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Corrigendum

Corrigendum to: Tendon Cell Biology: Effect of Mechanical Loading

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Following publication of the article, inaccuracies were identified in bibliographic metadata, duplicate and incorrectly assembled reference records, citation-to-statement assignments, the attribution and presentation of figures, and selected technical statements. The authors subsequently conducted a comprehensive review of the references and their assignment to statements in the article. The corrections below are limited to matters requiring correction of the scientific record and are not intended to update or stylistically revise the published review.

Textual and citation corrections

Abstract

Published: Abstract Tendons play a crucial role in the musculoskeletal system, connecting muscles to bones and enabling efficient force transfer. However, they are prone to acute and chronic injuries, which, if not properly repaired, can significantly impair function. Tendinopathy, a prevalent condition affecting approximately 20% of musculoskeletal complaints, arises from an imbalance between micro-injury accumulation and repair processes. The extracellular matrix (ECM) of tendons is a hierarchical structure comprising collagen fibrils, proteoglycans, and glycoproteins that regulate organization, hydration, and mechanical properties. Mechanotransduction pathways, mediated by integrins and focal adhesion complexes, activate signaling cascades such as MAPK/ERK and PI3K/Akt, driving tenocyte gene expression and ECM remodeling. Adaptations to load involve region-specific remodeling, with tensile regions favoring aligned Type I collagen and compressive regions promoting proteoglycans like aggrecan. Stress shielding or reduced loading disrupts these pathways, leading to matrix disorganization and inflammation, predisposing tendons to degenerative changes. Insights into these molecular mechanisms inform rehabilitation strategies to enhance tendon repair and mitigate tendinopathy progression in both athletic and general populations.

Corrected: Abstract Tendons play a crucial role in the musculoskeletal system, connecting muscles to bones and enabling efficient force transfer. However, they are prone to acute and chronic injuries, which, if not properly repaired, can

significantly impair function. Tendinopathy is a common tendon disorder associated with an imbalance between tissue loading and repair/remodelling processes. The extracellular matrix (ECM) of tendons is a hierarchical structure comprising collagen fibrils, proteoglycans, and glycoproteins that regulate organization, hydration, and mechanical properties. Mechanotransduction pathways, mediated by integrins and focal adhesion complexes, activate signaling cascades such as MAPK/ERK and PI3K/Akt, driving tenocyte gene expression and ECM remodeling. Adaptations to load involve region-specific remodeling, with tensile regions favoring aligned Type I collagen and compressive regions promoting proteoglycans like aggrecan. Reduced loading and stress shielding can impair tendon mechanical properties and matrix organization; the specific molecular responses depend on the experimental model. Insights into these molecular mechanisms inform rehabilitation strategies to enhance tendon repair and mitigate tendinopathy progression in both athletic and general populations.

p. 677, opening paragraph

Published: Tendons are primarily composed of longitudinal bundles of collagen fibers that connect muscle to bone [1]. The backbone of the tendon is formed by Type I collagen, which is crucial for force transmission [2]. Other components of the tendon extracellular matrix include various collagen isoforms, glycoproteins, proteoglycans, and water [3]. Collagen accounts for approximately 70-80% of the adult tendon's dry weight [4, 5], with Type I collagen constituting 65-80% of this total collagen content [6, 7]. Water makes up about 55-70% of the wet mass of the tendon [8, 9].

Corrected: Tendons are dense connective tissues that transmit force between muscle and bone [1,2]. Type I collagen is the predominant structural collagen of tendon and is central to force transmission [1,2]. Other extracellular-matrix components include additional collagen isoforms, proteoglycans, glycoproteins, glycosaminoglycans, and water [1]. Type I collagen constitutes approximately 65-80% of tendon dry mass and approximately 95% of total tendon collagen [3].

p. 678, tendon hierarchy/ECM paragraph

Published: Force transmission in tendons relies on the highly organized structure of long, rope- like Type I collagen proteins, which are packed into hierarchical bundles along the tendon's long axis [10, 11]. Type I collagen is the most common collagen type and is composed of a heterotrimeric molecule formed by two alpha 1 and one alpha 2 chains [12]. The triple helix region of the collagen chain features the characteristic amino acid motif (Gly-X-Y), with glycine occupying every third residue to fit into the center of the triple helix, while proline and hydroxyproline frequently occupy the X and Y positions [13]. Other relevant residues include lysine, hydroxylysine, and arginine [13, 14]. Each collagen chain is synthesized in the endoplasmic reticulum as a pre-pro-protein and undergoes several post-translational modifications before forming a mature triple helix procollagen molecule in the matrix. Key post-translational modifications include the hydroxylation of proline residues for helix stability [15, 16] and the intermolecular crosslinking of adjacent lysine residues [17]. The three procollagen chains assemble into a right-handed triple helix to form procollagen

I, which is then deposited into the extracellular matrix along the line of force [18]. Procollagen I is processed into a mature collagen molecule after the cleavage of the N and C terminal propeptides [19]. The collagen fibrils are free to assemble in the pericellular space where the N and C-termini telopeptides are enzymatically crosslinked by lysyl oxidase [17]. These collagen fibrils pack into fibers, which are surrounded by an endotenon and bordered by resident tendon cells that help maintain the matrix. Individual collagen fibers can slide past each other during movement, though this movement is resisted by intermolecular crosslinks. Bundles of collagen fibers can be further organized into fascicles, which are surrounded by an epitenon sheath and separated by the interfascicular space where nerves and blood vessels pass [20, 21]. Fascicles are absent in smaller organisms such as rodents [11]. In larger animals, fascicles can slide independently to accommodate differences in tendon excursion during complex movements, such as those seen in the supraspinatus tendon during shoulder adduction and abduction [22]. Fascicles within a single tendon are encased by a synovial sheath (as in hand and foot tendons) or a loose fibrillar tissue known as the paratenon (as in the Achilles tendon) [23]. Beyond Type I collagen, the tendon matrix contains numerous other collagen isoforms and non-collagenous proteins, which vary regionally within a tendon and between tendons with distinct functions [24]. Type III collagen accounts for up to 10% of the dry mass of a normal tendon [25] [7]. While the function of Type III collagen in healthy tendon is not fully understood, it tends to form smaller fibrils in vitro [26, 27] and assists in the longitudinal growth of Type I collagen fibrils by limiting lateral growth [28]. The patellar tendon and anterior cruciate ligament differ in collagen composition, with the patellar tendon having a greater Type I collagen concentration and lower Type III collagen concentration [7]. Other minor collagens such as types V, VI, XI, XII, and XIV are suggested to play roles in collagen fibril and fiber organization [29]. Type II collagen is most common in cartilage but can also occur in tendon fibrocartilage as an adaptation to compression, such as in wrap-around tendons, under an aponeurosis, or at the enthesis [30, 31]. Glycoproteins (GAGs) are a large class of non-collagen proteins characterized by a protein core with small covalently linked carbohydrate side chains. GAGs are linear polysaccharides containing an amino sugar. Tenomodulin (TNMD) and thrombospondin 4 (THBS4) are two glycoproteins highly expressed in tendon and ligament compared to other musculoskeletal tissues [32]. Tenomodulin is a transmembrane glycoprotein [33] with unknown binding partners [29] that is crucial for the proliferation of tendon stem/progenitor cells [34]. TNMD knockout mice exhibit reduced cell proliferation during development and abnormal collagen fibril diameter [35]. Thrombospondin 4 is an adhesive glycoprotein that forms complexes with cartilage oligomeric matrix protein (COMP) [36], a member of the thrombospondin protein family [37]. In weight-bearing tendons, COMP is more prevalent in regions that lack tension [38] and may play a role in collagen fibrillogenesis [39, 40]. Tenascin C is another glycoprotein associated with areas of tendon compression [31] and its levels are regulated by mechanical load [41].

