Relationship between compressive loading and ECM changes in tendons

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Summary

Tendons are designed to absorb and transfer large amounts of tensile load. The well organised, strong yet flexible, extracellular matrix allows for this function. Many tendons are also subject to compressive loads, such as at the entheses, as the tendon wraps around bony protuberances or from internal compression during tensile loading or twisting. Tendinopathy, the clinical syndrome of pain and dysfunction in a tendon is usually the result of overload. However, it is not only the tensile overload that should be considered, as it has been shown that compressive loads change tendon structure and that combination loads can induce tendon pathology. This review summarises how load is detected by the tenocytes, how they respond to compressive load and the resulting extracellular matrix changes that occur. Understanding the effect of compression on tendon structure and function may provide directions for future matrix based interventions.

KEY WORDS: compression, extracellular matrix, tendon, tendinopathy.

Tendon ECM changes and compression

Tendons are exposed to different types of load during normal function. Tensile load is the prime load that tendons endure, often functioning as elastic tissue to decrease the metabolic costs of high level function. In addition to tensile loads, compressive load is high at the enthesis and at points where the tendon has bony contact[1]. Pathology at these points of compression is common and some features of pathology in tensile and compressed regions are similar to fibrocartilage, which is a normal response to compressive load. To fully understand this response to compressive load, it is important to briefly review the structure of normal tendon.

Normal tendons are a three dimensional network of tendon cells (tenocytes), interspersed between tightly packed collagen fibres that are orientated along the line of tensile loading[2]. Also present in the extracellular matrix (ECM) are proteoglycans, glycoproteins and water as well as a range of enzymes, growth factors and cytokines.

Tenocytes synthesise all ECM proteins of tendon tissue[3] and are capable of expressing different phenotypes in response to differing mechanical stimuli[4]. The synthesis of the ECM components is based on load applied, therefore there is variation in tendon architecture and composition along the length of tendons and in tendons with different functions (e.g. elastic storage compared to positional tendons)[5]. The difference in structure in tendons that are subjected to differing mechanical stimuli clearly demonstrates a capacity of the tendon and its cell to detect and respond to load.

Cook and Purdam[1] examined the evidence for compression in the development of overuse tendinopathy and highlighted the many tendons subject to compression, particularly close to their insertion into bone. Tendons that develop tendinopathy where compression is an important factor include the Achilles insertion, proximal hamstring, tibialis posterior, biceps long head, supraspinatus, gluteus medius and minimus, adductor longus/rectus abdominus, peroneal tendons, quadriceps and pectorals. Given that most tendons are affected by compression, it is timely to review the cellular and matrix response to compressive loads. To understand the response, it is important to first appreciate how tendons detect, respond and transduce mechanical stimuli.

Overview of mechanotransduction in tendons

Mechanotransduction describes the conversion of a mechanical stimulus to a biochemical response and is important in tendon remodelling. The exact mechanisms by which tenocytes detect mechanical stimuli and thereby alter the ECM remains poorly understood[2]. It has been shown that the composition and tendon mi-

cro-architecture is continually adapting to the loads applied or removed, and that this adaptive process is driven by the tenocyte.

Tenocytes are sparsely distributed spindle shaped cells located end to end in rows in channels between collagen fibres. Tenocytes possess numerous cell processes extending between the cells in the rows and between rows of cells allowing communication between cells via the cell processes and gap junctions[6]. These gap junctions allow rapid exchange of ions and signalling molecules between cells, which can induce stimulatory and inhibitory responses to tensile load[7]. Whether these gap junctions play a role in compressive load is yet to be determined.

Tenocytes not only respond to mechanical loads[8] but to local stimuli (e.g., hydrostatic pressure changes, cytokines and growth factors)[9]. Different types of mechanical load may activate tenocytes differently (e.g. shear stress compared with substrate strain)[10]. That is, both the type and magnitude of the load may elicit a different cellular response.

The tenocyte has a number of mechanisms for detecting the mechanical environment such as their internal cytoskeleton, cellular projections (cilia), cell-cell communication and local/circulating chemical messengers. In the 1990's, Ingber described the 'tensegrity' model in an attempt to understand mechanotransduction and the role of cell deformation and the cytoskeleton[11-13]. The internal cytoskeletal structure forms a network of struts and cables that are placed in a state of isometric tension, due to the forces applied on the cell by the surrounding ECM, allowing the cell to be responsive to mechanical stresses. When under tensile strain, Type I collagen production is up-regulated in cultured tenocytes, however when the cytoskeleton is disrupted with cytochalasin D, collagenase mRNA expression is shown to be upregulated indicating increased catabolism[14]. This three dimensional internal network can detect and respond to tensile strain; however the ability of the cytoskeleton to detect compressive stresses has not been investigated.

