Lateral Elbow Tendinopathy

Development of a Pathophysiology-Based Treatment Algorithm

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Lateral elbow tendinopathy, commonly known as tennis elbow, is a condition that can cause significant functional impairment in working-age patients. The term *tendinopathy* is used to describe chronic overuse tendon disorders encompassing a group of pathologies, a spectrum of disease. This review details the pathophysiology of tendinopathy and tendon healing as an introduction for a system grading the severity of tendinopathy, with each of the 4 grades displaying distinct histopathological features. Currently, there are a large number of nonoperative treatments available for lateral elbow tendinopathy, with little guidance as to when and how to use them. In fact, an appraisal of the clinical trials, systematic reviews, and meta-analyses studying these treatment modalities reveals that no single treatment reliably achieves outstanding results. This may be due in part to the majority of clinical studies to date including all patients with chronic tendinopathy rather than attempting to categorize patients according to the severity of disease. We relate the pathophysiology of the different grades of tendinopathy to the basic science principles that underpin the mechanisms of action of the nonoperative treatments available to propose a treatment algorithm guiding the management of lateral elbow tendinopathy depending on severity. We believe that this system will be useful both in clinical practice and for the future investigation of the efficacy of treatments.

Keywords: tendinopathy; lateral; elbow; tendon injury; tendon healing; histopathology; biomechanics; treatment

Lateral elbow tendinopathy (LET), or tennis elbow, presents as pain due to tendinopathy of the common extensor tendon at the lateral epicondyle. It is most prevalent in the working-age population, generally affecting the dominant limb of both men and women. A Finnish observational study of 5871 subjects aged between 30 and 64 years reported a prevalence of 2.8%,[85] and similar rates have been cited in other parts of the world.[1,88] Traditionally, LET is considered to be the result of recurrent mechanical overuse or overloading at the lateral elbow whereby the ability of the tendon to repair itself is overwhelmed and ultimately fails. Subsequently, this leads to microscopic tears of the tendon and an immature, abnormal reparative response.[48] Although the disorder is considered self-limiting, with 89% of patients recovering within 1 year,[87] refractory cases have been known to last for several years and are often associated with functional disability and an inability to work. It may become resistant to many of the conservative therapies available, including rest, physical therapy, bracing, and extracorporeal shockwave therapy (ESWT) as well as injection of corticosteroid, hyaluronic acid, autologous blood, platelet-rich plasma, or autologous tenocytes. Surgical options aim to decompress, debride, and/or repair the diseased tendon insertion through percutaneous ultrasound tenotomy using open or arthroscopic techniques[5,51,66] or fractional lengthening of the tendon.[101]

Tendinopathy is a general term used to describe chronic overuse tendon disorders[84] encompassing a wide spectrum of histopathological changes. Tendinosis relates to these specific histological changes, as described by Nirschl and Pettrone.[66] It is important to recognize that each stage of the disease has the potential to respond differently to

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different treatment modalities. When trying to determine the most effective treatments for LET, it is crucial to understand the pathophysiological changes that occur. Most clinical trials have used binary inclusion criteria stating "tendinopathy" or "no tendinopathy" based on clinical features or radiological parameters when in fact they probably incorporate a very heterogeneous group of patients. As a result, some variance in response to treatment modalities is expected. Currently, nonoperative treatments do not target the underlying pathology of the condition, and this may contribute to the lack of significant long-term benefit of available interventions. The purpose of this review was to summarize the contemporary understanding of the histopathology and biomechanics of normal tendon and the disease progression of tendinopathy. We discuss the clinical efficacy and potential mechanism of available nonsurgical interventions, presenting a treatment algorithm based on the underlying grade of pathology.

