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Chapter

Exercise and Tendon Remodeling Mechanism

Rita de Cassia Marqueti, Ivo Vieira de Sousa Neto, Fabricio Reichert Barin and Gracielle Vieira Ramos

Abstract

Tendons connect muscles to bones and transmit the force exerted by the corresponding muscle to the skeleton and, therefore, are key components for locomotion. They are responsive to mechanical factors, which are essential for cellular functioning, tendon development, homeostasis, and repairing. Mechanical signals are transduced via molecular signaling pathways which trigger tendon adaptive responses. Previous data have already shown that exercise training promotes physiological adaptive responses, such as morphological properties and biomechanical and biochemical adaptations.

Keywords: tendon, exercise, extracellular matrix, mechanical loading

1. Tendon macro- and microscopic overview

Anatomically, tendons are located in muscle origin/insertion and, further, in tendon intersections within the muscles. These complexly arranged tissues have great importance in movement generation, having as main actions the transfer of tension produced by the muscles to the subsequent unit, thus determining the degree of articular movement produced [1, 2]. Moreover, tendons act as a mechanism of energy storage, improving movement economy and power amplification for activities as jumping and acceleration, based on their spring-like properties [1, 3]. More recently, studies have shown that a stretch applied to an active muscle-tendon unit (MTU) can be taken up solely by tendon stretch, with little or no muscle fascicle lengthening, acting like a mechanical buffer to protect muscle fascicles, attenuation damage associated with active lengthening [4]. In addition, the energy absorbed by the tendons during movement can be used to maximize the power generated, as it can also be dissipated as heat, increasing energy release time to the muscles, thus decreasing the peak force experienced by the MTU [3–5]. All these functional aspects can promote more efficient movements, consuming less energy and preventing muscle damage [1, 4, 5] (**Figure 1**).

The tendinous actions require an unrestricted slip by the adjacent tissue. For this reason, synovial sheaths form a closed system around many tendons to provide lubrication and to cushion the tendon during its action. Some tendons that do not have this system find in their periphery a loose peritendinous adipose and vascularized layer, which allows the free excursion of the tendon [6]. When healthy, they present white color, due to the presence of hypovascularized zones and fibroelastic texture, characterizing this tissue resistance to mechanical stresses [7]. In relation to

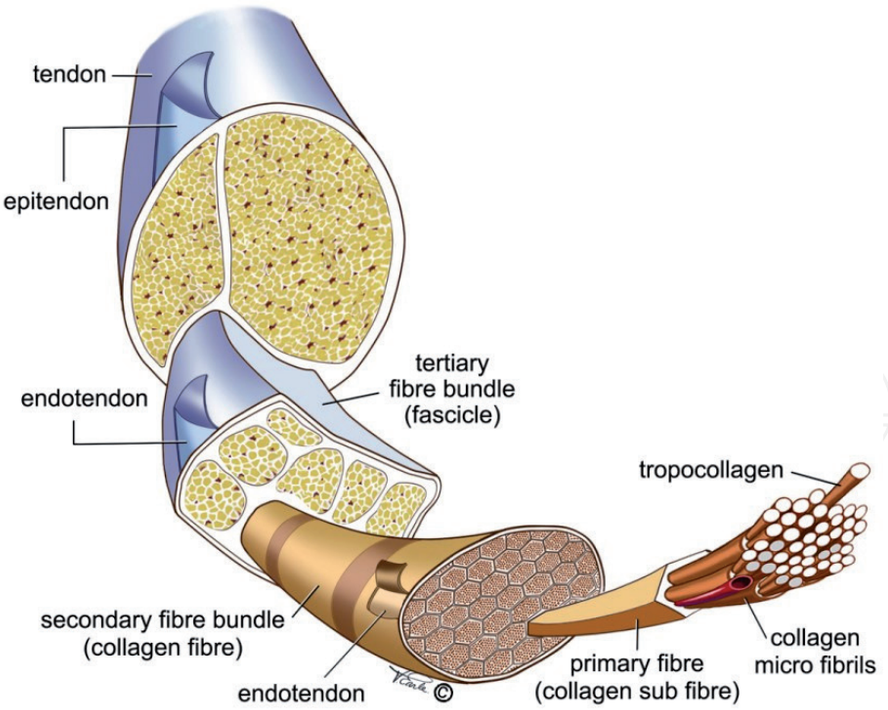

Figure 1.
Tendon hierarchical structure (adapted from Kannus, [8]).

its composition, because it is a connective tissue, the division happens between cells and the extracellular matrix (ECM) [7]. The ECM tendon is formed by approximately 70% of water, with great part associated with proteoglycans, glycosaminoglycans (GAGs), adhesion glycoproteins, non-collagenous proteins, and fibrous proteins (collagen and elastin) [1]. The water and GAG presence in the tendons is extremely important for maintaining the spacing among the collagen fibers, facilitating their slippage [9]. The highly organized collagen bundles represent 60–95% of the dry weight of the tendon, from which 90% are type I collagen and the remainder part is divided into types III (0–10%), IV (2%), V, and VI, respectively [2, 9].

The collagen formation occurs through the three spiral and helical peptide chains. Structural formation occurs intracellularly, with subsequent secretion into the ECM, where it is converted into collagen. The fibrillar structure is stabilized by various post-translational modifications, allowing the formation of intermolecular and interfibrillar cross-links. These cross-links' large amount makes this structure highly resistant to stresses, shear forces, and even compression [10]. There are two main types of cross-links—enzymatic cross-links, confined in the terminal domains, and advanced glycation end-products (AGEs)—which may be formed at various sites along the collagen length [11]. It has been shown that enzymatic cross-links are essential in the formation and functioning of collagen fibrils, stabilizing the structure, while AGEs accumulate with age and diabetes and may impair the normal function of fibrils, leading to decreased viscoelasticity of the tendon [12, 13].

Since tendons are attached to two totally distinctive structures in morphological and functional terms (muscles and bones), two types of tendon junctions are found and differ in relation to the number of cross-links. The myotendinous junction (MJT) is more compliant, thus having smaller amount of cross-links, so that the perfect junction can occur [14, 15]. This decrease occurs due to increased shear forces, mainly from muscle activity. On the other hand, the osteotendinous junction (OJT) is less compliant, with much greater amount of cross-links [16]. This regional difference is also identified by biomechanical studies, which show greater stress

in the tendon distal region, when compared to the proximal region. Thus, a study proposes that, besides that the tendon acts as a protective factor for the muscle (mechanical buffer), it seems that the tendon proximal region acts as a mechanical buffer of the tendon distal region, which undergoes greater mechanical loads and has greater stiffer [17].

Type I collagen molecules are generally heterotrimeric, composed of two α1 polypeptide chains and one α2 polypeptide chain, interlaced in a triple helix, as previously mentioned. Studies have shown that the α2 chain is the most hydrophobic, thus playing a stabilizing role for this molecule [18]. The type III collagen (second most commonly found type) is located mainly in the epitendon and endotendon. Authors have shown that their proportion changes under conditions of tissue injury. Among its functions, types I and V collagen heterotypic fibril formation and fibrillar diameter control stand out [1]. Type IV collagen is found primarily in the basement membrane, where it is considered the main structural component.

A small amount of elastin (2%) still contemplates the composition of tendon. This low proportion is directly related to the almost inelastic aspect of the tendon, its extensibility varying between 8 and 10% before reaching the point of total rupture. This aspect is extremely important, so that the function of conducting tension, performed by the tendon, is efficient [2, 9]. The tendinous arrangement is considered to be a highly organized hierarchical structure [9]. The tropocollagen molecules are organized and grouped into microfibrils and, later, into collagen fibrils. These primary beams bind to the formation of fascicles (smaller functional units of the tendon). Covering the fascicles is the endotendon, a layer of connective tissue, with nerve and vascular and lymphatic structures. By grouping the endotendons in an organizational way, we find the epitendon, the layer responsible for involving the tendon itself. Finally, the paratendon, a more vascularized layer, which can become a double layer, is filled with synovial fluid (produced by the synovial membrane) in tendons subject to friction [19, 20].

