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Evidence-Based Load Management for Tendon Adaptation and Injury Prevention in Athletes

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ABSTRACT

Background. Tendon health and performance are fundamentally dependent on the tissue's ability to adapt to mechanical loading through mechanotransduction. In elite sports and rehabilitation, understanding these molecular pathways is essential for optimizing training quality and preventing overuse injuries, such as tendinopathy.

Aim. This review aims to synthesize current knowledge on mechanosensitive pathways (including PIEZO1 and mTOR) and translate these biological findings into practical clinical implications for sports load management and injury prevention.

Materials and Methods. A comprehensive review of recent literature was conducted, focusing on the intersection of cellular mechanobiology and clinical sports medicine. Key areas of focus

included strain-induced signaling, the "adaptation gap" between muscle and tendon, and ultrasound-based monitoring.

Results. Research indicates that a specific "strain window" (approx. 4.5–6.5%) is required to trigger anabolic responses in tendons. A critical clinical finding is the "adaptation gap," where rapid increases in muscle strength outpace the slower stiffening of tendon tissue, creating a high-risk period for injury. Furthermore, effective tendon adaptation is driven more by changes in material properties (quality) than by gross hypertrophy.

Conclusion. To ensure high-quality sports outcomes, practitioners must shift from generic protocols to personalized load management. Integrating mechanobiological principles, such as specific loading magnitudes and adequate recovery intervals, allows for the correction of muscle–tendon imbalances. Utilizing advanced diagnostic tools like ultrasonography to monitor these adaptations is crucial for long-term athletic health and performance optimization.

Keywords: load management, tendon adaptation, injury prevention, sports quality, tendinopathy

1. Introduction

Physical activity is a fundamental component of holistic development, playing a vital role in the physical and functional maturation of an individual [1]. Within this context, the ability of the musculoskeletal system to tolerate and adapt to mechanical loading becomes essential. Tendons are dynamic structures that optimize the muscle-tendon unit's efficiency during the stretch-shortening cycle [2]. They transmit mechanical energy from muscles to the skeleton, representing a critical determinant of locomotor efficiency and joint integrity [3]. Any disruption in this force-transmission pathway, such as an Achilles tendon rupture, results in a complete loss of propulsive power, highlighting the pivotal role of tendons in the kinematic chain of athletic performance [4].

Data from elite athletes show that high-magnitude and long-duration loading lead induce significant increases in tendon stiffness and cross-sectional area (CSA), which directly correlates with improved rate of force development [5].These adaptations are both structural and metabolic: tendons act as biological springs that store and release elastic strain energy, thereby modulating the metabolic cost of movement [6].

Mechanotransduction is the cellular process of converting physical kinetic energy into biochemical responses [7]. During loading, deformation of the tendon extracellular matrix (ECM) is sensed by tenocytes, triggering intracellular signaling, changes in gene expression, collagen synthesis, and cross-linking, which together modify tendon material and morphological properties [3, 8, 9]. Mechanosensitive systems include integrins, which link the ECM to the cytoskeleton and growth factor signaling pathways [6, 10, 11]. More recently, ion channels such as PIEZO1 have been identified, they detect shear stresses from collagen fibre sliding and regulate tendon stiffness, cross-linking and energy storage [6, 10, 11]. Appropriate cyclic loading within a specific strain range stimulates anabolic remodeling, whereas chronic under- or over-loading can shift the balance toward matrix disorganization and tendinopathy [3, 8, 9].

Studying tendon mechanobiology is therefore highly relevant to sport science. Training and competition expose tendons to repetitive high mechanical loads, and the ability of tendons to adapt influences both athletic performance and the risk of overuse injury [3, 5, 9, 12]. Understanding mechanotransduction pathways provides opportunities to refine training prescriptions, identify the optimal range of mechanical loading, and develop targeted interventions for performance enhancement and injury prevention.

The aim of this review is to synthesize current knowledge on tendon mechanotransduction; from cellular shear-stress sensing and ion-channel signaling to matrix-

level remodeling; to link these processes to macroscopic changes in tendon mechanical properties and function relevant to sport. The scope includes experimental mechanobiology in cells and tissue-engineered constructs, *in vivo* human and animal studies of tendon adaptation to mechanical loading, and genetic or molecular factors such as *PIEZO1* that modulate tendon stiffness and athletic performance [3, 6, 8, 10, 11]. By integrating these perspectives, this review provides a mechanistic framework to inform evidence-based training, rehabilitation and injury-prevention strategies in athletic populations.

2. Research materials and methods

A narrative review was conducted to synthesize current evidence on tendon mechanobiology and its practical applications in sports science. The literature search was performed across electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar, covering publications from 2004 to early 2026, with a primary focus on high-impact studies from the last five years (2021–2026).

The search strategy utilized combinations of the following keywords: "mechanotransduction", "tendon adaptation", "*PIEZO1*", "load management", "tendon stiffness", "extracellular matrix remodeling", and "personalized loading". Data synthesis integrated findings across multiple scales—from molecular sensors (e.g., *PIEZO1*, *YAP/TAZ*) to macroscopic biomechanical properties—to develop the practical load-management guidelines presented in this work.

