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HIGHLIGHTED TOPIC | *Aging and Exercise*

Effect of aging and exercise on the tendon

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[1]*Institute of Sports Medicine Copenhagen, Department of Orthopedic Surgery, Bispebjerg Hospital and Center for Healthy Aging, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark;* [2]*Department of Biomedical Sciences, Center for Healthy Aging, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark; and* [3]*Musculoskeletal Rehabilitation Research Unit, Bispebjerg Hospital, Denmark*

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Svensson RB, Heinemeier KM, Couppé C, Kjaer M, Magnusson SP. Effect of aging and exercise on the tendon. *J Appl Physiol* 121: 1353–1362, 2016. First published May 5, 2016; doi:10.1152/japplphysiol.00328.2016.—Here, we review the literature on how tendons respond and adapt to ageing and exercise. With respect to aging, there are considerable changes early in life, but this seems to be maturation rather than aging per se. In vitro data indicate that aging is associated with a decreased potential for cell proliferation and a reduction in the number of stem/progenitor-like cells. Further, there is persuasive evidence that turnover in the core of the tendon after maturity is very slow or absent. Tendon fibril diameter, collagen content, and whole tendon size appear to be largely unchanged with aging, while glycation-derived cross-links increase substantially. Mechanically, aging appears to be associated with a reduction in modulus and strength. With respect to exercise, tendon cells respond by producing growth factors, and there is some support for a loading-induced increase in tendon collagen synthesis in humans, which likely reflects synthesis at the very periphery of the tendon rather than the core. Average collagen fibril diameter is largely unaffected by exercise, while there can be some hypertrophy of the whole tendon. In addition, it seems that resistance training can yield increased stiffness and modulus of the tendon and may reduce the amount of glycation. Exercise thereby tends to counteract the effects of aging.

exercise; fibril; fibroblast; stiffness; tendon

THE FORCE OF CONTRACTING MUSCLES is transmitted via tendons to bone and produce joint moments that achieve human movement. Therefore, conceivable changes in tendon composition, structure, and mechanical properties as a result of exercise and aging can influence the overall function of the muscle-tendon unit (65, 88). However, in contrast to muscle, our understanding of the effects of aging and exercise on the structure and function of the connective tissues is comparatively sparse. While connective tissues, i.e., tendons, have been historically thought of as relatively inert structures, more recent data suggest that tendons can respond and adapt to loading and aging (57, 121). Although we now know that connective tissue is not inert, its poor healing ability remains a clinical challenge, and both tendon ruptures (53) and chronic overload injuries (26, 35) of tendons are frequently occurring problems. Moreover, tendon tissue injuries appear to be more frequent with aging (3, 26, 51), and yet the underlying mechanisms have not been identified. A key problem is that the optimal properties of a given tendon are poorly understood, making it difficult to define what constitutes a detrimental or an advantageous change. Further, the cellular regulation of tendon tissue homeostasis and how such mechanisms contribute to overall tissue mechanical properties have yet to be clearly outlined, and while it appears that the mechanical function of tendon can be altered, little is known about the origins of these alterations. Here, we review the current understanding of how tendons respond and adapt to exercise and aging.

Tendon Structure and Composition

Tendons are connective tissues consisting mainly of extracellular matrix (ECM) made up of longitudinally aligned type I collagen fibrils (32, 57). Other components comprise cells, fibrillar collagens type III and type V, and proteoglycans. About 60-90% of the dry matter in adult tendon is type I collagen, which is responsible for the tensile load-bearing capacity of the tissue (63). Embryonic collagen fibrils are short (~10–200 μm), with a small uniform diameter (~40 nm). With maturation, the fibrils grow both longitudinally and laterally, reaching lengths in excess of a millimeter and diameters of 40–300 nm (14, 102). Type III collagen (~3%) can form heterotypic fibrils in combination with type I collagen and is mainly involved in tendon repair and growth, while type V

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collagen has been proposed as a nucleator, upon which type I collagen fibrils can form (13, 127). Proteoglycans (~0.5%) have protein cores covalently attached to negatively charged glycosaminoglycan chains, which are capable of retaining large amounts of water (63, 135). The most abundant proteoglycans in tendon are decorin and biglycan (135), which can bind to collagen fibrils and are more abundant (>3%) in regions of compression, indicating a role in compressive loads (63, 82), in addition to being important for collagen fibrillogenesis (126, 135).