PATHOLOGY AND BIOMECHANICS OF TENDINOPATHY AND TENDON HEALING

A normal, healthy tendon is primarily composed of type 1 collagen, tightly packed in a parallel longitudinal arrangement of microfibrils, fibrils, subfasciles, and fascicles. In between the rows of collagen, a small number of long, thin, fibroblast-like tenocytes are arranged along the line of the axis of the tendon. The collagen fibers and cells are embedded in a matrix of proteoglycans, glycosaminoglycans, and water.[48] There are at least 2 populations of tenocytes within the tendon, which respond differently to mechanical tendon loading.[36] It has been shown that induction of a substantial growth stimulus causes an overall increase in tendon cross-sectional area, where existing tendon fibroblasts remain terminally differentiated with growth occurring via the addition of new cells and matrix in the tendon's outer layers.[36] This supports the work of Heinemeier et al,[38] who suggested that adult tendons grow from the most superficial layers outward. The bulk of the tendon is avascular but there is an intrinsic supply from the myotendinous junction and the osteotendinous junction and an extrinsic supply from the paratenon.[29] Tendons subject to repetitive trauma, and in particular those that pass over a convex surface or cross 2 joints, are especially susceptible to overuse injury and microscopic tears.[48,85] The extensor carpi radialis brevis (ECRB) tendon is one such tendon and accounts for 90% of all cases of LET.[65]

Pathology of Tendinopathy

The principal elements of tendinosis are abnormalities of the cellularity, vascularity, and collagen arrangement within the tendon. Cellular changes associated with tendinosis are hyperplasia, hypertrophy, rounding of the tenocytes, and a decreased nucleus-to-cytoplasm ratio.[35,48,66] Some of the affected cells are immature, dedifferentiated fibroblasts, and many exhibit signs of increased metabolic activity and production of type 3 rather than type 1 collagen,[28,48,55] fibers that are no longer organized in parallel arrangement.[52] There is failure of cross-linkage between fibers, loss of distinct planes of the fascicles, and fibrils are fragmented with varying length and diameter.[48,52] Finally, vascular hyperplasia is seen as an invasion of immature, abnormal vessels. It is unlikely that many of these blood vessels are able to sustain adequate blood flow to induce tendon healing due to their closed or absent lumen.[29,48]

Recent attempts have been made to quantify these histological changes as to grade the severity of tendinopathy.[14,62] Movin et al[62] described a semiquantitative method of evaluating Achilles tendinopathy using a point scoring system to grade 8 parameters: fiber structure, fiber arrangement, rounding of nuclei, regional variations in cellularity, increased vascularity, decreased collagen sustainability, hyalinization, and glycosaminoglycan content. Each parameter was given a score from 0 to 3 (0 = normal, 1 = slightly abnormal, 2 = moderately abnormal, and 3 = markedly abnormal).[62] This system has been modified by Chen et al[14] to evaluate 6 parameters, with each parameter again scored from 0 to 3. In early tendinosis, the predominantly straight, parallel configuration of collagen fibers seen in healthy tendon changes to become slightly loose with a wave-like pattern. Increasing severity of tendinosis sees these fibers become more fragmented and disorganized, with increased cell hyperplasia and nuclei progressively become more rounded. Additionally, increasing neovascularity and infiltration of inflammatory cells is evident.[12,62]

Both of these scoring systems suggest increasing cell density with worsening tendinosis. However, recent study of the ECRB tendon has shown areas of high-grade tendinosis (grade 3, severe collagen fragmentation and loss of orientation), displaying programmed cell death and depletion of tenocytes.[12] Similar studies have shown apoptosis and cell depletion in tendinopathy of the rotator cuff[108] and Achilles[79] and patellar[86] tendons. It appears that cellular density peaks in areas of grade 2 tendinosis, before programmed cell death results in cell depletion as the disease process progresses. Cell depletion subsequently leads to reduction in the synthesis of type 1 collagen and disruption of the extracellular matrix,[12] which in turn could progress to complete structural failure of the tendon.

Thus, we propose 4 distinct grades of tendinopathy (Figure 1). In grade 1 disease, the collagen fiber pattern becomes increasingly wavy. Although cellular and vascular changes are minimal, there is an increase in the proportion of type 3 collagen. In grade 2, there is tendinosis and angiofibroblastic hyperplasia as first described by Nirschl and Pettrone,[66] with further disorganization and fragmentation of the collagen fibers, cellular hyperplasia, rounding of tenocytes, and neovascular hyperplasia. In grade 3 tendinopathy, programmed cell death leads to the depletion of functional tendon cells and breakdown of collagen and extracellular matrix. Finally, grade 4 presents with gross structural disruption and mechanical failure. These changes may cause malfunction of tendon and joint biomechanics.