3. Results

3.1. Structural and Functional Organization of Tendons

Tendons are specialized connective tissues that transmit muscle force to bone while withstanding high tensile loads and, in some cases, repeatedly storing and releasing elastic energy during movement [13, 14]. Their mechanical behavior and adaptability arise from a tightly coordinated hierarchical structure, distinct cell populations and a compositionally complex extracellular matrix [14, 15, 16].

3.1.1. Hierarchical Architecture and Cellular Composition

Tendons are organized across multiple scales, from nano- to macro-level; collagen molecules assemble into fibrils, which bundle into fibers, then fascicles, which together constitute the tendon mid-substance [15, 17]. Fascicles and tenocytes are embedded within interfascicular (endotenon) and outer peritendinous matrices, which are more cellular and vascularized than

the mid-substance, allowing fascicle sliding and contributing critically to overall tendon mechanics [14, 18, 19].

The main resident cells are tenocytes, elongated fibroblast-like cells aligned with collagen fibers that synthesize and remodel ECM [15, 18, 20]. In addition, tendon stem/progenitor cells (TSPCs) reside in specialized niches (paratenon, endotenon, perivascular regions), display clonogenicity and multipotency, and differ from tenocytes in morphology, marker expression, and proliferation [19, 21, 22]. Ageing and oxidative stress reduce TSPC numbers and functionality, impairing tendon regeneration [23].

3.1.2. Extracellular Matrix Composition

Water and ECM constitute the majority of tendon mass: type I collagen accounts for 60-85% of tendon dry weight, with smaller contributions from types III, V, VI, XII and others [15, 16, 20, 24]. Non-collagenous components include small leucine-rich proteoglycans (decorin, biglycan, lumican, fibromodulin) and larger proteoglycans (aggrecan, versican, COMP, CILP1) [14, 16, 24-28]. Elastin, and glycoproteins such as fibronectin and tenascin C further regulate fibrillogenesis, collagen cross-linking, fibril diameter, fascicle sliding, and viscoelasticity [14, 16, 24-28]. These compositional features underpin tendon specialization.

3.1.3. Functional Classification: Positional vs Energy-Storing

Tendons can be functionally categorized into positional and energy-storing tendons. Positional tendons (e.g., digital extensors) primarily control limb positioning; they experience lower strains and have more linear collagen architecture with modest elastic energy demands [24,29]. Energy-storing tendons (e.g., Achilles, superficial digital flexor) are adapted to cyclic high strains and efficient energy return [14, 24, 29]. They feature enhanced fascicle sliding via a specialized interfascicular matrix, distinct proteomic profiles, and collagen fibrils with increased strain-stiffening and molecular resilience [14, 24, 29]. These structural and compositional adaptations make energy-storing tendons crucial for efficient and explosive human movement, particularly in athletes performing repetitive high-intensity activities.

3.2. Mechanotransduction in Tendon Tissue

Mechanical loading of tendons is converted into biochemical signals through a multiscale mechanotransduction apparatus spanning the ECM, membrane receptors, cytoskeleton, and nucleus [30-33]. This system regulates tenocyte morphology, collagen synthesis, ECM organization, and gene expression, underpinning tendon adaptation and pathology [31-36].

3.2.1. Mechanical Signal Detection

Tenocytes detect strain via cell-ECM adhesions, the pericellular matrix, primary cilia, and cytoskeletal projections. The collagen VI-rich pericellular matrix and primary cilia modulate mechanosensor organization and downstream signaling pathways, including Akt (protein kinase B), ERK (extracellular signal-regulated kinase), p38 (mitogen-activated protein kinase), YAP (Yes-associated protein) [34]. *In vivo*, tenocytes extend microtubule-rich projections at myotendinous junctions that act as force sensors controlling ECM production through transforming growth factor-β (TGF-β)/mothers against decapentaplegic homolog 3 (SMAD3) signaling [33]. Engineered tendon constructs show endogenous cell-generated tension that maintains homeostatic force within the ECM [30].

3.2.2. Integrins and Focal Adhesion Complexes

Collagen-binding β1-integrins transmit forces from collagen fibrils into tenocytes, activating the integrin-linked kinase (ILK)/protein kinase B (Akt)/mechanistic target of rapamycin (mTOR), which regulates *mRNA* translation and collagen synthesis under cyclic loading [31]. Focal adhesion kinase (FAK) controls adhesion morphology, nuclear deformation, and mechanosensitive gene expression; loss of FAK *in vivo* alters tendon size, mechanics and ECM, establishing FAK as a central mechanotransduction hub [32]. Integrin nanoclusters and immobile “STARnodes” (Signaling Transit And Relay nodes) organize FAK. vinculin, and paxillin into relay nodes that propagate force-dependent phosphorylation and signal propagation [37, 38].

3.2.3. Intracellular Force Transmission and Ion Channel Activation

Actin, myosin, and microtubules transmit integrin-derived forces to the nucleus and coordinate contractility. Cytoskeletal tension is essential for tenocyte re-tensioning and mediates stretch-induced calcium signaling via the ECM [30]. During tendon development, microtubule-rich tenocyte projections rely on force-activated TGF-β to regulate ECM organization [33]. Proteins such as alpha-actinin, talin and vinculin orchestrate adhesion maturation and define how integrin forces are routed into actin networks [38, 39].

