No Strain, No Gain? The Role of Strain and Load Magnitude in Human Tendon Responses and Adaptation to Loading

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ABSTRACT

Transmission of force and energy storage and release are affected by the mechanical properties and morphology of tendons. Therefore, understanding the modulation of mechanical properties through training is key as part of optimising athletic task performance and rehabilitation. *In vivo* human tendon adaptation to exercise occurs in a non-graded manner, that is, there appears to be a threshold to which tendon responds and adapts to mechanical stimuli, whereas below this threshold, minimal or no adaptation is observed. However, this remains controversial as such findings have not always been universal. Modulation of strain magnitude (change in tendon length relative to its original length) or loading intensity (e.g. % one repetition maximum [1RM] or % maximal voluntary contraction [MVC]) therefore may play a fundamental role in enhancing tendon adaptation. This review outlines the key evidence of this phenomena through direct comparative studies of higher versus lower strain/ load magnitude, indirect non-comparative studies, and also explores some of the potential mechanobiological underpinnings of these adaptations. Furthermore, this review outlines practical considerations for exercise prescription using a strain magnitude-based approach, and why previous non-strain magnitude-based approaches may have been a confounding factor in load magnitude studies investigating tendon adaptation.

Key Words: extracellular matrix, mechanical, morphology, resistance training

INTRODUCTION:

Tendon forms the passive in-series link with the active muscle to form the muscle-tendon complex, which in turn is connected to bone. The primary functions of tendon are to transmit contractile forces to bone, and to store and return elastic energy following tendon stretch. Thus, monitoring and progressing tendon function should be a key variable in any larger physical performance or rehabilitation program. Tendons display time-dependant extensibility and have viscoelastic behaviour that has repercussions for muscle and joint function(21). That is viscoelastic behaviour such as force-relaxation, creep and hysteresis, due to the properties of the tendon collagen fibres and the inter-fibre matrix(22). These viscoelastic properties result in the modulation of tendon mechanical behaviour via strain rate, meaning at low strain rates tendons are more deformable and less deformable at high strain rates, ensuring more effective transmission of force to bone and return of stored energy(36).

In assessing tendon function, its mechanical properties are assessed most commonly by non-invasive, real-time imaging techniques such as Brightness-mode (B-mode) ultrasonography. Typical parameters describing the tendon mechanical properties are:(11)

1) Tendon strain, which describes the elongation/deformation of the tendon (ΔL) relative to the normal length (L0): Strain (%) = ΔL / L0 and is therefore dimensionless.

2) Tendon stress, which describes the tendon force (Ft) relative to the tendon CSA. Stress (MPa) = Ft / CSA

3) Tendon stiffness, which describes the change in tendon length (ΔL) (deformation) in relation to the force applied to the tendon (ΔFt). This parameter is dependent on the CSA and length of the tendon (greater CSA and shorter length will lead to greater stiffness). Stiffness (N/mm^2): ΔFt / ΔL.

4) Tendon modulus (or Young's modulus) describes the relationship between tendon stress and strain, representing the properties of the actual tendon material independently of the CSA. Modulus (GPa) = Stress/strain.

It is now well established that tendons are responsive and adaptive to loading (for reviews see (39),(5),(37)). Tendons rapidly adapt to prolonged exercise loading, and their extracellular environment has been shown to change along with their mechanical properties, morphology and regulatory proteins(10, 12, 13). Common changes in the mechanical properties of tendons, such as in the Achilles and patellar tendons of humans, include increases in tendon stiffness and modulus, with some studies also reporting morphological alterations such as increases in tendon CSA at various regions along its length(5, 39) following mostly moderate to longer-term durations of loading.

As recently suggested with its in-series counterpart muscle(35), the organisation and responsiveness of tendon tissue to loading suggests tendon is primarily responsive to mechanical stimuli to bring about adaptation or prevent maladaptation(36, 37). Also similar in some respects to muscle, there are many mechanical factors that can be manipulated when providing a loading stimulus to tendon that may alter the observed results of an intervention. The most common mechanical factors altered during an exercise intervention targeting human tendons are tendon strain magnitude, duration, rate and frequency(26). As mentioned above, tendon strain (or strain magnitude) is the relative increase in tendon length versus its original length and is usually depicted in a curvilinear stress/ strain relationship during *in vivo* mechanical testing. Therefore, it takes systematically higher stresses (force through tendon normalised to CSA), and/ or passive stretch through joint rotation to induce greater tendon strain magnitude. It has been noted for some time now that the mechanical properties of tendon appear to adapt in a non-graded manner i.e. improvements in tendon mechanical

properties do not display a linear relationship with increases in mechanical loading(5, 39). Rather, tendon appears to display a 'threshold' whereby only mechanical loading of a sufficient intensity or magnitude will induce notable mechanical adaptation, whereas below the threshold, minimal, no or even maladaptation occurs(3). What is not currently clear is 'how much strain is enough, or how much is too much?'