Primary cilia, solitary finger-like immotile projections that extend from the cell surface into the extracellular environment, have been observed in almost two-thirds of all tenocytes[2] and have a role in detecting tensile load. Cilia are microtubule based sensory organelles and shown to be aligned parallel to the collagen fibres forming a cantilevered beam with adhesions to the fibrillar matrix[2]. The cilia have been shown to deflect in response to tensile loading and lengthen when deprived of stress suggesting these cellular projections play an important role in detecting load[15, 16]. Although, it is not known how cilia react to compressive load in the tendon. In other tissues such as bone, cilia has been shown to detect fluid flow[17, 18], and this may be increased with compressive load.

How does tendon react to compression?

Pauwels[19] described connective tissue differentiation (fibrous, fibrocartilage, cartilage and bone) in response to differing mechanical stimuli, which as a result determines the expression of an appropriate form of connective tissue. Tissues respond to different loading parameters by altering their matrix structure to be suitable to transmit and absorb the applied loads[20]. Tendon, designed primarily to withstand tensile load, demonstrates several adaptive responses when subjected to compression. A substantial change in tendon composition and structure adjacent to a bony prominence has been described where the tendon is subjected to compressive forces. Gillard et al.[21] demonstrated fibrocartilage at the compressive region (where the tendon wraps around the calcaneus and talus) within the normal flexor digitorum profundus tendon of the rabbit, with a return to normal fibrous tissue upon removal of compression through surgical intervention. Milz et al.[22] also showed in the Achilles tendon that areas of fibrocartilage at, and proximal to, the insertion were normal adaptive changes.

What is the structure of compressed tendon (fibrocartilage)?

Tenocytes alter their phenotype as a result of compressive forces by becoming more rounded (chondrocytic) and express cartilage-like matrix proteins such as large proteoglycans and Type II collagen. They protect themselves by their position in lacunae and also by releasing large proteoglycans that slow the dissipation of fluid and reduce fluid shear stress (CJ Handley, personal communication[23]). Large proteoglycans such as aggrecan and versican are found in higher concentrations in both compressed and pathological tendon. This suggests that compression may be critical in the overload that drives the onset of pathology. These large proteoglycans may help with cell and/or tendon protection by limiting loads on the cell and decreasing stress on the tendon. Small proteoglycans are still synthesised by the tenocytes, but there is a greater predominance of large proteoglycans. In addition to the ongoing slow production of Type I collagen, there is some production of Type II collagen in the areas subject to compression within tendons[24]. Whether this production also exists in tendon pathology where compressive overload is a factor, is not yet known.

When does adaptation to compression become pathological?

A naturally occurring response to compressive load resulting in fibrocartilage occurs when tendon sustains compressive loads near a bony prominence that are not excessive but due to the normal positional and functional demands. The fibrocartilage is essential to allow the tendon to both tolerate the compressive load and maintain capacity to act in conjunction with the tensile load bearing part of the tendon.

When the compressive loads are excessive and/or suddenly increased in magnitude or volume, then tendinopathic changes occur. The cell and matrix changes in tendon pathology are described extensively. These

Table 1. Differences between fibrocartilage and tendon pathology (Reproduced with permission from Cook and Purdam: Is compressive load a factor in the development of tendinopathy?. British Journal of Sport Medicine 2012; 46:53).

	Normal tendon	Fibrocartilage	Pathological tendon
Cells	Few spindle shaped cells	No cell proliferation Cells rounder	Cell proliferation Cells rounder, more endoplasmic reticulum
Proteoglycans	Minimal mostly decorin and biglycan	5-10-fold higher than in tensile tissue, mostly aggrecan	3-fold higher than tensile tissue, 25-fold higher metabolic rate of normal tendon[32] Biglycan and aggrecan increase, decorin maintained[33]
Collagen	Predominately Type I	Type I & II	Type I collagen, some Type II, substantial increase in Type III collagen
Collagen structure	Ordered collagen network	Ordered collagen network	Disorganised collagen network
Vascularity	Minimal	None to minimal	Variable but can be abundant

changes include cell activation and proliferation, which leads to substantial matrix changes[25]. The cell proliferation drives a rapid increase in the production and degradation of large proteoglycans, with a half-life of around 2-3 days[26, 27]. The cells preferentially synthesise Type III collagen (some Type I and II is produced also) leading to increased collagen turnover. As Type III collagen is thinner and less capable of fibril formation, collagen disorganisation and neurovascular ingrowth results[28].