Stretch and matrix damage trigger Ca^{2+} signaling in tendon cells via mechanically activated ion channels, acting as a rapid functional readout of mechanotransduction [40]. In rodent tendons, the PIEZO1 ion channel senses shear stress, regulating tendon stiffness and elastic energy storage, influencing jumping performance in humans [6, 10]. Matrix maturation

and cytoskeletal tension define the strain thresholds required to activate these Ca^{2+} responses [6, 40].

3.2.4. Nuclear Mechanotransduction

Mechanical cues reach the nucleus through the LINC complex (Linker of Nucleoskeleton and Cytoskeleton complex) and the nuclear lamina, influencing chromatin organization and transcription [34, 39, 41]. Disruption of LINC complexes in developing tendons alters elastic modulus, collagen crimp, and cross-sectional area, with differential effects in energy-storing versus positional tendons [34]. In tenocytes, FAK-dependent intracellular tension modulates YAP/TAZ-mediated (Yes-associated protein and transcriptional coactivator with PDZ-binding motif) epigenetic regulation [31]. SUN1-dependent (Sad1 and UNC-84 domain-containing protein 1) nucleo-cytoskeletal coupling is required for actin organization, focal adhesion maturation, and integrin activation, supporting bidirectional crosstalk between the nucleus and adhesion machinery [39, 41].

Key mechanotransduction elements and their functional contributions to tendon homeostasis are outlined in Table 1.

Table 1. Key mechanotransduction elements in tendons

Level	Main Components	Functional role	Citations
Cell-ECM interface	Collagen VI pericellular matrix (PCM), primary cilia, integrins	Initial force sensing, pathway activation	[29, 30, 32, 33]
Focal adhesions	β1-integrin, ILK, FAK, paxillin, vinculin	Signal relay, collagen synthesis adhesion dynamics	[30, 31, 36, 37]
Cytoskeleton	Actin-myosin, microtubules, alpha-actinin, talin	Force transmission, projection formation, Ca^{2+} sensitivity	[29, 32, 39]
Ion channels	PIEZO1, stretch-activated Ca^{2+} channels	Rapid Ca^{2+} signals, stiffness and energy-storage regulation	[6, 10, 40]
Nuclear apparatus	LINC (SUN/nesprin), YAP/TAZ	Nuclear strain sensing, gene regulation, tendon development	[31, 34, 39, 41]

Tendon mechantransduction emerges as an integrated network: ECM and pericellular matrix focus forces onto integrin-FAK complexes, the cytoskeleton routes these forces to

mechanosensitive ion channels and the nucleus, and nuclear LINC-YAP pathways convert mechanical information into gene programs. This multilevel system governs tendon growth, remodeling, and functional specialization. It provides multiple potential targets for training optimization and mechanotherapy in sport and rehabilitation.

3.3. Molecular and Cellular Signaling Pathways

Mechanical loading reshapes tendon structure through multiple signaling cascades, including growth factor, redox, inflammatory, epigenetic and ECM-remodeling pathways. Mechanical overload increases levels of IGF-1 (insulin-like growth factor 1), TGF-β (transforming growth factor-beta) and PDGF (platelet-derived growth factor), which coordinate cell proliferation, differentiation and matrix deposition [42, 43].

3.3.1. Growth Factor Signaling

Tenocyte-specific deletion of IGF-1 receptor blunts overload-induced tendon growth, reducing cell proliferation and protein synthesis [44]. IGF-1 activates phosphoinositide 3-kinase (PI3K)-Akt and ERK pathways to drive collagen and ECM protein production [44]. Delivery of IGF-1, or scaffolds incorporating IGF-1 enhances matrix deposition and tendon biomechanics [42].

TGF-β upregulation in MSC-based (Mesenchymal Stem Cell-based) repairs promotes tendon-to-bone healing through TGF-β/MAPK (mitogen-activated protein kinase) signaling (ERK, p38, JNK), increasing fibroblast numbers, fibrocartilage formation, collagen content, and mechanical strength [45]. TGF–β also regulates tenocyte proliferation, migration, and collagen I/III synthesis in tendinopathy models [43, 45]. PDGF-BB stimulates mesenchymal and tendon cells, upregulating IGF-1, and promoting proliferation, migration, and ECM synthesis [21, 42]. Single-cell lineage tracing shows PDGF-responsive *Tppp3*$^{+}$*Pdgfra*$^{+}$ tendon stem cells generate new tenocytes after injury, while closely related Pdgfra^{+} fibro-adipogenic progenitors form fibrotic scar tissue, revealing a shared PDGF axis for regeneration versus fibrosis depending on target population and context [21]. Combined IGF-1 + PDGF-BB modulate proliferation, ECM gene expression, and mechanics in a complex, non-additive manner [42].

