tendon turnover is limited after adolescence. Tissue-based adaptation through increases in tendon dimensions may only be possible during puberty. This limited turnover in skeletally mature animals and humans may explain the equivocal results when investigating *in vivo* changes in tendon dimension in response to load.

Cross-sectional studies have found that high habitual tendon loading is associated with greater tendon dimensions[23-25]. However, it is unclear at what age these participants began this habitual loading, with early sport specialization during adolescence potentially driving these tissue-based adaptive changes. Bohm et al[7] revealed a small overall effect for an increase in cross-sectional area (CSA) in response to various exercise (eg isometric, eccentric, concentric and eccentric combined, etc)(weighted average effect size of 0.24 (CI 0.07-0.42). Importantly, 25 of the 33 interventions included in the meta-analysis showed no significant change in CSA. Increases in tendon dimensions in response to exercise have been consistently observed in younger participants (mean age <25 years old)[26-29]. In participants over 60 years old, no significant change in tendon CSA has been observed[30-32]. However, there are limited studies that have investigated the elderly population, with further work needed to determine whether increases in tendon dimensions through exercise are age-dependent and limited post-skeletal development.

It is logical to assume that increases in tendon CSA are adaptive and increase load capacity, as it decreases the stress placed on the tendon for the same force (stress = force/CSA). However, a link between increased tendon dimensions and a reduced risk of injury has not been established. Puberty may provide a critical window of opportunity where the tendon

can adapt by building new collagen tissue and be conditioned to tolerate high loads later in life. Inactivity during puberty may be a risk factor for the development of tendinopathy, as the individual may not have developed enough tendon tissue to tolerate high loads[33]. It is important to state that an absence of change in tendon CSA does not reflect an absence of tissue-based adaptation. The tendon may adapt via other mechanisms post-skeletal maturation, such as alteration of mechanical properties, or make up of the extracellular matrix.

Mechanical properties

Tendon mechanical properties have traditionally been quantified at the intra-muscular aponeurosis due to the difficulty in quantifying changes in length of the free tendon (ie lack of two clearly defined points where change in length can be measured)[34]. Currently, the term 'tendon mechanical properties' has been used to encompass both the aponeurosis and free-tendon. However, studies that have compared changes in mechanical properties between the two regions suggest that changes observed at the aponeurosis cannot be translated to the free tendon[35-37]. Techniques such as 3-dimensional ultrasound[38,39], speckle-tracking ultrasound[40], or shear-wave elastography[41] may allow for a better understanding of mechanical changes of the free tendon in response to exercise and how this relates to performance and injury[42].

Understanding the temporal sequence of changes in mechanical properties in response to load is critical[7,43]. A reduction in stiffness, both at the aponeurosis and free tendon, has been consistently demonstrated to occur immediately post-exercise[43]. Numerous authors have suggested that these transient (hours to days) changes increase the susceptibility of the tendon pain and pathology[43-46], with little supporting evidence. These changes may be as result of tendon creep due to the tendon's viscoelastic properties, and does not necessarily reflect mechanical fatigue. Furthermore, these changes may simply be a normal physiological response to load that normalises within ~24 hours[47,48].

Interestingly, exercise interventions produce contrasting effects when investigated over differing time frames. A decrease in aponeurosis/free tendon stiffness has been observed in the short-term (<24hours), however a meta-analysis of 37 medium- to long-term exercise interventions (total participants = 264) showed a significant increase in tendon stiffness and Young's modulus[7]. The majority of these studies suggested that these increases in tendon stiffness are adaptive, yet is unclear whether these changes contribute, and to what level they contribute, to person-level adaptation.

Few prospective studies have established a link between changes in tissue-level mechanical properties and improved athletic performance. Based on data from cross-sectional studies, a significant positive correlation has been reported between aponeurosis stiffness and both squat and countermovement jump height[49]. Interestingly, a large correlation was observed between rate of torque development and aponeurosis stiffness. Stiffening the aponeurosis may optimize its ability to transmit contractile forces from the muscle, leading to improvements in power tasks (ie jumping). In contrast, improved jump performance related to greater energy storage capability has been demonstrated in the more compliant aponeurosis[50]. A more compliant tendon may allow for greater elongation, greater storage of elastic energy, resulting in improved athletic performance (ie running, jumping, agility tasks). However, whether a stiffer or more compliant tendon is advantageous to physical performance is unclear.