In relation to non-collagenous proteins, proteoglycans and glycoproteins are essential to ensure the binding between collagen fibers, water molecule diffusion, and collagen fibrillogenesis and to maintain the matrix structure, being essential for tissue viscoelastic capacity [19]. There are two groups of proteoglycans in the tendon, accounting for 1–5% of the dry weight of the tendon, with high hydrophilicity, attracting water molecules. The small leucine-rich proteoglycans (SLRPs) (decorins, fibromodulins, biglicans, and lumicans), which have a small core protein (40 kDa) and large proteoglycans, also called modular proteoglycans (aggrecan and versican), have a core protein of about 220–370 kDa. The proteoglycan amount in the tendon can vary, depending on the tension and compression (mechanical stimuli) that it receives [21]. Among the glycoproteins, tenascin-C acts on the stability and structuring of ECM, and its expression is greater in tissues where ECM turnover is more active. About fibronectin, it serves as a bridge between cells and ECM [22].

Regarding the cellular environment, the tenoblasts and tenocytes comprise 90–95% of the elements, together with endothelial cells and mast cells [1, 9]. The tenoblasts are spindle-shaped cells, immature, and highly metabolic and present many cytoplasmic organelles. These cells, over time, differentiate into tenocytes, more elongated cells, and are distributed in rows among the collagen fiber bundles, located mainly in the peritendinous region [23, 24]. The tenocytes are arranged in parallel rows along the force transmission axis and interact with the ECM through the integrins (adhesion cell surface receptors) that connect the intracellular cytoskeleton to the matrix, allowing the propagation of mechanical signals from the outside to the inside and from the inside to the outside (bidirectional), a process known as mechanotransduction, that is, the cellular capacity to feel and respond to external mechanical stimuli, extremely important for the maintenance of the tendinous function,

besides the organization of its structure [25]. Additionally, tenocytes have extensive communication with adjacent cells through gap junctions. The communication junctions are extremely complex structures, having two hemicanals, also called connexons, with a central pore. These open connexons allow free metabolites and ion passage among the gap junctions [26, 27]. These connexons are numbered, and the most important ones, in terms of cellular communication and tendons regeneration, are those of number 32 and 43. Connexin 43 is responsible for the inhibition of the collagen syntheses within the tenocytes, as a response to mechanical loading. Connexin 32 may have a stimulatory role, but all we need to know is that they aid communication among cells within the tendon to help with regeneration and adaptation [27].

2. Biomechanical aspects inherent to tendon function

Tendons have biomechanical characteristics similar to springs. They are not able to produce mechanical energy, but are able to conserve energy, increase potency during functional activities, and absorb external forces to prevent injury in the muscle [1, 3, 4]. The parallel arrangement of its collagen fibers along the tendon long axis is directly correlated with its ability to control the tensile loads, mainly unidirectionally and making tendon highly effective in transmitting tension generated by the skeletal muscle to the bone. A good example of the opposite is the ligaments, which have an interlocking arrangement, thus having greater ability to control tension loads in different directions [1, 9].

Nevertheless, a look with microscopic scales identifies a zigzag pattern of collagen fibers, somewhat different from the perfect alignment along the tendon long axis described earlier, known as crimps [28]. Crimps form a "crimp angle" of 20° from the long axis of the tendon. When tendons are unloaded or in the low-load "toe region" of the stress-strain curve (this topic will be better described below), collagen crimps that are present, and they "disappear" when loaded to induce a tensile strain of about 4%. Thus, crimps are physiological markers of tendon tension [29, 30].

The ECM composition characterizes this tissue as viscoelastic, guaranteeing the return to its original size, after being submitted to a certain level of deformation force [31, 32]. Tendon deformation, which occurs during movement, is dependent on the applied load. With higher stress levels, the tendons deform less and become stiffer, maximizing their ability to carry mechanical loads. Otherwise, with lower tensions, tendons have greater ability to deform and thus generate greater gains and adaptations in their ability to absorb energy [33]. This feature guarantees metabolic expenditure reduction during locomotion, as well as strength and power maximization during movement, a strategy known as the stretch-shortening cycle, where there is the use of the elastic capacity of passive structures, such as the tendon, for the energy accumulation during its elongation, transformed into a more powerful movement and with less energy expenditure during muscle shortening (concentric contraction) [34, 35].

For a better understanding of the biomechanical aspects of this tissue, experimental tests are performed, trapping the muscle-tendon complex at one end and the bone at the other end [36]. The tendon is then exposed to a controlled load along its longitudinal axis, recording force, and displacement until tissue failure. The results about mechanical properties are described in four main ways in literature [37]. The tendon deformation/elongation capacity relative to its normal length is characterized as strain, while the tendon force relative to its cross-sectional area is known as stress. Changes in tendon length, relative to the forces applied on it, generate stiffness. Finally, Young's modulus, or modulus of elasticity, which describes the relationship between tendon stress and strain, represents the properties, independently of the cross-sectional area (CSA) [24, 36, 38].

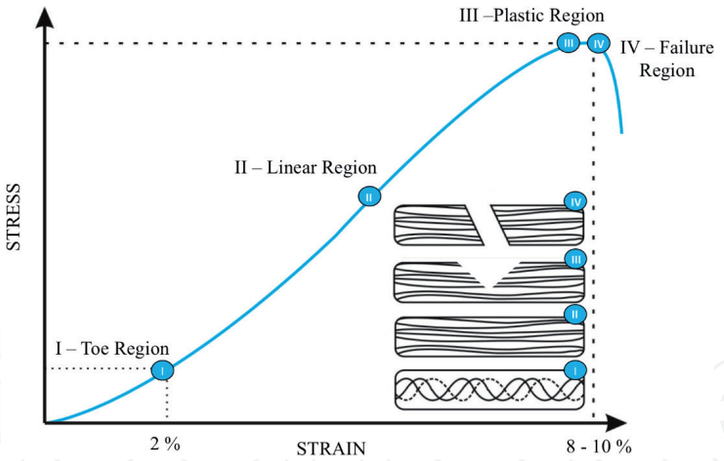

Figure 2.
Stress-strain curve and its four distinct regions: (I) toe region, (II) linear region, (III) plastic region, and (IV) failure region. The toe region represents the alignment of the collagen fibers. At 2% tension, all fibers are already out of their crimped state. In the linear region, the collagen fibers respond to the load in a linear fashion. The two subsequent regions (plastic and failure) represent the beginning and the total failure of the collagen fibers (accumulation of microdamages) (adapted from Robi et al. [39]).

A typical stress-strain curve has four distinctive regions. The first region is called *toe region*, where the crimped/zigzag pattern disappears when the strain of the tendon is below 2% and reappears when tension is released. Following the toe region, there is a linear region, in which the strain is lower than 4% (the physiological upper limit of strain in tendons) and the collagen fiber bundles are no longer crimped. If the strain remains lower than 4%, the fibers and fibrils have been shown to recoil back to their normal resting state, but strain greater than 4% can produce a microscopic damage (**Figure 2**). The slope of this region is Young's modulus, representing tendon stiffness. As the strain on the fibrils continues, the gap between the molecules increases and macroscopic failure can occur, with strain beyond 8–10%, eventually leading to tendon rupture [24, 38].