3.3.2. Redox Signaling and ROS (Reactive Oxygene Species)

Exercise, hypoxia-reoxygenation, and inflammatory mediators increase ROS in tendons [2, 46]. Oxidative stress contributes to tendon degeneration and failed healing, mitochondrial and ischemia/reperfusion-related ROS, together with cytokines and nitric oxide, are key sources in

injured tendons [47]. Platelet-rich plasma (PRP) protects tenocytes from H_2O_2-induced oxidative damage, reduces protein/lipid oxidation, and upregulates *Nrf2*-dependent (Nuclear factor erythroid 2-related factor 2) antioxidant enzymes (SOD2 - superoxide dismutase 2, catalase, HO-1 - heme oxygenase-1, NQO1 - NAD(P)H:quinone oxidoreductase 1, GCLC - glutamate-cysteine ligase catalytic subunit, GST - glutathione S-transferase), increasing catalase and GST activity and restoring homeostasis [47]. Antioxidant nanotherapies (cerium oxide nanoparticles or plant-derived exosomes) lower ROS levels, preserve stem cell viability, and improve tendon regeneration partly by suppressing NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells)/MAPK and other stress-responsive inflammatory pathways [43, 48].

3.3.3. Inflammatory Mediators and Adaptive Signaling

Inflammation initiates repair, but persistent signaling favors fibrosis and tendinopathy [3, 6, 42]. Canonical NF-κB remains active through all phases of repair; supporting tenocyte/myofibroblast survival but promoting scar formation and fibrotic progression [49]. Overactivation of IKKβ (inhibitor of nuclear factor kappa-B kinase subunit beta)/NF-κB in tendon fibroblasts leads to degenerative tendinopathy, whereas conditional IKKβ deletion partially protects against overuse-induced disease and improves healing after repair [50].

Pro-inflammatory cytokines IL-1β (interleukin 1 beta), TNF-α (tumor necrosis factor alpha), IFN-γ (interferon gamma) disrupt tenocyte matrix gene expression, increase MMPs (matrix metalloproteinases), and impair collagen gel contraction via NF-κB activation [51]. IL-17 cytokines further amplify tendon inflammation, activating p38 and NF-κB signaling [52]. Emerging therapies targeting inflammation include *IL-1RA* mRNA delivered via grapefruit-exosome microneedles and Zn-releasing tendon hydrogels, which reduce pro-inflammatory signaling, polarize macrophages towards M2 phenotypes, and restore ECM organization and biomechanics [43, 53, 54].

3.3.4. Epigenetic Regulation of Tendon Adaptation

Loss of tensile cues rapidly alters nuclear morphology and induces a matrix-catabolic gene program, associated with reduced chromatin accessibility near *YAP/TAZ* target loci [55]. Depletion of YAP/TAZ elevates catabolic gene expression, while YAP overexpression restores chromatin accessibility and represses this program even under loss of tension [55]. Paired assay for transposase-accessible chromatin using sequencing (ATAC-seq) and RNA sequencing show that mechanical signals control ECM homeostasis via a *YAP/TAZ*-dependent

mechanoepigenetic axis [55], providing a direct link between mechanical loads, chromatin state, and ECM transcription.

3.3.5. Collagen Synthesis and ECM Remodeling

Collagen synthesis and ECM remodeling integrate inputs from integrins, growth factors, inflammation, and redox signaling. Cyclic stretch of tendon cells activates β1-integrin-ILK-Akt-mTOR pathways; blocking integrin-ECM binding prevents upregulation of *COL1A1* (collagen type I alpha 1 chain), *COL3A1* (collagen type III alpha 1 chain) and *SCX* (scleraxis), and disrupts collagen fiber alignment [30].

IGF-1 signaling is essential for overload-induced tendon hypertrophy and ECM protein synthesis [44]. Increased Ca^{2+} influx via voltage-gated L-type calcium channel subunit alpha 1C (*CAV1.2*) in developing tendons induces hypertrophy, enhanced collagen fibrillogenesis, higher peak load and stiffness, and upregulation of matrix proteins (tenascin-C, tenomodulin, periostin, type XIV/VIII collagens) and remodeling enzymes (MMP14, MMP2, cathepsin K), as well as the myostatin [40]. PDGF-responsive tendon stem cells generate new tenocytes, whereas neighboring PDGFRα^{+} (platelet-derived growth factor receptor alpha-positive) fibro-adipogenic progenitors form fibrotic scar tissue [21]. Chronic inflammation, senescence, and NF-κB/MAPK activation sustain MMP activity, shifting ECM remodeling toward degradation and the formation of disorganized collagen, particularly under altered mechanical loading and in aged or senescent tendons.

A summary of key pathways roles in tendon adaptations is presented in Table 2.