The mechanical adaptations that improve performance may be sport specific, with the optimum mechanical properties of tendon likely to fall within a bell-curve, where too soft or too stiff a tendon will increase the risk of injury. An increase in stiffness may be beneficial for power athletes where transference of contractile forces through the tendon needs to be optimized. Kubo et al[36] demonstrated that isometric squat training increased quadriceps aponeurosis stiffness, along with increases in squat jump height. While not specific to the tendon, leg stiffness during a hopping task has been shown to influence maximum sprinting velocity[51,52]. Conversely, decreases in tendon stiffness and a more compliant tendon may be beneficial for endurance athletes who require the optimization of tendon elastic storage to keep the metabolic cost low[53]. While making theoretical sense, current evidence does not support this as strength training in runners resulted in an increase in aponeurosis stiffness, while reducing the energy cost during running[54].

The link between tendon mechanical properties and maladaptation has not been established. Chang and Kulig[55] reported decreased stiffness in the tendinopathic Achilles tendon, yet participants had similar levels of physical activity to structurally normal pain-free tendons. One of the few prospective studies that has attempted to answer this question has shown that medial gastrocnemius aponeurosis stiffness was not a risk factor for the development of Achilles tendon pain[56]. Measures of musculotendinous unit flexibility, which may be related to tendon stiffness, have found that reduced muscle flexibility in both the attached muscle and the antagonist is a risk factor for the development of Achilles and patellar tendinopathy[57-59]. As all of these studies have quantified aponeurosis or musculotendinous unit flexibility and it is unclear how these findings apply to the free tendon where injury occurs.

There is substantial evidence to suggest person-level adaptation is influenced by aponeurosis and/or tendon mechanical properties. However, it is unclear what specific tissue-level changes are required to induce specific person-level adaptation, for example it is unclear whether a stiffer or less stiff tendon is desirable for endurance athletes. Of particular interest, loading interventions that isolate the target musculotendinous unit tend to have a greater effect on mechanical properties. Changes to aponeurosis/tendon mechanical properties do not appear to occur at the same degree following multi-joint, functional activities (ie plyometric training, running)[7,43]. This may be due to the fact that multi-joint tasks do not apply adequate load to that

musculo-tendinous unit to induce adaptation. While there are studies that have reported changes in mechanical properties following multi-joint exercises[60,61], it appears that targeting the specific musculotendinous unit with isolated, single-joint tasks provides the greatest opportunity to induce adaptive changes to the tendon.

Internal tendon structure

Studies investigating *in vivo* changes in structure in response to load have been limited to imaging studies due to the difficulties in obtaining tissue. These studies can identify changes in structural integrity, but what specific proteins are involved is unknown (ie collagen fibre type and alignment, water content, proteoglycans etc). New imaging techniques that allow for semi-quantitative analysis may detect subtle changes in internal architecture in response to load. However, it needs to be noted that structural changes may occur within the tendon that is beyond the resolution of any *in vivo* imaging modalities.

Off-resonant saturation magnetic resonance imaging allows for the amount of free and bound water within tendon to be quantified[62]. Syha et al[63] reported a subtle, yet significant decrease in water content within the Achilles tendon after 6.6 km running. Interestingly, the same alteration was not observed after a 15 min rope skipping exercise, suggesting that this response may be load dependent (ie type, intensity or time of load). Conventional magnetic resonance imaging has also been used to quantify changes in tendon structure following extreme loading events. Increases in tendon dimensions and signal intensity (increase in water) were observed during a multi-stage ultramarathon covering 4487km over 64 consecutive days[64]. It is unclear whether this change was adaptive or maladaptive, however due to the extreme nature of the loading event it may be a maladaptive change driven by the accumulation of large proteoglycans, leading to increases in water content and tendon dimension.

Ultrasound tissue characterisation (UTC) has also shown a short-term change in tendon structure in response to maximal exercise. A subtle but significant change in the UTC echopattern was observed 2-days post-maximal exercise in both humans and horses that returned to baseline on day 3-4[65,66]. Based on the temporal sequence and nature of this response (ie an increase in echo-type II representing aligned yet slightly separated fibres/increased waviness), changes in proteoglycan composition and water content may have been responsible. Whether this transient change represents an adaptive or a maladaptive response is unknown and the authors simply termed this as a 'tendon response'.

Changes in the UTC echopattern have also been observed following medium-term load. An improvement in the UTC echopattern was reported in the normal pain-free Achilles tendons following a 5-month pre-season in elite Australian football players[67]. Similar findings were observed during a 4-month collegiate cross-country season, with it suggested that significant changes only occur after 3-months of chronic loading[68]. These changes may result in improved load capacity, as pre-season training involves the gradual increase in load and all athletes remained asymptomatic. However, it is unclear what specific extracellular matrix changes underlie this alteration in UTC echopattern and potential improved load capacity.