Corrected: Force transmission in tendons relies on highly organized type I collagen arranged hierarchically along the tendon's long axis [2]. Type I collagen is a heterotrimer composed of two alpha1(I) chains and one alpha2(I) chain [4]. The triple helix region of the collagen chain features the characteristic amino acid motif (Gly-X-Y), with glycine

occupying every third residue to fit into the center of the triple helix, while proline and hydroxyproline frequently occupy the X and Y positions [5]. Other relevant residues include lysine and hydroxylysine, which participate in collagen post-translational modification and crosslinking [5,6]. Each collagen chain is synthesized in the endoplasmic reticulum as a pre-pro-protein and undergoes several post-translational modifications before forming a mature triple helix procollagen molecule in the matrix. Key post-translational modifications include the hydroxylation of proline residues for helix stability [7,8] and the intermolecular crosslinking of adjacent lysine residues [6]. The three procollagen chains assemble into a right-handed triple helix to form procollagen I, which is then deposited into the extracellular matrix along the line of force [9]. Procollagen I is processed into a mature collagen molecule after the cleavage of the N and C terminal propeptides [10]. The collagen fibrils are free to assemble in the pericellular space where the N and C-termini telopeptides are enzymatically crosslinked by lysyl oxidase [6]. These collagen fibrils pack into fibers, which are surrounded by an endotenon and bordered by resident tendon cells that help maintain the matrix. Individual collagen fibers can slide past each other during movement, though this movement is resisted by intermolecular crosslinks. Bundles of collagen fibers can be further organized into fascicles, which are surrounded by an epitenon sheath and separated by the interfascicular space where nerves and blood vessels pass [11,12]. In larger animals, fascicles can slide independently to accommodate differences in tendon excursion during complex movements, such as those seen in the supraspinatus tendon during shoulder adduction and abduction [13]. Fascicles within a single tendon are encased by a synovial sheath (as in hand and foot tendons) or a loose fibrillar tissue known as the paratenon (as in the Achilles tendon) [14]. Beyond Type I collagen, the tendon matrix contains numerous other collagen isoforms and non-collagenous proteins, which vary regionally within a tendon and between tendons with distinct functions [15]. Type III collagen is a minor component of normal tendon and can influence fibril and bundle organization when present with type I collagen [1,16]. The patellar tendon and anterior cruciate ligament differ in collagen composition, with the patellar tendon having a greater Type I collagen concentration and lower Type III collagen concentration [17]. Other minor collagens such as types V, VI, XI, XII, and XIV are suggested to play roles in collagen fibril and fiber organization [18]. Type II collagen can occur in tendon fibrocartilage at sites adapted to compression, including wrap-around regions and entheses [19]. Glycoproteins are non-collagenous proteins with covalently attached carbohydrate chains. Glycosaminoglycans (GAGs), in contrast, are linear polysaccharides composed of repeating disaccharide units and commonly occur as carbohydrate chains in proteoglycans. Tenomodulin (TNMD) and thrombospondin 4 (THBS4) are two glycoproteins highly expressed in tendon and ligament compared to other musculoskeletal tissues [20]. Tenomodulin is a type-II transmembrane glycoprotein involved in tenocyte and tendon stem/progenitor-cell proliferation [21,22]. TNMD knockout mice exhibit reduced cell proliferation during development and abnormal collagen fibril diameter [21]. Thrombospondin 4 can form heterooligomeric complexes with cartilage oligomeric matrix protein (COMP) [23], a member of the thrombospondin protein family [24]. COMP distribution varies with tendon region and mechanical environment, and COMP can participate in

collagen fibrillogenesis [25]. Tenascin-C is an extracellular-matrix glycoprotein whose expression at the osteotendinous junction is regulated by mechanical loading [26].

p. 679, proteoglycans and tendon-cell populations

Published: Proteoglycans (PGs), a subgroup of glycoproteins, are characterized by the covalent attachment of long carbohydrate glycosaminoglycan side chains (GAGs) to a core protein. PGs are embedded within the collagen matrix and help regulate collagen organization and tissue hydration. The abundance of specific PGs varies depending on the biomechanical environment. Canonical small leucine-rich proteoglycans (SLRPs) are a class of PGs with collagen binding domains characterized by a leucine-rich repeat region [42]. Decorin and biglycan are modified with one or two dermatan sulfate GAG side chains, respectively [43]. Shortly after birth, biglycan content is nearly twice that of decorin. As animals begin to walk, gene expression and protein levels of decorin increase while those of biglycan decrease [44, 45]. Decorin binds procollagen to assist with collagen fibril assembly [46] and may prevent the association of collagen fibrils with each other. Decorin is moderately expressed into adulthood, while biglycan expression is minimal in mature tendons [44][45]. In adult tendons, decorin and biglycan are essential for maintaining collagen fibril diameter and mechanical properties [47]. Fibromodulin and lumican are two other SLRPs common in tendons that contain two keratan sulfate GAG chains [43]. Lumican and fibromodulin inhibit collagen fibril assembly early in post-natal tendon development, transitioning to assist with fibril growth, with fibromodulin continuing to promote fibril growth throughout adolescence [48]. SLRPs are more highly expressed in cells under tension, whereas tendon cells under compression synthesize more large PGs [49]. Large PGs, such as aggrecan, hold substantially more water, helping to resist matrix compression [50]. Consequently, aggrecan is more prevalent in compressed tendon regions and cartilage [51, 52, 53, 50]. Versican, another large proteoglycan, is present in tendons but is more concentrated in ligaments [7, 54]. Tendons have relatively few cells compared to other tissues, yet they contain multiple cell types, each with distinct functions. Over 70% of cells in a tendon are tenocytes, which synthesize high levels of collagen and function to maintain the matrix. Endothelial cells are the next most abundant cell population, with the remaining cells comprising pericytes, nerve cells, red blood cells, and immune cells [55][56]. Tenocytes are elongated, spindle-shaped fibroblast cells with extended cell processes located between collagen fibers in the endotenon and outside collagen fascicles in the epitenon [20]. In larger organisms with fascicles, most cells are located in the interfascicular matrix [57][24]. Tendons are surrounded by a paratenon, which contains a thin layer of cells that do not express scleraxis [58]. The tendon proper cells and peritenon cells have different transcriptional characteristics, with tendon proper progenitor cells expressing higher levels of scleraxis (Scx) and mohawk (Mkx) [59]. Multiple studies have demonstrated the existence of stem/progenitor cells within tendons, though their exact location and markers vary. In 2007, Marian Young's group identified cells isolated from human and mouse tendons that met stem cell classification criteria: self-renewal capacity, clonogenicity, and multipotency [60]. Subsequently, tendon stem cells were identified in the middle region of rabbit patellar and Achilles tendons [61]. Mienaltowski and

colleagues later showed that stem/progenitor cells within the tendon proper and peritenon are regionally distinct [59][62]. Tendon stem cells were also identified in the patellar tendon sheath of adult rats [63]. Tendon cells are linked to each other and the extracellular matrix through cell junctions, which facilitate communication between tenocytes. The main classes of cell junctions are occluding junctions (e.g., tight junctions), anchoring junctions (e.g., cadherins and integrins), and communicating junctions (e.g., gap junctions) [64]. These cell junctions persist in adult tendon despite the lower cellularity and higher matrix composition compared to embryonic and early post-natal development [51][65]. Gap junctions in vertebrates, composed of connexin proteins, allow for cell-cell communication via ion and small molecule diffusion. Connexin-32 and -43 are present at high levels in embryonic tendon and decline post-natally [66]. In adult tendons, connexin 43 is found at meeting points between cell processes and cell bodies, whereas connexin 32 is only found between cell bodies [67].

