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THE ROLE OF MECHANOBIOLOGY IN TENDON HEALING

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Abstract

Mechanical cues affect tendon healing, homeostasis, and development in a variety of settings. Alterations in the mechanical environment are known to result in changes in the expression of extracellular matrix proteins, growth factors, transcription factors, and cytokines that can alter tendon structure and cell viability. Loss of muscle force *in utero* or in the immediate postnatal period delays tendon and enthesis development. The response of healing tendons to mechanical load varies depending on anatomic location. Flexor tendons require motion to prevent adhesion formation, yet excessive force results in gap formation and subsequent weakening of the repair. Excessive motion in the setting of anterior cruciate ligament reconstruction causes accumulation of macrophages, which are detrimental to tendon graft healing. Complete removal of load is detrimental to rotator cuff healing, yet large forces are also harmful. Controlled loading can enhance healing in most settings; however, a fine balance must be reached between loads that are too low (leading to a catabolic state) and too high (leading to micro-damage). This review will summarize existing knowledge of the mechanobiology of tendon development, homeostasis, and healing.

Keywords

shoulder; mechanotransduction

Tendon structure-function

Tendons are critical for the function of joints, connecting muscles to bones and allowing for the transmission of forces between the tissues, leading to joint motion. The mechanical properties of tendons derive largely from type I collagen fibers that are arranged in dense, parallel arrays.[127] This arrangement results in a resilient tissue with high tensile stiffness in the direction of fiber orientation. The organization of tendon and ligament is hierarchical in nature, from the molecular to the tissue scales (Figure 1).[63] Triple-helix type I collagen molecules (300 nm in length, 1.5 nm in diameter) pack together to form microfibrils.[57] Microfibrils are typically defined as five collagen molecules, stacked in a quarter-stagger array. Neighboring microfibrils interdigitate, imposing order upon a mildly twisted lattice

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that forms the next level structure termed a fibril (50–200nm in diameter). At the next level of structural hierarchy, fibrils close-pack into larger structures to form fibers (3–7 μm in diameter). Fibers combine to form fascicles (with diameters on the order of micrometers); at this level a characteristic "crimp" pattern can be seen histologically.[62,63] Finally, fascicles are bundled together through a fascicular membrane to form tendon (diameter on the order of millimeters or centimeters).

Approximately 20–30% of the dry weight of tendon is made up of proteoglycans, glycosaminoglycans, minor collagens (e.g., type III, type XII), elastin, and cellular material.[71,119,127] These minor compositional constituents play important roles in the development of the tissue. For example, type V collagen and the proteoglycans biglycan and decorin regulate fibril diameter during collagen fibrillogenesis [15,95,124].

The attachment of tendon to bone is of major concern in many repair scenarios, including rotator cuff tears. Due to the large difference in mechanical properties between tendon and bone[19,125], large stress concentrations will arise at the attachment point of these two materials and the connection will be at risk for failure. The natural (uninjured) tendon insertion site (the "enthesis") overcomes this challenge via a number of strategies[76]: 1) gradations in its composition and structure[45,76,86,106], 2) a shallow attachment angle at the insertion[76,111], 3) shaping of tissue morphology of the transitional tissue[76], and 4) interdigitation of transitional tissue with bone[84]. These four mechanisms provide a nano- through macro-mechanical description of how a robust tendon-to-bone attachment is achieved.[45,76] However, the complex composition, structure, and mechanical behavior of the tendon/ligament-to-bone insertion result in a particularly difficult challenge for effective response to injury.