Table 2. Key pathway roles in tendon adaptation

Pathway	**Main effects on tendon adaptation**	**Citation**
IGF-1-PI3K/Akt-ERK	Tenocyte proliferation, protein synthesis, tendon hypertrophy	[42, 44]
TGF-β/MAPK	Tenogenesis, tendon-bone healing, risk of fibrosis	[43, 45]
PDGF/PDGFRα	Stem-cell-driven regenerations versus fibrotic scarring	[21, 42]
ROS-Nrf2	Antioxidant defense, protection from oxidative damage	[47]

NF-κB/IL-1β/TNF-α/IL-17	Initiates repair; chronic activation causing degeneration, scar	[49-52]
YAP/TAZ mechanoepigenetics	Chromatin state, balancing anabolic versus catabolic ECM genes	[53]
β1-Integrin-ILK-mTOR and *CAV1.2* Ca^{2+}	Collagen synthesis, fibrillogenesis, tendon stiffness	[30, 40]

3.4. Biomechanical Adaptation of Tendons

Mechanical loading reshapes tendon stiffness, internal organization, and viscoelastic function Conversely, unloading, aging, and genetic factors can render tendons weaker and more prone to injury.

3.4.1. Stiffness and Elasticity Changes

Training generally increases tendon stiffness and modulus, with only minor changes in cross-sectional area [56]. Meta-analyses indicate moderate-to-large gains in stiffness and modulus, primarily driven by changes in material properties rather than size [61]. High-strain resistance training yields the largest increases [56].

A human *PIEZO1* gain-of-function variant (E756del) is associated with 45-46% higher patellar tendon stiffness and modulus without geometric changes, highlighting intrinsic material stiffening [57]. In contrast, reduced loading (bed rest, paralysis, immobilization) typically decreases Achilles stiffness *in vivo* and reduces modulus in animal models [58, 59].

3.4.2. Fascicle and IFM (Interfascicular Matrix) Adaptation

Unloading leads to crimped, disorganized fibers, altered fibril strain partitioning, and decreased cell density in rat Achilles tendons [58]. Computational modeling shows that impaired mechanics largely result from dispersed collagen fiber orientations and geometric changes [59].

The IFM enables fascicle sliding and recovery, behaving more elastically in energy-storing tendons; with aging it becomes stiffer, shows more stress relaxations, and loses sliding capacity, predisposing to injury [60, 61]. Single-nucleus mapping in humans demonstrates that interfascicular fibroblasts rapidly upregulate ECM genes related to lubrication and resilience after single loading bout [62].

3.4.3. Viscoelastic Properties and Energy Storage

Achilles tendons are viscoelastic energy-storing tissues; nanoscale studies reveal that individual collagen fibrils strain less than the whole tissue and exhibit fibril-level viscoelasticity (increased stretchability, relaxation) under cyclic loading [63].

IFM in energy-storing tendons shows lower stress relaxation (more elastic behavior) than positional tendons, which is crucial for efficient energy storage and return [61]. Aging increases IFM stress relaxation and alters force-extension behavior [61]. Short-term unloading or altered *in vitro* loading can reduce the elastic modulus and increase stress relaxation, partly due to changes in glycosaminoglycan (GAG) content [64].

3.4.4. Load-Dependent Structural Remodeling

Prolonged unloading produces larger, more heterogenous crimp, disorganized nano- and meso-structures, and reduced modulus; tendons may lengthen, forming thicker but mechanically weaker tissue [58, 59].

During healing, lower loads increase collagen and elastin staining but produce thinner, poorly organized matrices with rounded, misaligned cells and higher angiogenesis, showing that matrix quality and alignment depend on load level, not only quantity of ECM [20]. Overload models reveal early adaptive increases in CSA and ultimate load, followed by later decreases in modulus and ultimate stress, accompanied by upregulation of inflammatory and degradative genes, marking a shift from adaptation to degeneration [65].

3.4.5. Age and Sex Effects on Tendon Adaptation

Aging generally reduces stiffness and modulus, though some mechanosensitivity is preserved [40]. Adaptive responses to loading are smaller in older adults [40]. At the multiscale level, aged tendons show altered, less strain-dependent ECM remodeling, with fewer structural changes across a range of applied strains, indicating a blunted adaptive window [66].

In energy-storing tendons, IFM stiffens and loses elasticity with age, limiting fascicle sliding and increasing injury risk [61]. GAGs modulate regional mechanics near the Achilles insertion in young tendons but have diminished effects in middle-aged or older tendons, suggesting age-dependent roles in local modulus and injury susceptibility [67].

Sex-specific fibril data are limited; some nanoscale studies report age and sex differences in fibril mechanics, but detailed *in vivo* sex comparisons remain sparse [56].

3.5. Exercise-induced Tendon Adaptation

Chronic exercise reshapes tendon properties through load-sensitive mechanotransduction. The pattern, intensity, and timing of loading strongly determine whether adaptation is protective or maladaptive.

3.5.1. Resistance Training

Systematic reviews show moderate increases in stiffness and modulus and small increases in cross-sectional area (CSA) after resistance training, with changes in stiffness driven mainly by material property (modulus) rather than size [3, 56]. High-strain resistance protocols involving a tendon strain of ~4.5-6.5% and loads reaching ≥70% of the one-repetition maximum (1RM), produce the largest gains in stiffness and modulus [9, 56].