Corrected: Proteoglycans (PGs) consist of a core protein with one or more covalently attached glycosaminoglycan (GAG) chains. PGs are embedded within the collagen matrix and help regulate collagen organization and tissue hydration. The abundance of specific PGs varies depending on the biomechanical environment. Canonical small leucine-rich proteoglycans (SLRPs) are a class of PGs with collagen binding domains characterized by a leucine-rich repeat region [27]. Decorin and biglycan are small leucine-rich proteoglycans carrying chondroitin/dermatan sulfate GAG chains [28]. Shortly after birth, biglycan content is nearly twice that of decorin. As animals begin to walk, gene expression and protein levels of decorin increase while those of biglycan decrease [29,30]. Decorin binds procollagen to assist with collagen fibril assembly [31] and may prevent the association of collagen fibrils with each other. Decorin is moderately expressed into adulthood, while biglycan expression is minimal in mature tendons [29][30]. In adult tendons, decorin and biglycan are essential for maintaining collagen fibril diameter and mechanical properties [32]. Fibromodulin and lumican are additional SLRPs found in tendon and contribute to collagen fibril organization [28,33]. Lumican and fibromodulin inhibit collagen fibril assembly early in post-natal tendon development, transitioning to assist with fibril growth, with fibromodulin continuing to promote fibril growth throughout adolescence [33]. Large PGs, such as aggrecan, hold substantially more water, helping to resist matrix compression [34]. Consequently, aggrecan is enriched in compression-adapted tendon regions [19,35]. Tendons have relatively few cells compared to other tissues, yet they contain multiple cell types, each with distinct functions. Tenogenic fibroblasts/tenocytes constitute a major resident tendon-cell population, alongside endothelial, perivascular, immune, and other cell populations [36]. Tenocytes are elongated, spindle-shaped fibroblast cells with extended cell processes located between collagen fibers in the endotenon and outside collagen fascicles in the epitenon [11]. In larger organisms with fascicles, most cells are located in the interfascicular matrix [2][15]. Tendons are surrounded by a paratenon, which contains a thin layer of cells that do not express scleraxis [37]. Tendon-proper and peritenon-derived progenitor populations show distinct transcriptional and tenogenic properties [38,39]. Multiple studies have demonstrated the existence of stem/progenitor cells within tendons, though their exact location and

markers vary. In 2007, Marian Young's group identified cells isolated from human and mouse tendons that met stem cell classification criteria: self-renewal capacity, clonogenicity, and multipotency [40]. Subsequent work identified distinct progenitor populations within tendon proper and peritenon [38,39]. Tendon cells are linked to each other and the extracellular matrix through cell junctions, which facilitate communication between tenocytes. The main classes of cell junctions are occluding junctions (e.g., tight junctions), anchoring junctions (e.g., cadherins and integrins), and communicating junctions (e.g., gap junctions) [41]. Cell-cell adhesion structures persist in adult tendon [42]. Gap junctions in vertebrates, composed of connexin proteins, allow for cell-cell communication via ion and small molecule diffusion. Adult tendon cells form a three-dimensional network of cell processes linked by gap junctions [43].

p. 680, cadherin/integrin paragraph

Published: Cadherins, a type of cell-cell anchoring junction, are crucial in tendon development. Cadherin-11 and N-cadherin are the most commonly studied cadherins. Embryonic tendons require cadherin-11 and N-cadherin for proper formation, with N-cadherin localized to the tendon periphery and cadherin-11 restricted to the midsubstance [68][69]. In adult tendon, N-cadherin is found at cell-cell junctions, and its amount increases with radial stretch of adult tendon cells [70]. Integrins play a critical role in transmitting mechanical information by linking the extracellular matrix to the intracellular actin cytoskeleton. Integrin subunits α1 and α2 are widely expressed [35], with integrin α11 specifically localized around dense Type I collagen and binding Type I collagen at high affinity [71][35]. The integrin α11 promoter contains consensus sequences for binding a tendon/ligament-specific transcription factor, scleraxis, indicating its relevance in tendon mechanotransduction [71]. Mechanical stretch of tendon stem/progenitor cells increases the expression of multiple integrin subtypes (including α1/2/11) and activates downstream kinases ERK and p38 [72]. Integrins are essential for tendon mechanotransduction, as evidenced by studies showing that fibroblasts with ligand- bound integrins can stiffen their cytoskeleton in response to restraining forces [73].

Corrected: Cadherins, a type of cell-cell anchoring junction, are crucial in tendon development. Cadherin-11 and N-cadherin are the most commonly studied cadherins. Cadherin-11-mediated cell-cell junctions are required for normal tendon development [44]. In adult tendon, N-cadherin is found at cell-cell junctions, and its amount increases with radial stretch of adult tendon cells [42]. Integrins play a critical role in transmitting mechanical information by linking the extracellular matrix to the intracellular actin cytoskeleton. Integrin subunits α1 and α2 are widely expressed [21], with integrin α11 specifically localized around dense Type I collagen and binding Type I collagen at high affinity [45][21]. The integrin α11 promoter contains consensus sequences for binding a tendon/ligament-specific transcription factor, scleraxis, indicating its relevance in tendon mechanotransduction [45]. Mechanical loading can alter integrin-related and downstream signaling in tendon cells [46]. Integrins are essential for tendon mechanotransduction, as evidenced by studies showing that fibroblasts with ligand- bound integrins can stiffen their cytoskeleton in response to restraining forces [47].

p. 680, loading-type paragraph

Published: Tendons possess a remarkable ability to adapt to various types of mechanical loads, with the most notable adaptations occurring in response to tensile and compressive forces. There are three primary types of mechanical loads experienced by tendons within the musculoskeletal system: tension (where the tissue is pulled in one direction), compression (where the tissue is pushed from one or more directions), and shear (where the tissue is subjected to sliding forces). These adaptive processes begin as early as in utero or ovo. Tendons that develop under tensile loads exhibit a dense, well-aligned matrix predominantly composed of Type I collagen. Conversely, tendons subjected to compressive loads display a fibrocartilage phenotype, characterized by sparsely connected, unaligned, and smaller Type I collagen fibers, alongside larger proteoglycans. Tendons exposed to shear forces exhibit a partially aligned collagen matrix and produce high levels of surface lubricating proteins such as lubricin (proteoglycan 4) and hyaluronic acid [51][74][75][76] [77]. During embryonic and post-natal development, most tendons experience an increase in collagen content and a decrease in cellularity [51][65][78]. These changes in tissue composition during fetal development are associated with an increase in lysyl oxidase- mediated crosslinks, resulting in greater modulus [78]. Although significant differences in collagen organization between tensile and compressive tendon regions become apparent

Corrected: Tendons possess a remarkable ability to adapt to various types of mechanical loads, with the most notable adaptations occurring in response to tensile and compressive forces. There are three primary types of mechanical loads experienced by tendons within the musculoskeletal system: tension (where the tissue is pulled in one direction), compression (where the tissue is pushed from one or more directions), and shear (where the tissue is subjected to sliding forces). These adaptive processes begin as early as in utero or ovo. Tendons that develop under tensile loads exhibit a dense, well-aligned matrix predominantly composed of Type I collagen. Conversely, tendons subjected to compressive loads display a fibrocartilage phenotype, characterized by sparsely connected, unaligned, and smaller Type I collagen fibers, alongside larger proteoglycans. Compression-adapted tendon regions contain increased proteoglycan-rich fibrocartilaginous matrix, and cyclic compression can increase lubricin expression in tendon cells [19,48]. During embryonic and post-natal development, tendon matrix maturation includes increasing collagen organization and lysyl-oxidase-mediated crosslinking, accompanied by increasing mechanical properties [49]. Although significant differences in collagen organization between tensile and compressive tendon regions become apparent

p. 681, adult adaptation and early turnover discussion

Published: Once tendons reach their adult length, changes in loading can lead to circumferential growth, enhancing mechanical properties. In humans, two to three months of training can significantly increase tendon stiffness and cross-sectional area. High-intensity training, which involves greater jerk forces, has a more substantial effect than lower intensity exercise, while the type of muscle contraction does not affect tendon stiffness [81]. Studies show that intercollegiate male and female cross-country runners increased their Achilles tendon cross-sectional area (CSA) during the first three to six weeks of the season [82], and lifelong distance runners have larger Achilles tendon CSA compared to non-runners [83]. Similarly, intercollegiate female soccer players increased their anterior cruciate ligament (ACL) volume throughout the competitive season [84]. In animal models, six weeks of running in mice increased Achilles tendon mass, fibroblast density, and CSA [85]. Swimming exercise for one hour a day over five to seven weeks also increased total protein in rat Achilles tendons, indicating that jerk is not necessary to drive tendon adaptations [86]. These tendon adaptations are attributed to the direct load applied to the tendon rather than a systemic exercise effect. For instance, in humans, only the loaded patellar tendon increases in CSA and stiffness after twelve weeks of unilateral resistance training [87]. Long-term training of one limb more than the other results in significantly larger and stiffer tendons in the dominant leg [88]. Conversely, two weeks of immobilization in elderly men resulted in an 80% reduction in tendon collagen synthesis [89]. These findings suggest that connective tissues are highly dynamic and acutely responsive to load. The collagen content in tendons and ligaments is balanced between collagen synthesis and incorporation versus degradation. Degradation can occur through the breakdown of the existing dense collagen matrix or the degradation of newly synthesized collagen before its incorporation. One of the early studies examining collagen metabolism in response to load involved hanging a weight on a chicken wing for 45-50 hours, which resulted in a fivefold increase in collagen synthesis and a two-and-a-half-fold decrease in degradation before incorporation [90]. The extent of collagen turnover in adult tendons is debated. Early studies using the 14C bomb pulse method suggested that the central core of adult tendons does not turnover after the age of 17 [91][92]. During the period of nuclear bomb testing from 1955-1963, there was a sharp increase in 14C content in the atmosphere, which began to decrease exponentially after the Test Ban Treaty in 1963. The correlation between 14C levels in the core of the Achilles tendon and atmospheric 14C levels on subjects' seventeenth birthdays suggested that tendon cores only turnover during skeletal growth or regeneration [91]. This method showed no regional differences in collagen turnover in human patellar tendons [5]. Supporting this, collagen proteins in horses have a 100-fold longer half-life than non-collagen proteins in high-strain superficial digital flexor tendons (SDFTs) and a 10-fold longer half- life in low-strain common digital extensor tendons (CDETs) [93]. However, studies using...