Tendon injury and repair

Tendinopathies limit mobility and joint function and often lead to disability and pain.[93] Damage to tendons can be the result of an acute injury (e.g., laceration or sports injury) or chronic impairment (e.g., overuse injury or degeneration), and the capacity of the tendon to heal varies depending on its magnitude, duration, and location.[96,103,128] Effective repair of short and intracapsular tendons (e.g., rotator cuff tendons) often relies on tendon-to-bone integration[59,112] whereas effective repair of long and sheathed tendons (e.g., flexor tendons) often depends on prevention of repair-site gapping and maintenance of tendon gliding.[20,44,126] Tendon healing, in general, follows a typical wound-healing course[75]: a short inflammatory phase (lasting on the order of days) is followed by a proliferative phase (lasting on the order of weeks), which in turn is followed by a remodeling phase (lasting on the order of months). The inflammatory phase is characterized by increased vascular permeability and an influx of local inflammatory cells including platelets, macrophages, monocytes, and neutrophils that release chemotactic agents to recruit blood vessels, fibroblasts, and intrinsic tenocytes. In the proliferative phase of healing, fibroblasts at the injury site multiply and begin producing collagen. During the remodeling phase, cellularity decreases and collagen is crosslinked and oriented parallel to the direction of muscle force.

Tendon healing depends on the contributions of mulitple cell sources, which may include fibroblasts from the endotendon and epitendon[2], inflammatory cells from the vasculature[21,39], cells from the synovial sheath[1,3,9], and mesenchymal stem cells[128], which may migrate to the area of tendon injury or proliferate from within the tendon. The contribution of each cell type to the repair depends on the anatomy and physiology of the particular tendon. For example, healing of flexor tendon injuries begins with angiogenesis and epitenon fibroblast migration to the wound site.[40,43] Cells from the intrasynovial sheath infiltrate to the repair site, leading to adhesions between the sheath and the tendon surface,

which impairs tendon gliding (and hence decreases digital range of motion).[40,43] In the rotator cuff, on the other hand, injuries typically require repair of tendon to bone.[59] In this case, abundant fibroblasts from the tendon and surrounding tissues produce a disorganized collagen scar tissue at the attachment site of the two tissues.[109,112] Osteoclasts are also attracted to the repair site, and resorption of bone at the repair site can impair healing.[24,28] Understanding how different tendons heal is an important consideration for post-operative treatment and rehabilitation.

Tendon mechanobiology during development and homeostasis

The importance of mechanical loading on the development and homeostasis of tendon is evident from a number of studies.[14,80,107,108,122] Mechanical loading has been implicated in changes to tendon size[29,50,68] and mechanical properties[29,34,77], and this mechanosensitive tissue responds to loading in an adaptive manner.[8] Mechanotransduction, or the ability of cells to respond to mechanical cues with biochemical signals, is an important component of musculoskeletal tissue development, homeostasis, healing, and degeneration.[11,122] Tendon homeostasis is maintained with regulated levels of extracellular matrix turnover via production of both matrix degrading enzymes (e.g., matrix metalloproteinases [MMPs]) and extracellular matrix (ECM; e.g., collagen).[80,81] Of particular recent interest are the roles of the transcription factor scleraxis (necessary for tenogenesis) and transforming growth factor-β (TGF-β; a master regulator of differentiation, proliferation, and ECM production), both of which have been shown to act as mediators of tendon development.[88,94,97,100] Altered mechanical loading can promote changes in the expression of scleraxis as well as TGF-β, leading to changes in tendon structure, cell viability, and ECM production.[18,73,107,109] Murcheson *et al.* demonstrated that the regulation of tendon differentiation by scleraxis distinguished force-transmitting tendons from muscle anchoring tendons, implying a mechanosensitive role for the transcription factor.[88] A number of MMPs[81], cytokines (e.g., interleukin-1[5,6,13,61,72,85,114–116,130], and cyclo-oxygenase-2[5,13,72,123,130]), and growth factors (e.g., platelet-derived growth factor) [14,87] can also be affected by mechanical loading. This can result in either a catabolic environment leading to decreased tendon mechanical properties or an anabolic environment leading to increases in tendon mechanical properties.

