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Tendinopathy: Investigating the Intersection of Clinical and Animal Research to Identify Progress and Hurdles in the Field

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Abstract

- Biological treatments, surgical interventions, and rehabilitation exercises have been successfully used to treat tendinopathy, but the development of effective treatments has been hindered by the lack of mechanistic data regarding the pathogenesis of the disease.
- While insightful, clinical studies are limited in their capacity to provide data regarding the pathogenesis of tendinopathies, emphasizing the value of animal models and cell culture studies to fill this essential gap in knowledge.
- Clinical pathological findings from imaging studies or histological analysis are not universal across patients with tendinopathy and have not been clearly associated with the onset of symptoms.
- There are several unresolved controversies, including the cellular changes that accompany the tendinopathic disease state and the role of inflammation.
- Additional research is needed to correlate the manifestations of the disease with its pathogenesis, with the goal of reaching a field-wide consensus on the pathology of the disease state. Such a consensus will allow standardized clinical practices to more effectively diagnose and treat tendinopathy.

Tendinopathy, which is a chronic clinical syndrome typically defined by longstanding pain and tendon dysfunction, is a common and costly condition that is prevalent among the general public and athletes¹. However, tendon abnormalities are not always associated with pain or dysfunction². Diagnosis in the absence of symptoms or dysfunction is limited by our lack of understanding of its unclear pathophysiology and disease progression.

Previous clinical and basic-science studies have yielded contradictory findings regarding tendon pathophysiology. Tendinopathy has a varied presentation both clinically (in terms of symptoms and imaging findings) and histologically^{3,4}. Clinical trials are limited by the heterogeneous nature of the population under investigation. Even studies that have investigated a specific manifestation of tendinopathy have had equivocal results⁵. This

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varied clinical presentation may be due to the complex interactions of psychosocial factors, genetic differences, and molecular/cellular responses to an injury. Consequently, the definition lacks consensus in the scientific community and there is no objective method to assess tendinopathy or tendon repair. Unfortunately, the efficacy of current treatments to restore function and to promote adaptation is limited as the pathophysiology of the disease is largely unknown.

The purpose of the present report is to provide insight on the current state of the research on tendinopathy and to identify promising areas for future investigation. This review discusses the current understanding of the clinical and scientific definitions of tendinopathy, the role of inflammation, therapeutics, gene expression, mechanical loading, factors that contribute to a patient's susceptibility to the development of tendinopathy, the contributions of animal studies to clinical approaches, and areas in need of continued research.

Materials and Methods

In August 2014, we performed a preliminary search for articles published over the past 5 years using the PubMed database with the following search terms: "tendinopathy," "insertional tendinopathy," "midsubstance tendinopathy," "Achilles," "supraspinatus," "rotator cuff," "patellar," "gene expression," "tendon development," "tendon degeneration," "tendinosis," "tendinitis," "enthesitis," "enthesitis degeneration," and "tendon imaging." As manuscript preparation and submission was not complete until June 2015, the literature search was extended to June 2015, for a total of 6 years. A single reviewer screened the resulting titles and abstracts to determine the eligibility of each study for inclusion. A total of 10,377 records, including duplicates, were obtained after searching PubMed. Articles cited in these manuscripts and seminal supporting manuscripts were also reviewed and included in the present report if relevant. As the manifestations of tendinopathy can involve different combinations of the tenosynovium, peritenon, and tendon, to achieve more depth, we limited the breadth of the review to focus on the manifestations that affect the tendon itself. We focused our search on studies that investigated histological changes, gene expression, tendon development, the effects of mechanical loading, cellular changes, the controversial role of inflammation, therapeutics, and diagnostics. There were 48 basic science studies, 15 imaging studies, 25 outcomes studies, and 26 literature reviews. A review of the current literature is presented in this report.

The Clinical Definition

The diagnosis of tendinopathy is primarily based on patient history and physical examination⁶. The major clinical feature is longstanding pain¹. The findings from the physical examination include tenderness of the affected part of the tendon(s), pain with tendon loading, and, occasionally, palpable nodular thickening⁷. Tendon pain long has been thought to be moderately well localized⁸, suggesting that injured tendons would be easily identifiable. Yet, tissue abnormalities recently have been associated with widespread mechanical hyperalgesia and motor control deficits^{9,10}, suggesting that localized pain may be obscured by generalized pain. Consequently, physicians use magnetic resonance imaging (MRI) and/or ultrasound to confirm the pathology of the clinical findings. A number of

studies have evaluated the accuracy and sensitivity of ultrasound (range, 0.63 to 0.83 and 0.68 to 0.87, respectively) and MRI (range, 0.68 to 0.70 and 0.50 to 0.57, respectively)^{11–16}. Because of its greater accuracy, lower cost¹⁷, and potential for improved resolution as new transducers and contrast agents become available¹⁸, ultrasound is becoming more widely used by physicians.