Corrected: Once tendons reach their adult length, changes in loading can lead to circumferential growth, enhancing mechanical properties. In humans, two to three months of training can significantly increase tendon stiffness and cross-sectional area. Higher-magnitude loading interventions generally produce greater tendon adaptation than low-magnitude loading, whereas contraction mode alone is not a consistent determinant of tendon stiffness [51]. Studies show that intercollegiate male and female cross-country runners increased their Achilles tendon cross-sectional area (CSA) during the first three to six weeks of the season [52], and lifelong distance runners have larger Achilles tendon CSA compared to non-runners [53]. Similarly, intercollegiate female soccer players increased their anterior cruciate ligament (ACL) volume throughout the competitive season [54]. In animal models, six weeks of

running in mice increased Achilles tendon mass, fibroblast density, and CSA [55]. These tendon adaptations are attributed to the direct load applied to the tendon rather than a systemic exercise effect. For instance, in humans, only the loaded patellar tendon increases in CSA and stiffness after twelve weeks of unilateral resistance training [56]. Habitual asymmetric sport loading is associated with greater patellar-tendon cross-sectional area and stiffness in the more heavily loaded limb [57]. Conversely, two weeks of lower-limb immobilization in elderly men markedly reduced tendon collagen synthesis [58]. These findings suggest that connective tissues are highly dynamic and acutely responsive to load. The collagen content in tendons and ligaments is balanced between collagen synthesis and incorporation versus degradation. Degradation can occur through the breakdown of the existing dense collagen matrix or the degradation of newly synthesized collagen before its incorporation. The extent of collagen turnover in adult tendons is debated. Bomb-pulse radiocarbon analysis demonstrated very limited renewal of collagen in the core of the adult human Achilles tendon after skeletal maturity [59]. During the period of nuclear bomb testing from 1955-1963, there was a sharp increase in 14C content in the atmosphere, which began to decrease exponentially after the Test Ban Treaty in 1963. The correlation between 14C levels in the core of the Achilles tendon and atmospheric 14C levels on subjects' seventeenth birthdays suggested that tendon cores only turnover during skeletal growth or regeneration [59]. In healthy human patellar tendon, radiocarbon analysis found no detectable regional differences in lifelong collagen turnover [60]. In equine tendons, aspartic-acid racemization indicates markedly longer collagen half-life than non-collagenous-protein half-life, with differences between tendon types [61]. However, studies using...

p. 682, stable isotopes/IGF-1/ERK/estrogen/transcriptome

Published: stable isotopes suggest that whole tendon and ligament protein synthesis rates are similar to muscle [94]. Although stable isotope measurements do not account for protein breakdown, they suggest that collagen turnover in tendons or ligaments is much higher than previously thought. This discrepancy indicates that while the core of the tendon may not turnover, the outer part does, at rates faster than the whole tissue turnover rate. The molecular and cellular mechanisms mediating collagen content increases with load are not fully understood. Progenitor cells are thought to migrate towards the core of the tendon in response to loading. Six weeks of treadmill running in young mice localized scleraxis (Scx) expression to the epitenon and between collagen fibers, suggesting that tendon cells emerge from the outer layer and migrate towards the core [85]. Insulin-like growth factor 1 (IGF-1) is one of the first molecules identified to play a role in tendon hypertrophy in response to load. In the rat Achilles tendon, loading increased IGF- 1 concentration within tendon cells, while unloading decreased it [95]. Furthermore, IGF-1 expression increased 24 hours after four days of training, regardless of muscle contraction type [96]. In a model of plantaris tendon hypertrophy, mice with IGF-1 receptor knockout in scleraxis-positive cells experienced reduced tendon hypertrophy after loading. In vitro, IGF- 1 application activates PI3K/Akt and ERK signaling pathways, promoting tenocyte protein synthesis and cell proliferation [97]. IGF-1 also increases collagen

and mechanical properties in engineered ligaments [98]. ERK signaling, which can be activated directly by load, also plays a role in increasing collagen content. Ten minutes of loading is sufficient to activate ERK, and intermittent loading optimized for ERK1/2 phosphorylation increases collagen content more than continuous loading [99][100]. ERK may increase collagen content through EGR1, a transcription factor for collagen Iα1 [101]. Both male and female tendons hypertrophy with load, but the mechanisms of increasing collagen content may differ due to the role of estrogen. In men, a leg-kicking protocol increased patellar tendon collagen fractional synthesis rates (FSR), peaking 24 hours post-exercise and remaining elevated 72 hours later [102]. In women in their follicular phase, the same exercise did not increase patellar tendon collagen FSR 24 hours post-exercise [103]. However, post- menopausal women not on estrogen replacement therapy (ERT) had lower tendon collagen FSR but higher PINP (synthesis) after resistance exercise than those on ERT. At rest, ERT users had more medium-sized and fewer larger collagen fibrils than non-ERT users [103]. Proteomics studies support estrogen's beneficial effects on collagen incorporation, with pre-menopausal females having higher Type I collagen content in the ACL and patellar tendon compared to males [7]. However, estrogen can also result in smaller Achilles tendon CSA, as observed in monozygotic twins where only one took ERT and in active women on ERT [104] [105]. These data indicate that estrogen modulates collagen synthesis and incorporation in response to load, and this response changes as women transition through menopause. Adult tendons in different mechanical environments (tension vs. compression) exhibit regional gene expression variations. For example, energy-storing tendons like the rat Achilles and patellar tendons have similar transcriptomes, while the supraspinatus tendon, subjected to compressive loads, shows distinct gene expression profiles [106]. In adult bovine flexor tendons, tensile regions show no expression for collagen I, II, decorin, and biglycan, while compressed regions show varied expression depending on the distance from the tendon surface [53]. Over time, loading history leads to epigenetic encoding of gene expression differences. Tendon cells from tensile regions produce more small proteoglycans and fewer large proteoglycans than cells from compressed regions or chondrocytes [49]. Acute changes in load, however, can dramatically alter gene expression. Ex vivo compressive loading of tendons for 72 hours increases aggrecan mRNA and protein levels [80]. These studies highlight the role of tensional loads in promoting a tendon cell phenotype and compressive loads in inducing fibrocartilage gene expression. Tendon cells in normally structured, healthy tendons primarily experience tensile loads, while cells near entheses or where tendons wrap around bones experience compressive loads and adopt a fibrocartilage- like phenotype. Over time, cells become epigenetically tuned to their loading environment, though acute load changes can lead to phenotypic shifts.