The classic, general depiction of the biomechanical stress-strain curve is that there are three distinct regions. The first (Toe) region describes the initial curvilinear portion of the stress-strain relationship of strains ~ ≤2% (range 1-4% depending on tendon in question). This flatter portion of the curve is usually attributed to the loss of the crimp pattern and the nonlinear resistance of the non-aligned collagen fibrils within the crimp pattern(37). However, a more contemporary view is that this occurs due to the slide and rotation of collagen fascicles within the interfascicular matrix of tendons(34). The exact mechanism is beyond the scope of this review, however ultimately, at lower stresses and strains, the actual tendon collagen fibrils themselves are not stretched. The second region is the linear (or elastic) region of strains ≥2%, where the parallel aligned collagen fibrils are stretched representing the 'stiffness' of the tendon. Within this region, the tendon displays elastic behaviour, in that, when the tensile load is removed the tendon returns to its original, size/ shape/ length. Strains ≥8% may result in macroscopic damage to the tissue and eventually rupture, where the tendon does not return to its original size, shape and length (i.e. plastic region)(37). The extracellular matrix (ECM) is made up almost exclusively of collagen with other non-collagenous subcomponents and few cells, predominantly fibroblasts(12). The ECM acts as a flexible network that integrates information from loading and converts it into mechanical signals, serving as a scaffold for adhesion of cells, permitting the processes of mechanotransduction(12). The stretching of the ECM components and collagen fibrils during

loading allows for the cell-to-cell communication and co-ordinated responses for intracellular signalling and upregulation of proteins that potentially promote tendon adaptation (12). This provides a potential direct link, whereby unless the magnitude of strain is high enough then the mechanical stretch of the tendon fibres/ ECM components is unlikely to occur, and therefore will not initiate the signalling pathways of mechanotransduction and adaptation.

Resistance training is a potentially effective intervention to induce mechanical load and adaptation in the muscle-tendon complex in humans. However, results from such interventions can have varying outcomes, with positive adaptation not always observed, likely due to the unfavourable combination of tendon strain magnitude, duration, rate and frequency within the training prescription. To date, only a few studies have attempted to characterise the potential modulation of tendon mechanical properties through strain/ load magnitude by directly comparing groups undertaking resistance training under distinctly different strain/ load magnitudes. In addition, whilst other studies have not performed or quantified systematic manipulation of both low and high strain training within the same study, indirect evidence of low or high strain training provide further adjunct evidence to direct comparative studies. The focus of this review is to therefore explore the literature demonstrating the impact of strain/load magnitude on the resistance training-induced adaptation on *in vivo* mechanical properties of healthy human Achilles/ patellar tendons, and also some of the potential strain magnitude-dependent physiological responses underpinning these observations. Computerized electronic databases PubMed/ MEDLINE, SPORTDiscus, and Google Scholar were searched from March to June 2021 using the following key words; tendon, human, patella, Achilles, mechanical properties, material properties, strain, stiffness, stress, Young's Modulus, resistance training, strength, cross-sectional area, adaptation, ultrasound, MRI.

High Vs. Low Comparison Studies and effects on Tendon Mechanical Properties and Morphology

Arampatzis et al.(1) systematically altered the cyclical strain magnitude on the Achilles Tendon into high versus low strain conditions, whilst controlling for strain frequency and volume. In a within-subjects design, 11 participants (8 females, 3 males) took part in 14 weeks of isometric plantar flexor training, performing 5 sets of either 4 (high strain group) or 7 (low strain group) repetitions, 4 times per week. The disparity in repetition number was to control and equate for the total volume of exercise between the two legs (integral of the plantar flexor moment over time). Each participant's legs were randomly assigned to a high strain (4.55±1.38%) or low strain (2.85±0.99%) condition, which were analogous to approximately 90% and 55% MVIC respectively, whilst a control group performed no exercise. Following resistance training, both exercise groups showed a significant increase in tendon force and moment, indicating an improvement in muscle strength. However, in the high strain group only, there was a significant increase in the GM tendon-aponeurosis stiffness (~36%) and significant decreases in tendon-aponeurosis strain per 100N force ≥600N. Additionally there were significant increases in the modulus, plantar flexion moment: strain ratio at ≥1200N, and region specific increases in Achilles CSA (60% and 70% of Achilles length) in the high strain group only. Furthermore, which is of interest, was that in the low strain group only, tendon elongation and strain actually increased following resistance training. This is the result of the training intervention stimulating gains in strength in the low strain group (increased force and MVC) and lack of concurrent adaptation at the tendon level, where the muscle is then able to stretch the tendon to greater strains. In a subsequent study, Arampatzis et al.(4) in a within-subject design (*n*=11), again compared a high tendon strain condition (4.72±1.08%) to low tendon strain condition (2.97 ±0.47%) following 14 weeks of plantar flexor resistance training. However, in contrast to the previous

study, the authors employed a higher tendon strain frequency (0.5Hz, 1secs on, 1 secs relaxation vs. 0.17Hz, 3secs on, 3secs relaxation previously). Again, strain magnitudes corresponded to ~55%MVC in low strain group and 90%MVC in high strain group, with the authors not only matching training volume (integral of the plantar flexor moment over time) between groups in this study, but also to the previous study(1) to allow direct comparisons. The results mirrored the previous study, whereby tendon elongation and strain increased in the low strain group, yet there were significant increases in GM tendon-aponeurosis stiffness (17%) and modulus, and significant reductions in tendon-aponeurosis strain per 100N force ≥600N in the high strain group only.