An important process for connective tissue mechanics is the formation of covalent cross-links between collagen molecules, which improve the strength and stability of collagen fibrils (9). There are two broad groups of cross-links; the enzymatic and the nonenzymatic. Enzymatic cross-links are formed as a result of lysyl oxidase (LOX) enzyme activity, which turns the amino group on specific lysine residues into aldehydes at the ends (telopeptides) of the type I collagen molecule (9, 40). The aldehyde can react with amino groups on neighboring collagen molecules to produce different cross-links, which initially form so-called immature divalent linkages that can, in some cases, react further to form mature trivalent bonds (9). The relative amount of these various cross-links differs between tissues (29, 40). Nonenzymatic cross-links are mainly formed by the so-called Maillard reaction in which glycation of amino acids by reducing sugars eventually form advanced glycation endproducts (AGEs) (7, 80). In contrast to enzymatic cross-linking, formation of AGEs is an erratic process that may occur at many locations along the collagen molecule and can form a wide array of different cross-linking (e.g., pentosidine, glucosepane) and non-cross-linking compounds (e.g., carboxymethyllysine) (86).

The primary cells of the tendon are fibroblasts, which are responsible for producing the various ECM components discussed above. In the mature tendon, cells are elongated and located between larger bundles of collagen fibrils called fibers (54, 106). Cellular processes spread in between collagen fibers and provide contacts to neighboring cells, which enables cell-cell signaling (82).

Effects of Aging

The effect of age on tendon cell function and morphology. Tendon cell function changes with increasing age in regard to both cell density and cell activity. As the postnatal tendon develops from an immature to mature tissue, there is a dramatic drop in cell density (54, 72, 89, 91), which presumably is due to the large expansion of extracellular matrix (54, 72). In addition, it has been suggested that further decrease in cell density occurs with aging (89, 91). An early study showed that the cell density in rat-tail tendon dropped to one-third from 1.5 to 9 mo of age with a smaller decrease from 9 to 25 mo (89). Several other studies on rabbit, horse, and rat tendons support the dramatic drop in cell density early in life (54, 72, 87, 91, 113). However, most of these studies focused on the tendon maturation phase (54, 72, 87), and it is likely that the drop in cell number is mainly a maturation rather than an aging phenomenon per se. In support of this notion, no age-related change in cell density or DNA content was found in horses between 2 and 30 yr of age (113, 117). On the basis of these observations and the lack of human studies, it remains unknown whether changes occur in tendon cell density from maturity to old age in human tendon.

In addition to a decrease in cell-to-matrix ratio with maturation, there is also evidence of changes in cell morphology from relatively round cells in the young/immature tendon to very long spindle-shaped cells, with low amounts of cytoplasm and reduced synthetically active organelles, in the mature/old tendon (54, 91). This maturation-associated change suggests a decrease in cell synthetic activity, which is supported by data showing much higher collagen synthesis in response to tendon injury in immature (21 days) compared with young (8–10 wk) rats, but without further change at older age (4–6 mo) (4). Other studies have also observed little to no difference between adult and old animals in metabolic activity of cultured cells from rats as well as collagen synthesis in horse tendon (117, 120). Chronological decline in synthetic activity, therefore, appears to be a maturation rather than an aging phenomenon.

Changes in cell function with age are also supported by in vitro studies on primary tendon cell cultures. Cell proliferation has been reported to decrease with old age both in injured human supraspinatus, as well as rat and mouse Achilles tendon (6, 58, 119). The studies in rat and mouse also observed an age-related reduction of cell migration speed in vitro (6, 119).

In recent years, there has been considerable focus on the presence and function of stem and progenitor cells in tendon tissue, including the potential effect of aging on these cells. In cells derived from human Achilles tendon, a decrease in the number of colony-forming units was seen with aging (28 ± 5 vs. 63 ± 14 years), and a lower rate of proliferation, as well as reduced migration, were observed in stem/progenitor cells from the aged tendon (59). Similar results have been shown for progenitor cells from rat patellar tendon (136, 137). There is no consensus with regard to the multipotency of the tendon stem/progenitor cells based on the currently available data. One study showed no effect of age on multipotency of human tendon cells (59), while another found poorer differentiation both in the adipogenic, chondrogenic, and osteogenic direction in 9-mo-old compared with 2.5-mo-old mice (136). Yet a third study found that aged (24 mo) rat stem/progenitor cells had a greater tendency toward adipogenic cell lineage compared with young (3 mo) cells (137).