The exact molecular profile and processes driving the histopathological changes seen in tendinopathy are yet to be fully understood. It is thought that angiofibroblastic
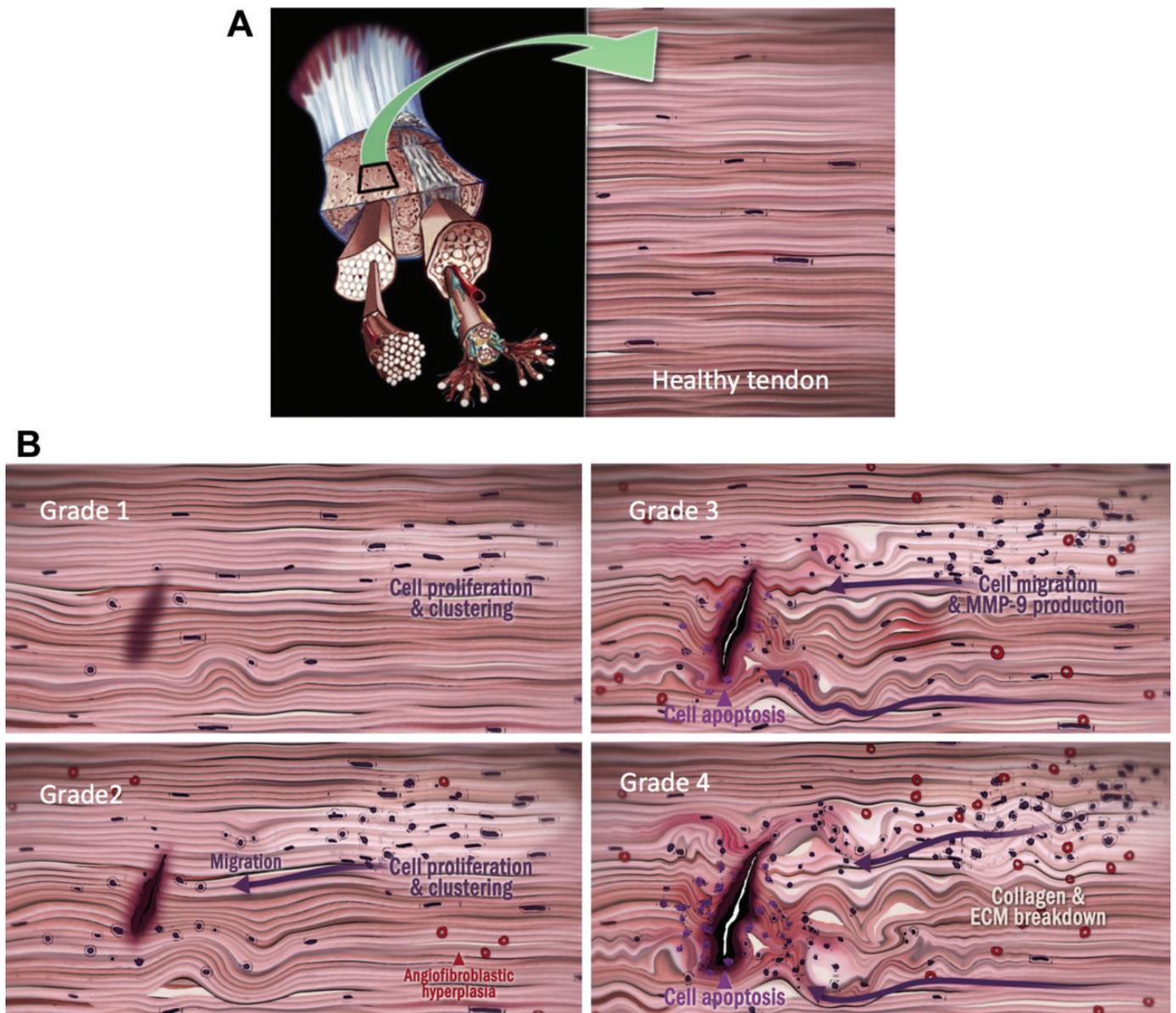
Figure 1. Schematic diagram displaying the histological features of (A) healthy tendon and (B) the 4 grades of tendinopathy. In healthy tendon, type 1 collagen fibers are organized and layered side-to-side and end-to-end. They are essentially parallel but with a very slight wave pattern. The tenocytes are elongated and uniform in number. In grade 1 tendinopathy, the tight array of collagen fibers loosens with increasing waviness. There is a relative increase in type 3 collagen and minimal cell proliferation. In grade 2 tendinopathy, there is increasing cell proliferation and clustering as well as angiogenesis. The nuclei of the cells become rounded and the collagen fibers are further disrupted and start to fragment. In grade 3, tendinopathy there is cell death by apoptosis. There is increased cell migration and matrix metalloproteinase (MMP) production. The extracellular matrix begins to breakdown until, in grade 4 tendinopathy, there is structural and mechanical failure.