Tendon blood flow

The response of blood flow to exercise has been proposed as a tissue-based change influencing maladaptation. Using real-time contrast-enhanced ultrasound, Pingel et al[69] described an increase in the microvascular volume immediately after a 1 hr run that returned to baseline 24 hrs post-exercise. Interestingly, the changes in blood flow were not affected by the presence of pathology or pain[69]. Boesen et al[70] investigated changes in Doppler signal before and after two badminton games in the Achilles and patellar tendon. A significant increase in Doppler signal was observed at the patellar insertion of the dominant leg following loading. As the pathological/painful tendon demonstrates increased blood flow[71-73], any increase in blood flow in response to exercise has been suggested as a maladaptive response. To date, changes in blood flow in response to exercise can best be described as tissue-based temporal response as it has not been linked to the development of pathology or pain, and returns to baseline levels within days.

Tendon load capacity in tendon pathology and pain

Improving load capacity in the normal tendon is important in injury prevention and improving athletic performance, yet the clinician's primary concern is how we improve load capacity in the pathological tendon. Tendon pain is associated with abnormal tendon structure, reduced load capacity, and decreased performance[74]. The reduction in load capacity may be due to the presence of pain or compromised tendon structure, or both.

The tendons capacity to tolerate load in tendinopathy will be limited by pain. As pain results in a reduction of load, this reduction in load will negatively affect the tendon's structural and mechanical properties[75], resulting in maladaptation and a shift in the tendons 'mechanostat point' (Figure 2). Furthermore, pain and its associated disuse will negatively affect muscle strength and kinetic chain function. In simply removing pain with a medical intervention, it will not necessarily result in an immediate increase in load capacity, or a change in the 'mechanostat point', as it does not address the local tendon maladaptation. While pain needs to be considered and reduced in tendinopathy, load capacity needs to be improved through adaptation or re-injury may occur. The critical question is how does the pathological tendon adapt to increase its load capacity?

Load capacity is not related to the presence or extent of pathology. A high proportion of asymptomatic pathological tendons have been observed in various tendons and populations[76-82]. Furthermore, the presence of pathology does not appear to affect the load capacity of the individual.

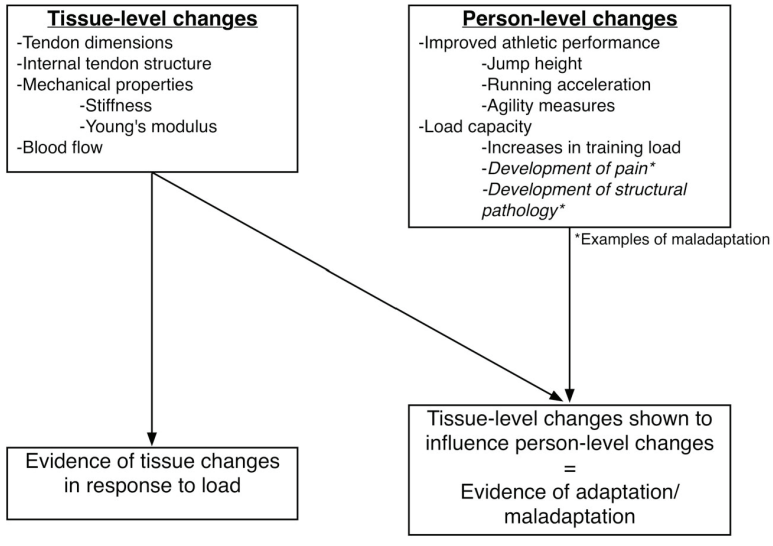

Figure 3. Defining adaptation based on contribution of tissue-level response to person-level changes.

Twenty-six percent of junior basketball players demonstrated asymptomatic patellar tendon pathology, yet no difference in training hours per week suggesting that load capacity was not altered due to structural pathology[83]. The 'jumpers knee paradox' demonstrated that those with patellar tendinopathy (pain and pathology) had no difference in countermovement jump performance compared to those with normal tendons, despite having inferior tendon structural and mechanical properties (stiffness and Young's Modulus)[84-87]. Furthermore, maximal voluntary isometric contraction was similar in those with patellar tendinopathy and activity matched controls[88].

The high prevalence of asymptomatic pathology combined with the evidence that training volume and performance are similar between normal and pathological tendons suggests that the presence or extent of structural disorganisation is not critical in determining load capacity. It suggests that the body adapts and compensates to account for tendon pathology. This adaptation/compensation may occur at more metabolic active tissues, such as the musculature and/or central nervous system[15,55]. It is unclear what changes, if any, occur at the local tendon level that may facilitate positive adaptation.

How does the pathological tendon adapt?

How the degenerative tendon increases load capacity is poorly understood, but the degenerative tendon rarely recovers normal structure. Prospective studies have shown that degenerative tendons have a limited ability to normalise[89,90]. However, improvement/normalisation of tendon structure properties (Doppler signal, anteroposterior thickness, UTC echopattern) following load-based interventions has been demonstrated[91,92]. However, these changes do not relate to clinical improvements[92,93] and improvement in tendon structure is not the sole mechanism by which the pathological tendon adapts.