In summary, in vivo, there is a marked drop in both cell numbers and cell synthetic activity in the transition from immature to mature tendon tissue (Fig. 1). However, currently available data do not clearly identify whether a decline takes place from mature to aged tendon tissue, particularly in humans. The in vitro data suggest that aging leads to a decrease in the potential for cell proliferation, as well as a decrease in the amount of stem- and progenitor-like cells in the tendon, while changes in the multipotency of the stem and progenitor cells are less clear. Furthermore, the distinction between maturation and aging is not well established for these observations.

Effect of age on tendon tissue turnover. The data on tendon cell numbers and activity discussed above indicate that cell synthesis activity is high during the postnatal growth of tendon and that it slows down after maturity. This fits well the limited tissue turnover in human adult tendon recently found with the use of carbon-14 (^{14}C), generated by nuclear bomb tests performed in the 1950-1960s. It was shown that large amounts of ^{14}C were retained in the core of healthy Achilles tendon

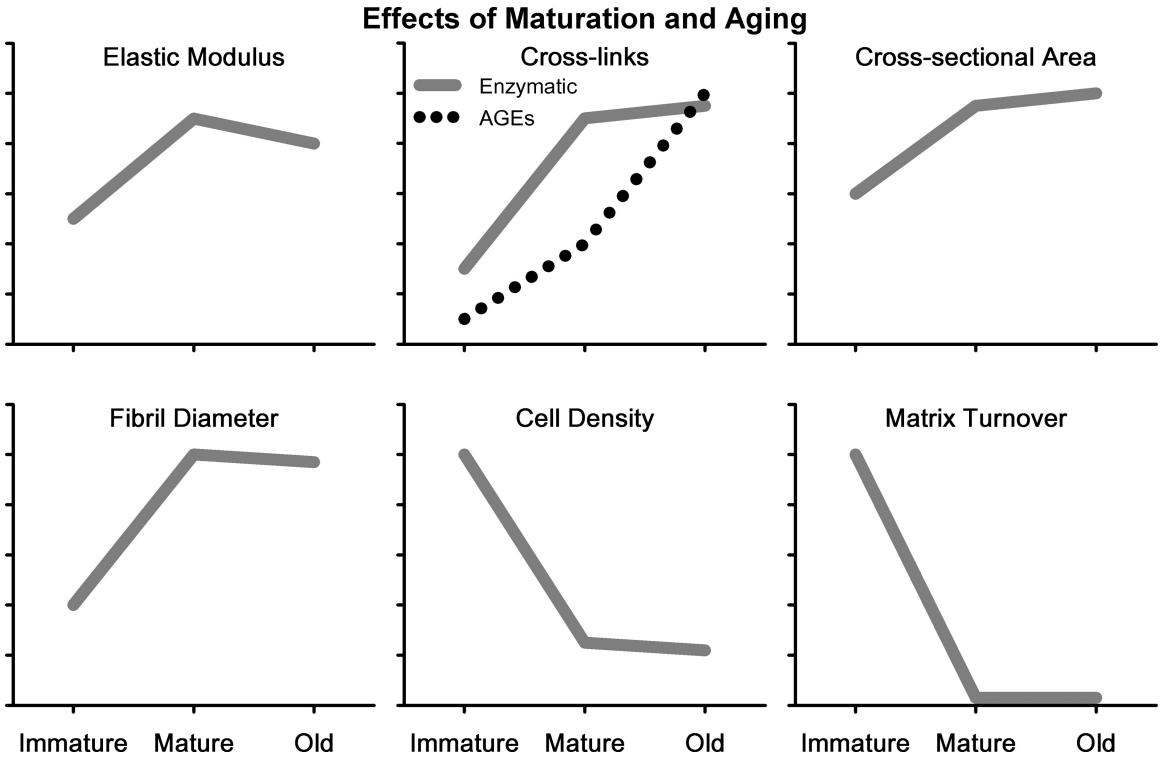

Fig. 1. Schematic overview of changes occurring in tendon tissue with maturation and aging. The graphs do not represent actual data values but simply illustrate the overall trends. Values are placed such that the situation with the highest value is at the top of the graph and the remaining points illustrate the relative trends. AGEs, advanced glycation endproducts.

from adults born during the peak of the ^{14}C bomb pulse (49). The pattern of retained ^{14}C indicated that at least the core of the tendon is formed during the first 17 years of life, with extremely limited turnover after this point (49). The evidence of a very slow tendon turnover after maturity is also supported by earlier studies measuring accumulation of pentosidine (nonenzymatic cross-link) and racemization from L- to D-aspartate to estimate long-term tissue turnover in adult human biceps tendon (11) and mature horse tendon (118). Whether an additional drop in the turnover of collagen happens from maturity to old age is unclear; however, it is unlikely since the bulk of the tendon matrix is already relatively inert in mature human tendon.