These imaging modalities led to the identification of additional criteria for diagnosis. On MRI, tendinopathy is diagnosed through the visualization of macroscopic tears, thinning, thickening, or hyperintensities (fluid) (Fig. 1-A)^{12,19–21}. On ultrasound, tendinopathy is diagnosed by observation of hypoechoic areas, increased blood flow (neovascularization), and/or irregular fiber structure (Figs. 1-B and 1-C)^{12,22}. Although imaging studies have proven useful for the diagnosis of symptomatic tendinopathy, clinical studies have demonstrated that structural changes can be visualized on ultrasound and/or MRI in the absence of clinical symptoms^{15,23}. Therefore, abnormal imaging findings do not necessitate physician intervention; however, they do alert the physician that a pathological process is occurring. The pathological features that trigger the onset of symptoms are unknown; there are no correlations thus far between clinical symptoms and either pathological changes on imaging studies, histological findings, or the mechanical strength of a tendon.

Despite inherent limitations associated with the assessment of pain in animal models, animal studies are necessary to further define the relationship between pathological changes and pain (or its seemingly unexplainable absence). Studies have investigated central nervous system pain-related peptides (including calcitonin gene-related peptide, substance P, and dynorphin A) and tendon sensitivity via an instrumented plier test²⁴. In addition, animal studies have utilized functional measures, such as gait analysis, to relate tendon abnormality and the onset of loss of function²⁵.

Despite the prevalence of tendinopathy, clinical samples, mostly from surgical discards collected at the end stage of the disease, provide limited but valuable insight into its pathogenesis. For instance, degenerative changes in ruptured tendons, commonly seen in cases of rotator cuff tears, suggest that subrupture damage accumulation contributes to the development of tendinopathy^{26,27}. Similarly, increased cellularity^{3,28–30} and vascularity³¹ during end-stage tendinopathy suggest that its progression is the result of a process in which degeneration outpaces effective healing. Clinical studies have shown that end-stage tendinopathy is associated with increased matrix metalloproteinase (MMP) activity³², suggesting that, despite failed repair, an attempt to remodel, albeit ineffective, is a component of its pathogenesis. However, clinical studies are limited in their capacity to provide data regarding the pathogenesis of tendinopathies. Basic-science studies, despite their inherent limitations, help to fill the gaps in knowledge by investigating underlying mechanisms and directly characterizing the pathogenesis of the disease.

Disease Pathophysiology and Histopathology

Clinical studies have shown healthy tendons to be shiny, white, and firm on gross examination²⁸. Healthy tendons have collagen fibers aligned in the direction of loading, relatively few cells, and minimal vasculature^{29,30,33}. In contrast, diseased tendons grossly

appear dull, yellow, and soft²⁸. Pathological changes are diagnosed with imaging, yet current modalities do not have sufficient resolution to demonstrate such changes at the microstructural level. Histological analysis of diseased and healthy tendons in humans is not commonly performed as it would require a biopsy and possibly compromise the tendon's biomechanical strength³⁴. Therefore, animal studies are useful for investigating the histological appearance of native and tendinopathic tendons.

There are 2 methods to induce tendinopathy in animal models: (1) chemical induction of injury from injections of collagenase, prostaglandin E (PGE), corticosteroids, or fluoroquinolone; and (2) mechanical loading, such as fatigue loading or treadmill running³⁵. Chemical-induction methods do not replicate the process of human tendinopathy, but they provide a rapid method to induce tendon damage and to investigate potential treatments. Mechanical-overuse models are similar to human tendinopathy secondary to overuse. Although animal models are not without their limitations, they provide a valuable platform to assess the pathogenesis of tendinopathy and potential therapeutics.