In another within-subjects study design by Kongsgaard et al.(15), the authors randomly allocated one leg to a 'heavy-resistance' and the other leg to a 'light-resistance' condition for 12 weeks, in 12 healthy untrained males. Participants in the 'heavy' condition completed 10 sets of 8 repetitions at 70% 1RM with 3mins recovery between sets, targeting knee extension. The 'light' condition completed 10 sets of 36 repetitions with 30secs of rest between sets, in order to match overall work performed by the heavy leg, however the authors did not quantify this relative to % 1RM. Due to the amount of repetitions performed with limited inter-set recovery, the current author believes it is reasonable to assume that the intensity of the light condition exercise was likely to have been in the 20-40%1RM range. Along with significantly greater increases in quadriceps CSA, 1RM and MVC in the heavy vs light condition, there was also a significant increase in patellar tendon stiffness in the heavy condition only. Furthermore, patellar tendon CSA was significantly larger at the proximal site post-training compared to baseline in the light condition, whereas tendon CSA was significantly greater at both proximal and distal sites post-training compared to baseline in the heavy condition.

Grosset et al.(9) investigated the effects of 12 weeks RT at either 40% (*n*=9) or 80% (*n*=8) 1RM on the mechanical and material properties, CSA and dimensions of the patellar tendon in older (>65 years old) individuals. The participants trained three times per week, progressing from 8-11 reps and 2-4 sets at the designated exercise intensity (i.e. 40% or 80% 1RM). The results demonstrated that there were significant increases in maximal tendon stiffness at 100% MVC (57.7±15.7%), mean stiffness over 10-100%MVC, modulus at 100%MVC (57.9±17.8%) and modulus at every force level (10-100%MVC) in the high intensity training group compared to both baseline and the low intensity training group. The authors however, reported no effects of the training on tendon CSA in either training group.

Taken together, these intervention studies suggest that tendon strain magnitude during resistance training, matched for total work or not, may play a pivotal role in enhancing the mechanical properties of tendon at the whole tendon level, and to a lesser extent, can also alter regional tendon morphology.

Cross-sectional studies without direct High vs. Low comparison

This section will look at the evidence of studies where there is no direct comparison of a high and low strain/ load condition, but rather data from either condition, or observations from groups undergoing distinctly different loading regimes (but not quantified).

Kubo et al.(16) investigated the effects 6 months of low load resistance training (*n*=11, body weight squats, 5× per week, 44±17 repetitions per day) vs. a non-training control group (*n*=7) on the mechanical properties of the patella tendon-aponeurosis in middle-aged and older females. There were no changes maximal tendon length, stiffness or hysteresis yet maximal strain actually increased following training, with no changes in controls. These results are consistent with the findings of Grant et al.(8) who found that 8 weeks of low intensity

physical activity in older females (*n*=26, 73±5 years) resulted in a lack of adaptation of the Achilles tendon. McMahon et al.(24) investigated patella tendon mechanical properties in response to 8 weeks to high load (80% 1RM) resistance training with the muscle-tendon complex in a shortened or lengthened position (both *n*=10). A third training group performed training at 55% 1RM in the lengthened position (*n*=11), matched for forces through the tendon as the 80% 1RM shortened position. This is because of the length of the patellar moment arm is altered via knee joint angle (i.e. muscle-tendon complex length). However, the strain of the tendon was higher in the 55% 1RM group compared to the 80% shortened group because of the additional passive strain via joint angle. The results showed that performing resistance training with increased strain via increased forces (80% 1RM lengthened position), or combination of active/ passive strain on the tendon (55% 1RM lengthened position), increased patella tendon stiffness and modulus to a greater extent, even when stress was normalised between the shorter and longer muscle-tendon complex conditions. Therefore, even when all training conditions were sufficient to induce mechanical adaptations at both muscle-tendon complex lengths, the two training groups experiencing the highest overall strain found greater adaptation. These data are partially supported by Kubo et al.(18) who also had 9 male participants isometrically train the knee extensor muscle-tendon complex for 9 weeks, with one leg training in a shortened position (50^{o} knee flexion) versus the other leg in a lengthened position (100^{o} knee flexion) at 70% 1RM. Again, the lengthened training leg significantly increased tendon stiffness post-training, whereas the shortened training leg did not. Critically internal muscle forces were 2.3 times higher through the tendon in the lengthened position due to the patella tendon moment arm despite training at the same relative intensity. Unfortunately the authors did not report tendon strain in the training positions, however these findings, along with those of McMahon et al.(24), suggest an additional layer of complexity into tendon training prescription, whereby joint angle, and

the associated change in passive strain and internal force production should be considered within a training prescription framework.