Effect of age on tendon structure and composition. Changes to the tendon structure and composition take place with aging and may influence the mechanical function. The average stress (N/m^2, Pa) imposed on the tendon during loading can be expressed as the force transmitted through the tendon divided by its cross-sectional area (CSA). Increased CSA, thereby, leads to reduced stress, at least to the extent that forces are distributed evenly throughout the tendon. Animal data suggest that tendon CSA may increase (12, 90) or remain unchanged (131) with age. Similarly, cross-sectional studies in humans indicate that the tendon CSA may increase (25, 76, 114) or remain unchanged (19, 23, 25) with aging. Human cross-sectional studies can be hampered by the challenges of accounting for physical activity and its potential effects on tendon CSA (109). However, it was recently shown that young and old men of similar activity levels displayed similar tendon CSAs (23, 25). Overall, this suggests that unlike muscle, there is no loss of tendon tissue with increasing age, and there may even be a small increase.

The fibril is the principal tensile load-bearing unit and is made up of type I collagen. In both animals and humans, age has been associated with a reduction in collagen content in some (23, 44, 125), but not all, studies (25). The apparent reduction in collagen content with age implies that the tensile properties may be impaired, although it should be noted that the typical measurements cannot differentiate free collagen from the incorporated fibrillar form, and only the latter is a tensile bearing component. Furthermore, because the content is a relative measure (usually to dry weight), it may not be collagen itself that is reduced, but rather some other component, such as lipid that is increased (2).

Collagen fibrils do not appear to change appreciably following maturation. The mean diameter of collagen fibrils remains unchanged with aging, or may be slightly reduced, while the relative distribution of fibril sizes may change (25, 98, 131). The total content of collagen fibrils (volume fraction) remains largely unaltered with aging in both animals and humans as well (25, 98, 131).

Both enzymatic and nonenzymatic cross-links can be affected by age. In tendons, the enzymatic cross-link composition changes greatly with maturation, replacing divalent with trivalent cross-links (10, 18). A smaller increase with further aging has been reported (23), although it is not found consistently (25), and the significance of this difference is unknown but likely modest. In contrast, nonenzymatic cross-links formed by glycation probably play a more important role in relation to aging. The glycation reaction is a largely uncon-

trolled process where sugar molecules are continuously added to the collagen molecules leading to accumulation of increasing amounts of AGEs throughout life (11, 25, 38). AGE accumulation is dependent on collagen turnover rates (11) and, therefore, accumulates to a higher extent in tissues with low turnover [tendon and cartilage (49, 122)] compared with tissues with higher turnover [skeletal muscle (42) and skin (122)]. Glycation has been reported to increase the distance between collagen molecules within tendon collagen fibrils, therefore, affecting their molecular structure (55), although to what extent molecular packing is influenced by age is unclear (55, 92). AGEs likely also contribute to the loss of water with age observed in the tendon (54), since cross-links cause dehydration of collagen (84). In animals, it has been shown that the proteoglycan content is reduced with age, at least in some tendons (54, 118), which would also contribute to a reduction in water content. Using magnetic resonance imaging (MRI) of human tendon in vivo, it has been shown that the MRI signal intensity is altered with aging, reflecting a change in the internal milieu of the tendon (19, 25), although the underlying cause is unclear.

In summary, there may be small increases in tendon CSA and enzymatic cross-links, as well as minor reductions in collagen content, fibril diameter, proteoglycan content, and molecular packing; however, these findings are not consistent. The only major and consistent compositional change with age is the accumulation of AGE cross-links (Fig. 1).