Animal studies have demonstrated that healthy tendons are structurally organized with aligned collagen fibrils having a bimodal diameter distribution and a specialized tendon-bone insertion site. In addition, native tendon cells are elongated in the midsubstance³⁶, are more rounded at the enthesis³⁶, and express tenomodulin³⁷. With the development of tendinopathy, collagen bundles become increasingly disorganized, losing their parallel alignment and overall hierarchical structure^{38–40}. Alterations in cellularity and cell morphology, neovascularization, glycosaminoglycan (GAG) deposition, and dystrophic changes, including calcification and lipid deposition, also develop^{28,41–43}. Even with the identification of many histological changes, the lack of their universal presence confounds our capacity to determine their role in the disease process.

For instance, cellular proliferation has been associated with tendinopathy and tendon rupture and is used as a histological marker in research studies^{3,28–30,44}. Increased cellularity could be a manifestation of an ultimately ineffective repair. Yet, some evidence suggests that early and late-stage tendinopathy are associated with hypocellularity and apoptosis^{45–47}. In a case-control trial of patellar tendinosis, apoptotic cell death was increased⁴⁶. This finding was supported by an in vivo rat patellar tendon study in which apoptosis increased early in the degenerative process and correlated with the extent of damage to the tendon⁴⁷. Excessive cell death and proliferation are associated with tendinopathy, suggesting that cellularity may change with disease progression and as a result of the mechanism of injury.

Researchers have endeavored to create a grading scale to determine the severity of tendinopathy on the basis of its histological appearance. Unlike the Osteoarthritis Research Society International scoring system for arthritis, there is no universally objective way to grade tendinopathy or tendon-healing. Over the past 2 decades, several scales have been applied to grade the extent of tendinopathy and the quality of repair^{43,48–53}.

The disparate criteria used by various tendinopathy and tendon-repair grading scales are shown in Table I^{43,48–53}. Collagen organization is the only criterion assessed by every scoring system. Vascularity and cellularity are the next most common markers evaluated,

with 5 of the 7 scales taking these morphological changes into account. Cell morphology, continuity, and fibrocartilage are used in 3 of the 7 scales. The remainder of the criteria are used in only 1 or 2 scales. Only the Rosenbaum scale is correlated with ultimate tensile load ($R^2 = 0.91$)⁵¹. Interestingly, none of those scales are commonly used in research; different criteria are applied for each new study.

A hurdle to the application of these so-called markers of disease to the clinical setting is that few of them are measurable with current diagnostic modalities. Ultrasound and/or MRI can identify neovascularization through increased blood flow, the continuity of fiber structures, collagen organization, and cellularity (deduced from changes in tendon thickness). Inflammation cannot be directly measured⁵⁴. Even experimental confocal arthroscopy, which has better resolution for observing fiber structure and orientation, cannot visualize all markers³⁴.

Inflammation

Clinical studies have suggested that overt inflammation is absent in chronic tendinopathy²⁹. Yet, Schubert et al. observed the presence of macrophages, T-lymphocytes, and B-lymphocytes in samples from patients with painful human Achilles tendinosis⁵⁵. The same authors also found large numbers of granulocytes in spontaneously ruptured tendons⁵⁵. While an overt systemic inflammatory response with cell infiltration is controversial, molecular-level inflammation has been demonstrated in numerous clinical, cadaveric, animal, and cellular studies in association with chronic tendinopathy and after tendon over-exercise, suggesting that molecular inflammation plays a role in tendinopathy and adaptation. Specifically, increased levels of cyclooxygenase-2 (COX-2), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-21 (IL-21), transforming growth factor- β (TGF- β), substance P, and prostaglandin E2 (PGE2) have been observed^{28,55–60}.

Animal and in vitro studies are needed to determine the direct role of such inflammatory markers in tendon disease and repair. For instance, the level of PGE2 (a prostaglandin closely associated with inflammation) increased in a mouse patellar tendon in response to rigorous treadmill running⁶¹. When PGE2 is cultured with tendon stem cells (TSCs), adipogenesis and osteogenesis are induced whereas cell proliferation decreases⁶¹.

Therapeutics

Despite the controversial role of inflammation, nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed, although largely ineffective⁶², conservative treatment to reduce inflammation by inhibiting prostaglandins. COX-2 inhibitors, which have anti-inflammatory and analgesic effects while avoiding the adverse gastrointestinal side effects, have been found to inhibit tendon-healing⁶³. Platelet-rich concentrates are thought to improve healing because of their abundance in growth factors and cytokines, some of which are anti-inflammatory⁶⁴.

Platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) have been shown to improve the healing process⁶⁴; however, their effects have not been consistently reported. This inconsistent outcome may be attributable to the large number of preparation methods or to

the composition of platelet-rich concentrates. Protocols vary greatly with regard to velocity and duration of centrifugation. This variation alters the composition of platelet concentrates, leading to patterns of growth factor expression^{65–67}, some of which may have an adverse effect by potentially enhancing the fibrotic response⁶⁷. While promising, the optimal preparation of platelet concentrates and the time during healing wherein they might promote an effective response have not been identified.

Mesenchymal stem cells (MSCs) have been thought to be a promising therapeutic as a source of cells to promote regeneration. Gulotta et al.⁶⁸ delivered MSCs to a rotator cuff repair site in a rat model and reported that the treatment did not improve the biomechanical strength or histological appearance of the tendon, although the MSCs were shown to be metabolically active. While promising, the lack of outstanding results could be due to the lack of an optimal carrier for delivery (e.g., fibrin glue, various scaffolds, or direct injection of cells) or due to the need to enhance the cells through gene modification. Gulotta et al. also reported that, after delivery of Sox-9 and/or scleraxis-transfected MSCs, the enthesis had increased amounts of fibrocartilage at the insertion and improved biomechanical strength⁶⁹. Improvements also were seen after transfection of membrane type-1 matrix metalloproteinase (MT1-MMP)⁷⁰. However, not all transfected stem cells have produced improved tendon-healing⁷¹, suggesting that there is much room for improvement prior to translation of cell-based therapies to the clinical setting.

Human adipose stem cells (hASCs) are another stem cell source. They can trilineage differentiate⁷². An advantage to this cell source is that there is an abundance of stem cells in this tissue, which could eliminate the need for in vitro expansion⁷³. Deng et al. reported that hASCs delivered to rabbit Achilles tendon defects increased the tendon tensile strength and collagen fiber diameter⁷⁴.

Gene Expression

Gene-expression studies have been performed to identify the biological factors implicated in the pathogenesis of ten-dinopathy. The main findings of human and animal studies are summarized in Table II^{75–81}. Since human studies typically harvest tendons at the time of surgical intervention, the gene expression from several patients will reflect a large variation in disease state. Therefore, animal studies could provide insight into gene expression that is associated with a particular state of injury.

Diseased tendons exhibited a change in extracellular matrix gene expression, specifically those (MMPs, TIMPs [tissue inhibitors of metal-loproteinases], ADAMs [a disintegrin and metalloproteinase]) involved with remodeling, focal adhesion, integrin signaling, collagen synthesis, and non-collagen glycoprotein synthesis. These changes in gene expression suggest active remodeling, yet clinical data do not suggest that all tendons effectively remodel induced damage. For instance, despite advances in surgical technique, rotator cuff tears have high postoperative retear rates⁸² whereas Achilles tendon ruptures have been shown to typically heal with nonoperative treatment⁸³, suggesting that tendons exhibit different capacities for healing.

Jelinsky et al.²⁸, in a study of 23 patients with tendinopathy, identified 983 transcripts that had significantly increased expression in diseased tendons as compared with controls ($p < 0.01$). Most interestingly, they found an increased expression of components of the JAK/STAT (Janus kinase/signal transducers and activators of transcription) pathway, which can lead to the activation of MMP-9 and MMP-14²⁸. Castagna et al.³² found that MMPs and TIMPs were altered in the pathological portion of the tendon, the normal portion of the diseased tendon, and nearby “control” tendons. This finding suggests that tendon injuries affect the entire joint, with altered biomechanics in the uninjured tendon regions as well. However, control human tendons are harvested from patients typically undergoing orthopaedic surgery and may exhibit minimal pathological changes. Still, clinical studies provide limited but valuable insight into the pathogenesis of tendinopathy.

Andarawis-Puri et al.⁸⁴, using an early-onset tendinopathy animal model, found an inverse relationship between gene expression of collagen types I and XII, MMPs, and TIMPs and the severity of tendon damage. Minor tendon damage due to fatigue loading can lead to an adaptive response, whereas a high level of damage elicits an ineffective and substantially reduced repair response.