Mechanical cues are necessary for the development of tendon microstructure and strength, especially during prenatal and postnatal growth.[18,32,66,83,108,110] Embryonic immobilization leads to a decrease in tenascin expression and protein levels in avian synovial joints.[83] Compressive loading is critical for the production of proteoglycans in developing flexor tendons.[32] Other skeletal structures are dependent on tendon mobility *in utero* as well. For example, the development of sesamoid bones has been shown to be dependent on embryonic mobilization, specifically localized mechanical stress and musculotendinous loading.[82,99] In neonates, muscle paralysis has been shown to result in delayed tendon and fibrocartilage maturation as well as impaired mineralization at the enthesis.[66,110] Muscle paralysis of supraspinatus muscles induced at birth via botulinum toxin A[110] or microsurgical transection of the superior trunk of the brachial plexus[66] led to musculoskeletal deformities[66], delayed maturation of tendon-to-bone insertion[110] (Figure 2), and increased intramuscular fat accumulation[26]. Understanding the role of mechanical loading during development may aid in designing rehabilitation strategies and other therapies for adults with tendon injuries.

The sensitivity of tendon fibroblasts to their mechanical loading environment has been well characterized *in vitro* and *in vivo*.[11,12,47,52,53,79,97,117,118,120–122,129] Nuclei of tendon fibroblasts have been shown to deform when subjected to tensile strain *in situ*.[80] Arnoczky *et al*. demonstrated that tendon fibroblasts, when subjected to tensile loads *in vitro*, respond

biochemically via the stress-activated protein kinases (SAPK) in both strain- and frequency-dependent manners[12]. While over-expression of biochemical pathways such as the c-Jun N-terminal kinase (JNK) have been linked to deleterious effects such as apoptosis and increased cytokine activity[60], such loading may also have a therapeutic role in tendon biology. For example, Scott *et al*. identified upregulation of insulin-like growth factor 1 (IGF-1) following increased loading[101], which may encourage cellular proliferation and tendon remodeling[55]. Stress deprivation induces a catabolic state in tendon cells[11,35,52]. Removal of load for one day led to a marked increase in mRNA and protein expression of MMP-1 in an *ex vivo* model[11]. Similarly, while cyclic loading increased the ratio of TIMP-1 to MMP-13 (resulting in an anabolic state), stress deprivation reversed this ratio through an increase in MMP-13 expression (resulting in a catabolic state)[35]. In the section that follows, we will discuss both beneficial and detrimental effects of mechanical loading on tendon healing.

Tendon mechanobiology during healing

Joint immobilization and temporary muscle paralysis

Proper post-surgical rehabilitation strategies for tendon repair are persistently debated in the field of orthopaedics. Recent research has suggested a beneficial effect of sling or cast immobilization to prevent post-repair rupture and aid in healing of repaired rotator cuff tendons.[89,112] In some animal models of tendon injury and healing, cast immobilization has been shown to enhance healing of tendon to bone when compared to other post-repair loading regimes like exercise or complete tendon unloading.[25,34,46,112] For example, in the repaired rotator cuff, immobilization has been shown to play a beneficial role in tendon-to-bone healing.[34,46,112] Using a rat model of rotator cuff injury and repair, Thomopoulos *et al*. found that cast immobilization led to reduced expression of collagen type III (indicative of scar) and increased expression of aggrecan, collagen type II, and collagen type XII when compared to injured rats with exercise.[112] Immobilization promoted the improvement of viscoelastic parameters compared to exercise post-repair.[112] Similarly, Gimbel *et al*. found that immobilization led to increased elastic properties and improved collagen organization at the repaired insertion in the rat rotator cuff repair model compared to cage activity or post-repair exercise.[46]

Understanding the role of immobilization on other connective tissues, such as ligaments, may provide insight into tendon repair as well. Rodeo *et al*. has described the role of macrophage infiltration on the healing tendon-to-bone following anterior cruciate ligament (ACL) reconstruction.[17,23,25,54,64,98] Macrophage activity has been shown to be deleterious to the healing tendon graft, and macrophage-depleted rats (treated with the bisphosphonate, liposomal clodronate) have demonstrated accelerated ACL graft healing compared to untreated rats,[64] Immobilization has also led to reduced phagocytic macrophage accumulation in the healing graft tunnel following ACL repair, with concurrent improvements in tendon-to-bone integration.[25]

Short-term muscle paralysis has been used as a rehabilitation strategy for tendon injuries. The implementation of botulinum toxin A, a pharmacological agent that temporarily inhibits the pre-synaptic release of acetylcholine, has been used in tendon healing experiments in an effort to protect the repair from excessive muscle loads. Such treatment has been shown to lead to favorable clinical results in patients with spasticity.[22,70] Additionally, botulinum toxin A has been implemented as a tool for unloading the tendon during the healing process post-repair.[34,56,78] However, as described in the next section, caution must be taken when completely unloading the repair site.