Effect of age on tendon mechanics. The mechanical properties of the tendon influence the overall function of the muscle-tendon complex, affecting parameters, such as the rate of force development, elastic energy return, and electromechanical delay (16, 79, 94). These parameters can affect balance and mobility, which are reduced in elderly people (97). Numerous studies on mechanics have been performed in animal models, and some of these show increased modulus and strength with age in rodents (93, 124, 131), while others show that the tendon is weaker and more compliant (28, 69, 110, 125), and yet others demonstrate a status quo (43, 44, 90). Maturation is normally associated with an increase in modulus and strength (43, 90, 95), and therefore, it is important to consider whether there is a component of maturation involved when studying aging, especially in short-lived species where maturity may differ markedly from that of humans (107). Several animal studies that include a middle-aged group show a tendency toward increased stiffness and strength from young to adult, with a decrease from adult to old (22, 69, 90), with one exception finding a major increase from adult to old, which may be related to calcification (131).

Tissues from human tendons have also been tested in vitro. Overall, these data suggest that there are either no changes or a reduction in the mechanical properties (modulus and strength) of the tendon with aging (30, 52, 56), which is in agreement with most of the findings in the animal data. In the past, investigating mechanical properties on living tissue has not been possible, but the arrival of ultrasound-based methods 20 years ago (31) made it possible to measure tendon deformation on humans in vivo (108). Of course, failure strength cannot be assessed in vivo, but studies on the modulus have reported unchanged (19, 23), as well as reduced (67, 97, 114), values with aging. In vivo measurements rely on voluntary muscle force to load the tendon, and, therefore, the strength of the subject will determine how much of the tendon stress-strain curve is probed. As strength tends to decline with age, an age-associated reduced tendon strain may, therefore, be due to a lower force placed on the tendon (64, 68). However, the overall picture suggests that with age, there is no change or a decrease in the modulus of the tendon. Although outside the scope of this review, it should be noted that estrogen may play a role in the homeostasis of female connective tissue, which could give rise to sex differences (36, 77).

In summary, there is not complete agreement on mechanical changes with age, but when the possible influence of maturation in animal studies is considered, a reduction in modulus and strength appears to be the most common finding (Fig. 1). Somewhat paradoxically, the most notable structural change with age is an increase in AGE cross-links (see *Effect of age on tendon structure and composition*), which would be expected to increase tendon modulus and strength. In vitro, it appears that glycation generally does lead to increased mechanical properties (8, 75), but in vivo, there is no clear evidence for such a relation. It is possible that the increase in AGEs is countered by a reduction in collagen content with age as mentioned above.

Effects of Exercise

Effect of exercise on tendon cell function. As people get older, they also tend to become less physically active and since the tendon is heavily loaded during exercise, it is reasonable to think that some of the changes seen with age may be related to physical activity. Tendon mechanical properties and cross-sectional area have been shown to increase in response to training in humans and animals (see below), which indicates that mechanical stimuli can lead to adaptive responses of the tendon cells and yield an altered extracellular matrix. However, the mechanisms responsible for these adjustments are still unclear, and there is a relatively large discrepancy between results from animal and human studies.

One hypothesis is that mechanical loading of tendon tissue during exercise or training initiates a signaling cascade that stimulates the cells located in the tissue to increase their production of matrix proteins, ultimately leading to tendon hypertrophy. This phenomenon—which is termed mechanotransduction—is well established and described in vitro (21). Cell culture studies on tendon and ligament fibroblasts show that they respond to mechanical stretch by increasing their production and secretion of certain growth factors, which, in turn, act on the fibroblasts to induce expression and synthesis of collagen (21). Growth factors involved in this signaling cascade include transforming growth factor-β1 (TGF-β1) and connective tissue growth factor (CTGF) (105, 133). In addition, more indirect evidence suggests that insulin like growth factor-I (IGF-I) could act as a link between mechanical load and collagen synthesis in tendon tissue (1, 41). Growth factor-mediated mechanotransduction is supported by animal experiments observing increases in IGF-I, TGF-β1, and collagen expression, following both extreme mechanical stimulus (electrostimulation, synergist ablation) (47, 48, 96), as well as more moderate treadmill exercise (41). Thus, it seems likely that the tendon cells respond to load by increasing growth factor production and that the action of these growth factors leads to induction of collagen expression. However, a causal link between growth factor and collagen expression has not been

proven, and the exact signaling pathways involved in transforming mechanical stimuli into biochemical signals in tendon remain unknown (34). In addition to growth factors, a study in rats showed a substantial increase in mRNA expression of the collagen cross-linking enzyme lysyl oxidase (LOX) in response to 4 days of strength training (47). This indicates that cells may also modify the matrix quality and not just quantity in response to exercise.