More recently in an older population (62-67 year olds), Eriksen and colleagues(7) compared a high (*n*=10, 70-85% 1RM) vs. moderate (various manipulations of body weight or TheraBands, *n*=13) load groups following 12 months of RT. Even though both moderate and high load groups were able to significantly enhance patella tendon mechanical properties, common force tendon stiffness and modulus were significantly higher in the high vs. moderate training group. Finally, Arampatzis et al.(2) investigated whether the mechanical properties (i.e. force strain relationship) of the triceps surae tendon and aponeurosis relate to the performed sport activity in an intensity-dependent manner, comparing 28 sprinters and 28 endurance runners with 10 non-sport controls. Body mass, maximal tendon length and maximal strain was not different between the groups, however strain levels up to 400N were significantly lower, normalised tendon-aponeurosis stiffness and maximal plantar flexor moment were significantly higher in sprinters than both endurance runners and controls. There were no differences between endurance runners and control in any of these parameters. The authors concluded that this reaffirms a non-graded adaptation of mechanical properties to exercise loading by tendon and that the finding of a significant relationship between maximal tendon force and stiffness demonstrates the importance of the sprinters' strength (therefore increasing stress and strain during training) for inducing mechanical adaptation.

The observations outlined in this section provide further context to the direct comparative interventions whereby distinctly different training intensities give rise to specific mechanical properties, reaffirming strain/ load magnitude's potentially fundamental role in their development.

Effects of strain/ load magnitude on the acute responses of tendon structural and regulatory components

Loading of tendon *in vivo* induces a number of physiological responses via transmission of external tendon forces through the ECM to mechano-sensitive cells and ultimately changes in anabolic/ catabolic gene expression within the tendon(19, 36). Evidence from different areas of tendon regulation and function suggest there is a strain-magnitude dependent response of these cells which may underpin the observations from intervention studies.

Transforming Growth Factor Beta -1 (TGFβ-1) is a polypeptide member of the TGFβ superfamily of cytokines that performs many cellular functions. In tendon, TGFβ-1 plays an important role in tendon repair and adaptation through stimulating ECM protein production including a central role in Type I collagen, the main structural component of tendon(25, 40). Yang et al.(40) stretched tendon fibroblasts under different strain conditions; 0% (control), 4% and 8% strain. Significant increases in fibroblast proliferation were only observed in the 8% condition, with Collagen Type I, Collagen Type I mRNA and TGFβ-1 expression all increased in a strain-magnitude dependent manner (8% > 4% > 0% respectively). Collagen is encoded by the Col1A1 and Col1A2 genes. Wang et al.(38) showed using a bioreactor system, that a strain magnitude of 6% enhanced Col1A1 expression to a greater extent than 3% strain in harvested rabbit Achilles tendons. Wang et al.(38) also demonstrated that Type III Collagen mRNA was increased in the 3% strain condition whereas Type III Collagen showed similar levels as native tendon in the 6% strain condition. Furthermore, histological scoring of the 6% strain condition was similar to the native tendon, whereas the 3% strain condition showed evidence of a disrupted ECM and significant changes in cellular morphology.

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases that digest collagen and other structural proteins. Whilst necessary for basal ECM homeostasis, MMP activity can become dysregulated. MMP-1 activity results in the degradation of Type I and Type III collagen, and has been implicated in models of injury and pathology in tendon(29). Several investigations have shown that MMP-I expression can be modulated in a strain-magnitude manner with higher strains of 6% abolishing MMP-1 expression completely(20) *in vitro* and lower strains of 3% inducing higher levels of MMP-1(38). In addition, tendon strain of 3% has also been demonstrated to increase the expression of MMP-3 and MMP-12 which also may be involved in degradation of tendon collagen(38).

There is also evidence to suggest however there may be an upper limit to the positive effects of increased strain magnitude, which if surpassed may induce maladaptive signalling within the tendon. Wang et al.(38) demonstrated that when rabbit Achilles tendons were loaded under 9% mechanical strain in a bioreactor system, they displayed distorted structural arrangement, increased cell apoptosis rate and higher Type III Collagen turnover and gene expression. It should be noted that the percentage of strains used in *in vitro* work on fibroblasts do not scale up to match the strains of mechanically tested whole tendon (e.g. 6% strain at macroscopic [whole tendon] level does not mean a 6% strain at microscopic [fibroblast] level and vice versa). Therefore, one must exercise caution in interpreting, comparing and extrapolating the strain values investigated at different tendon structural hierarchies.

PRACTICAL APPLICATIONS

The evidence from the above sections has led to the proposition that there is an ‘optimal’ or ‘sweet spot’ range of strain magnitudes in order to induce positive mechanical property and