3. General aspects of tendon mechanical properties in response to exercise

Similar to the skeletal muscle, the tendon has the capacity to adapt according to their mechanical environment. In general, human movement occurs through force-generated muscle contraction, which is transmitted to the bone by aponeurosis and tendon [40]. On the other hand, movement is also essential for tendons [33, 41]. Since 1977, Beckham and coworkers have already noticed incomplete formation of cheek tendons during embryogenesis when muscle contraction was inhibited [42]. This result showed us that the relationship between the tendon and mechanical stimulus could be essential for tendon survival. Currently, we know the tendon answers metabolically to mechanical stimulus, and this exists in humans, for instance, tendon stiffness increase is related to mechanical loading imposed over it following a period of enhanced mechanical loading [33]. Moreover, short-term bout, as well as long-term loading-bearing, produces elevated collagen synthesis response [40]. A possible mechanism that explains the structural changes noticed following mechanical loading is the tendon responsiveness to mechanotransduction, promoting the interaction between fibroblasts and ECM. It is believed that this interaction between fibroblasts and ECM permits the cells to sense and respond to mechanical stimuli, promoting intracellular signaling that will improve protein synthesis and, consequently, tendon structures through collagen and growth factor autocrine/paracrine release (**Figure 3**).

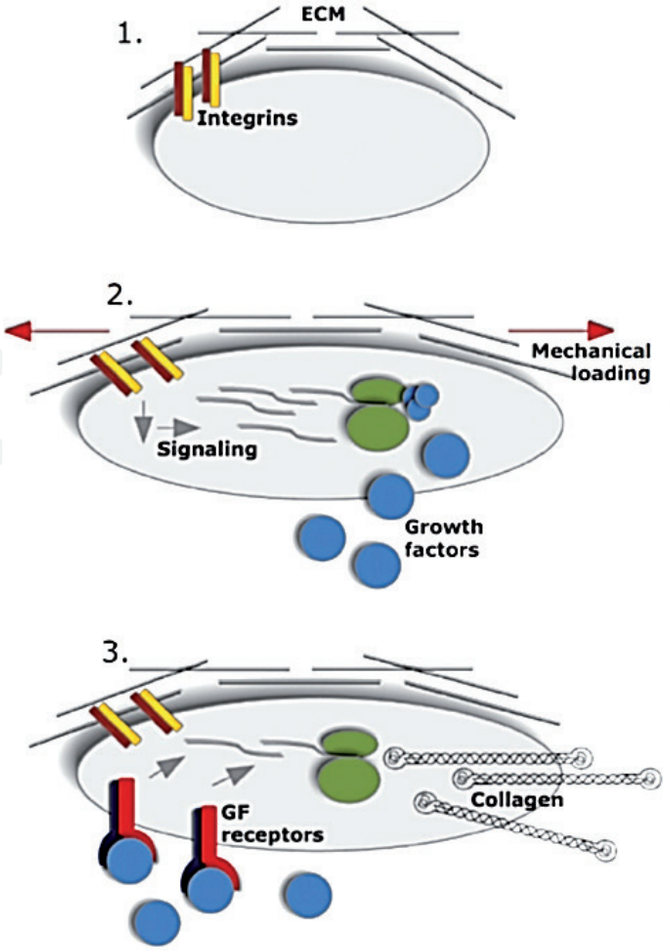

Figure 3.
Possible mechanism for loading induced collagen synthesis: (1) fibroblast connected to extracellular matrix via integrins. (2) Transcription and synthesis of growth factors induced by mechanical loading via changed intracellular signaling. (3) Autocrine-paracrine action of growth factors leading to increased collagen transcription and synthesis. Adapted from Heinemeier and Kjaer [43].

4. Biomechanical adaptations of the tendon in response to exercise training

Evidence-based interventions that elucidate biomechanical adaptations in the tendon are valuable to monitor the effectiveness of training programmers, as well as for the development, evaluation, and implementation of effective intervention programs aimed at injuries. The technique improvement for biomechanical evaluation in the tendon has directly influenced sports medicine, ergonomics, manufacturing sports equipment, and many other aspects of human life. Exercise training potentiates an increase of tensile strength, energy absorption, and stiffness, which may help to enhance the tendon quality. Several reports have already described that these alterations in tendon mechanical properties, due to changes in the loading levels, can improve the muscles' operating range and, consequently, the athletic performance [43].

4.1 Stiffness

Tendon stiffness is a crucial component for human locomotion and athletic performances because it keeps strain energy storage and returns properly and facilitates the muscle force potential due to force-length-velocity relationship [44]. Stiffness properties permit tendon to receive more or less stress, and this is directly related to tendon size. Thus, tendon stiffness is characterized by change in tendon length (ΔL) (deformation) in relation to the force applied to the tendon (ΔFt),

but this parameter is dependent on the cross-sectional area (CSA) and length of the tendon, for instance, greater CSA and shorter length (deformation) will lead to greater stiffness [3] (**Figure 4**).

It has been demonstrated that tendon stiffness can increase after exercise training to maintain physiological ranges of strain. Tendon has been shown to undergo mechanical changes in response to diverse training regimens, including resistance and endurance training. The stiffness may vary according to limb dominance and specific activity. For example, patellar tendon stiffness was greater in the lead leg of badminton and fencing athletes [40]. The changes of the tendon material and morphological properties are among the prime candidate mechanisms, which could account for an increase of tendon stiffness in response to exercise. Running exercises can improve the tendon stiffness. Investigation that used ultrasonography reports greater tendon stiffness in long-distance runners than sedentary subjects [45]. The tendon stiffness may be a potential parameter for improving athletic performance in running, such as peak ground reaction force and ground contact time. The recent findings suggest that stiffer tendon may help achieve better running performance, with greater running economy, in endurance runners [46]. The sprinters had higher normalized stiffness (relation between tendon force and tendon strain) of the triceps sural tendon than the endurance runners and subjects not active in sports, which suggest that higher muscle strength possibly increases the margin of tendon tolerated mechanical loading due to tendon greater stiffness [47].

The resistance training (RT) potential for modulate tendon stiffness in individuals with connective tissue disorders, healthy individuals, athletes, and the elderly are largely described [48–50]. Eccentric exercise, isometric and plyometric training, and vascular occlusion are commonly used as forms of loading exercise for increasing tendon stiffness and represent important strategies for training and rehabilitation [51–53]. However, adding RT to endurance training did not affect stiffness patellar tendon compared to endurance training only [54]. The effects of RT on tendon stiffness can be potentiated by training variable manipulation, such as exercise intensity and duration program [33]. Several studies demonstrated that higher muscle contraction intensity (i.e., 70% of RM) showed higher stiffness values than low-intensity exercise (30% of RM), which indicates that exercise intensity exerts important regulation on tendon adaptation following mechanical loading exercise, regardless the muscle contraction type.

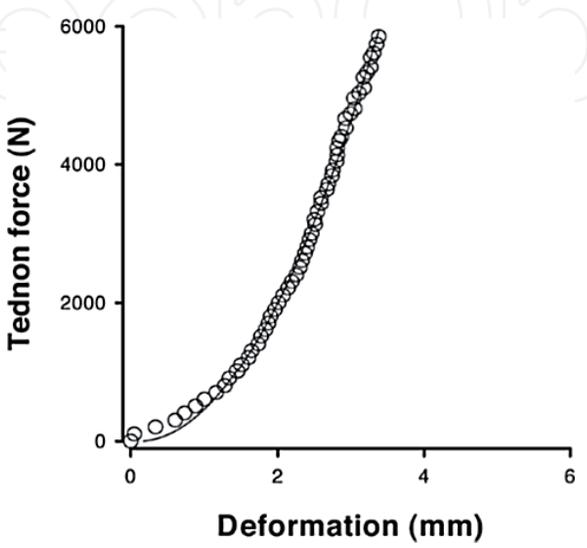

Figure 4.
Patella tendon force-derformation curve. Relationship between the force applied to the tendon (Ft) and the tendon deformation (elongation (ΔL). Adapted from Heinemeier and Kjaer [43].

In relation to the duration of the exercise program, several investigations suggest significant adaptations of tendon stiffness with only 8 weeks of intervention [33]; however, reduced elongation/strain over the whole force range can occur only after years of overload, indicating that there is a force-/strain-specific time course to these adaptations [55]. Although the use of RT may predict important biomechanical adaptations induced by training, the link between changes of tendon stiffness with different rest intervals, exercise order, and training volume remains to be determined.