Eccentric high-load plantarflexion increased Achilles stiffness by ~80% and CSA by 17% over 12 weeks, with material property adaptations appearing by week 4 and hypertrophy by week 8 [68]. Low-load blood-flow-restriction training (20-35% 1RM) can produce comparable stiffness and CSA gains, indicating that local mechanical strain, rather than external load per se, drives adaptation [69]. Shorter interventions (≤8 weeks) often yield robust muscle but minimal tendon changes, highlighting the slower responsiveness of tendons [9, 70, 71].

3.5.2. Eccentric and Isometric Loading

Meta-analyses suggest that muscle contraction type (concentric, eccentric, or isometric) has minimal effect on chronic stiffness adaptation when overall tendon strain is matched [3, 56, 70]. Both concentric and eccentric protocols at ~60% 1RM increased patellar tendon modulus in young and older men, with a slower but still positive response in older tendons [70].

Eccentric contractions allow higher peak forces, efficiently reaching an “effective” strain window (~4.5-6.5%) that stipulates collagen synthesis and cross-linking [9, 68, 70]. Isometric loading is particularly useful to control load duration and intensity [72]. Long-duration, high-intensity isometrics acutely reduce tendon volume and stiffness more than brief or low-intensity efforts, likely enhancing fluid flow and mechanostimulation of tenocytes, which may favor long-term adaptation [72].

3.5.3. Plyometric Loading

Evidence for plyometric training is more heterogeneous. Meta-analyses report changes in Achilles tendon stiffness ranging from +28% to -9%, with only one study showing a significant,

27% increase [3]. Broader analyses found moderate improvements in tendon stiffness and jump performance, but CSA often remained unchanged [73].

Short ground-contact times and high strain rates in plyometrics may limit tenocyte deformation duration, constraining mechanotransduction despite high peak loads [3, 56, 73]. Comparison with sustained resistance or isometric training indicate greater stiffness gains after prolonged loading, emphasizing the importance of load duration for tendon adaptation [3, 56].

3.5.4. Endurance and Cyclic Loading

Aerobic and moderate-intensity endurance training generally induce smaller or absent increases in stiffness and modulus compared with resistance training [56]. In a large meta-analysis, only resistance and jump-based activity consistently enhance tendon stiffness; concurrent resistance plus aerobic training can blunt tendon adaptation, similar to the “interference effect” observed in muscle [56].

High-intensity cyclic isometric loading at 90% of the maximum voluntary contraction (MVC) (~4.5-6.5% strain) increased Achilles stiffness and CSA over 16 weeks, regardless of whether sessions were clustered or distributed [74]. Within 2.5-5 sessions per week and 180-300 seconds of total loading, the timing of loading relative to recovery and total volume were secondary, provided high strain was achieved [74].

3.5.5. Sport-Specific Tendon Adaptation

Habitual sport loading leads to region- and sport-specific remodeling [12]. For example, volleyball athletes performing frequent jumps show patellar tendon adaptations corresponding to mechanical and psychophysiological load, suggesting a narrow window between positive and tendinopathy [75].

Across sports, tendons exposed to frequent high-strain, stretch-shortening cycles (e.g., jumpers) exhibit higher stiffness than endurance-dominant athletes, likely optimizing energy storage and recoil [3, 12, 56]. Genetic factors modulate this phenotype: carriers of *PIEZO1* gain-of-function variant exhibit ~46-46% higher patellar tendon stiffness and modulus without CSA change, supporting a mechanosensitive, cross-linking-dependent regulation of tendon material properties that may benefit explosive performance [6, 57].

3.6. Mechanoadaptation, Tendon Pathology and Tissue Remodeling

Tendons adapt to mechanical load through mechanotransduction pathways that can promote either beneficial strengthening or progressive degeneration, depending on load profile, tissue architecture and cellular state [6, 9, 65, 76].

3.6.1. Adaptive vs. Maladaptive Remodeling

Physiological loading within the optimal strain window (~4.5–6.5%) induces anabolic remodeling, whereas excessive loads or biological risk factors such as cellular senescence drive maladaptive changes [6, 9, 65, 76, 77].

In a rat synergist-ablation model, tendons initially exhibit increased CSA and load capacity, but prolonged overload (8-16 weeks) reduces modulus and elevated matrix-degrading gene expression, marking the onset of degenerations [65]. Senescent or aged tendons exacerbate this effect, maintaining sustained MMP activity despite reduced protein synthesis [77].

3.6.2. Mechanobiology of Tendinopathy

Tendinopathy represents a failure of homeostatic mechanobiological control [7]. While PIEZO1 signaling contributes to healthy tendon stiffening (Section 3), dysregulated PIEZO1 can drive pathology [6, 76]. Chronic over-activation of mTOR in tendon progenitor cells promotes maladaptive differentiation into adipogenic, chondrogenic, or osteogenic lineages, contributing to the heterotopic ossification and lipid infiltration in degenerated tissue [40, 78].

Disruption of the pericellular matrix, such as in collagen VI deficiency, impairs primary cilia, focal adhesions, and downstream Akt/ERK/YAP signaling, blunting mechanosensitive gene expression and suggesting that defects in the mechanosensory niche predispose to tendinopathy [33, 55]. Inflammatory cues further bias tendon fibroblasts toward catabolic programs, whereas aligned matrices mitigate these adverse responses [79, 80].