morphological changes to tendon(3, 26, 38). Authors have suggested that strain magnitudes of ~4.5-6.5% may be the most appropriate for inducing such adaptations in tendons such as the Achilles and patellar(3). Whilst the author agrees there is likely a more optimal range of strains to train within, particular caution must be exercised when evaluating the upper range of strains. For example, although the study of Wang et al.(38) and other studies provide very interesting data in terms of a potential catabolic zone at higher strains as outlined above, these observations have never been verified in an acute study *in vivo* in humans. Whilst the author does not contend that the proposed zones are a reasonable estimate, it is plausible that more work is necessary before using such animal model data as a potential yardstick for human training intervention prescription. For example, data from the author's previous lab and from other labs demonstrate that it is not uncommon to find maximal strains of 9-12% in the patellar tendon during a ramped isometric maximal voluntary contraction in young adults(3). Data within our lab has shown that prescribing adults with 9-12% maximal patellar tendon strains high-load resistance training such as 80% 1RM, which resulted in tendon strains during training of >6.5%, did not result in negative mechanical adaptation but rather the participants increased tendon stiffness and modulus. Although as Arampatzis et al.(3) highlight, the strain magnitudes suggested (4.5-6.5%) are not intended to represent discrete cut-off thresholds more of transitional zones between lower and higher strain. Furthermore, the recommended strain values of 4.5-6.5% appear to be based specifically on the Achilles tendon. If higher maximal strains are possible in the patellar tendon this may also shift the lower threshold of effective strain to higher strains than in the Achilles.

One of the main practical considerations in designing a resistance training intervention aimed at improving tendon mechanical properties or morphology based off strain-magnitude is the de-coupled relationship within some individuals between training intensity (defined as a % of task 1RM) and strain magnitude. For a more detailed review on this please refer to

Arampatzis et al.(3). When prescribing resistance training, one cannot assume on an individual basis that performing training at a certain percentage of one repetition maximum (%1RM) that they will necessarily induce sufficient tendon strain per se. This is a result of a mis-match between the relative strength of the individual versus the existing mechanical properties of their tendons. For example, in an individual who is relatively weak in terms of muscle strength but has a relatively stiff tendon, the maximal strain of the tendon may be fairly low such as (4-5%). Therefore, prescribing exercise at 70% of 1RM or MVIC for example may be ineffective for this individual, because this intensity may not induce sufficient strain (<4%) to induce adaptation to mechanical properties. Conversely, one may be able to strain the tendon to a higher magnitude (>9%) if the individual has good muscle strength but a more compliant tendon, which may facilitate adaptations at slightly lower intensities such as <70% MVIC (See Figure 1). A recent study from Quinlan et al.(28) showed that following 8 weeks of RT using either isolated concentric or eccentric contractions at 60% 1RM in younger and older males, patellar tendon Young's Modulus significantly improved. This is below the ≥70% 1RM commonly reported that is needed to improve the mechanical properties of tendons(5) and reinforces the need to individualise the assessment of a person's tendon stress-strain relationship if one is to adequate target mechanical adaptation, to ensure sufficient strain is induced(3, 26). Although higher magnitude of loading studies using percentage 1RM as the prescriptive method have proved successful, this calls into the question the certainty with which one could prescribe tendon training via a percentage of 1RM or MVIC when using more moderately high loads (i.e. ~60-80% 1RM). It also confounds our ability to critically appraise studies that use %1RM as a descriptor basis for their intervention. For example, without knowing the strain on the tendon, we cannot with any certainty describe the load as being low (<50% 1RM), moderate (50-65% 1RM) or high (≥ 70% 1RM), which in the author's opinion has led to much ambiguity with

practitioners trying to use an evidence-based approach. Therefore, the training descriptor must be relative to the tissue of interest, that is, percentage 1RM or MVIC should be used for muscle strength, and percentage strain for tendon. For more detailed potential frameworks of implementing individualised tendon assessment for training prescription please see Arampatzis et al.(3) and Pizzolato et al.(27).

There is no doubt that it is likely to be most beneficial for athletic performance to have co-ordinated adaptation and balanced muscle-tendon interaction (i.e. a strong muscle with a stiff tendon), with research showing the strong relationship between higher muscle strength and tendon stiffness in athletes(2). Recently Arampatzis et al.(3) suggested that if an individual has weaker muscle strength and a relatively stiff tendon (i.e. low maximal strain in an MVIC) that they may wish to include low intensity training (possibly to failure) that could conceivably increase muscle strength without further increases in tendon mechanical properties. Whilst this seems a fair and sensible approach, the author would also suggest an alternative approach. Whilst light intensity training can be effective in producing strength gains, a recent systematic review and meta-analysis suggests that heavy strength training is even more beneficial for strength gains(30). Adaptations in *in vivo* mechanical properties of tendons may plateau after a relatively short period of time (e.g.4-8 weeks(28, 39)) whereas muscle strength can continually be developed over longer periods of time (e.g. 3-12 months). Therefore depending on the overall aims and objectives of the resistance training program, performance needs and length of training blocks, it may not be necessary to include light intensity resistance training to try and specifically address a muscle strength-to-tendon stiffness deficit, as heavy strength training may close this gap over time naturally to provide a more balanced muscle-tendon interaction.

Is there evidence for adaptation without sufficient strain magnitude?