hyperplasia observed after microtrauma is an attempt by the tendon to heal.[31] Resting tenocytes may be activated to multiply and produce collagen by mechanoreceptor stimulation in response to shear stress after an initial insidious injury.[48,64] The lack of an effective vascular system prevents the influx of any humoral mediators that are necessary for optimal tendon remodeling, leading to progressive degeneration.[48,56] A number of in vitro studies have shown that cytokines such as platelet-derived growth factor

(PDGF) and transforming growth factor beta (TGF-β) can upregulate the expression of type 1 collagen in fibroblasts.[32,40,69,104] It seems plausible that without such cytokines, the tendon healing process is impaired, leading to a disorganized collagen arrangement.[56] Thus, the cycle of microtrauma and improper healing that occurs is thought to lead to tendinosis and eventual structural failure in LET. This continual process of injury and repair with matrix remodeling is also reflected in changes in the expression

of proteolytic enzymes such a matrix metalloproteinases (MMPs) and ADAMTS (disintegrin and metalloproteinase with thrombospondin motifs) as well as tissue inhibitors of metalloproteinase (TIMPs) in tendinopathic tissue.[26] For example, samples of tendinopathic patellar tendon display increased expression of MMP-9 and TIMP-1.[70]

Biomechanics

Another important concept to consider when discussing tendon healing is the amount and type of load placed on the tendon. Amiel et al[3] showed that changes in the biochemical composition of periarticular fibrous connective tissue after immobilization included a reduction in glycosaminoglycans, water, and alterations in collagen crosslinking. Biomechanical changes thus resulted, with a 39% decrease in maximum failure load after 8 weeks of anterior cruciate ligament (ACL) immobilization. As a major contributor to tissue tensile strength, it was suggested that collagen turnover dynamics may be altered under conditions of stress and immobilization. These authors concluded that synthesized collagen fibers in such immobilized ligaments must be laid down in a haphazard manner due to the absence of the usual controls of matrix orientation as imposed by physical forces.

Wang et al[102] designed a bioreactor system allowing the application of mechanical stimulation on ex vivo rabbit Achilles tendons. They showed that in the absence of any load, tendons bathed in growth medium displayed typical histological features of tendinosis after only 6 days. By 2 weeks, 95% of the cells in these unloaded tendons had undergone apoptosis. Tendons subject to 3% cyclical tensile strain displayed similar but milder features, without the high rates of apoptosis. In contrast, tendons subject to 6% cyclical strain were histologically normal. At the other end of the spectrum, tendons subject to 9% strain had partially torn and again showed histological features of severe tendinosis. These findings complement the results from previous studies[37,44] and begin to identify the ideal strain conditions for tendon homeostasis. It is clear that some tensile mechanical loading as opposed to immobilization is essential for tendon integrity and strength, and within that, there is a narrow range of ideal strain that stimulates an anabolic effect in tendon tissue (Figure 2).[102]

In summary, by understanding the different histological grades of tendinosis and optimal conditions for healing, one can begin to appreciate the requirements of the nonoperative interventions for tennis elbow.

TREATMENT

Rest

The primary aim of "relative rest" is to halt the injury process by removing mechanical overload, providing the tendon a chance to repair itself through the restriction and modification of provocative daily activities. It has previously been inferred that LET is a self-limiting condition, with pain and symptoms running a "natural course" and
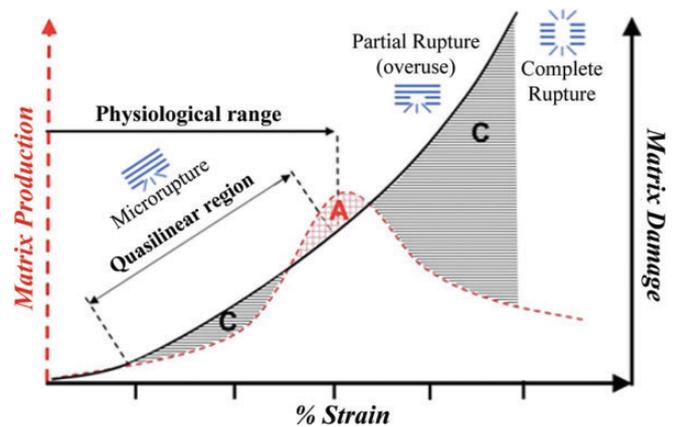