3.6.3. Structural and Molecular Changes in Overuse

In vivo models show that collagen is not stretched but proteolytically denatured after exercise; chronic denaturation leads to collagen accumulation and clinical tendinopathy [76]. Histological analyses of human Achilles tendinopathy reveal higher degenerative scores in chronic cases, with matrix disorganization, hypercellularity, altered collagen I/III balance, and dysregulated MMP/TIMP (tissue inhibitors of metalloproteinases) expression [81]. Nuclear and cellular morphology shifts from elongated, aligned tenocytes to round, heterogenous shapes,

particularly in proteoglycan-rich and injured regions; these nuclear changes correlate with injury markers, reflecting a collapsed mechanotransductive state [82].

Biofabrication and microtissue models show that reduced nuclear confinement and matrix alignment are sufficient to drive pathological gene programs, recapitulating diseased-like states [79, 83]. Single-cell and spatial transcriptomics reveal loss of homeostatic tenocyte subsets and emergence of inflammatory, chondrogenic, and ossifying mesenchymal populations, alongside disease-specific endothelial and macrophage subsets, mapping cellular reprogramming during overuse pathology [84].

3.6.4. Continuum Model of Tendon Pathology

Current evidence supports a progression from normal adaptation to reactive changes, disrepair, and final degeneration [9, 65, 76, 84]. Early reactive responses involve transient swelling and increased synthesis [9, 76, 81]. Crossing the threshold of cumulative demand triggers persistent inflammatory signaling and proteolytic denaturation [9, 76, 81].

Single-cell analyses indicate that inflammatory infiltration precedes chondrogenesis and endochondral ossification along the trajectory of tendinopathy, consistent with late-stage degenerative and mineralized lesions [84]. Computational models suggest that structural disorganization, such as dispersed fiber orientations, permanently reduces tendon functional capacity and impairs mechanobiological responses [59].

3.6.5. Recovery and Regeneration Mechanisms

Successful recovery requires re-establishing a mechanotransduction environment that favors balanced ECM turnover [79, 80]. As aligned, anisotropic matrices significantly enhance tendon cell remodeling potential. [89, 80]. Bioengineered mini-tendon and microtissue platforms show that restoring matrix stiffness and nuclear confinement drives elongated nuclear morphology and homeostatic signaling, providing a template for reparative loading and pharmacological interventions [83].

Cellular senescence and aging blunt regenerative responses by reducing protein synthesis and maintaining MMP activity, shifting remodeling toward degradation even under mechanical stimulation [77]. Mapping myeloid and mesenchymal subpopulation trajectories identifies critical windows in which modulating immune responses can promote functional regeneration over scar formation [85].

Neural mediators, including nerve growth factor (NGF), calcitonin gene-related peptide (CGRP) and galanin (GAL), support matrix maturation, highlighting a neuro-mediated component in successful tendon recovery [86].

4. Discussion

The synthesis of evidence presented in this review highlights that tendon adaptation is not merely a byproduct of mechanical loading, but rather a highly regulated mechanobiological process. The translation from molecular signaling to clinical performance requires a precise "dosage" of strain, in which the PIEZO1-YAP/TAZ-mTOR axis acts as a key mediator of structural integrity.

4.1.1. Practical Implications for Training and Rehabilitation

Mechanotransduction principles translate directly into the organization of training load, variation, and monitoring, guiding adaptive tendon remodeling while minimizing overload and overuse risk. Effective training protocols expose tendons to ~4.5-6.5% strain at high relative intensity (70-90% MVC or 1RM), for at least 8-12 weeks [3, 9, 56, 74].

Because tendons are more sensitive to strain magnitude than to metabolic stress and adapt slower than muscle, load management must specifically prevent situations in which rapid muscle strength gains outpace tendon stiffening, which otherwise elevates mechanical demand and injury risk [8, 12, 61].

Mechanical redundancy allows for variability modalities. For example, low-load blood-flow restriction (BFR) training can induce increases in tendon stiffness and CSA comparable to heavy resistance training, when sufficient local strain is achieved [69]. Tendons also respond most effectively to sustained or slower-rate loading (isometric or controlled concentric-eccentric) than to brief, plyometric contacts, which may generate high peak forces but do not always optimally stimulate mechanocellular signaling pathways [56].

Functional loading alterations can also drive structural adaptation. For instance, gait retraining from rearfoot to non-rearfoot strike pattern has been shown to induce morphological changes, including increased Achilles CSA and length, highlighting the tendon’s sensitivity to changes in loading patterns [87].

Personalized loading strategies targeting the “sweet spot” strain range of ~4.5-6.5% can stabilize the muscle-tendon unit (MTU) across a competitive season [88-91]. In adolescent and adult athletes (e.g., handball and volleyball), individualizing loads to prevent high-strain peaks

(>9%) reduce muscle-tendon imbalances and stabilize tendon strain, serving as an effective primary prevention strategy [88-91].