While immobilization has been shown to be beneficial for post-repair treatment in rotator cuff tendons[46,89,112] and ACL reconstruction[25], such post-operative repair methods may be detrimental for other types of injured tendons[20,44]. For example, immobilization after flexor tendon repair leads to fibrous adhesions between the tendon and its synovial sheath[42], which can severely limit range of motion. Complete immobilization of flexor tendon repairs can also lead to a reduction in repair strength.[40,44,126] Long-term (9 week) immobilization of the knee leads to a reduction in tissue stiffness, particularly of the patellar tendon and medial collateral ligament, which has been attributed not to atrophy but rather to increased collagen turnover.[4]

Complete repair-site unloading

Stress deprivation by immobilization or short-term paralysis can benefit recovery and healing of tendons in certain scenarios.[27,78] However, complete unloading of the repair site is detrimental to healing. Complete removal of load has been shown to limit the organization and structure of the healing tendon and insertion as well as to decrease the mechanical properties of the unloaded tendon.[34,113,116] Galatz *et al*. showed that complete removal of load from the healing site using immobilization and botulinum toxin A application to the muscle resulted in decreased structural properties of the repair tissue (Figure 3).[34] This was largely due to a decreased production of extracellular matrix. Hettrich *et al*. found similar results using chemical removal of load in the same rat model without immobilization.[56] Repairs treated with botulinum toxin A had significantly lower cross sectional area at later time points with subsequent reduction in load to failure. Experiments *in vitro* have demonstrated a quick and sustained release of MMPs as well as a decrease in tissue inhibitors of MMPs when tendon cells are deprived of mechanical stress.[35] Rotator cuff tendon unloading following tenotomy and muscle denervation leads to an increase in fatty degeneration and atrophy of muscle[34,56,65], increased adipogenesis[65,110], and increased fibrosis[16,110]. Similarly, removal of load after flexor tendon-to-bone repairs via a proximal tenotomy led to unfavorable results in mechanical strength and collagen organization.[113]

Passive motion

Tendons requiring long excursions for function (e.g., the flexor tendons of the hand) are typically encased in synovial sheaths. Successful repair of these tendons requires recovery of tissue strength and maintenance of intrasynovial gliding properties. In order to maintain gliding, adhesions between the tendon surface and its sheath must be prevented. Therefore, post-operatively rehabilitation strategies must balance the detrimental effects of immobilization (which will lead to adhesions) with the detrimental effects of active motion (which increase the risk for repair-site rupture). Passive motion, where the tendon is moved within its sheath without active muscle forces, has been established as optimal loading environment for healing.[20,37,40,41,44,126] Passive mechanical rehabilitation methods have been shown to be an effective post-repair treatment for preventing fibrotic adhesions in long tendons, and the optimal timepoint of initiation of such treatment is about 5 days post-repair[31]. By mobilizing the tendon in the synovial sheath, adhesion formations are reduced, injured tendons become stronger than if immobilized, and cell activity and collagen deposition at the repair site are improved[40].

Although passive mechanical loading of the repaired flexor tendon is clearly beneficial, the same may not be true of the repaired rotator cuff. Recent work by Peltz *et al*. using the rat model of rotator cuff injury demonstrated that passive mobilization post-repair can lead to decreased range of motion in joints compared to immobilization.[90] However, clinical studies have demonstrated a reduction in pain scores for patients undergoing continuous passive motion following rotator cuff repair[30], and some suggest continuous passive motion to be clinically more beneficial than immobilization[36]. In contrast, active motion rehabilitation

protocols have been proposed for flexor tendon healing which involve moving the tendon within its sheath using active muscle force. This can lead to high loads on the tendon repair site, and a higher risk for rupture.[74] Similarly, high loads across the repair site during tendon-to-bone healing may lead to gaps, microtears, or repair-site rupture and poor healing outcomes.[20,38,67,102,132]