Corrected: stable-isotope measurements show that protein synthesis rates in tendon and cruciate ligament are of the same order of magnitude as skeletal muscle [62]. Stable-isotope measurements assess short-term protein synthesis rather than lifelong collagen replacement and therefore should not be used to infer a specifically rapid peripheral turnover rate. The molecular and cellular mechanisms mediating collagen content increases with load are not fully understood. Progenitor cells are

thought to migrate towards the core of the tendon in response to loading. Six weeks of treadmill running in young mice localized scleraxis (Scx) expression to the epitenon and between collagen fibers, suggesting that tendon cells emerge from the outer layer and migrate towards the core [55]. Insulin-like growth factor 1 (IGF-1) is one of the first molecules identified to play a role in tendon hypertrophy in response to load. Short-term strength training increased expression of IGF-I isoforms in rat tendon across contraction types [63]. EGR1 is a transcriptional regulator involved in tendon differentiation and type-I-collagen expression [64]. The published specific IGF-1 engineered-ligament and ERK loading claims are removed because their assigned references do not support those experiments. Both male and female tendons hypertrophy with load, but the mechanisms of increasing collagen content may differ due to the role of estrogen. In men, one-legged kicking exercise increased patellar-tendon collagen synthesis over the post-exercise period, with a peak at approximately 24 hours [65]. In women, tendon collagen fractional synthesis was lower than in men, and the studied exercise response differed from that observed in men [66]. In postmenopausal women, estrogen replacement therapy was associated with differences in tendon collagen synthesis, structural characteristics, and the response to exercise [67]. Sex-associated proteomic differences have been reported in the ACL and patellar tendon [17]. Hormone-replacement therapy has been associated with differences in Achilles-tendon size in monozygotic twins and with smaller Achilles-tendon diameter in active postmenopausal women [68,69]. These data indicate that estrogen modulates collagen synthesis and incorporation in response to load, and this response changes as women transition through menopause. Adult tendons in different mechanical environments (tension vs. compression) exhibit regional gene expression variations. Functionally divergent limb tendons show distinct transcriptomic profiles [70]. In adult bovine flexor tendons, tensile regions show no expression for collagen I, II, decorin, and biglycan, while compressed regions show varied expression depending on the distance from the tendon surface [71]. Over time, loading history leads to epigenetic encoding of gene expression differences. Acute changes in load, however, can dramatically alter gene expression. Ex vivo compressive loading of tendon for 72 hours increases aggrecan mRNA and promotes aggrecan synthesis and accumulation [50]. These studies highlight the role of tensional loads in promoting a tendon cell phenotype and compressive loads in inducing fibrocartilage gene expression. Tendon cells in normally structured, healthy tendons primarily experience tensile loads, while cells near entheses or where tendons wrap around bones experience compressive loads and adopt a fibrocartilage- like phenotype. Over time, cells become epigenetically tuned to their loading environment, though acute load changes can lead to phenotypic shifts.

p. 683, immobilization paragraph
Published: The detrimental impact of extended immobilization or disuse on the mechanical strength of tendons and ligaments was first documented in 1977. In a controversial study, primates were subjected to eight weeks of total body plaster immobilization (no weight-bearing) or single lower limb immobilization. Following eight weeks of total body immobilization, the maximum load capacity of the ACL

decreased by 40%, from 78 kg to 46.79 kg, and the linear stiffness reduced by approximately 30%. After five months of reloading, the maximum tensile load (MTL) recovered to 79% of the baseline value. Twelve months of reloading saw MTL return to 91% of the baseline, which was not statistically different from the control group. In contrast, linear stiffness recovered to 90% of baseline after five months and was fully restored by twelve months. This suggests that a complete lack of weight-bearing for eight weeks causes a disproportionate loss in tissue material, contributing to maximal load (such as collagen content), which cannot be fully recovered within a year. However, tissue structures contributing to stiffness (such as collagen crosslinks) are lost more slowly and can be recovered more rapidly during the reloading period. In the single leg immobilization part of the study, the ACL's maximal load and stiffness decreased by 22% over eight weeks. This single leg immobilization posed a different challenge from full body immobilization because the animal's overall activity was maintained, and the non-immobilized leg was loaded normally. This indicates that there may be a systemic signal from loading that helps mitigate the reduction in tissue mechanics. It appears that tissue stiffness is less sensitive to a direct mechanical load signal compared to MTL, as it similarly reduced under both full body (30% reduction) and single leg (22% decrease) immobilization. These findings suggest that a systemic signal from loading may better mitigate the reduction in MTL than stiffness during immobilization, as MTL decreases by half as much in the single leg immobilization (22% decrease) compared to full body immobilization (40% decrease) [107].
Corrected: After eight weeks of total-body plaster immobilization in rhesus monkeys, ligament units showed a 39% decrease in maximum failure load and a 32% decrease in energy absorbed to failure, together with a significant decrease in stiffness [72]. After five months of resumed activity, ligament strength had only partially recovered, although stiffness/compliance had returned to control values; complete recovery of strength parameters required up to 12 months [72]. The published single-limb percentage comparison and the proposed systemic/collagen-crosslink mechanisms are removed because they are not established by the cited source.

pp. 683-684, tendon mechanics and viscoelasticity
Published: Tendons are essential connective tissues that play a key role in force transmission between muscles and bones, enabling complex movements such as running, jumping, and lifting. They serve as an intermediary between muscle-generated forces and the skeletal system, ensuring that forces are transmitted efficiently and accurately to produce controlled movements [108]. To achieve this function, tendons must combine strength, flexibility, and resilience, properties that are derived from their unique mechanical characteristics, including elasticity, viscosity, and viscoelasticity. These properties are essential for tendons to withstand both high tensile forces during muscular contraction and compressive forces at bone insertion points [109]. Viscoelasticity refers to a material's ability to exhibit both elastic (spring-like) and viscous (fluid-like) behaviors, which allows tendons to respond to mechanical loading in a time-dependent manner [110]. This viscoelastic behavior is crucial for the efficient transmission of muscular forces and the absorption of mechanical shocks during high-intensity activities [111]. Furthermore, this viscoelastic nature

allows tendons to buffer and dissipate mechanical energy, preventing excessive stress concentration that could lead to microdamage and eventual injury [112]. The primary component of tendons responsible for their high tensile strength is type I collagen, which makes up approximately 65-80% of the tendon's dry weight [113]. Collagen is organized into hierarchical structures, starting from the molecular level and extending to fibrils, fibers, fascicles, and the whole tendon [114]. At the molecular level, collagen molecules form a triple helix structure, which assembles into microfibrils and then into larger fibrils, providing the tendon with its characteristic crimped pattern. This crimp pattern is essential for allowing tendons to elongate with minimal resistance under low tensile forces, providing initial flexibility [115]. As tension increases, the collagen fibers...

Corrected: Tendons are essential connective tissues that play a key role in force transmission between muscles and bones, enabling complex movements such as running, jumping, and lifting. They serve as an intermediary between muscle-generated forces and the skeletal system, ensuring that forces are transmitted efficiently and accurately to produce controlled movements [73]. To achieve this function, tendons must combine strength, flexibility, and resilience, properties that are derived from their unique mechanical characteristics, including elasticity, viscosity, and viscoelasticity. These properties enable tendons to withstand tensile forces and, at insertional/wrap-around regions, adapt to compressive loading [19,74]. Tendons exhibit time-dependent viscoelastic behavior, including creep, stress relaxation, and hysteresis [74]. The primary component of tendons responsible for their high tensile strength is type I collagen, which makes up approximately 65-80% of the tendon's dry weight [75]. Collagen is organized hierarchically from molecules and fibrils to fibers, fascicles, and the whole tendon [2,76]. At the molecular level, collagen molecules form a triple helix structure, which assembles into microfibrils and then into larger fibrils, providing the tendon with its characteristic crimped pattern. At low strain, recruitment and straightening of collagen crimp contribute to the nonlinear toe region of the tendon stress-strain response [77,78]. This linear region of the stress-strain curve represents the tendon's primary load-bearing phase, where it functions optimally in force transmission. Repeated or excessive tensile loading can produce microstructural fatigue damage and, at sufficiently high loads, tendon failure [79,80]. Non-collagenous extracellular-matrix components and water contribute to tendon viscoelastic behavior, which includes creep, stress relaxation, and hysteresis [1,74]. Understanding these mechanical properties is crucial for developing training and rehabilitation protocols that optimize tendon loading without causing injury. In addition to their mechanical properties, tendons demonstrate remarkable adaptability to different mechanical environments [81]. Chronic mechanical loading can increase tendon stiffness and cross-sectional area [51]. Tendon regions subjected to compression can develop fibrocartilaginous characteristics with increased proteoglycan content [19]. This adaptability involves mechanotransduction pathways that convert mechanical signals into cellular responses affecting matrix homeostasis [82,83]. Such adaptability is essential for maintaining tendon health and function in diverse physical activities, ranging from high-impact sports to static postures [82]. Tendinopathy is associated with disordered matrix remodeling and altered

mechanical function [84]. These changes are associated with disorganized collagen fibers, increased glycosaminoglycan content, and the presence of non-collagenous scar tissue, all of which impair the tendon's ability to transmit force effectively [84]. The development of tendinopathy is often linked to repetitive overloading, poor biomechanics, and inadequate recovery, which create a catabolic environment within the tendon, disrupting normal matrix homeostasis [12]. These mechanical and matrix changes are relevant to the clinical understanding of tendinopathy [84,85].