Meta-analyses and intervention studies support protocols based on isometric or slow concentric-eccentric contractions performed at 70-90% MVC, typically organized into multiple sets totaling 180-300 seconds of high-strain loading per week [3, 56, 74, 91]. More recently, personalized loading concepts have been proposed in which external load is adjusted to achieve approximately 6.2% tendon strain during exercise rather than prescribing intensity solely as %MVC or %1RM [74, 88, 90]. This approach improves normalized tendon stiffness or prevents excessive strain increases without compromising strength gains [74, 88-90].

Importantly, aging tendons remain mechanosensitive. In older adults, 14 weeks of high-strain cyclic exercise increased Achilles stiffness, modulus, and CSA by ~6%, demonstrating that similar loading principles can be effective across the lifespan [8].

Because tendon adaptation is slow and exhibits substantial inter-individual variability, ongoing monitoring is essential [12,88]. Ultrasound-based assessments of mechanical properties (e.g., stiffness, strain during MVC) and micromorphology (e.g., peak spatial frequency analysis) can detect subtle structural alterations and identify maladaptive responses [75, 88-90,92].

The integration of point-of-care ultrasound into routine athletic monitoring enables a dynamic assessment of the musculoskeletal system, allowing early detection of subclinical tendon changes [93]. Repeated measurements of tendon strain allow classification of muscle-tendon imbalances and enable individualized load adjustments, reducing seasonal fluctuations and aligning muscle strength with tendon stiffness [88-90].

Finally, combining imaging markers with external and internal workload metrics such as jump count and session rating of perceived exertion (sRPE), offers a comprehensive load profile that supports precise training adjustments and promotes the long-term resilience of the muscle-tendon unit [75].

4.1.2. Future Directions and Research Perspectives

Emerging tools in imaging, computational modeling, and molecular profiling are beginning to bridge tendon mechanobiology with individualized diagnosis, training, and therapy.

High-resolution synchrotron-based X-ray tomography and scattering now enable quantification of collagen crimp, fiber orientation, and nano- to mesoscale architecture [58,59]. These techniques reveal how unloading increases structural disorganization and alters multiscale tendon mechanics [58,59].

At the clinical level, integration of freehand 3D ultrasound with shear-wave elastography and UTE-MRI enables *in vivo* quantification of tendon volume and stiffness [72,94]. These approaches can capture fluid-flow-driven mechanobiological responses and non-collagenous ECM components that were previously inaccessible with standard imaging techniques [72, 94].

The future of tendon management will likely rely on finite-element frameworks and mechanoregulated healing models that incorporate individual collagen fiber orientations and geometry [59, 95]. Such computational models enable patient-specific simulations of how rehabilitation protocols influence tissue composition and viscoelastic properties [59, 95]. In this context, clinicians could eventually stimulate "what-if" scenarios, to optimize loading magnitudes according to each tendon's structural state.

Mechanosensitive ion channels and signaling pathways are also emerging as candidate biomarkers of mechanoadaptation [6, 10]. Load-responsive transcriptional signatures and genetic variants, such as gain-of-function *PIEZO1* mutations associated with superior jumping performance, may eventually allow genetic screening to estimate mechanoadaptive capacity and injury susceptibility [6, 89, 93].

Beyond diagnostics, molecular targets involved in mechanotransduction may become therapeutic modulators. Regulators such as focal adhesion kinase or *CaV1.2*-mediated calcium influx could enhance *in situ* mechanotransduction and collagen fibrillogenesis during tendon recovery [31, 40]. In parallel, force-responsive transcriptional programs identified in embryonic tendon development and stem-cell-derived engineered tissues are expanding the pool of candidate mechanosensitive genes for future biomarker panels [94, 96].

Multimodal, multiscale research frameworks are increasingly integrating mechanical and molecular datasets [58]. Engineered tendon tissues derived from embryonic stem cells or adult stromal cells provide a controlled experimental system for mapping mechanotransduction markers to defined strain histories [94, 95]. When combined with synchrotron imaging, these models allow nanoscale collagen remodeling to be directly linked to whole-tendon mechanical behavior, bridging cellular signaling with functional outcomes [58, 59].

Ultimately, the convergence of advanced imaging, computational modeling, and molecular profiling is paving the way toward "precision tendon training". This emerging paradigm moves beyond external workload metrics toward real-time assessments of internal tissue state and mechanosensitivity, enabling truly individualized tendon loading strategies.

5. Conclusions

Tendons are dynamic, mechanosensitive tissues that rely on a coordinated interplay of molecular signaling, epigenetic regulation, and structural remodeling to maintain homeostasis. The evidence synthesized in this review indicate that optimal mechanical strain (~4.5-6.5%) promotes robust adaptive strengthening through pathways such as PIEZO1, YAP/TAZ and mTOR, whereas chronic overload or underloading can lead to maladaptation and pathological remodeling.

The future of tendon health lies in bridging advances in molecular biology with applied sport and rehabilitation science. By integrating biomechanical loading principles with individualized biological profiles, exercise prescription, recovery strategies, and adjunct therapies may be tailored to each athlete's structural mechanosensitivity. Such a personalized, strain-guided approach has the potential to better align muscle-tendon adaptation, reduce injury risk and optimize the functional capacity of the muscle-tendon unit across the lifespan.

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