Overuse

Tendon overuse is a common problem in sport and work settings.[8,10] Repeated overloading can lead to tendinosis, tendinitis, and/or micro-tearing of collagen fibrils, weakening the tendon and eventually leading to rupture.[48,58,92,104,105] This is a significant problem for individuals who perform repetitive activities and manual labor.[8,10,33,105] A number animal models have been used to investigate the influence of overuse on rotator cuff and Achilles tendon degeneration.[48,58,92,104,105] These studies have demonstrated that overuse activity can lead to increased inflammation, changes in tendon structure, and decreased material properties. In a rat model of rotator cuff tendinosis, Soslowsky *et al*. demonstrated that increased loading on the supraspinatus due to exercise resulted in decreased collagen organization and increased cellularity, implicating overuse as one likely etiology for the development of tendinopathy.[105]

Repetitive mechanical overloading has been shown to lead to elevated inflammatory markers such as prostaglandin E_2 (PGE_2)[130,131], IL-1β[7] and tumor necrosis factor-α (TNF-α)[7]. In an animal study on healthy tendon, Archambault *et al*. found that chronic repetitive loading did *not* induce inflammatory or degenerative changes to Achilles tendons in rabbits[7]. However, changes in cytokine expression were observed, leading to increased expression of collagen type III (indicative of scar) and MMP-3 (indicative of a catabolic state). In the injured Achilles tendon, loading with treadmill exercise has been shown to induce macrophage activation, scar formation, and loss of tendon function.[49] In the rat rotator cuff model, repair of the supraspinatus tendon to its humeral head insertion followed by exercise demonstrated significant decreases in mechanical, structural and compositional properties of the tendon-to bone insertion site. Exercise also led to reduced joint range of motion compared with rats exposed to immobilization or normal cage activity.[91,112] Overloading via exercise led to increased production of extracellular matrix at the repair site. However, the material properties of the repair were not improved with increased load; rather, more material of lesser quality was produced. Exposure to overloading has detrimental effects for tendon properties and joint biomechanics in tendon mid-substance healing as well. After injury and repair of canine flexor digitalis profundus, increased levels of force applied during postoperative rehabilitation did not improve tendon strength nor accelerate healing.[51]

Clinical application of mechanobiology for tendon healing

Tendon is a mechanosensitive tissue; this responsiveness provides the opportunity for treatments based on mechanical loading. However, care must be taken in the application of load for enhanced tendon healing. The rehabilitation protocol should be chosen based on the particular tendon injured and the pathology associated with the injury (Figure 4). Multiple factors impact tendon healing in a clinical setting including age, tear size, tear chronicity, and patient biology. However, consideration of the existing research can guide an informed approach to postoperative rehabilitation after tendon repair.

In general, a fine balance must be met between understimulating and overloading the healing tendon-to-bone interface (Figure 4). Studies reviewed in earlier sections demonstrate that complete removal of load from the healing site is detrimental, but excessive load is also harmful. For example, in the study by Galatz *et al*., complete removal of load from the repair site led to decreased matrix production and decreased structural properties.[34] Similar

results were reported by Hettrich *et al*.[56] These studies indicate that the production of extracellular matrix at the repair site is largely dependent upon mechanical stimulation. However, excessive motion and load can also be detrimental to healing. Thomopoulos *et al*. compared immobilization, cage activity, and treadmill running in the rat model after rotator cuff repair.[112] Although, higher load across the repair site stimulated the production of extracellular matrix, this additional scar-like material did not improve the material properties of the repair. These studies illustrate the sensitivity of the repair to postoperative rehabilitation for the example of rotator cuff repair.