p. 685, YAP/TAZ sentence

Published: Integrins, which are transmembrane receptors, play a pivotal role in mechanotransduction by linking the ECM to the cytoskeleton and serving as the primary sensors of mechanical forces [141]. Upon mechanical stimulation, integrins cluster and recruit focal adhesion complexes, including focal adhesion kinase (FAK) and Src kinases, which initiate downstream signaling cascades [142]. Activation of these pathways can lead to the phosphorylation of transcription factors such as YAP/TAZ, which translocate to the nucleus and modulate the expression of genes involved in cell proliferation, differentiation, and matrix remodeling [143]. These signaling events ultimately influence the composition and mechanical properties of the tendon ECM, ensuring that it remains resilient and functional under different mechanical conditions [144]. The complexity of mechanotransduction is further illustrated by the diverse cellular responses observed under different types of mechanical loading. For example, cyclic tensile loading, which simulates physiological stretching forces, has been shown to upregulate the expression of collagen types...

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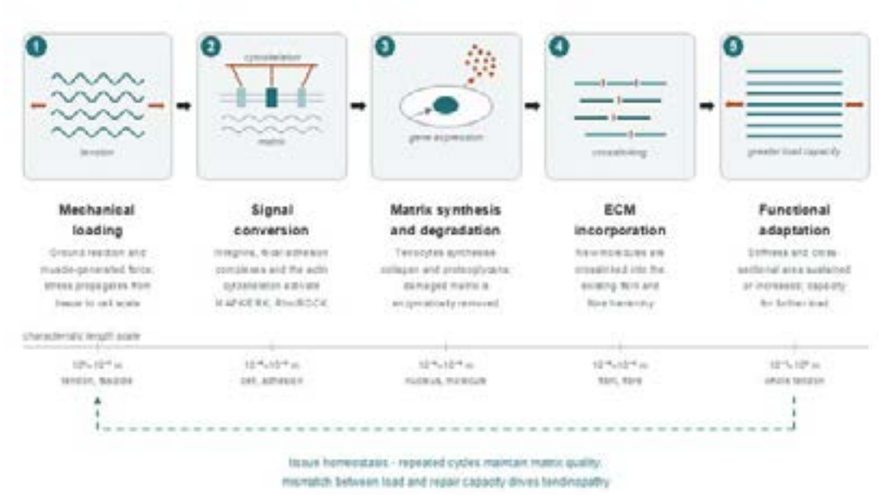
Figure 1 legend

Published: Fig. 1. The Fig. illustrates the process of mechanotransduction in tendons in response to mechanical loading, highlighting the molecular pathways that regulate tendon adaptation. Upon the application of mechanical loading, such as ground reaction forces during running or strength training, the extracellular matrix (ECM) experiences stress propagation from the macro to the micro-level, activating

mechanosensitive receptors on tenocytes (1) [mechanical loading phase]. This mechanical signal is then converted into biochemical signals within the tendon cells through ECM-cell interactions (2), involving integrins, focal adhesion complexes, and cytoskeletal elements, initiating intracellular pathways like MAPK/ERK and Rho/ROCK [signal conversion]. As a result, tenocytes increase the synthesis of new matrix components such as collagen and proteoglycans, promoting the remodeling of the ECM and degradation of damaged matrix (3) [matrix synthesis and degradation]. This remodeling process leads to the incorporation of newly synthesized molecules into the ECM, enhancing its structural and functional integrity (4) [ECM incorporation]. The end result is a sustained or improved tendon function, ensuring that the tissue can better withstand subsequent mechanical loads (5) [functional adaptation]. Ultimately, the cycle contributes to tissue homeostasis and adaptation, preventing overuse injuries and maintaining tendon health.)

Corrected: Fig. 1. Load-driven mechanotransduction in tendon, shown as five sequential stages. (1) Mechanical loading: ground reaction and muscle-generated forces propagate as stress from the tissue to the cell scale. (2) Signal conversion: integrins, focal adhesion complexes and the actin cytoskeleton couple the extracellular matrix (ECM) to the cell interior and activate intracellular cascades including MAPK/ERK and Rho/ROCK. (3) Matrix synthesis and degradation: tenocytes increase synthesis of collagen and proteoglycans while damaged matrix is enzymatically removed. (4) ECM incorporation: newly synthesised molecules are crosslinked into the existing fibril and fibre hierarchy. (5) Functional adaptation: tendon stiffness and cross-sectional area are sustained or increased, raising capacity for subsequent load. The axis beneath the sequence indicates the characteristic length scale at which each stage operates. The dashed return path denotes the repeating cycle that maintains matrix homeostasis; a mismatch between applied load and repair capacity shifts this cycle towards tendinopathy. Schematic prepared for this correction; the staged organisation of the mechanotransduction cycle follows the framework reviewed by Siadat et al. (2021) [91].



p. 686, load-dependent mechanotransduction paragraph

Published: I and III, as well as the glycoprotein tenascin-C, which contribute to tendon strength, elasticity, and resistance to tensile stress [145]. Additionally, cyclic loading enhances the production of lubricin, a glycoprotein that reduces friction between tendon fibers, thereby protecting the tissue from shear-induced damage [146]. On the other hand, compressive loading, which is commonly experienced at bone-tendon junctions, stimulates the production of large proteoglycans like aggrecan and decorin, which increase tissue hydration and provide resilience against compressive forces [147]. The upregulation of these molecules helps protect tendons from compression-induced degeneration, as seen in fibrocartilaginous regions of tendons that are subjected to high compressive loads [148]. In addition to the classical outside-in signaling, where external mechanical forces influence intracellular processes, mechanotransduction can also occur in an inside-out manner. Changes in the actin cytoskeleton, such as polymerization and depolymerization, can alter the distribution and conformation of integrins on the cell surface, modulating the cell's sensitivity to external mechanical stimuli [149]. This bidirectional communication between the cytoskeleton and ECM is essential for maintaining the dynamic balance of tendon homeostasis and for adapting to changes in the mechanical environment, such as increased physical activity or immobilization [150]. For instance, during mechanical unloading, as seen in immobilization or reduced physical activity, tendon cells exhibit reduced expression of collagen and other ECM proteins, leading to a decrease in tendon stiffness and strength [151]. Conversely, during periods of increased loading, such as during resistance training, tendon cells increase the production of collagen and cross-linking enzymes, enhancing the mechanical properties of the tendon [152]. The

actin cytoskeleton also plays a crucial role in mechanosensing by providing structural support and regulating the mechanical properties of cells [153]. Actin filaments connect integrins to the nucleus through the LINC (linker of nucleoskeleton and cytoskeleton) complex, enabling the transmission of mechanical signals to the nuclear lamina [154]. This mechanotransduction pathway allows cells to sense changes in the stiffness of the ECM and adjust their gene expression accordingly. For example, increased matrix stiffness promotes the activation of YAP/TAZ transcription factors, which enhance the expression of matrix proteins and increase cell proliferation, leading to tissue stiffening [155]. Conversely, a softer ECM inhibits YAP/TAZ signaling, reducing matrix synthesis and promoting a more compliant tissue phenotype [156]. These adaptive responses are essential for maintaining tendon function under different mechanical conditions and preventing the onset of pathological changes associated with altered mechanotransduction, such as tendinopathy and fibrosis [157].