As demonstrated in Table II, gene expression varies between tendinopathies of specific tendons, yet there has been little exploration of their similarities and differences. Shadwick⁸⁵ suggested that functional differences were the major drivers for biological, structural, and compositional differences. However, recent studies have demonstrated that there are molecular differences during tendon development, likely when functional differences are minimal^{86,87}. Brown et al. explored the differences between axial and limb development by using embryonic mouse tendon progenitor cells (TPCs) isolated from tendons at different embryonic days of development and anatomical origin. In vitro, it was found that at baseline and after mechanical loading, gene-expression levels of scleraxis and elastin differed between limb and axial TPCs⁸⁶. This difference may be due to inherent difference between cell types or the effects of their different microenvironments early in their development^{86,87}. This difference between axial and limb TPCs suggests that different cell types are partly programmed to respond uniquely to exogenous factors in the setting of development, adaptation, regeneration, and injury. Zhang and Wang reported that rabbit patellar TPCs had larger colonies and proliferated more rapidly than Achilles TPCs in monolayer culture⁸⁸. Williamson et al. reported that equine superficial digital flexor tendon TPCs had restricted differentiation capabilities in monolayer culture in that they were unable to undergo adipogenesis⁸⁹.

The effectiveness of TPCs also may be influenced by the health status of the tendon. Lui and colleagues reported that TPCs from a collagenase-induced failed-healing patellar tendon injury model had limited proliferative and differentiation capabilities and higher levels of bone morphogenetic protein (BMP)-2, BMP-4, BMP-7, and BMP receptors⁹⁰ and that these findings could contribute to the chondro-ossification seen in tendinopathy⁹¹. However, the cells in those studies were cultured in monolayer, which fails to replicate the cell-matrix interactions of the natural 3-dimensional environment. Still, to our knowledge, no studies have directly addressed the fate and roles of tendon stem cells after tendon injury in vivo.

Mechanical Loading

In addition to their innate biological differences, tendons have different loading environments due to their function and anatomy, which may affect the regulation of growth factors and gene expression. For instance, tendons in the wrist experience different loads than the Achilles tendon^{92,93}. Excessive mechanical loading can lead to tendon injury. However, clinical studies have shown that mechanical loading can facilitate tendon adaptation and can improve tendon repair⁹⁴. A recent animal study supported the contextual effect of loading by showing that the time of initiation of loading after the onset of fatigue injury can lead to further injury or repair⁹⁵. However, the mechanisms by which loading promotes a therapeutic effect or leads to further degeneration are unknown. For instance, despite a similar load being transmitted through the tendon in eccentric and concentric exercises, eccentric Achilles tendon exercises have been shown to further reduce pain more than concentric exercises involving the same load⁹⁶. Concentric and eccentric Achilles tendon exercises have been shown to differ in terms of the amount of high-frequency oscillation and the direction of tendon deformation, but not in terms of peak tendon force or tendon length change⁹⁷. Therefore, the distribution of mechanical loading may influence the tendon response.

A myriad of clinical projects have investigated the therapeutic effects of mechanical loading⁶, the optimal type of mechanical loading^{96,97}, and the intrinsic factors that alter the loading environment^{92,93}. However, most of the research regarding the physiology and microstructural changes in tendon adaptation and/or progression of tendinopathy secondary to mechanical loading has involved animal studies and in vitro studies^{38,98,99}. Low levels of mechanical stretching of healthy rat patellar and Achilles tendons promoted tenocyte differentiation and increased tenocyte-related genes, whereas high levels led to increases of non-tenocyte-related genes and promoted histological findings associated with later stages of tendinopathy, including increased levels of lipid accumulation, mucoid formation, and tissue calcifications^{98,99}. Similarly, low levels of loading (preconditioning) of horse tendons initially caused microstructural changes, but the tendons fully recovered³⁸. Tendons that experience intense levels of loading (fatigue loading) had visual evidence of damage and decreased ability to recoil, increasing their likelihood of injury³⁸. The severity of damage from fatigue loading may impact the course of adaptation, the disease progression, and gene expression.