Figure 2. The effect of mechanical loading on tendon homeostasis. The black curve represents matrix damage with increasing strain. The red dotted curve represents matrix production by tenocytes. Zone "A" indicates the anabolic zone where matrix production overcomes matrix damage, such that the tendon can maintain its structural integrity. There are 2 "C" zones (catabolic zones) in which matrix disruption overcomes production, leading to tendinopathy. Image adapted from Wang et al[102] with permission.

resolving spontaneously in up to 89% at 1 year.[87,89] However, awaiting spontaneous recovery may be associated with the loss of economic productivity and might be an imprudent approach in patients with crippling pain and disability.

Bracing

Application of a brace or splint, often employed simultaneously with relative rest, aims to offload the common extensor tendon.[9] Two popular methods of bracing include wrist extension splints and forearm counterforce straps.

Extension splints provide passive assistance to wrist extension necessary to counteract the wrist flexion forces that occur with gripping.[41] Jansen et al[43] investigated electromyographic (EMG) changes in the wrist extensors during activity and lifting tasks with and without a wrist orthosis, reporting significantly reduced muscular activity using the orthosis. However, this may prove counterproductive by contributing to further physical deconditioning and regression.[27]

Forearm counterforce straps apply compression over the common extensor muscle mass to reduce muscle expansion and contraction. Inadvertently, this lessens tension across the muscle-tendon unit, thereby reducing painful inhibition and allowing the patient to contract more forcefully.[9] Furthermore, it is thought the direct compression provided by the counterforce strap creates a secondary origin of the extensor tendons, therefore unloading the true origin at the lateral epicondyle.[34] While biomechanical studies have demonstrated reduced force and stress at the origin of the ECRB,[58,91] clinical evidence is scarce. Wuori et al[107] compared a counterforce strap with a simple elbow support sleeve, placebo brace, or no brace in patients with LET and

found no significant difference in both grip strength and pain between any of the groups. Other studies have shown no difference in clinical outcomes between using forearm or elbow straps and wrist extension splints.[2,34] Braces and splints are hence considered a somewhat archaic management modality for LET, with contemporary evidence of their effectiveness lacking.

Physical Therapy

As already discussed, tendons respond adversely to stress-shielding or immobilization. Appropriate physiological loads are necessary for optimal tendon development and maintenance and thought to be best achieved by controlled exercise rehabilitation.[33] A direct link between tenocytes and the extracellular matrix allows the cells to sense and respond to mechanical stimuli by converting the stimulus into a cellular response promoting tissue repair and remodeling via a process termed *mechanotransduction*.[46] Recent years have seen a growing interest in exercise as a treatment for chronic tendinopathies, including LET. Studies have reported a clear tendency in favor of physical therapy modalities compared with "relative rest."[7,71,89] Pienimaki et al[72] demonstrated improved pain scores and less medical sick leave in patients with chronic LET who received a graduated program of strengthening and stretching exercises compared with those treated with pulsed ultrasound. A recent systematic review by Cullinane et al[24] concluded eccentric exercise, in isolation or as an adjunctive therapy, decreases pain and improves function in patients with LET. However, despite these results, up to 10% of patients continue to deteriorate and develop chronic refractory symptoms.[20] It is possible that these patients have a higher grade of tendinopathy, either with an immature vascular supply preventing cytokine-induced tendon repair, cell depletion, or even large tendon tears. Therefore, introducing mechanical loading via exercise therapy as part of a robust physical therapy regimen is considered beneficial in the early stages of LET.