In humans, there is some support for a comparable loading-induced increase in tendon collagen synthesis. Increased levels in markers for collagen synthesis in response to both acute and long-term exercise have been measured by microdialysis in the peritendinous tissue surrounding the human Achilles tendon (70, 71). However, these data likely reflect the collagen synthesis at the very periphery of the tendon, or even outside the tendon, rather than that of the core tendon tissue. A more direct way of measuring collagen synthesis within the tissue is to trace incorporation of labeled amino acids in a tendon biopsy. With this approach, one study observed an increased rate of collagen synthesis in patellar tendons of young men in response to acute kicking exercise (85). However, several other studies have not confirmed this loading-induced collagen synthesis in human tendon using the same technique and exercise model (27, 36, 37, 101).

With regard to gene expression of growth factors and collagen in response to tendon loading, results in adult humans are inconsistent with the robust expression seen in rodents (discussed above). Studies have shown decreased or unchanged growth factor and collagen mRNA expression in the mid-portion of the tendon (45, 115), while one study found modest increases in collagen and CTGF mRNA expression in tissue from the proximal part of the patellar tendon in response to acute exercise (27). In other words, adult human tendon tissue seems less responsive than that of small animals. Such differences may relate to the fact that rats and mice are still in a growth phase when they are typically used in experiments (10–12 wk of age for rats) (47, 48, 96), and consequently, their tendons may have more potential for adaptation than adult human tendons. In addition, differences exist between different types of tendons; for example, data from horses show that high-load tendons have slower turnover than tendons subjected to more moderate loads (118). Finally, there are also regional differences within tendons, and animal studies commonly use the whole tendon, including the periphery, whereas samples from humans likely contain less of the peripheral material.

In summary, exercise markedly increases the expression of growth factors and matrix proteins in animals, while in humans the effect appears to be more modest. This discrepancy is possibly due to differences in maturation of animals compared with humans, or the result of sampling different tendon regions.

Effect of exercise on tendon structure and composition. It is well established that muscle can adapt to increased loading by hypertrophy, but to what extent tendons adapt to altered loading patterns has until recently largely been unknown. Animal studies investigating whether exercise yields a larger tendon have not provided a coherent picture (17, 50, 112). In humans, there is cross-sectional data, suggesting that endurance training is associated with a larger Achilles tendon cross-sectional area, which is more pronounced close to the insertion (25, 62, 78). Moreover, resistance training in humans appear to result in increases in tendon cross-sectional area (5, 61, 109), and it has been shown that subjects with a side-to-side difference (22%) in knee extensor strength as a result of habitual sport-specific high loading have a greater tendon cross-sectional area (20%) on the stronger side (24). Collectively, these studies support the notion that tendons hypertrophy in response to increased loading. If the hypertrophy represents tensile bearing components, i.e., principally collagen fibrils, the larger cross-section means that the stress across the tendon is reduced, which may play a role in injury prevention. However, a possible caveat is that exercise-induced hypertrophy could represent increased water content and not an actual accrual of collagen matrix.

Assuming that the hypertrophy is not just water, it indicates some level of synthetic activity, which is difficult to reconcile with the apparently slow rate of tendon tissue renewal after maturity (described previously). A possible explanation is that loading-induced tendon growth takes place at the very periphery of the tendon. This could be reconciled both with the 14C bomb pulse data that show very low turnover rates in the tendon core, as well as the fact that microdialysis experiments consistently indicate a loading-induced collagen synthesis in peritendinous tissue (49, 71). This hypothesis is supported by recent data on 6-mo-old mice, which showed that overload-induced plantaris tendon hypertrophy was based on growth and cell proliferation only in the most superficial layers of the tendon tissue, while the "original" core tendon remained relatively unchanged (33). Preferential hypertrophy at the tendon periphery is further supported by greater IGF-I protein expression and improved potential for growth and cell proliferation observed in cells located at the tendon periphery compared with those in the deeper parts of the tendon (41, 81, 116). It can be speculated that tendon growth occurs through the addition of new external "layers" of collagenous matrix, comparable with the growth rings of a tree.