Corrected: I and III and the extracellular-matrix glycoprotein tenascin-C; tendon-cell matrix expression is load-responsive [26,46]. Cyclic compression can increase lubricin expression in tendon cells [48]. Compression-adapted tendon regions are characterized by proteoglycan-rich fibrocartilaginous matrix, and cyclic compression can increase large-proteoglycan synthesis [19,35]. Mechanical coupling between integrins, the actin cytoskeleton, and the extracellular matrix enables bidirectional mechanosensing and regulation of matrix homeostasis [83,86]. Mechanical unloading reduces tendon/ligament mechanical competence and collagen synthesis, whereas chronic loading can increase tendon stiffness and cross-sectional area [51,58,72]. The actin cytoskeleton also plays a crucial role in mechanosensing by providing structural support and regulating the mechanical properties of cells [92]. Actin filaments connect integrins to the nucleus through the LINC (linker of nucleoskeleton and cytoskeleton) complex, enabling the transmission of mechanical signals to the nuclear lamina [92]. This mechanotransduction pathway allows cells to sense changes in the stiffness of the ECM and adjust their gene expression accordingly. Increased matrix stiffness promotes nuclear YAP/TAZ activity, whereas softer matrix tends to reduce YAP/TAZ mechanosignaling [88,93]. Dysregulation of mechanotransduction and extracellular-matrix homeostasis can contribute to pathological tissue remodeling [83].

pp. 686-687, tendinopathy pathogenesis/classification

Published: Tendinopathies are a group of chronic tendon disorders characterized by pain, swelling, impaired function, and structural changes within the tendon matrix. They are most commonly observed in high-use tendons such as the Achilles, patellar, and rotator cuff tendons, where repetitive loading, microtrauma, and insufficient recovery contribute to pathological changes over time [158]. Tendinopathies often result from a mismatch between tendon loading and repair capacity, leading to a cumulative cycle of micro-injuries, inflammation, and degeneration [159]. While tendinopathies were traditionally thought to be primarily degenerative, recent studies suggest that inflammatory processes play a more significant role than previously believed, particularly in the early stages of the condition [160]. The pathogenesis of tendinopathies is complex and multifactorial, involving mechanical, biochemical, vascular, and cellular factors that disrupt the normal balance between matrix synthesis

and degradation, leading to progressive tendon degeneration [161]. Mechanical overloading, whether due to repetitive microtrauma or sudden high-intensity forces, initiates a cascade of events at the cellular level. Tendon cells, known as tenocytes, become activated and release pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis...

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pp. 688-689, "Radiocarbon Dating and Collagen Turnover"

Published: Radiocarbon dating, particularly the use of the 14C bomb-pulse method, has emerged as a powerful tool for estimating collagen turnover and understanding the dynamics of protein synthesis in human tendons and other tissues [182]. This method exploits the significant spike in atmospheric 14C levels caused by nuclear bomb testing in the 1950s and 1960s, which created a distinct chronological marker

that was incorporated into biological tissues formed during this period [183]. By measuring the levels of 14C in collagen, researchers can accurately date when specific collagen molecules were synthesized, providing insights into the rates of protein turnover and tissue renewal [184]. This technique has been used to study various tissues, including bone, cartilage, and the brain, but has been particularly informative in assessing tendon turnover rates due to the unique structural properties and low metabolic activity of tendons [185]. Studies utilizing the 14C bomb-pulse method have revealed that the core of adult tendons exhibits very low collagen turnover after skeletal maturity, suggesting that tendons are relatively static tissues compared to more dynamic tissues such as muscle or skin [186]. This finding challenges the traditional view that tendons are continuously remodeling throughout life, indicating instead that collagen turnover in tendons may be highly localized and dependent on mechanical loading or injury [187]. The low turnover in the core regions of tendons implies that tendons may accumulate age-related damage over time, making them more susceptible to degenerative changes and injuries, such as tendinopathies, in older adults [188]. Interestingly, radiocarbon dating has also shown that while the central core of the tendon is relatively quiescent, the outer layers of tendons—particularly those closer to the bone-tendon junction—exhibit higher turnover rates [189]. This suggests a more dynamic remodeling process in these peripheral regions, potentially due to higher mechanical loads and greater cellular activity in response to stress or micro-injury [190]. This spatial variation in collagen turnover within tendons reflects the heterogeneous nature of tendon tissue, where different regions are subjected to varying mechanical environments and metabolic demands [191]. Such findings have significant implications for understanding tendon aging and the development of degenerative conditions, as the inability of the tendon core to effectively repair micro-damage could contribute to the onset of tendinopathy and other chronic tendon pathologies [192]. Moreover, the 14C bomb-pulse method has been used to investigate the turnover of other extracellular matrix (ECM) proteins in tendons, such as elastin and proteoglycans, which play key roles in tendon elasticity and resistance to compressive forces [193]. These studies have shown that, similar to collagen, the turnover rates of these ECM proteins are also remarkably low in the core regions of adult tendons, indicating that the overall matrix composition of tendons is highly stable after maturity [194]. This stability may be advantageous for maintaining the mechanical integrity of tendons under repetitive loading conditions but could also predispose tendons to accumulate damage over time, especially in individuals engaged in high-impact activities or sports [195]. The findings from radiocarbon dating studies have important clinical implications. For example, the low turnover rates in adult tendons suggest that therapeutic strategies aimed at enhancing collagen synthesis and matrix remodeling, such as mechanical loading protocols or growth factor treatments, may be necessary to promote tendon healing and prevent age-related degeneration [196]. Furthermore, understanding the differential turnover rates in various tendon regions could help inform the development of region-specific rehabilitation strategies for tendon injuries, such as eccentric loading exercises targeting areas of high metabolic activity [197]. In addition to the 14C bomb-pulse method, stable isotope labeling has been used as a complementary approach to study

tendon protein turnover [198]. This technique involves the incorporation of stable isotopes, such as deuterium or 13C, into newly synthesized proteins, allowing for the tracking of protein synthesis and degradation over shorter time
Corrected: Bomb-pulse radiocarbon dating uses the atmospheric increase in 14C produced by mid-twentieth-century nuclear testing as a chronological marker for long-lived tissue proteins. In human Achilles tendon, this approach demonstrated very limited renewal of core collagen after skeletal maturity [59]. In healthy human patellar tendon, radiocarbon analysis across multiple anatomical regions found no detectable regional difference in lifelong collagen turnover [60]. In equine tendons, aspartic-acid racemization indicates substantially longer collagen half-life than non-collagenous-protein half-life, with differences between tendon types [61]. Stable-isotope approaches measure protein synthesis over much shorter time scales and demonstrate active protein synthesis in human muscle, tendon, ligament, cartilage, and bone [62]. Radiocarbon and stable-isotope measurements therefore address different temporal aspects of matrix biology. The published claims of systematically higher peripheral tendon turnover, region-specific anabolic therapeutic targets, and associated treatment implications are removed because the cited records do not establish those conclusions.

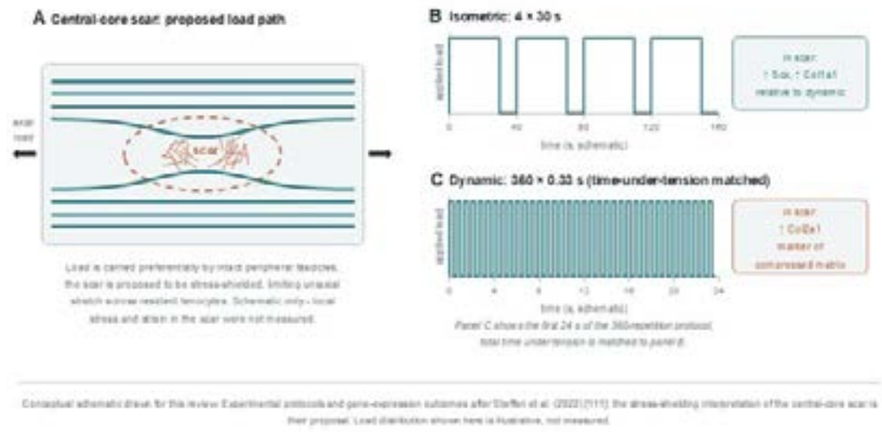
pp. 689-691, "Molecular Role of Stress Shielding in Tendinopathy Development"
Published: The development of tendinopathy often stems from repetitive mechanical loading that does not lead to adequate tendon remodeling, resulting in compromised structure and function [204]. However, this mechanical model alone fails to capture why the remodeling process stalls initially. The main hypothesis posits that stress shielding contributes to the onset of tendinopathy, with biochemical and cellular responses leading to tissue dysfunction and weakening (Fig. 2). Stress shielding occurs when weaker tissue regions are protected from mechanical stress by surrounding stronger tissues, a phenomenon shown in experiments where unloading the patellar tendon in rabbits revealed critical molecular pathways impacted by stress shielding [205]. At a cellular level, stress shielding initiates significant biochemical changes. For instance, fibroblast density in the mid-substance of the tendon rapidly increases four-fold within two weeks, suggesting an immediate attempt at tissue repair under reduced mechanical load [208]. The fibroblasts shift from spindle- shaped to a more rounded...
Corrected: Stress shielding refers to a reduction in local mechanical load when load is carried preferentially by surrounding tissue. Experimental rabbit patellar-tendon models demonstrate that prolonged stress shielding reduces tendon mechanical properties and produces histological and collagen-fibril changes [104-106]. These studies support mechanical and structural consequences of unloading but do not directly demonstrate the specific cytokine, integrin, ERK, MMP, collagen-I-to-III switching, or collagen-crosslink mechanisms attributed to them in the published text; those mechanistic statements are therefore removed. Restressing of previously stress-shielded rabbit patellar tendon can produce recovery of some mechanical properties, although recovery may be incomplete [107]. Experiments with beta-aminopropionitrile (BAPN) separately demonstrate that inhibition of collagen