As this review has demonstrated, strain magnitude appears to play a fundamental role in the enhancement of the *in vivo* mechanical properties in healthy human tendons. In practical terms, this means that achieving strain of sufficient magnitude is the most likely means to elicit desired tendon adaptation and thus it should be the focus when prescribing interventions. Explanatory models of tendon adaptation which deviate from assigning strain-magnitude a causal role will require a significant body of evidence to establish both their need and plausibility. For instance, it has recently been suggested that blood flow restriction could significantly reduce the minimum strain threshold needed to see adaptation. Centner et al.(6) trained the plantarflexor muscle-tendon complex for 14 weeks in young males using either a high load group (70-85% 1RM, *n*=14), low-load with blood flow restriction (20-35% 1RM, *n*=11) or a control group. The authors reported a significant increase in post-training Achilles tendon-aponeurosis CSA, Achilles stiffness, muscle CSA and strength in both high load and low-load BFR groups with no differences between groups. This contrasts to the findings of Kubo et al.(17) also in young males (*n*=9) using a within-subjects design, 12-week unilateral resistance training program of the knee extensor muscle-tendon complex. The authors found that the stiffness of the muscle-tendon aponeurosis was significantly higher in the high load (80% 1RM) vs low-load (20% 1RM) BFR group, despite significant increases in muscle size and strength with no differences between groups. There are many methodological differences and limitations between these studies which preclude any real direct comparison of the main opposing outcome, i.e. BFR training's ability to enhance the mechanical properties and morphology of tendon. A major limitation of both studies is that neither employed a non-BFR low-load training group or a high-load BFR training group, meaning isolating the precise effect of BFR was not possible with either experimental design. Centner et al.(6) estimated tendon stiffness at 50-80% MVC, whereas tendon stiffness

calculations should include upper regions of the force-elongation curve(31), such as those included by Kubo et al.(17) (50-100% MVC). Each of the studies measured tendon CSA using ultrasound, whose questionable lack of sensitivity limits its ability to detect changes in CSA, which also creates significant uncertainty around the stiffness calculations derived from these measures. The aforementioned studies on BFR also present with the same limitations as other studies that prescribe training using a relative muscle strength descriptor (%1RM or MVIC). An individual who has sufficient muscle strength or sufficiently compliant tendon to reach higher maximal strains (≥9%) at MVIC and is assigned to BFR training at 30-40% 1RM, may find that tendon strain is sufficient to induce some detectable adaptation. In this instance, the observed adaptation would again be due to sufficient strain magnitude and independent of the effects of restricting blood flow. Therefore, future BFR studies must prescribe training based off higher and lower strain magnitudes to truly isolate the effects on tendon.

Reviews of tendinous adaptation to loading(5, 12-14, 23, 39), the mechanobiology of tendon(36, 37) and tendon remodelling(32) all place mechanical signals as the pivotal consideration in tendon adaptation, without any hypoxic or metabolic (or downstream effect of either) mechanism considered a major potential modulator of mechanical adaptation. Furthermore, tendons are poorly vascularised tissues(33) so it would appear counter-intuitive that a major mechanical adaptive mechanism would be induced via manipulation of blood flow. As such, a small study that fails to reject the null hypothesis based on NHST provides more of an interesting anomaly than support for any particular hypothesis that might be proposed as an alternative explanation to strain magnitude-based tendon adaptation. Whilst this does not preclude the potential for BFR training, nor limit its potential mechanism to either metabolism or hypoxia-mediated per se, based on current knowledge, the evidence is

much too limited for BFR to be recommended as an established, reliable and effective strategy in improving tendon mechanical properties at this time.

Future Investigations:

Further direct comparative strain-magnitude based *in vivo* intervention studies are needed in humans to progress our understanding of strain's role in adaptation. Further research should focus on the range of strains which permit the tendon to move from non-responsive to responsive e.g. between 3-6% strain and also upper strain ranges (>8%) to identify where tendon moves from adaptive to non-adaptive. Importantly, this research needs to be conducted in females, clinical (including tendon pathological states such as tendinopathy) and older populations, and in a range of contexts as the overwhelming data is from young, healthy males. Performance measures should be included alongside tendon mechanical properties and morphology to extend our knowledge on the impact of mechanical/ material property changes on task performance. In addition, acute *in vivo* human studies are also needed to investigate the response to exercising under different strain magnitudes and identify the mechanisms by which strain may modulate tendon adaptation. Future BFR studies in tendon should also avail of these considerations in experimental design.

Perspectives:

Promising evidence thus far suggests higher tendon strains during resistance training appear to provide the most appropriate stimulus for inducing improvements in the *in vivo* mechanical properties of healthy tendons in humans. The potential positive adaptation from higher strains may be due to an enhanced anabolic response relative to any catabolic response of mechano-sensitive regulatory and structural proteins within the extracellular matrix. Effective

resistance training prescription may require personalised tendon assessment to ensure sufficient strain to induce adaptations, with percentage 1RM or MVIC being a less reliable test to base prescription off. There are various options open to practitioners in order to address potential imbalances between muscle strength and stiffness identified during the assessment of maximal muscle strain based off the individual's training program priority outcomes.

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REFERENCES:

1. Arampatzis A, Karamanidis K, and Albracht K. Adaptational responses of the human Achilles tendon by modulation of the applied cyclic strain magnitude. *Journal of Experimental Biology* 210: 2743-2753, 2007.
2. Arampatzis A, Karamanidis K, Morey-Klapsing G, De Monte G, and Stafilidis S. Mechanical properties of the triceps surae tendon and aponeurosis in relation to intensity of sport activity. *Journal of biomechanics* 40: 1946-1952, 2007.
3. Arampatzis A, Mersmann F, and Bohm S. Individualized muscle-tendon assessment and training. *Frontiers in Physiology* 11, 2020.
4. Arampatzis A, Peper A, Bierbaum S, and Albracht K. Plasticity of human Achilles tendon mechanical and morphological properties in response to cyclic strain. *Journal of biomechanics* 43: 3073-3079, 2010.