Increased levels of proteoglycans with exercise have been reported in animals and may counteract the age-related loss previously mentioned, although little is known about the functional impact of these changes (134). The water-retaining properties of these proteoglycans may also be involved in the observed hypertrophy. While not always observed (25), some studies have reported increased mature enzymatic cross-linking with exercise (20, 60) in agreement with the increased LOX expression previously mentioned. There are also a number of studies that have reported reductions in nonenzymatic AGE content with exercise in tendon, especially in relation to aging, indicating that exercise may counteract the age-related increase in AGEs (25, 60, 132). It is unclear whether AGEs on existing collagen molecules are removed, but it appears more likely that the reduction is due to formation of new nonglycated collagen.

Data regarding the effect of exercise on the collagen fibril are relatively sparse. In animal models, mechanical loading has been shown to yield decreased, increased, or unchanged fibril diameter (83, 99, 100). Part of this variability is likely due to regional differences (103); in particular, if growth occurs at the tendon surface, as described above, then samples from the core region may be unchanged, while those from peripheral regions could display changes. Tissue for such analyses is harder to come by in humans, but in recent years, it has been possible to obtain microstructural and compositional data with the use of percutaneous tendon biopsies, although repeated biopsies remain a challenge (46). It has been proposed that exercise during skeletal maturation can influence the tendon fibril de-

velopment, but the fibril morphology of long-distance runners who were physically active did not differ from those who were physically inactive during their maturation (74). Similarly, life-long habitual running did not appear to appreciably influence fibril morphology compared with age-matched nonrunners (25). These relatively scant human data suggest that the collagen fibrils are largely unaffected by exercise. To what extent the various other ECM components are modulated in response to loading remains poorly understood.

In summary, exercise can produce tendon hypertrophy, possibly by growth in the peripheral region. In addition, proteoglycan content appears to increase and, in some cases, also enzymatic cross-linking, while AGEs can be reduced (Fig. 2). In general, the changes are consistent with formation of new tissue.

Effect of exercise on tendon mechanics. Endurance running in rabbits has been shown to not appreciably influence the mechanical properties of tendon (123), while others have shown that endurance training in swine augments both tendon stiffness and modulus (129, 130). In rats, it has been shown that endurance training may (50) or may not (73) augment the mechanical properties and that any increase may be intensity-related (12, 112). The effect of resistance training has very rarely been examined in animal models; only one study has examined its effect and could not demonstrate an augmentation of the mechanical properties of the tendon (110). Collectively, these data do not provide a clear depiction, and, in addition, species, exercise type, load magnitude, intensity, frequency, and duration differ between studies.

Numerous studies have been published using the in vivo ultrasound-based method previously mentioned (for a systematic review, see Refs. 15 and 128). Although it has been shown in cross-sectional studies that endurance athletes have a similar (104) or greater (66) tendon stiffness than untrained persons, a rare longitudinal study showed that 9 mo of running in previously sedentary persons did not alter the mechanical properties or size of the Achilles tendon in spite of conferring cardiovascular improvements (39). Because of the low tendon turnover in adults, it has been suggested that exercise prior to skeletal maturity may yield a stronger tendon that is more resistant to injury (111). However, recent data suggest that high or low activity during youth does not appreciably influence the mechanical, structural, or biochemical properties of the Achilles tendon of adult runners (74). In contrast to the few studies done on the effects of endurance training in humans, there have been numerous studies on the consequences of resistance training (128). Although the reported response is associated with considerable variation, it seems that resistance training yields increased stiffness and modulus along with a modest hypertrophy of the tendon (128). Most of these studies are of limited duration (12–14 wk); however, a cross-sectional study on athletes with large differences in leg strength (22%) due to habitual asymmetric loading, reported a robust increase in patellar tendon stiffness (36%) on the stronger side (24). In contrast the modulus did not differ significantly due to the previously mentioned increase in CSA (20%), which implies that the change in mechanical properties was primarily due to increased size, rather than a material change (24). In contrast, most short-term studies (weeks) do see changes in modulus (128). This indicates that there may be a rapid mechanism to alter the material properties (modulus), possibly through changes in enzymatic cross-linking, which is then followed by hypertrophy without altered material properties in the long term.