Clinical practice and clinical research have influenced postoperative rehabilitation approaches. For example, in the past decade there has been a gradual transition from open rotator cuff repair to arthroscopic repair. The use of minimally invasive techniques for repair, and studies showing a failure of tendon-to-bone healing, have initiated a trend toward slower, more conservative rehabilitation protocols. Unfortunately, few clinical studies have addressed this directly. Parsons *et al* evaluated patients who underwent a 6 week period of immobilization after rotator cuff repair compared to patients who underwent early initiation of passive motion.[89] In the early postoperative group, 23% of patients had relative loss of motion at the early time point of 6 weeks. However, there was no difference between the patients with early stiffness compared to the rest of the group one year after surgery. Although the numbers were small, there was a trend toward better healing in the stiffer group as assessed by MRI. Duzgun, *et al*. compared a slow and accelerated postoperative range of motion protocol with patients initiating active range of motion at 6 and 3 weeks respectively.[31] The accelerated program was associated with less pain and improved DASH (Disabilities of the Shoulder and Hand) scores. Another small study comparing two rehabilitation protocols, one initiating early motion and muscle activation and another with early immobilization, found no differences in functional outcome at 2 years after surgery.[69] However, there was no assessment of healing in either study. Overall, strong clinical evidence for a specific rehabilitation protocol over another does not exist, but early mobilization in a controlled fashion does not appear to be harmful.

In conclusion, tendon responds to mechanical cues in a variety of settings, including the post-injury and post-operative scenarios. In general, some controlled loading is necessary for development, homeostasis, and healing. However, excessive force will produce a negative effect on tendon resulting in injury and impaired healing post-repair. Although clinical evidence supporting specific rehabilitation protocols is limited, basic science research can contribute to the formation of logical approaches to postoperative management.

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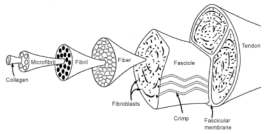

Figure 1.

The organization of tendon is hierarchical in nature, from the molecular (i.e., collagen molecule) to the tissue scales. [Adapted from: Kastelic, J., A. Galeski, and E. Baer. 1978. The multicomposite structure of tendon. Connective Tissue Research 6 (1):11–23].