On the other hand, aging can harm tendon biomechanical properties directly, as a result of biological change degeneration in the tendon and indirectly due to inactivity. In this context, studies suggest that RT is a therapeutic approach to minimize the deleterious effects of aging on biomechanical parameters in the tendon. In a recent review, the study suggests that the interventions should implement high mechanical loads with repetitive loading for up to 3–4 months to counteract age-related changes in muscle-tendon unit biomechanical properties [56]. Exercise training has demonstrated to promote stiffness [44] and increase the elastic modulus in elderly individuals [57]. Increased tendon stiffness is associated with a more rapid development of joint torque (~25%), which may be beneficial in the elderly. In rodent models, RT in old rats was effective for an increase in the stress-strain relationship, which improved the tendon capacity to support stress [36].

4.2 Tensile strength

The tendons need to be strong enough to sustain high magnitudes of loading, while their mechanical properties must remain functionally adequate for optimal muscle shortening or elastic energy storage. The tendons' tensile strength represents the pull which a tendon can resist without rupturing. This biomechanical parameter is a key measure to evaluate tendon injury risk [1]. It is worth highlighting that tendon injuries are extremely common, with the top three being tears of the rotator cuff, Achilles, and wrist flexor tendon. Exercise training has been able to produce excellent outcomes in about 75% of cases, with increased tensile strength being a key component. Several factors can affect the mechanical forces on tendons during locomotion and exercise [58]. In general, different tendons in the body are subject to different levels of mechanical loads, and both muscle contraction level and tendon relative size influence mechanical forces on a tendon.

In the past, the studies about exercise effects on tensile strength were based on in vitro animal investigations [59]. Recent advanced practices allow for noninvasive, in vivo assessment of fascicle movement and cross-sectional area of human tendons. The different athletic activities induce distinct levels of force, even on the same tendon. The tensile strength of a tendon is dependent on collagen and many proteoglycans, which proportionate viscoelastic properties, possessing both solid and fluid-like characteristics and exhibiting changes to the stress-strain relationship regarding the rate at which they are loaded [58]. This dynamic entity remodels permanently in response to mechanical stimulation. Most studies with heavy resistance exercise and endurance activity seem to indicate that systematic exercise strengthens the tendon complex [33].

There is a paradox regarding the exercise effects on tensile strength since acute exercise can induce a decrease in this biomechanical parameter, which may be detrimental to tendon functions. However, chronic exercise stands out as a remarkable non-pharmacological strategy for increasing tensile strength. It has been

demonstrated that Australian football athletes' tendons presented a disorganization response to the mechanical loading of a game and that this disorganization returned to normal only after 4 days [60]. In the same research line, the football players showed an improvement in tendon structure over a 5-month preseason training period with increased fibrillar alignment [61]. Thus, exercise seems to improve tendon mechanical quality, including tensile strength. Tendons are able to withstand considerable forces during exercise, adapting to changes in mechanical load over time. Athletes of different modalities demonstrated improved viscoelastic properties, such as greater maximum tendon strain and suitable strain fluctuations when compared to nonathletes [62].

5. Tendon morphological properties in response to exercise training

Tendons' morphological properties are crucial to their ability to function effectively in situations of greater demand, such as the exercise training. The measures are determined from both the geometrical form and material properties. In general, the technological advances for tendon elongation evaluation, by means of an ultrasound-based methodology, as well as the determination of the tendon CSA from magnetic resonance images, enabled more robust elucidations. Although morphology analysis appear to be relatively simple measurements, researchers still encounter several difficulties that must be taken into account and that still limit current techniques [63].

5.1 Cross-sectional area

The tendons need to adapt based on the ratio of their peak operating stress to their ultimate stress. In this aspect, the modulation in CSA is an adaptive mechanism required for keeping suitable safety factors in response to larger stress levels. Several studies in vivo reported that tendon stiffening after exercise training is accompanied by increases in CSA, which indicated that tendon hypertrophy can also occur with mechanical loading. In a recent systematic review and meta-analysis about human tendon adaptation in response to mechanical loading, it was demonstrated that exercise training induces positive effect for CSA, regardless of type of applied loading regimens. Accumulating evidences from animal and human studies suggest increases in tendon CSA following exercise interventions. In these studies an increase of 20–30% of CSA was noticed in athletes that performed weight-bearing exercise (running and jumping) compared to athletes that did not performed weight-bearing exercise (kayakers) [64, 65]. Interestingly, a tendon CSA increase of 30% in athletes that performed sports where one lower extremity is normally submitted to more loading (leading leg) than the contralateral side was also observed.

In addition, Konsgaard et al. [66] have showed that 12 weeks of heavy RT in healthy young men were efficient to promote increase in both quadriceps tendon CSA in middle and distal regions, as well as in stiffness when compared to other leg that accomplished light RT. Therefore, it is known that loading magnitude could interfere in tendon size. Interestingly, athletes with tendon degeneration cannot present pain symptoms after tendon damage has occurred. It has been demonstrated that around 52% of distance runners will sustain an Achilles tendon injury during their career. In the context, it is extremely essential to determine the difference between tendon remodeling and tendon degeneration. Tendon CSA changes may further indicate positive exercise adaptations or initial degeneration and tendon tissue repair [67].

On the other hand, Wiesinger et al. investigated the tendon structural integrity in athletes engaged in sports with contrasting requirements [68]. Curiously, researchers showed that tendon CSA area normalized to body mass was smaller in water polo players than in other athletes (patellar and Achilles tendon, −28 to −24%) or controls (patellar tendon only, −9%). In contrast, the normalized cross-sectional area was larger in runners (patellar tendon only, +26%) and ski jumpers (patellar and Achilles tendon, +21% and + 13%, respectively) than in controls, which indicate that tendon morphological properties can be modulated by functional requirements.

At last, some studies have demonstrated that there are differences in tendon plasticity between men and woman. It was noticed that men's tendons hypertrophy with training, whereas trained women's tendons are the same size as those of untrained women. This work suggests that gender-specific humoral factors may be involved in the training-induced adaptive morphological response of the human tendon. In fact, tendon adaptation inhibition following exercise when levels of estrogen are high was observed [3, 10].

5.2 Tendon elongation

Tendon elongation correlates significantly with clinical outcome, and lengthening is an important cause of morbidity and may produce permanent functional impairment [69]. Increases in tendon stiffness and tensile strength reported following exercise training could conceivably be attributed to tendon elongation. Nevertheless, current literature does not offer conclusive evidence to support this premise. Several research lines about the positive effects of exercise on tendon elongation are controversial [33, 45]. Few studies considered all relevant methodological aspects (e.g., accounting for gravitational forces, axes misalignment of joint and dynamometer, averaging multiple trials to reliably assess tendon elongation, measuring the tendon moment arm directly). Possibly these aspects affect the validity of the applied method. In addition, whenever variations between measured and calculated tendon elongations are observed, it should be standard practice to confirm that there are no shortcomings in the original elongation calculations or the standard stressing procedures.

On the other hand, in tendon injury mechanical theory, tendon tissue overload is blamed for the pathologic process. Sports injuries, such as Achilles tendon rupture, are serious injuries for which the best treatment is still controversial. The main objective of intervention strategies must be to restore normal length, thus obtaining an optimal function [69]. Once tendon lengthening has become permanent, its clinical management is often difficult. The emphasis on exercise programs should be placed on muscle strengthening.

6. Tendon molecular signaling in response to exercise training

In general, the maintenance or changes in tendon CSA, as well as in tendon elongation, are regulated by interaction between synthesis and degradation molecular pathways [70–73]. In the tendon, the molecular adaptations stimulated by different types of exercise occur similarly to the skeletal muscle. Therefore, it is important to notice that in cases where training stimulates muscle hypertrophy and strength increase, the adaptations of muscles and tendons, which are collagen-rich tissues, are essential to maintain muscle-tendon unit integrity [74].