The pathological tendon may have a fail-safe adaptive mechanism to maintain a level of homeostasis and compensate for areas of disorganisation. Docking and Cook[94] demonstrated that the pathological Achilles and patellar tendon contained greater levels of aligned fibrillar structure on UTC compared to structurally normal tendons. This cross-sectional study showed that the pathological tendon compensates for areas of disorganisation by increasing in dimensions to ensure a sufficient level of aligned fibrillar structure to tolerate load. While this aligned fibrillar structure is likely not to be 'normal', with subtle changes in composition while maintaining parallel collagen fibrils[95], the compensation of aligned fibrillar structure may allow the tendon to tolerate load. Adaptation and increases in load capacity may not occur within the degenerative area due to its inability to sense mechanical stimuli[96].

Areas of tendon degeneration may be non-resolving due to a loss of normal tendon architecture leading to this area being stress-deprived. With little ability to sense tensile load, the cell may be under-stimulated and not receive the necessary mechanical stimuli to remodel, explaining the limited capacity of the pathological tendon to remodel and normalise. Thornton and Hart[96] proposed that non-resolving pathology can have considerable matrix turnover without the formation of mature tissue that is associated with acute wound healing. Adaptation may occur in the surrounding aligned fibrillar structure, rather than changes within the degenerative area.

One mechanism by which the pathological tendon may adapt independent of structural changes may be through alterations in mechanical properties. However due to the

limitations stated above in measuring mechanical properties, studies that have attempted to quantify the mechanical properties of the pathological tendon have been equivocal. A reduction in tendon stiffness and increase in tendon strain in the tendinopathic tendon has been reported[84], where other studies have reported little difference in mechanical properties[97]. Further, how the mechanical stimuli affects the tendinopathic tendon is poorly understood. A decrease in patellar tendon stiffness occurred following heavy-slow resistance training[97], despite stiffness of the tendinopathic tendon being no different to control tendons. In a larger RCT, Kongsgaard et al[91] found that eccentric training and heavy slow resistance training had little effect on mechanical properties. While changes in mechanical properties are a likely candidate to explain adaptation in the pathological tendon, the current evidence is a long way from stating this as fact.

Future directions to investigate tendon adaptation

Understanding adaptation is critical in allowing the development of load-based interventions to harness mechanotransduction to build more resilient tendons and improve physical performance. To be able to do this, we need to consider the following points to further our understanding of adaptation:

1. **A robust and repeatable measure of person-level adaptation is needed, whether it measures load capacity or athletic performance**. Measures of tendon load capacity are limited to the development of pain or pathology. Reliance on pain as a measure of load capacity is complex. As the incidence of tendon pain is low, a large number of individuals would be required potentially making the study unfeasible. Measures such as jump performance, squat jump, and drop jumps may be a useful measure to determine athletic performance at the person-level.
2. **For tissue-level changes to be termed adaptation, it needs to exhibit a significant relationship to a person-level change (Figure 3).** With the lack of a person-level marker of adaptation, any observed changes should be termed a 'response to load'. An example of comparing tissue-level changes to person-level adaptation is in the hamstring literature. Following a load-based intervention, changes in muscle fascicle length and pennation angle resulted in improved strength and reduced risk of injury[98]. As tissue-level changes were shown to influence person-level changes, the term adaptation is appropriate.
3. **Measure the relative contribution of tendon properties in person-level adaptation.** Any load-based intervention will affect the tendon, muscle, kinetic chain, and nervous system. While improvement in tendon properties may contribute to person-level adaptation, it is possible that the majority of adaptation occurs within the more metabolically active neuromuscular system[15]. Similarly, maximum tendon capacity may be reached during puberty and cannot be significantly altered after skeletal maturity. Future studies need to investigate system contribution to better understand their role in adaptation, as well as the temporal nature of their contribution. Changes in the neuromuscular system may contribute greater in the short-term (days to weeks), where local tissue changes having a greater contribution in the long-term (months)[15].

Conclusion

Our understanding of tendon adaptation is incomplete. Research in the field of tendon adaptation has focused on observing changes in tissue properties and terming this adaptation, yet provided little information on what this means for the person. The lack of mechanistic evidence means that any observed change can only be termed as a "tendon response", as it is unclear whether these changes have an affect on the individual. Care needs to be taken not to overstate changes in tissue properties as relating to adaptation or maladaptation without a person-level comparator to support this. It is clear that the tendon responds to load, but how we apply these interventions to create a more robust athlete and prevent tendon injuries is unclear. Future research needs to investigate the effect of tendon-level changes on athletic performance or risk of injury.

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