crosslink formation alters tendon mechanical properties [108]; they should not be presented as a direct experimental model of stress shielding. Fetal sheep tendon studies demonstrate regenerative healing capacity [109,110], but they do not establish reduced stress shielding as the causal mechanism of fetal healing. The published posterior-patellar-region and broad molecular-signaling conclusions are removed because the assigned sources do not establish those mechanisms.

Figure 2 legend

Published: Fig. 2. It has been proposed that ‚stress shielding' happens when loads are applied to a tendon, such as during jumping or isotonic strength exercises. In this scenario, the healthier regions of the tendon absorb the force, effectively shielding the disorganized parts by bearing the load. Theoretically, this load distribution should support tendon repair and enhance the tensile strength of the misaligned fibrils. However, due to the ‚stress shielding' effect, the disorganized section of the tendon remains unloaded, potentially leading to continued deterioration. Stress-relaxation reduces the stiffness of surrounding collagen, making it less rigid than the injured area, which allows the load to transfer through the damaged region. When uniaxial loading passes through this injured area, it triggers a response that boosts the expression of genes associated with both mature and developing tendons (Left). Dynamic loading, such as that experienced during running or jumping, occurs rapidly, causing the load to divert around the injured area. In cases of central core injury, the injured region experiences radial compression as the tendon lengthens without a change in volume (Right). Interpretation form Steffen et al., 2022)

Corrected: Fig. 2. Loading-pattern experiment in the central-core rat patellar tendon model. Panel A depicts a hypothetical load path around a central defect; it is an interpretive schematic, not a measurement of scar stress or strain. Panels B and C summarize the protocols reported by Steffen et al. [111]: four 30-s isometric contractions and a dynamic condition matched for total time under tension (360 x 0.33 s). Isometric loading increased scleraxis (Scx) and type I collagen (Col1a1) expression in scar tissue relative to the dynamic condition, whereas the dynamic protocol produced greater type II collagen (Col2a1) expression. The figure is retained to distinguish the experimentally observed loading-pattern response from the subsequent stress-shielding interpretation [112].



p. 691, Conclusion

Published: Tendons play a fundamental role in the musculoskeletal system by linking muscles to bones and facilitating force transmission. Despite their critical function, tendons are prone to both acute and chronic injuries, which can significantly hinder their ability to transfer force if not properly repaired. Tendinopathy, a common condition resulting from an imbalance between micro-injuries and the tendon cells' ability to repair the matrix, accounts for about 20% of musculoskeletal complaints in the general population. In the United States, musculoskeletal injuries such as strains, sprains, and tears have consistently accounted for a substantial portion of missed workdays, significantly affecting productivity and quality of life. This chapter has explored the complex interplay between mechanical load and the biology and mechanics of both healthy and tendinopathic tendons, providing insights into potential strategies for treating tendinopathy. Tendons are primarily composed of collagen fibers, with Type I collagen being the most prevalent and crucial for force transmission. The organization and composition of tendons are highly adaptive to mechanical loads, with distinct responses to tensile, compressive, and shear forces. During development, tendons exhibit significant changes in collagen content and cellularity, which continue into adulthood as tendons respond to varying mechanical environments. These adaptations are driven by intricate molecular and cellular mechanisms, including the synthesis of specific proteins and the modulation of gene expression in response to mechanical stimuli. In adults, tendons continue to adapt to mechanical loads, with changes in loading leading to increased tendon stiffness and cross-sectional area. High-intensity training and specific types of exercise can significantly enhance tendon properties, while immobilization or disuse can lead to a reduction in mechanical strength. The balance between collagen synthesis and degradation is crucial for maintaining tendon health, and the extent of collagen turnover remains a topic of ongoing research. The molecular pathways involved

in tendon adaptation to load, such as those mediated by IGF-1 and ERK signaling, highlight the complex regulatory networks that govern tendon biology. Additionally, the role of systemic signals and hormones, such as estrogen, further complicates the understanding of tendon adaptation, particularly in response to loading and unloading. In summary, tendons are dynamic tissues capable of significant adaptation to mechanical loads throughout life. Understanding the underlying mechanisms of these adaptations is essential for developing effective treatments for tendinopathy and other tendon-related injuries. Future research should continue to elucidate the molecular and cellular processes involved in tendon adaptation, paving the way for innovative therapeutic strategies to enhance tendon repair and function.

Corrected: Tendons play a fundamental role in the musculoskeletal system by linking muscles to bones and facilitating force transmission. Despite their critical function, tendons are prone to both acute and chronic injuries, which can significantly hinder their ability to transfer force if not properly repaired. This review has examined the complex interplay between mechanical load and the biology and mechanics of both healthy and tendinopathic tendons, providing insights into potential strategies for treating tendinopathy. Tendons are primarily composed of collagen fibers, with Type I collagen being the most prevalent and crucial for force transmission. The organization and composition of tendons are highly adaptive to mechanical loads, with distinct responses to tensile, compressive, and shear forces. During development, tendons exhibit significant changes in collagen content and cellularity, which continue into adulthood as tendons respond to varying mechanical environments. These adaptations are driven by intricate molecular and cellular mechanisms, including the synthesis of specific proteins and the modulation of gene expression in response to mechanical stimuli. In adults, tendons continue to adapt to mechanical loads, with changes in loading leading to increased tendon stiffness and cross-sectional area. High-intensity training and specific types of exercise can significantly enhance tendon properties, while immobilization or disuse can lead to a reduction in mechanical strength. The balance between collagen synthesis and degradation is crucial for maintaining tendon health, and the extent of collagen turnover remains a topic of ongoing research. Molecular pathways associated with tendon responses to mechanical loading, including IGF-I-related signaling and broader mechanotransduction mechanisms, highlight the complex regulatory networks that govern tendon biology. Additionally, the role of systemic signals and hormones, such as estrogen, further complicates the understanding of tendon adaptation, particularly in response to loading and unloading. In summary, tendons are dynamic tissues capable of significant adaptation to mechanical loads throughout life. Understanding the underlying mechanisms of these adaptations is essential for developing effective treatments for tendinopathy and other tendon-related injuries. Future research should continue to elucidate the molecular and cellular processes involved in tendon adaptation, paving the way for innovative therapeutic strategies to enhance tendon repair and function.

Reference-list corrections

The reference list has been comprehensively corrected to address inaccurate bibliographic metadata, duplicate entries, incorrectly assembled records, and

citation-to-reference mismatches identified during the post-publication review. Duplicate records have been consolidated, records that did not correspond to the cited publications have been corrected or removed, and references have been reassigned where necessary to ensure that the cited sources support the corresponding statements. As a consequence of these corrections, the reference list and all corresponding in-text citations have been consecutively renumbered. The complete corrected reference list below supersedes the reference list in the original article.

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Effect of the correction

These corrections address errors in attribution, bibliographic information, citation mapping, figure presentation, and the level of support for selected technical statements. Statements for which the originally assigned literature did not support the stated level of specificity have been corrected, narrowed, or removed. The corrections do not alter the general subject or principal conclusion of the review that tendon cells and the extracellular matrix respond and adapt to mechanical loading. The authors apologize for the inaccuracies and thank the Editorial Office for the opportunity to correct the scientific record.