Tendons are distinct structures from muscles; however, tendon tissue has a direct continuation with the muscle ECM. This characteristic develops an essential mechanism that permits the communication of the mechanical properties of both muscles and tendons, allowing suitable force transmission between them [75]. Based on this communication, the externally applied mechanical load can stimulate ECM components through fibroblasts; however, ECM composition seems to be adapted specifically to changes in load. Therefore, it is possible to understand that mechanical stress can modulate the synthesis of ECM proteins, stimulating paracrine growth factor release, indirectly or directly triggering intracellular signaling pathway that will permit some ECM gene activation [76].

In order to investigate molecular signaling in response to exercise training, different approaches have been used, for instance, microanalysis, incorporation of stable isotope labeled proline into tendon tissue (C-13-proline), and mRNA gene expression of molecules present in the ECM. These approaches have been employed with the goal to analyze the modulations of several molecular mediators responsible for EMC remodeling, as well as molecules that present role key in tendon structure maintenance, such as collagens, proteoglycans, growth factors, as well as collagenases that could response to both endogenous and exogenous stimuli.

Currently, it is known that exercise induces collagen synthesis in the tendon, but the cellular mechanisms are still unclear. In the same way, growth factors as transforming growth factor-β-1 (TGF-β-1), connective tissue growth factor (CTGF), insulin-like growth factor (IGF), and mediator upstream involved in the collagen synthesis also might be involved in the ECM remodeling [77]. Enzymes involved in collagen processing, such as lysyl oxidase (LOX), in favor to cross-linking of collagen [78], as well as matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) might contribute with tendon remodeling aggravated by exercise [79].

6.1 Collagens fibers and growth factors

The microanalysis has been employed to measure collagen pro-peptides which are responsible in the mature collagen synthesis.

Based on the microanalysis, it was possible to notice, in humans, elevated levels of collagen synthesis in peritendinous tissue in response to mechanical stimuli, in both acute and prolonged exercises [41]. These data corroborate with a previous study that used qPCR to investigate synthesized collagen by mRNA expression, but, in rats. In this study, the rats were submitted to 4 days of concentric, eccentric, or isometric training in the medial gastrocnemius muscle through sciatic nerve stimulation, simulating short-term strength training. Interestingly, in humans, high levels of type I and III collagen mRNA in the Achilles tendon in response in short-term resistance training were found, but no difference was seen between training types [77]. In this same study, researchers also investigated the regulation of TGF-β and CTGF key mediators for collagen fiber mRNA transcription.

TGF-β family is composed of more than 30 members identified in humans. This family orchestrates several cellular processes as proliferation, differentiation, protein metabolism, and growth and remodeling of the ECM in the tendon [80]. In the tendon, in particular, three TGF-β isoforms are known (TGF-β1, TGF-β2, and TGF-β3), but the most studied and that receive more attention is TGF-β1 isoform. In theory, latent TGF-β1 molecules are stored in ECM, in association with other ECM components such as fibrillin-1 and fibronectin. In cases when there is ECM remodeling necessity, for instance, injury tendon or overload following training,

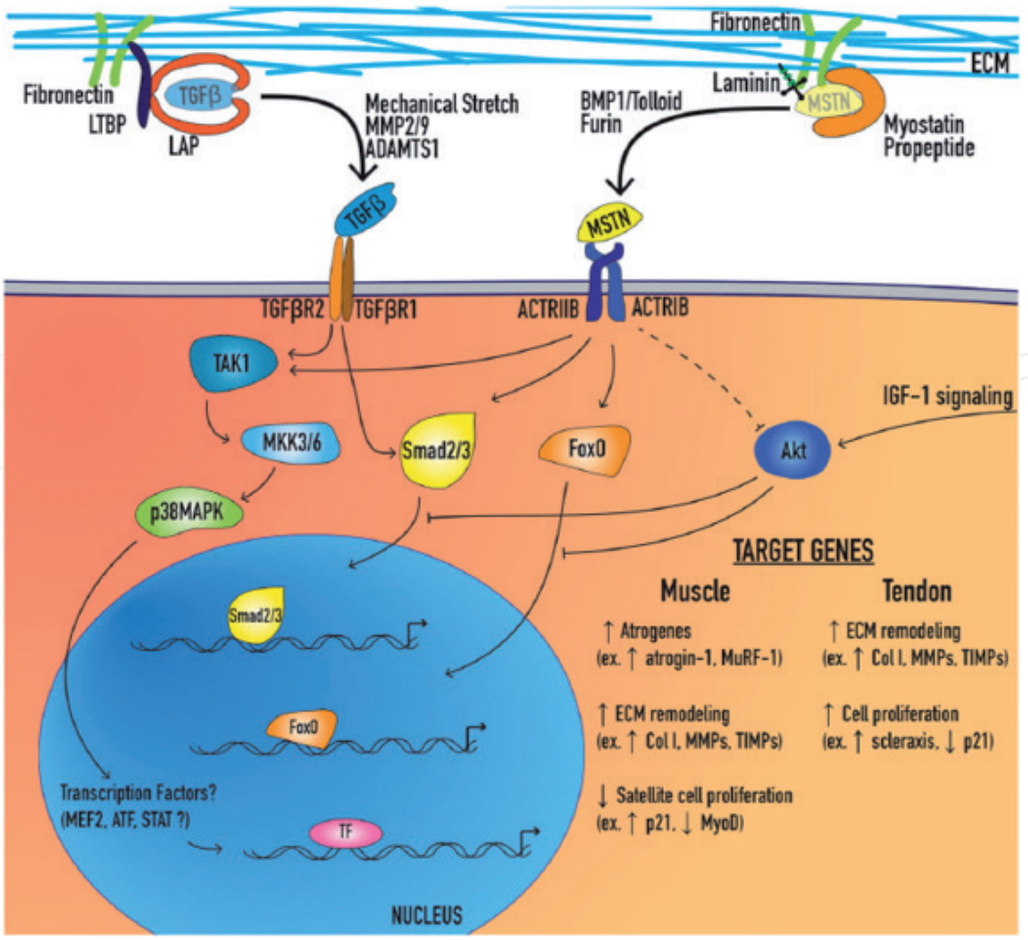

Figure 5.
Overview of TGF-β signaling pathways. Adapted from Gumucio et al. [75].

active TGF-β can be released of ECM through mechanical force or by matrix proteolytic enzymes as ADAMTS1, MMP-2, and MMP-9 [75]. In the case of mechanical force-mediated TGF-β activation, αvβ6 integrin, transmembrane proteins that connect intracellular cytoskeleton proteins together with ECM, suffers a conformational change that signals to liberate latent TGF-β; now matrix biologically active to binding in surface receptors are found in ECM cell. The binding between ligand (TGF-β) and their receptor permits activation of downstream intracellular signaling pathways, responsible for gene transcription, essential to ECM remodeling (for instance, collagen, MMPs, and TIMPs) (**Figure 5**) [75].

Interestingly, Heinemeyer et al. [77] confirmed in their study that TGF-β could be involved in collagen I and collagen III regulations in different types of training (concentric, eccentric, or isometric). Following 24 hours post training, a TGF-β increased gene expression in all types of training (concentric, eccentric, or isometric) with no difference among training types was noticed. These results are in accordance with previous studies that showed eccentric training is also accompanied by fibroblast proliferation, main cells responsible for synthesizing collagen in response to exercise [81, 82].

About ECM, connective tissue growth factor (CTGF), downstream mediator of TGF-β, in fibroblastic cells, also seems to be responsible for tendon ECM remodeling by exercise. It was noticed in human patellar tendon submitted to 1 hour of unilateral kicking exercise (workload of 67%) with frequency of 35 kicks per min and 2100 concentric contractions that CTGF gene expression total volume was increased, together with COL1A1 mRNA levels, 24 hours postexercise. On the other

hand, tendon collagen protein synthesis between trained and untrained groups was not modified [83]. Despite that literature is still unclear about the mechanism that links mechanical loading, TGF-β-1, and CTGF, some results have reported that habitual loading is firstly related to stimulating proximal and distal portions of the tendon [40, 66]. However, future studies are necessary to obtain a better understating about the effect of exercise in this gene expression. Another point is inconsistency among loading protocol, so it is possible that some protocols have not reached to threshold enough stress-strain to stimulate the CTGF expression.