5. Bohm S, Mersmann F, and Arampatzis A. Human tendon adaptation in response to mechanical loading: a systematic review and meta-analysis of exercise intervention studies on healthy adults. *Sports medicine-open* 1: 7, 2015.

6. Centner C, Lauber B, Seynnes OR, Jerger S, Sohnius T, Gollhofer A, and König D. Low-load blood flow restriction training induces similar morphological and mechanical Achilles tendon adaptations compared with high-load resistance training. *Journal of applied physiology* 127: 1660-1667, 2019.

7. Eriksen CS, Svensson RB, Gylling AT, Couppé C, Magnusson SP, and Kjaer M. Load magnitude affects patellar tendon mechanical properties but not collagen or collagen cross-linking after long-term strength training in older adults. *BMC geriatrics* 19: 1-15, 2019.

8. Grant D, Tomlinson D, Tsintzas K, Kolić P, and Onambélé-Pearson G. Minimizing sedentary behavior (without increasing medium-to-vigorous exercise) associated functional improvement in older women is somewhat dependent on a measurable increase in muscle size. *Aging (Albany NY)* 12: 24081, 2020.

9. Grosset J-F, Breen L, Stewart CE, Burgess KE, and Onambélé GL. Influence of exercise intensity on training-induced tendon mechanical properties changes in older individuals. *Age* 36: 1433-1442, 2014.

10. Hansen P, Aagaard P, Kjaer M, Larsson B, and Magnusson SP. Effect of habitual running on human Achilles tendon load-deformation properties and cross-sectional area. *Journal of Applied Physiology* 95: 2375, 2003.

11. Heinemeier K and Kjaer M. In vivo investigation of tendon responses to mechanical loading. *J Musculoskelet Neuronal Interact* 11: 115-123, 2011.

12. Kjaer M. Role of extracellular matrix in adaptation of tendon and skeletal muscle to mechanical loading. *Physiological Reviews* 84: 649-698, 2004.

13. Kjaer M, Langberg H, Heinemeier K, Bayer M, Hansen M, Holm L, Doessing S, Kongsgaard M, Krogsgaard M, and Magnusson S. From mechanical loading to collagen synthesis, structural changes and function in human tendon. *Scandinavian Journal of Medicine & Science in Sports* 19: 500-510, 2009.

14. Kjaer M and Magnusson S. Mechanical adaptation and tissue remodeling, in: *Collagen*. Springer, 2008, pp 249-267.

15. Kongsgaard M, Reitelseder S, Pedersen TG, Holm L, Aagaard P, Kjær M, and Magnusson S. Region specific patellar tendon hypertrophy in humans following resistance training. *Acta physiologica* 191: 111-121, 2007.

16. Kubo K, Kanehisa H, Miyatani M, Tachi M, and Fukunaga T. Effect of low-load resistance training on the tendon properties in middle-aged and elderly women. *Acta Physiologica Scandinavica* 178: 25-32, 2003.

17. Kubo K, Komuro T, Ishiguro N, Tsunoda N, Sato Y, Ishii N, Kanehisa H, and Fukunaga T. Effects of low-load resistance training with vascular occlusion on the mechanical properties of muscle and tendon. *Journal of applied biomechanics* 22: 112-119, 2006.

18. Kubo K, Ohgo K, Takeishi R, Yoshinaga K, Tsunoda N, Kanehisa H, and Fukunaga T. Effects of isometric training at different knee angles on the muscle–tendon complex in vivo. *Scandinavian Journal of Medicine & Science in Sports* 16: 159-167, 2006.

19. Lavagnino M and Arnoczky SP. In vitro alterations in cytoskeletal tensional homeostasis control gene expression in tendon cells. *Journal of Orthopaedic Research* 23: 1211-1218, 2005.

20. Lavagnino M, Arnoczky SP, Tian T, and Vaupel Z. Effect of amplitude and frequency of cyclic tensile strain on the inhibition of MMP-1 mRNA expression in tendon cells: an in vitro study. *Connective tissue research* 44: 181-187, 2003.

21. Maganaris CN, Narici MV, Almekinders LC, and Maffulli N. Biomechanics and pathophysiology of overuse tendon injuries. *Sports Medicine* 34: 1005-1017, 2004.

22. Maganaris CN, Narici MV, and Maffulli N. Biomechanics of the Achilles tendon. *Disability and rehabilitation* 30: 1542-1547, 2008.

23. Magnusson SP, Narici MV, Maganaris CN, and Kjaer M. Human tendon behaviour and adaptation, in vivo. *The Journal of Physiology* 586: 71-81, 2008.