Extracorporeal Shockwave Therapy

ESWT is an increasingly popular therapeutic approach for the treatment of a number of soft tissue complaints including LET. Extracorporeal shock waves are single-pressure pulses of microsecond duration that can be focused on a site using ultrasound guidance. Although the exact mechanisms for pain reduction are unclear, the basic premise is that these shock waves may stimulate tissue healing, reduce calcification, inhibit pain receptors, and cause denervation.[92] Rompe et al[76] showed ESWT to be more effective than sham treatment, while Sarkar et al[77] later reported that a combination of low-energy ESWT and exercise was superior to exercise alone. However, a randomized controlled trial undertaken by Staples et al[93] found little evidence to support the use of ESWT as a longer term treatment for LET despite early (3-6 months) improvements in pain and functional outcomes. Systematic reviews investigating the efficacy of ESWT in patients with LET have concluded there is little evidence to suggest it provides greater benefits than other therapies, including placebo.[8,10,94]

Injection Therapy

A number of substances may be injected around the insertion of the common extensor origin for LET, including corticosteroids, prolotherapy, polidocanol, botulinum toxin, hyaluronic acid, autologous blood, and platelet-rich plasma (PRP). Many randomized controlled trials (RCTs) have attempted to study the clinical effects of these compounds, with a number of recent systematic reviews and meta-analyses summarizing these trials.

A systematic review of 41 trials[21] and a more recent meta-analysis of 10 trials[49] both failed to demonstrate any long-term benefit of corticosteroid injection over either placebo or no intervention for the treatment of LET. There is evidence to suggest that beyond 26 weeks, patients who received a corticosteroid injection were more symptomatic than those who received no treatment or physical therapy.[21] These findings are consistent with in vitro studies, showing that corticosteroids may be detrimental by inhibiting tenocyte proliferation, tenocyte activity, and collagen synthesis.[80,106]

A review of a smaller number of studies of noncorticosteroid injections reveal a paucity of evidence from unbiased clinical trials to support the use of polidocanol, botulinum toxin, or hyaluronic acid.[21,49] Although 1 small trial has suggested improved clinical outcomes from prolotherapy injection with hyperosmolar irritants,[78] it is likely that this promotes an inflammatory response followed by scar tissue and disorganized collagen rather than healthy tendon at the site of injection.[54,57,74]

Recently, therapies focusing on the use of growth factors as a stimulant of tendon repair have become increasingly popular for their potential application in the treatment of tendinopathy. The premise behind injection of PRP or autologous blood is to promote tendon healing and generate repair tissue capable of withstanding tensile load. These biological therapies contain growth factors and other bioactive molecules that modulate cell signaling and enhance chemotaxis, cell proliferation, and differentiation.[56,59] The key cytokines are stored in alpha granules of platelets; as such, there is a greater concentration of these in PRP when compared with autologous whole blood. Molecular biologists have identified several hundred proteins released from platelets, including platelet-derived growth factor (PDGF), TGF-β, vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1), and basic fibroblast growth factor (bFGF).[22,59] PDGF in particular has been shown to upregulate the expression of type 1 collagen by tenocytes,[103] while TGF-β and bFGF increase the production of collagen types 1 and 3 in rat tenocytes.[47,105] IGF-1 plays an important role in the initial stages of tendon healing through stimulation of chemotaxis and migration of tenocytes and fibroblasts.[45] VEGF is thought to play a role in angiogenesis around healing tendons, with a less pronounced role in collagen synthesis.[104]

A meta-analysis by Krogh et al[49] included 3 clinical trials evaluating autologous blood and 2 trials studying PRP.

They report both autologous blood and PRP injection to be superior to placebo; however, only 1 trial was considered to be at low risk of bias. In a comprehensive systematic review of platelet-rich therapies for several soft tissue musculoskeletal conditions, Moraes et al[61] examined 19 trials in 8 clinical conditions. Data pooled from 10 trials in 5 different clinical conditions concluded that there was no difference between PRP and control for function in the short, medium, or long term, with a very small reduction in pain in the short term in favor of PRP. Three trials specifically looked at PRP for the treatment of LET. None of these were considered as having low risk of bias, with high rates of loss to follow-up and inconsistent blinding and allocation.[61] Nevertheless, pooled results from these 3 trials showed a statistically significant difference in favor of PRP at 3 and 6 months. The authors of the individual trials suggest their results support the use of PRP over placebo or autologous blood.[23,50,95] However, the effect size of the pooled results was small and of uncertain clinical significance, leaving Moraes et al[61] to conclude that as yet, there is insufficient evidence to support the use of PRP for the treatment of tendinopathy.