6.2 Proteoglycans

Other molecules, such as proteoglycans, are essential for fibrillogenesis regulation and tendon structure maintenance [84]. The proteoglycan regulation from exercise is still not clear on the literature, whereas most studies have observed the exercise effects over collagen and some growth factors responsible for gene expression of those molecules. However, it seems that resistance exercise appears not to induce changes in proteoglycan gene regulation. In the previous study, there were no observed changes in mRNA expression of the proteoglycans: decorin, biglycan, fibromodulin, and versican from resting levels at 4 or 24 hours after resistance training that corresponded to workload of 70% of the subject's concentric maximum repetition [84]. Although, this study hasn't found changes between proteoglycans, it is possible to infer that the regulation of these molecules could be related to mode, duration, and intensity of the exercise.

6.3 Matrix metalloproteinases

The ECM surrounding tendon provides structural support, protection, and maintenance of the functional integrity. The modulation of ECM function is controlled by matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs). The MMPs constitute a large family of endopeptidase zinc dependent that modulates ECM functions, degrading their constituents, such as proteoglycans, collagen, fibronectin, laminin, and other proteins during normal and pathological tissue remodeling. It has been reported that gelatinases (MMP-2 and MMP-9) play an important role in the ECM turnover induced by tissue injury and exercise training [84].

In order to compare exercise types (concentric, eccentric, or isometric) over gene expression of MMPs, a previous study noticed that MMP-2 mRNA expression increases moderately in the tendon in concentric and isometric exercises. On the other hand, MMP inhibitor, TIMP-1, and TIMP-2 increased gene expressions in response to all training types [77]. These data suggest a self-regulatory mechanism in attempt to protect the ECM against a high degradation of ECM compounds. In humans, it was found that MMP-2 mRNA decreased significantly 4 hours posteriorly to resistance training but returned to resting levels 24 hours after exercise. The mRNA expression of TIMP-1 did not change 24 hours post-acute exercise.

Interestingly in rodent models, previous data has already shown that acute or chronic exercises upregulate MMP-2 activity in the tendon, which is considered substantial mechanisms to tendon adaptation [85]. In contrast, anabolic-androgenic steroid treatment strongly inhibited this activity. Thus, anabolic-androgenic steroid treatment (AAS) can impair tissue remodeling in animal's tendons undergoing physical exercise by downregulating MMP activity, thus increasing the potential for tendon injury [86].

In the same research line, it has been demonstrated that the effects of exercise training on tendon repair are not the same for different tendon types and tendon regions (distal, proximal, and intermediary). For example, Marqueti et al. [87], showed that the intermediate region of the trained animals with AAS supplementation differed from the proximal and distal regions. Moreover, trained animals with AAS supplementation decreased MMP-2 activity form in three regions of the calcaneal tendon (distal, proximal, and intermediary) but not on the deep flexor tendons. The results suggest that the differences in the response to exercise and AAS treatment are a result of distinct metabolism and recruitment of these tendon regions in the exercise program. In another study, Pereira et al. [85] investigated MMP-2 activity in different regions of the calcaneal tendon after RT in ovariectomized rats. The authors demonstrated that ovarian hormones modulate MMP-2 activity differently in proximal region when compared to distal region; however, acute and chronic RT promote sufficient local stimuli to increase total and active MMP-2. Furthermore, proximal region of the calcaneus tendon seems to be more sensitive than the distal region to both acute and chronic RT due to greater MMP-2 activity increase, even in the ovariectomy condition.

7. Conclusions

In summary, tendons are highly responsive to morphological, biochemical, and biomechanical modifications in response to exercise training. Those changes emphasize the importance of extracellular matrix investigation and its remarkable characteristics in this tissue type. With respect to mechanical loading, is well known that exercise exerts beneficial effects in distinct regions of tendons. However, tendon remodeling is not the same in different tendon regions concerning the same mechanical loading application. Also, muscle contraction intensity is a key element in tendon adaptive responses. Finally, accumulating evidence from animal and human studies suggests several beneficial effects of exercise on the tendon remodeling, which might contribute to clinical conditions and performance, as well as understanding the potential of mechanical loading in different types of exercise conditions.

Author details

Rita de Cassia Marqueti*, Ivo Vieira de Sousa Neto, Fabricio Reichert Barin and Gracielle Vieira Ramos
University of Brasilia, Distrito Federal, Brazil

*Address all correspondence to: marqueti@gmail.com

References

[1] Wang JH, Guo Q, Li B. Tendon biomechanics and mechanobiology—A minireview of basic concepts and recent advancements. Journal of Hand Therapy. 2012;**25**(2):133-140; quiz 41

[2] Benjamin M, Kaiser E, Milz S. Structure-function relationships in tendons: A review. Journal of Anatomy. 2008;**212**(3):211-228

[3] Roberts TJ, Azizi E. The series-elastic shock absorber: Tendons attenuate muscle power during eccentric actions. Journal of Applied Physiologyl (1985). 2010;**190**(2):396-404

[4] Konow N, Azizi E, Roberts TJ. Muscle power attenuation by tendon during energy dissipation. Proceedings of the Biological Sciences. 2012;**279**(1731):1108-1113

[5] Wilson A, Lichtwark G. The anatomical arrangement of muscle and tendon enhances limb versatility and locomotor performance. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences. 2011;**366**(1570):1540-1553

[6] Ackermann PW, Renström P. Tendinopathy in sport. Sports Health. 2012;**4**(3):193-201

[7] Riley G. The pathogenesis of tendinopathy. A molecular perspective. Rheumatology (Oxford). 2004;**43**(2):131-142

[8] Kannus P. Structure of the tendon connective tissue. Scandinavian journal of medicine & science in sports. 2000;**10**(6):312-320

[9] Kjaer M. Role of extracellular matrix in adaptation of tendon and skeletal muscle to mechanical loading. Physiological Reviews. 2004;**84**(2):649-698

[10] Shoulders MD, Raines RT. Collagen structure and stability. Annual Review of Biochemistry. 2009;**78**:929-958

[11] Depalle B, Qin Z, Shefelbine SJ, Buehler MJ. Influence of cross-link structure, density and mechanical properties in the mesoscale deformation mechanisms of collagen fibrils. Journal of the Mechanical Behavior of Biomedical Materials. 2015;**52**:1-13

[12] Couppe C, Hansen P, Kongsgaard M, Kovanen V, Suetta C, Aagaard P, et al. Mechanical properties and collagen cross-linking of the patellar tendon in old and young men. Journal of Applied Physiology (1985). 2009;**107**(3):880-886

[13] Snedeker JG, Gautieri A. The role of collagen crosslinks in ageing and diabetes—The good, the bad, and the ugly. Muscles, Ligaments and Tendons. 2014;**4**(3):303-308

[14] Kostrominova TY, Calve S, Arruda EM, Larkin LM. Ultrastructure of myotendinous junctions in tendon-skeletal muscle constructs engineered in vitro. Histology and Histopathology. 2009 May;**24**(5):541-550

[15] Charvet B, Ruggiero F, Le Guellec D. The development of the myotendinous junction. A review. Muscles, Ligaments and Tendons Journal. 2012;**2**(2):53-63

[16] Schweitzer R, Zelzer E, Volk T. Connecting muscles to tendons: Tendons and musculoskeletal development in flies and vertebrates. Development. 2010;**137**(17):2807-2817

[17] Reeves ND, Cooper G. Is human Achilles tendon deformation greater in regions where cross-sectional area is smaller? The Journal of Experimental Biology. 2017;**220**(Pt 9):1634-1642