24. McMahon GE, Morse CI, Burden A, Winwood K, and Onambélé-Pearson GL. The manipulation of strain, when stress is controlled, modulates in vivo tendon mechanical properties but not systemic TGF-β1 levels. *Physiological Reports* 1, 2013.

25. Müller SA, Todorov A, Heisterbach PE, Martin I, and Majewski M. Tendon healing: an overview of physiology, biology, and pathology of tendon healing and systematic review of state of the art in tendon bioengineering. *Knee Surgery, Sports Traumatology, Arthroscopy* 23: 2097-2105, 2015.

26. Pizzolato C, Lloyd DG, Zheng MH, Besier TF, Shim VB, Obst SJ, Newsham-West R, Saxby DJ, and Barrett RS. Finding the sweet spot via personalised Achilles tendon training: the future is within reach. BMJ Publishing Group Ltd and British Association of Sport and Exercise Medicine, 2019.

27. Pizzolato C, Shim VB, Lloyd DG, Devaprakash D, Obst SJ, Newsham-West R, Graham DF, Besier TF, Zheng MH, and Barrett RS. Targeted achilles tendon training and rehabilitation using personalized and real-time multiscale models of the neuromusculoskeletal system. *Frontiers in Bioengineering and Biotechnology* 8: 878, 2020.

28. Quinlan JI, Franchi MV, Gharahdaghi N, Badiali F, Francis S, Hale A, Phillips BE, Szewczyk N, Greenhaff PL, and Smith K. Muscle and tendon adaptations to moderate load eccentric vs. concentric resistance exercise in young and older males. *GeroScience*: 1-18, 2021.

29. Riley GP, Curry V, DeGroot J, van El B, Verzijl N, Hazleman BL, and Bank RA. Matrix metalloproteinase activities and their relationship with collagen remodelling in tendon pathology. *Matrix biology* 21: 185-195, 2002.

30. Schoenfeld BJ, Grgic J, Ogborn D, and Krieger JW. Strength and hypertrophy adaptations between low-vs. high-load resistance training: a systematic review and meta-analysis. *The Journal of Strength & Conditioning Research* 31: 3508-3523, 2017.

31. Seynnes OR, Bojsen-Møller J, Albracht K, Arndt A, Cronin NJ, Finni T, and Magnusson SP. Ultrasound-based testing of tendon mechanical properties: a critical evaluation. *Journal of applied physiology* 118: 133-141, 2015.

32. Sharma P and Maffulli N. Biology of tendon injury: healing, modeling and remodeling. *Journal of musculoskeletal and neuronal interactions* 6: 181, 2006.

33. Tempfer H and Traweger A. Tendon vasculature in health and disease. *Frontiers in Physiology* 6: 330, 2015.

34. Thorpe CT, Godinho MS, Riley GP, Birch HL, Clegg PD, and Screen HR. The interfascicular matrix enables fascicle sliding and recovery in tendon, and behaves more elastically in energy storing tendons. *journal of the mechanical behavior of biomedical materials* 52: 85-94, 2015.

35. Wackerhage H, Schoenfeld BJ, Hamilton DL, Lehti M, and Hulmi JJJJoAP. Stimuli and sensors that initiate skeletal muscle hypertrophy following resistance exercise. 2018.

36. Wang JH, Guo Q, and Li B. Tendon biomechanics and mechanobiology—a minireview of basic concepts and recent advancements. *Journal of hand therapy* 25: 133-141, 2012.

37. Wang JHC. Mechanobiology of tendon. *Journal of biomechanics* 39: 1563-1582, 2006.

38. Wang T, Lin Z, Day RE, Gardiner B, Landao-Bassonga E, Rubenson J, Kirk TB, Smith DW, Lloyd DG, and Hardisty G. Programmable mechanical stimulation influences tendon homeostasis in a bioreactor system. *Biotechnology and bioengineering* 110: 1495-1507, 2013.

39. Wiesinger H-P, Kösters A, Müller E, and Seynnes OR. Effects of increased loading on in vivo tendon properties: a systematic review. *Medicine and science in sports and exercise* 47: 1885, 2015.

40. Yang G, Crawford RC, and Wang JHC. Proliferation and collagen production of human patellar tendon fibroblasts in response to cyclic uniaxial stretching in serum-free conditions. *Journal of biomechanics* 37: 1543-1550, 2004.

FIGURE CAPTION:

Fig.1 Theoretical relationship between macroscopic tendon strain and likelihood of tendon adaptation. *Note:* There are likely a range of 'optimal' strains that may induce adaptation as opposed to a single point estimate. Also, either side of this 'optimal' strain range adaptation is not completely abolished, some may occur but is reduced. Dash-dot line depicts potential zone of further adaptive strains that is not well characterised in humans. *Top left*: Example of how training prescription at the same relative intensity (70%) using percentage of maximal voluntary contraction (% MVC) or percentage one repetition maximum (% 1RM) without

consideration of the existing mechanical properties of the tendon, may lead to training at insufficient strains to induce adaptation. Top example depicts an individual who has higher muscular strength and/ or a more compliant tendon resulting higher maximum strain (9%). Bottom example depicts an individual with poor muscular strength and/ or stiffer tendon with lower maximal strain (5%).