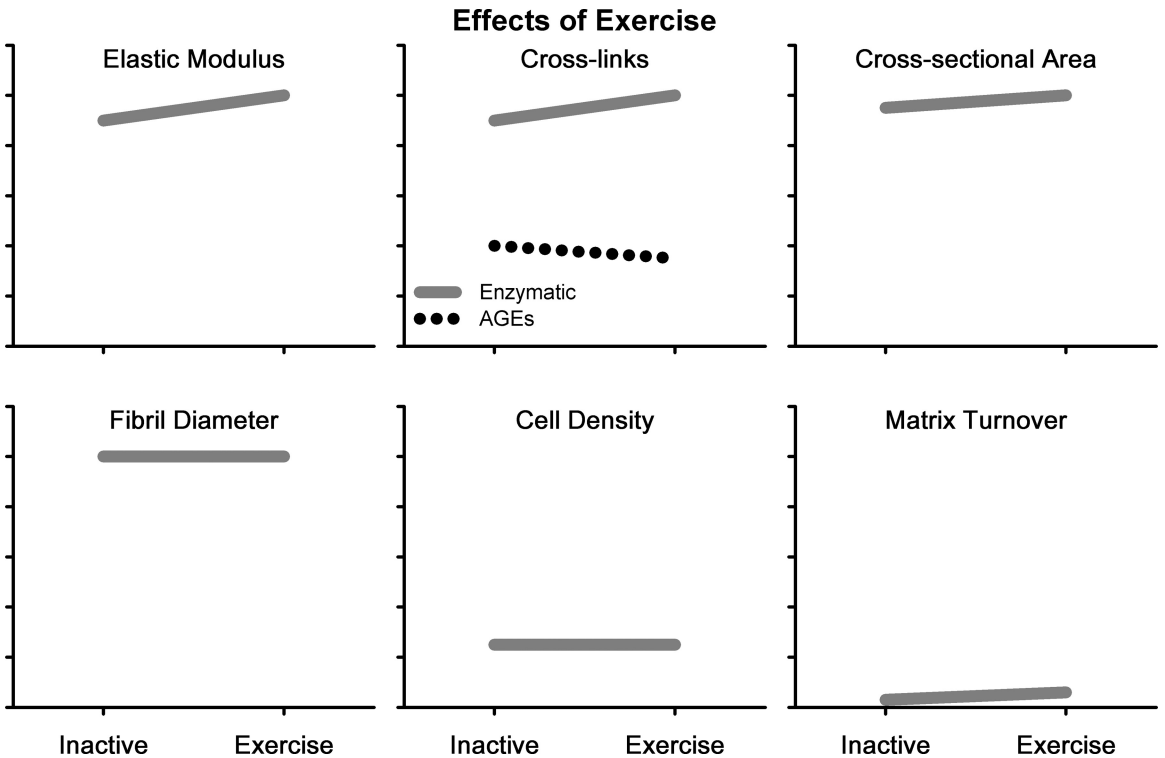

Fig. 2. Schematic overview of changes occurring in tendon tissue with exercise. The graphs do not represent actual data values but simply illustrate the overall trends. Values are placed on the same scale as in Fig. 1, such that the "Inactive" value corresponds to the "Mature" value. AGEs, advanced glycation endproducts.

Summary. Major cellular, structural, and mechanical changes largely take place during maturation, rather than during aging. Yet there appears to be a reduction in modulus and strength with aging that may contribute to the increased injury risk, although the mechanism for this alteration remains unknown. Exercise can stimulate the production of growth factors, and there is some evidence for an increase in tendon collagen synthesis, which is likely at the periphery rather than the core of the tendon. Collagen fibrils seem to be largely unaffected by exercise, while there can be some hypertrophy of the whole tendon. In contrast to aging, it appears that resistance training can yield increased stiffness and modulus of the tendon, which may help mitigate the risk of injury. These conclusions are based on a fair amount of contradictory data, and an important reason for these contradictions is likely the variation in experimental protocols regarding animal species, tendon types, tendon regions, age groups, and exercise regimes. More work is needed to clear up the influence of these parameters and enable more certain conclusions.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

R.B.S., K.M.H., C.C., M.K., and S.P.M. conception and design of research; R.B.S., K.M.H., C.C., M.K., and S.P.M. analyzed data; R.B.S., K.M.H., C.C., M.K., and S.P.M. interpreted results of experiments; R.B.S., K.M.H., C.C., M.K., and S.P.M. prepared figures; R.B.S., K.M.H., C.C., M.K., and S.P.M. drafted manuscript; R.B.S., K.M.H., C.C., M.K., and S.P.M. edited and revised manuscript; R.B.S., K.M.H., C.C., M.K., and S.P.M. approved final version of manuscript.

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