The Role of Systemic Effects on Tendinopathy

In addition to tendon-specific factors, it is believed that systematic factors influence tendinopathy development and/or progression. Specifically, it has been repeatedly hypothesized that central neuronal mechanisms play a role in tendinopathy, but, to our knowledge, no research has directly identified such mechanisms. After a tendon injury, the risk of injury to the contralateral counterpart increases; the odds ratio of a contralateral Achilles tendon rupture after a unilateral rupture is 176 when compared with the general population¹⁰⁰. This increased risk may be a result of high bilateral loads and/or systematic factors. Miniaci et al.¹⁰¹ observed degenerative changes in the throwing and non-throwing rotator cuffs of asymptomatic baseball players. Rabbits that performed unilateral lower limb

exercises had bilateral Achilles tendinosis-like changes after 3 and 6 weeks of exercise¹⁰². In addition to pathological changes following a tendon injury, it is common for patients to develop symptoms at the injury site and on the healthy, contralateral side. This finding can be attributed to changes in loading patterns and/or central neuronal mechanisms^{103,104}.

Factors That Increase Susceptibility to Tendinopathy

Systemic diseases^{33,105}, sex, and age are thought to increase a patient's susceptibility to tendinopathy. For instance, muscle and tendon strength and the ability to withstand injury differ between women and men. Women have less tendon hypertrophy, lower protein turnover, and less collagen synthesis in response to exercise^{106–108}. This sex difference is thought to be due to higher estrogen levels and/or lower insulin-like growth factor (IGF)-1 concentrations in females^{106–108}. Estrogen reduces tendon stiffness, which may be mitigated by physical training¹⁰⁸. Longo et al. found that the prevalence of Achilles tendinopathy in male and female track-and-field athletes, who have similar exercise plans, did not differ¹⁰⁹. Therefore, sex may impact the biomechanical environment of tendons because of anatomical differences and pathogenesis due to hormonal differences.

In addition, age is associated with increased susceptibility to tendinopathy, although the mechanisms are not well understood^{110,111}. The hierarchical structure of energy-storing tendons becomes increasingly compromised with age, and, following fatigue loading, there is evidence of greater matrix damage and fiber sliding³⁹. Yu et al. reported that, as rats aged, MMP-2 and MMP-9 mRNA expression increased¹¹², whereas Kostrominova and Brooks reported that TIMP-1, TIMP-2, and collagen-I, III, and V expression decreased (although collagen-I and V protein levels did not differ compared with controls)¹¹³. These findings identify possible players in tendinopathy and demonstrate the importance of studying mRNA expression and protein levels.

Overview

Current biological treatments, tendon-specific operations, and rehabilitation exercises are limited by the paucity of data on the disease process. Further insight into the pathogenesis of tendinopathy may shed light on the relationship between diagnostic imaging findings and patient symptoms and/or projected therapeutic outcomes.

Future work should focus on the contributors to and manifestations of disease progression by investigating histological findings, gene expression, protein levels, and the effects of growth factors as well as mechanical loading in animal and in vitro/in vivo models in a tendon-specific manner. More insight into the microstructural changes associated with tendinopathy and their effects on pain and function is needed to determine which structural changes need to be identified to diagnose tendinopathy and which should be targeted for therapy. It is known that different tendon precursors have different responses to exogenous factors (growth factors and/or the extracellular matrix), yet it is unclear if the same is true of mature tenocytes. To identify potential therapeutics, the relationship between tenocytes and exogenous factors needs to be elucidated. Additionally, it is known that mechanical loading influences tendon healing¹¹⁴, disease progression⁹⁵, differentiation of stem cells into

tenocytes⁹⁹, and tendon development⁸⁶, yet the optimal duration and amount mechanical loading to produce therapeutic effects needs to be investigated. Reaching a field-wide consensus on the pathology of the disease state will allow physicians to create standardized clinical practices to more efficiently diagnose and treat tendinopathy.

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Fig. 1-B

Fig. 1-C

Figs. 1-A, 1-B, and 1-C.

Imaging studies for patients with tendinopathy. **Fig. 1-A** Proton-density-weighted MRI (repetition time, 3450 ms; echo time, 35 ms) of the knee of a symptomatic 29-year-old man. The patellar tendon has increased signal intensity (large arrow), antero-posterior thickening (arrowheads), and loss of definition in the posterior tendon border (small arrows). These findings are consistent with tendinopathy. (Reproduced from: Warden SJ, Kiss ZS, Malara FA, Ooi AB, Cook JL, Crossley KM. Comparative accuracy of magnetic resonance imaging and ultrasonography in confirming clinically diagnosed patellar tendinopathy. *Am J Sports Med.* 2007 Mar;35[3]:427–36, copyright © by SAGE Publications, Inc. Reproduced with permission from SAGE Publications, Inc.) **Figs. 1-B and 1-C** Ultrasound images of the knee