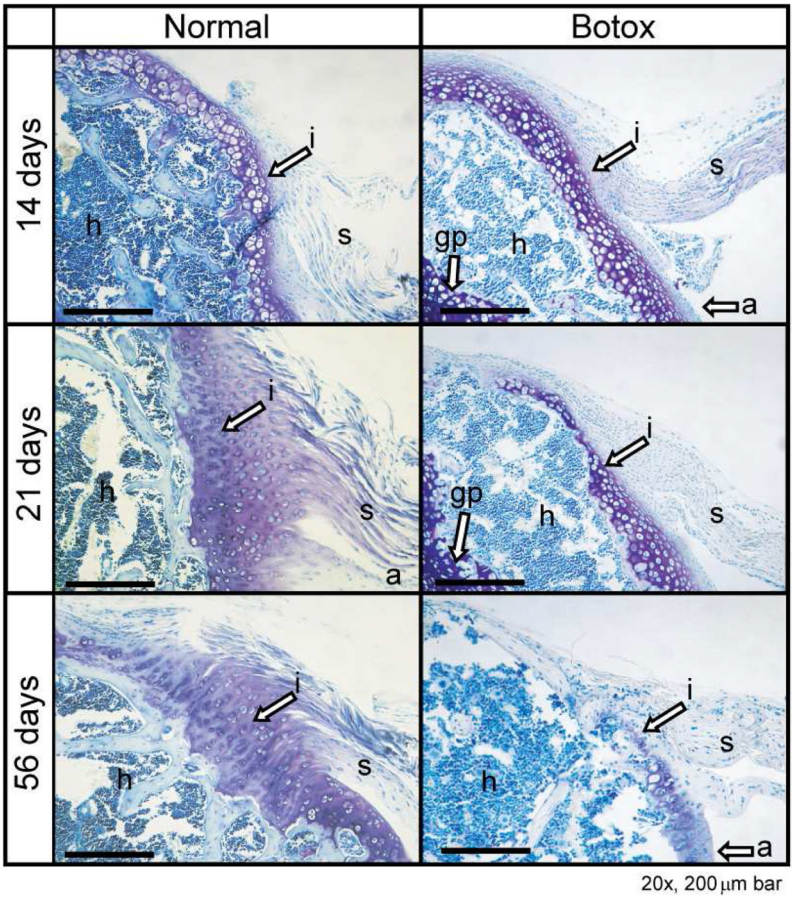

Figure 2.
Development of the tendon-to-bone insertion was dramatically delayed in the Botox group compared to the Normal group. i, tendon-to-bone insertion; s, supraspinatus tendon; a, articular surface of the humeral head; h, humeral head; gp, growth plate. Scale bar: 200 μm. [Adapted, with permission, from: Thomopoulos S, Kim HM, Rothermich SY, Biederstadt C, Das R, Galatz LM. Decreased muscle loading delays maturation of the tendon enthesis during postnatal development. J Orthop Res 2007;25:1154–63.]

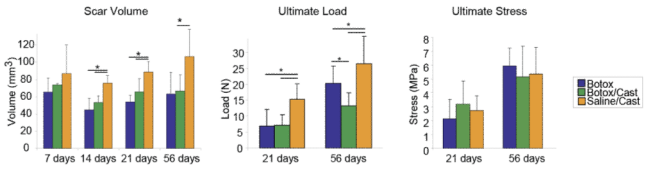

Figure 3.

Complete removal of load (Botox/Cast group) led to significantly lower scar volume and ultimate load (a structural property), but did not affect ultimate stress (a material property). * $p < 0.05$. [Adapted, with permission, from: Galatz LM, Charlton N, Das R, Kim HM, Havlioglu N, Thomopoulos S. Complete removal of load is detrimental to rotator cuff healing. Journal of Shoulder and Elbow Surgery 2009;18:669–75.].

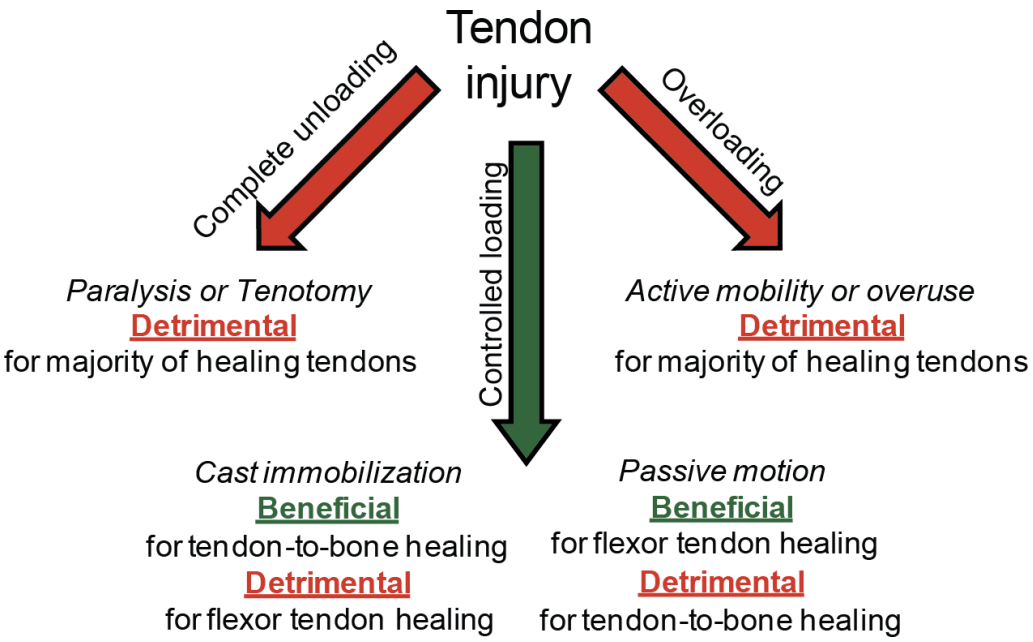

Figure 4.
Complete removal of load is detrimental to tendon healing, yet large forces are also harmful. Controlled loading can enhance healing in most settings; however, a fine balance must be reached between loads that are too low (leading to a catabolic state) and too high (leading to micro-damage).