These changes associated with pathology are sometimes referred to as fibrocartilaginous metaplasia[29, 30] due to the similarity to fibrocartilage[31]. However, despite the role of compressive stresses in pathology and the obvious similarities between tendon pathology and fibrocartilage, the term fibrocartilaginous metaplasia in reference to pathology is incorrect due to key differences as listed in Table 1.

Compressive loads, in isolation and in combination with tensile load have been investigated for their ability to induce tendon pathology. Soslowsky et al.[34] investigated the effect of different loads on rat supraspinatus tendon and examined the effect of compressive load, tensile load and the combination of both. They showed that compressive load (by interposing tissue between the tendon and acromion) in itself had minimal effect in the tendon, tensile load (running downhill) was clearly detrimental, but the combination of loads was especially damaging to the tendon[35]. Increased cross-sectional area and decreased mechanical properties were maximal in tendons exposed to both compressive and tensile loads. This has immediate clinical relevance as many tendons are subject to an environment of both tensile and compressive loads in relative combinations.

How does this relate to tendinopathy?

Normal adaptation to compression is present within the tibialis posterior tendon as it passes posterior to the medial malleolus and presents as an appropriate model for understanding compression in the development of tendinopathy[36, 37]. Within these areas of fibrocartilage the presence of aggrecan binds with water, slowing the permeability of fluid and protecting the fibrillar and cellular components of the tendon from lateral forces[23]. In contrast, the tensile region of the tendon is proposed to have higher fluid permeability due to low concentrations of aggrecan, allowing the tendon to withstand high tensile load. However, this zone of fibrocartilage is not well demarcated and a zone of transitional tissue exists between the two mechanical distinct regions. As this transitional zone is unsuited to compressive loads, this area of tendon may be implicated in the development of tendinopathy. If excessive loading (tensile, compressive or more likely combination load) is placed upon tendon, this may lead to the flow of fluid and the depletion of bound water within the high fluid permeability areas (tensile and transitional zones). Grigg et al.[38] reported a reduction in the Achilles tendon AP diameter at these high fluid permeability areas (mid-substance of the tendon) as a result of repeated eccentric load. In pathological tendons, which have been shown to contain high levels of aggrecan, this alteration in AP diameter was not observed[38].

The movement and loss of water through the tendon may expose the tenocyte to compressive load. In response to the loss of water from the tendon, the tendon may synthesise and release large water binding proteoglycans in an attempt to maintain homeostasis. This process has been shown to occur in a pathological state and occurs within days[39]. As previously discussed, this would bind water to the matrix and protect the cellular and fibrillar components of the tendon against future insult by reducing the permeability of water through the matrix. Further loading to the tendon may perpetuate the response and result in extensive disorganisation of structure[40]. Pathological features similar to fibrocartilage (cell rounding, aggrecan deposition) have been induced in the supraspinatus tendon in the rat within the transitional zones normally occupied by normal spindle shaped tenocytes[41].

Compression may not only occur as a result of the tendon being adjacent to a bony prominence, but occur

during tensile loading such as in the midsubstance of the Achilles tendon. Lavagnino et al.[42] developed a finite computational model to measure mechanical stresses placed on the cell during tensile strain. Cellular tensile strain was suggested to be similar to the strain on the tendon yet shear stress (perpendicular to the long axis of the tendon) was significantly increased when strain rate was increased. The reason for this lateral shear stress was suggested to be due to fluid flow perpendicular to tensile strain. This increase in lateral compression placed on to the tenocyte may help explain why high elastic storage (high strain rate) movements are deleterious to the tendon and implicated in tendinopathy[34, 43] yet heavy slow resistance loads (low strain rate) are more beneficial[44].

In summary, tendons adapt to the loads placed on them either with normal adaptive responses or with a pathological response. The exact mechanisms that lead to adaptation versus pathological change are not completely understood but are likely to be related to the frequency and type of load (with a combination of tensile and compression load being the most provocative). Characterisation studies of the clinical and imaging presentation of tendinopathy at various tendons[45, 46] identify the site of compression adjacent to the tendon insertion as a predominant site of pathology, strongly suggesting that compression is an important consideration in the development and management of tendinopathy. Compression to the tendon is not solely isolated to the insertion and can occur due to normal anatomical bony prominences away from the insertion, due to alterations in biomechanics that induce compression from an adjacent bony prominence or changes to fluid flow and matrix structure. Compression is not responsible for all tendinopathies as some tendons lack a nearby bony prominence (e.g. flexor tendons of the forearm, proximal insertion of the patellar tendon). However, clearly compression appears to be implicated in pathology and results in substantial changes to the structure and function of the ECM and therefore of the tendon. Opportunities to reduce compressive loads on the tendon, especially when in combination with tensile loads may prevent a deleterious tendon response.

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