In 2014, Mishra et al[60] published a multicenter double-blind RCT of 230 patients with chronic LET. Patients received multiple needle perforations of the common extensor tendon with or without PRP. A successful outcome was considered to be a $\geq 25\%$ improvement on a visual analog scale for pain. There were no significant differences in the percentage of successful outcomes at 12 weeks, but at 24 weeks, 84% of patients in the PRP group had a successful outcome compared with 68% in the control group ($P < .05$).[60] Although these results appear encouraging, some aspects of the study's methodology and resultant conclusions have been criticized.[4,25,67] Nevertheless, a recent meta-analysis investigating the efficacy of PRP for treatment of various tendinopathy has shown sound evidence to support the use of leukocyte-rich PRP in tendinopathy when used under ultrasound guidance.[30]

Percutaneous Ultrasonic Tenotomy

Ultrasound-guided percutaneous tenotomies are offered as an alternative to surgical intervention. Ultrasonography is highly sensitive for hypoechoic lesions, proving to be a useful tool for the localization and targeted ablation of pathologic tissue in recalcitrant LET.[82] Recent understanding of the pain-generating mechanisms associated with chronic tendinopathies suggests a process of abnormal neural ingrowth manifesting as peritendinous hypervascularity.[82] In addition to hypoechoicity and calcification as present on ultrasonography, this has been correlated with the location of pain in symptomatic LET.[82] The TX1 (Tenex Health Inc) technique is the favored procedure in literature. Performed under local anesthesia and standard ultrasound guidance, the technique uses ultrasonic energy to produce low-amplitude, high-frequency longitudinal oscillation of an 18-guage hollow-tip needle that cuts through the tendon, emulsifying the tissue at approximately 1 mm distal to the needle tip. The outer hollow shaft of the double-lumen tip contains fluid that flows to the tip region to cool the oscillating tip while outflow occurs through the inner lumen removing heated fluid, emulsified tissue, and debris. Postprocedural wound dressings are required, with activity restriction and modification for the next 6 weeks.

Recently published data indicate that the TX1 procedure provides sustained pain relief and functional improvement for recalcitrant LET at both 1- and 3-year follow-up.[6,82] The most dramatic clinical results typically occur within the first 6 to 12 weeks after treatment, with little to no complications reported.[6] It is noteworthy that this technique has achieved the same outcomes that have traditionally been associated with surgical intervention without the morbidity, complications, and cost associated with surgery.

Cellular Regenerative Therapy

In an attempt to revitalize degenerate tendon tissue, augment regeneration of normal tendon, and limit the amount of scar tissue that is formed in response to injury, it has been proposed that the restoration of functional cells capable of synthesizing the extracellular matrix and repairing the damaged tissue may be an effective therapeutic strategy for tendon repair in patients with tendinopathy.[13,14,100] Injection with autologous differentiated fibroblasts or tenocytes has shown promising results in laboratory studies and early clinical trials. Animal models have demonstrated that autologous tenocytes or dermal fibroblasts can bridge 3- to 4-cm defects in tendons, with the newly formed tendon tissue displaying the histological features of normal healthy tendon by 14 weeks.[11,53] In a rabbit model of Achilles tendinopathy, autologous tenocytes improved the histological appearance and biomechanical properties of the tendon by 8 weeks.[13] Tenocytes synthesize both fibrillar and nonfibrillar components of the tendon extracellular matrix, and it seems plausible that implanted autologous tenocytes might replace the apoptosed/autophaged cells in the latter stages of tendinopathy.[12,98]

To date, there are 4 published trials that have examined the effects of autologous cell implantation on tendinopathy in humans. Three of the 4 trials have used "collagen-producing skin-derived fibroblasts,"[16,18,68] while 1 trial used tendon-derived cells. The advantage of using a population of tendon-derived progenitor cells is the capacity for collagen synthesis and the homologous application. Wang et al[98,99] have used autologous tendon cell injection (ATI) for the treatment of chronic resistant LET. In the pilot study, 17 patients who had suffered chronic LET for more than 6 months despite a course of nonoperative treatment, including physical therapy, corticosteroid injection, and bracing received a single ATI under ultrasound guidance. The results showed that there was a significant improvement in pain, function, and grip strength from 3 months postinjection, with continued improvement at 12 months. A midterm follow-up of 4.5 years on this group of patients further showed that ATI significantly improved clinical function and magnetic resonance imaging (MRI) tendinopathy scores for up to 5 years in patients with chronic resistant LET who had previously undergone unsuccessful nonsurgical treatment. This study provides evidence for the midterm durability of ATI in the treatment of LET.