of a symptomatic 24-year-old man. **Fig. 1-B** Sagittal ultrasound image. The patellar tendon has hypoechoic thickening (arrowheads), suggestive of tendinopathy. **Fig. 1-C** Color Doppler ultrasound image. Increased blood flow is observed in the hypoechoic region seen in Figure 1-B, indicative of neovascularization. (Reproduced from: Warden SJ, Kiss ZS, Malara FA, Ooi AB, Cook JL, Crossley KM. Comparative accuracy of magnetic resonance imaging and ultrasonography in confirming clinically diagnosed patellar tendinopathy. *Am J Sports Med.* 2007 Mar;35[3]:427–36, copyright © by SAGE Publications, Inc. Reproduced with permission from SAGE Publications, Inc.)

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TABLE I

Recently Applied Scoring Systems of Tendinopathy *

	Ide et al. ⁴⁸	Soslowsky et al. ⁴⁹	Koike et al. ⁵⁰	Fearon et al. ⁴³	Rosenbaum et al. ⁵¹	Yokoya et al. ⁵²	Schon et al. ⁵³
Collagen organization	✓	✓	✓	✓	✓	✓	✓
Vascularity	✓			✓		✓	✓
Cellularity	✓	✓		✓		✓	✓
Cell morphology		✓		✓		✓	
Continuity	✓	✓				✓	
Fibrocartilage	✓		✓			✓	
Cartilage formation					✓		
Tidemark	✓						
Bone ingrowth	✓						
Fiber diameter	✓						
Ratio of chondrocytes to non-chondrocytes			✓				
Aligned chondrocytes			✓				
Aligned cells						✓	
Ground substance				✓			
Collagen typing						✓	

* Check marks indicate that the criterion was included in the scoring system

TABLE II

Tendinopathic Gene-Expression Profiles⁷⁵⁻⁸¹

	Human Supraspinatus Tendon	Human Achilles Tendon	Rat Achilles Tendon	Human Tibialis Posterior Tendon	Human Patellar Tendon	Rat Patellar Tendon
MMP-1	+				NC	
MMP-2		+		+	NC	+
MMP-3		+	+	-	NC	+
MMP-8						NC
MMP-9	+	+		+	+	NC
MM-13					NC	+
MMP-14						+
MMP-23				+		
ADAMTS-1				NC	NC	
ADAMTS-4				NC	NC	
ADAMTS-5			NC	-	NC	
ADAM-12L				+		
TIMP-1		NC			+	+
TIMP-2		+				NC
TIMP-3						+
TIMP-4						NC
VEGF		NC		NC		
TGF- β		+				
bFGF		-				
CTGF		NC				
IGF-1		NC				
CNTF		+		NC		
COX-2	+	+, NC		NC		
COX-1		NC				
Col I	+	+	+	+		+
Col II			+			
Col III	+		+	+		+
Col V						+

	Human Supraspinatus Tendon	Human Achilles Tendon	Rat Achilles Tendon	Human Tibialis Posterior Tendon	Human Patellar Tendon	Rat Patellar Tendon
Col XII						-
Disintegrin				+		
Fibronectin		+	+			
Tenascin-c		+				
Agg/biglycan	+			+		
ACAN			+			
Ki67		-				
IL-1B	+	NC				
IL-6		+, NC		NC		
IL-6R		-		NC		
IL-21R	+					

* Blank spaces indicate that data are not currently available. A plus sign (+) indicates that an increase in gene expression was observed. A minus sign (-) indicates that a decrease in gene expression was observed. "NC" indicates that there was no significant change in expression. MMP = matrix metalloproteinase, ADAMTS = a disintegrin and metalloproteinase with thrombospondin motifs, ADAM = a disintegrin and metalloproteinase, TIMP = tissue inhibitor of metalloproteinase, VEGF = vascular endothelial growth factor, TGF- β = transforming growth factor- β , bFGF = basic fibroblast growth factor, CTGF = connective tissue growth factor, IGF = insulin-like growth factor, CNTF = ciliary neurotrophic factor, COX = cyclooxygenase, Col = collagen, Agg = aggrecan, IL = interleukin.