[18] Miles CA, Sims TJ, Camacho NP, Bailey AJ. The role of the alpha2 chain in the stabilization of the collagen type I heterotrimer: A study of the type I homotrimer in oim mouse tissues. Journal of Molecular Biology. 2002;**321**(5):797-805

[19] Sharma P, Maffulli N. Biology of tendon injury: Healing, modeling and remodeling. Journal of Musculoskeletal & Neuronal Interactions. 2006;**6**(2):181-190

[20] O'Brien M. The anatomy of the Achilles tendon. Foot and Ankle Clinics. 2005;**10**(2):225-238

[21] Rees SG, Flannery CR, Little CB, Hughes CE, Caterson B, Dent CM. Catabolism of aggrecan, decorin and biglycan in tendon. The Biochemical Journal. 2000;**350**(Pt 1): 181-188

[22] Peffers MJ, Thorpe CT, Collins JA, Eong R, Wei TK, Screen HR, et al. Proteomic analysis reveals age-related changes in tendon matrix composition, with age- and injury-specific matrix fragmentation. The Journal of Biological Chemistry. 2014;**289**(37):25867-25878

[23] Abate M, Silbernagel KG, Siljeholm C, Di Iorio A, De Amicis D, Salini V, et al. Pathogenesis of tendinopathies: Inflammation or degeneration? Arthritis Research & Therapy. 2009;**11**(3):235

[24] Freedman BR, Sarver JJ, Buckley MR, Voleti PB, Soslowsky LJ. Biomechanical and structural response of healing Achilles tendon to fatigue loading following acute injury. Journal of Biomechanics. 2014;**47**(9):2028-2034

[25] Lavagnino M, Wall ME, Little D, Banes AJ, Guilak F, Arnoczky SP. Tendon mechanobiology: Current knowledge and future research opportunities. Journal of Orthopaedic Research. 2015;**33**(6):813-822

[26] Maeda E, Ye S, Wang W, Bader DL, Knight MM, Lee DA. Gap junction permeability between tenocytes within tendon fascicles is suppressed by tensile loading. Biomechanics and Modeling in Mechanobiology. 2012;**11**(3-4):439-447

[27] McNeilly CM, Banes AJ, Benjamin M, Ralphs JR. Tendon cells in vivo form a three dimensional network of cell processes linked by gap junctions. Journal of Anatomy. 1996;**189**(Pt 3): 593-600

[28] Franchi M, Ottani V, Stagni R, Ruggeri A. Tendon and ligament fibrillar crimps give rise to left-handed helices of collagen fibrils in both planar and helical crimps. Journal of Anatomy. 2010;**216**(3):301-309

[29] Mountain KM, Bjarnason TA, Dunn JF, Matyas JR. The functional microstructure of tendon collagen revealed by high-field MRI. Magnetic Resonance in Medicine. 2011;**66**(2):520-527

[30] Shim V, Fernandez J, Besier T, Hunter P. Investigation of the role of crimps in collagen fibers in tendon with a microstructually based finite element model. Conference Proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society. 2012;**2012**:4871-4874

[31] Screen H, Birk D, Kadler K, Ramirez F, Young M. Tendon functional extracellular matrix. Journal of Orthopaedic Research. 2015;**33**(6):793-799

[32] Kubo K, Kanehisa H, Fukunaga T. Effects of viscoelastic properties of tendon structures on stretch-shortening cycle exercise in vivo. Journal of Sports Sciences. 2005;**23**(8):851-860

[33] Bohm S, Mersmann F, 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. Dec 2015;**1**(1):7:1-18

[34] Zhang J, Wang JH. The effects of mechanical loading on tendons—An in vivo and in vitro model study. PLoS One. 2013;**8**(8):e71740

[35] Fukutani A, Kurihara T, Isaka T. Factors of force potentiation induced by stretch-shortening cycle in plantarflexors. PLoS One. 2015;**10**(6):1-12

[36] de Cassia Marqueti R, Almeida JA, Nakagaki WR, Guzzoni V, Boghi F, Renner A, et al. Resistance training minimizes the biomechanical effects of aging in three different rat tendons. Journal of Biomechanics. 2017;**53**:29-35

[37] Shepherd JH, Screen HRC. Fatigue loading of tendon. International Journal of Experimental Pathology. 2013;**94**(4):260-270

[38] Wren TAL, Yerby SA, et al. Mechanical properties of the human achilles tendon. Clinical Biomechanics. 2001;**16**(3):245-251

[39] Robi K, Jakob N, Matevz K, Matjaz V. The physiology of sports injuries and repair processes. In Current issues in sports and exercise medicine. IntechOpen. 2013;**2**:48-49

[40] Couppe C, Kongsgaard M, Aagaard P, Hansen P, Bojsen-Moller J, Kjaer M, et al. Habitual loading results in tendon hypertrophy and increased stiffness of the human patellar tendon. Journal of Applied Physiology. 2008;**105**(3):805-810

[41] Beckham C, Dimond R, Greenlee TK Jr. The role of movement in the development of a digital flexor tendon. The American Journal of Anatomy. 1977;**150**(3):443-459

[42] Reeves ND. Adaptation of the tendon to mechanical usage. Journal of Musculoskeletal & Neuronal Interactions. 2006;**6**(2):174-180

[43] Heinemeier KM, Kjaer M. In vivo investigation of tendon responses to mechanical loading. Journal of Musculoskeletal & Neuronal Interactions. 2011;**11**(2):115-123

[44] Maganaris CN, Narici MV, Reeves ND. In vivo human tendon mechanical properties: Effect of resistance training in old age. Journal of Musculoskeletal & Neuronal Interactions. 2004;**4**(2):204-208

[45] Buchanan CI, Marsh RL. Effects of exercise on the biomechanical, biochemical and structural properties of tendons. Comparative Biochemistry and Physiology. Part A, Molecular & Integrative Physiology. 2002;**133**(4):1101-1107

[46] Takahashi C, Suga T, Ueno H, Miyake Y, Otsuka M, Terada M, et al. Potential relationship between passive plantar flexor stiffness and sprint performance in sprinters. Physical Therapy in Sport. 2018;**32**:54-58

[47] Arampatzis A, Karamanidis K, Morey-Klapsing G, De Monte G, Stafilidis S. Mechanical properties of the triceps surae tendon and aponeurosis in relation to intensity of sport activity. Journal of Biomechanics. 2007;**40**(9):1946-1952

[48] Han SW, Lee DY, Choi DS, Han B, Kim JS, Lee HD. Asynchronous alterations of muscle force and tendon stiffness following 8 weeks of resistance exercise with whole-body vibration in older women. Journal of Aging and Physical Activity. 2017;**25**(2):287-294

[49] Moller MB, Kjaer M, Svensson RB, Andersen JL, Magnusson SP, Nielsen RH. Functional adaptation of tendon and skeletal muscle to resistance training in three patients with genetically verified classic Ehlers Danlos

Syndrome. Muscles, Ligaments and Tendons Journal. 2014;**4**(3):315-323

[50] Waugh CM, Korff T, Fath F, Blazevich AJ. Effects of resistance training on tendon mechanical properties and rapid force production in prepubertal children. Journal of Applied Physiology (1985). 2014;**117**(3):257-266

[51] Roig M, Macintyre DL, Eng JJ, Narici MV, Maganaris CN, Reid WD. Preservation of eccentric strength in older adults: Evidence, mechanisms and implications for training and rehabilitation. Experimental Gerontology. 2010;**45**(6):400-409

[52] Hirayama K, Iwanuma S, Ikeda N, Yoshikawa A, Ema R, Kawakami Y. Plyometric training favors optimizing muscle-tendon behavior during depth jumping. Frontiers in Physiology. 2017;**8**:16

[53] Kubo K, Komuro T, Ishiguro N, Tsunoda N, Sato Y, Ishii N, et al. Effects of low-load resistance training with vascular occlusion on the mechanical properties of muscle and tendon. Journal of Applied Biomechanics. 2006;**22**(2):112-119

[54] Vikmoen O, Raastad T, Seynnes O, Bergstrom K, Ellefsen S, Ronnestad BR. Effects of heavy strength training on running performance and determinants of running performance in female endurance athletes. PLoS One. 2016;**11**(3):e0150799

[55] Massey GJ, Balshaw TG, Maden-Wilkinson TM, Folland JP. Tendinous tissue properties after short- and long-term functional overload: Differences between controls, 12 weeks and 4 years of resistance training. Acta Physiologica (Oxford, England). 2018;**222**(4):e13019

[56] McCrum C, Leow P, Epro G, Konig M, Meijer K, Karamanidis K. Alterations in leg extensor muscle-tendon unit biomechanical properties with ageing and mechanical loading. Frontiers in Physiology. 2018;**9**:150

[57] Grosset JF, Breen L, Stewart CE, Burgess KE, Onambele GL. Influence of exercise intensity on training-induced tendon mechanical properties changes in older individuals. Age (Dordrecht, Netherlands). 2014;**36**(3):9657

[58] Maganaris CN. Tensile properties of in vivo human tendinous tissue. Journal of Biomechanics. 2002;**35**(8):1019-1027

[59] Viidik A. Elasticity and tensile strength of the anterior cruciate ligament in rabbits as influenced by training. Acta Physiologica Scandinavica. 1968;**74**(3):372-380

[60] Rosengarten SD, Cook JL, Bryant AL, Cordy JT, Daffy J, Docking SI. Australian football players' Achilles tendons respond to game loads within 2 days: An ultrasound tissue characterisation (UTC) study. British Journal of Sports Medicine. 2015;**49**(3):183-187

[61] Docking SI, Rosengarten SD, Cook J. Achilles tendon structure improves on UTC imaging over a 5-month pre-season in elite Australian football players. Scandinavian Journal of Medicine & Science in Sports. 2016;**26**(5):557-563

[62] Mersmann F, Bohm S, Schroll A, Marzilger R, Arampatzis A. Athletic training affects the uniformity of muscle and tendon adaptation during adolescence. Journal of Applied Physiologyl (1985). 2016;**121**(4):893-899

[63] de Carvalho KL, Silva PE, Castro J, Babault N, Durigan JLQ, de Cassia Marqueti R. Height, weight, and age predict quadriceps tendon length and thickness in skeletally immature patients: Letter to the editor. The American Journal of Sports Medicine. 2017;**45**(9):NP26

[64] Kongsgaard M, Aagaard P, Kjaer M, Magnusson SP. Structural Achilles

tendon properties in athletes subjected to different exercise modes and in Achilles tendon rupture patients. Journal of Applied Physiology. 2005;**99**(5):1965-1971

[65] Rosager S, Aagaard P, Dyhre-Poulsen P, Neergaard K, Kjaer M, Magnusson SP. Load-displacement properties of the human triceps surae aponeurosis and tendon in runners and non-runners. Scandinavian Journal of Medicine & Science in Sports. 2002;**12**(2):90-98

[66] Kongsgaard M, Reitelseder S, Pedersen TG, Holm L, Aagaard P, Kjaer M, et al. Region specific patellar tendon hypertrophy in humans following resistance training. Acta Physiologica. 2007;**191**(2):111-121

[67] Sponbeck JK, Perkins CL, Berg MJ, Rigby JH. Achilles tendon cross sectional area changes over a division I NCAA cross country season. Journal of Exercise Science & Fitness. 2017;**10**(8):1226-1234

[68] Wiesinger HP, Rieder F, Kosters A, Muller E, Seynnes OR. Are sport-specific profiles of tendon stiffness and cross-sectional area determined by structural or functional integrity? PLoS One. 2016;**11**(6):e0158441

[69] Maquirriain J. Achilles tendon rupture: Avoiding tendon lengthening during surgical repair and rehabilitation. The Yale Journal of Biology and Medicine. 2011;**84**(3):289-300

[70] Cohen S, Nathan JA, Goldberg AL. Muscle wasting in disease: Molecular mechanisms and promising therapies. Nature Reviews. Drug Discovery. 2015;**14**(1):58-74

[71] Egerman MA, Glass DJ. Signaling pathways controlling skeletal muscle mass. Critical Reviews in Biochemistry and Molecular Biology. 2014;**49**(1):59-68

[72] Gundersen K. Muscle memory and a new cellular model for muscle atrophy and hypertrophy. The Journal of Experimental Biology. 2016;**219**(Pt 2):235-242

[73] Schiaffino S, Dyar KA, Ciciliot S, Blaauw B, Sandri M. Mechanisms regulating skeletal muscle growth and atrophy. The FEBS Journal. 2013;**280**(17):4294-4314

[74] Kjaer M, Magnusson P, Krogsgaard M, Boysen Moller J, Olesen J, Heinemeier K, et al. Extracellular matrix adaptation of tendon and skeletal muscle to exercise. Journal of Anatomy. 2006;**208**(4):445-450

[75] Gumucio JP, Sugg KB, Mendias CL. TGF-beta superfamily signaling in muscle and tendon adaptation to resistance exercise. Exercise and Sport Sciences Reviews. 2015;**43**(2):93-99

[76] Chiquet M, Renedo AS, Huber F, Fluck M. How do fibroblasts translate mechanical signals into changes in extracellular matrix production? Matrix Biology. 2003;**22**(1):73-80

[77] Heinemeier KM, Olesen JL, Haddad F, Langberg H, Kjaer M, Baldwin KM, et al. Expression of collagen and related growth factors in rat tendon and skeletal muscle in response to specific contraction types. The Journal of Physiology. 2007;**582**(Pt 3):1303-1316

[78] Kagan HM, Li W. Lysyl oxidase: Properties, specificity, and biological roles inside and outside of the cell. Journal of Cellular Biochemistry. 2003;**88**(4):660-672

[79] Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: Structure, function, and biochemistry. Circulation Research. 2003;**92**(8):827-839

[80] Massague J. TGFbeta signalling in context. Nature Reviews Molecular Cell Biology. 2012;**13**(10):616-630

[81] Kjaer M, Langberg H, Heinemeier K, Bayer ML, Hansen M, Holm L, et al. From mechanical loading to collagen synthesis, structural changes and function in human tendon. Scandinavian Journal of Medicine & Science in Sports. 2009;**19**(4):500-510

[82] Mendias CL, Gumucio JP, Bakhurin KI, Lynch EB, Brooks SV. Physiological loading of tendons induces scleraxis expression in epitenon fibroblasts. Journal of Orthopaedic Research. 2012;**30**(4):606-612

[83] Dideriksen K, Sindby AK, Krogsgaard M, Schjerling P, Holm L, Langberg H. Effect of acute exercise on patella tendon protein synthesis and gene expression. SpringerPlus. 2013;**2**(1):109

[84] Sullivan BE, Carroll CC, Jemiolo B, Trappe SW, Magnusson SP, Dossing S, et al. Effect of acute resistance exercise and sex on human patellar tendon structural and regulatory mRNA expression. Journal of Applied Physiology. 2009;**106**(2):468-475

[85] Pereira GB, Prestes J, Leite RD, Magosso RF, Peixoto FS, Marqueti Rde C, et al. Effects of ovariectomy and resistance training on MMP-2 activity in rat calcaneal tendon. Connective Tissue Research. 2010;**51**(6):459-466

[86] Marqueti RC, Parizotto NA, Chriguer RS, Perez SE, Selistre-de-Araujo HS. Androgenic-anabolic steroids associated with mechanical loading inhibit matrix metallopeptidase activity and affect the remodeling of the achilles tendon in rats. The American Journal of Sports Medicine. 2006;**34**(8):1274-1280

[87] Marqueti RC, Prestes J, Paschoal M, Ramos OH, Perez SE, Carvalho HF, Selistre-de-Araujo HS. Matrix metallopeptidase 2 activity in tendon regions: Effects of mechanical loading exercise associated to anabolic-androgenic steroids. European Journal of Applied Physiology. 2008;**104**:1087-1093