Connell et al[18] showed a similar clinical response to injection with skin-derived tenocyte-like fibroblasts in 12 patients with chronic tennis elbow. Both of these trials were pilot studies with no control groups. However, both seemed to show a good response to autologous cell injection, with no reported adverse events. Clarke et al[16] randomly assigned 46 patients with patellar tendinopathy to receive either skin-derived fibroblasts suspended in autologous plasma or autologous plasma alone. At 6 months, there was a significantly greater improvement in the symptoms and function of the patients in the cell therapy group. Obaid et al[68] conducted a double-blind RCT of 32 patients with Achilles tendinopathy comparing injection of skin-derived tenocyte-like fibroblasts against treatment with a local anesthetic injection and physical therapy. Again, pain and function scores at 6 months were significantly better in the group treated with autologous fibroblasts. These initial results seem to favor autologous cell therapy, but larger RCTs with longer follow-up times are needed to truly determine the clinical efficacy of this treatment.

RELATING CLINICAL OUTCOMES TO INTRINSIC CHANGES WITHIN THE TENDON

While the myriad clinical studies published provide some useful information with regard to the response to various treatments, they cannot provide specific insight into the effects of these therapies on the intrinsic changes that occur within diseased tendons. Although the scientific principles behind physical therapy, PRP, and tenocyte injections appear robust, as already discussed, the term *tennis elbow* incorporates a wide spectrum of disease. At least part of the reason for the discrepancy in the results of large clinical trials may be due to the fact that they study a heterogeneous group of patients. In addition, the validity of clinical scores has been shown to be compromised by a ceiling effect such that they may fail to show differences in outcome in high-functioning patients.[39,90,97] For obvious ethical reasons, no studies have looked at the histological changes before and after nonoperative treatment. However, a limited number of studies have attempted to use radiological measures to assess structural changes within the tendon after treatment.

Areas of contrast enhancement on MRI correspond with areas displaying histological evidence of tendinosis in Achilles tendons.[63,73,83] Change in MRI signal intensity has been used to grade tendinopathy in lateral elbow[96] and rotator cuff tendinopathy.[81] Treatment of LET with autologous tenocytes led to a significant decrease in the MRI severity score by 12 months.[98] In addition, there was a reduction in the bone-tendon separation (tear size) in these patients. However, it is not evident from MRI whether this represents infilling with scar tissue or healthy tendon tissue with a parallel collagen arrangement.

Four characteristic sonographic features of tendinopathy have also been shown to correspond with areas of collagen degeneration and cellular hyperplasia: increase in tendon size, areas of decreased focal echotexture, interstitial clefts or tears, and neovascularity.[17] Patients with larger intrasubstance tears and tears of the lateral collateral ligaments have worse clinical scores.[15] Connell et al used these 4 sonographic features within a semiquantitative scoring system to demonstrate improvements in radiological outcomes in small groups of patients with LET after treatment with autologous blood[19] and autologous skin-derived tenocyte-like fibroblasts.[18] Treatment with autologous blood injections led to a 6.4% reduction in tendon size and statistically significant reductions in hypoechogenic foci and neovascularity.[19] In addition, there was an alteration in the appearance of the interstitial clefts, with blurring of margins and replacement of the clefts with echogenic foci. The authors propose that these changes represent immature scar tissue formation.[19] In contrast, treatment with autologous tenocyte-like fibroblasts resulted in a return to near-normal tendon appearance, including the resolution of interstitial clefts and a reduction in tears and in tendon size.[18] Similar differences were noted in the treatment of patellar tendinopathy with autologous blood[42] and autologous fibroblasts.[16] Of interest, 1 patient with patellar tendinopathy treated by autologous fibroblasts underwent late surgery, and histology at the time showed normal healthy tendon tissue.[16]

The findings from these studies suggest that treatment of tendinopathy with autologous tenocytes might promote tendon healing and structural repair. Using these imaging modalities as a surrogate for histological evaluation of the tendon obviously provides substantial information, and similar studies assessing the structure of tendons before and after treatment with physical therapy might also be useful. However, it is difficult to confirm the quality of newly repaired tissue without visualizing the cellularity and collagen fiber arrangement within the tendon. Furthermore, these studies have relatively small numbers and again do not stratify the patients according to the severity of disease to assess the effect of the interventions on different disease grades.

TREATMENT ALGORITHM BASED ON THE UNDERLYING PATHOLOGY

Having extensively reviewed the histological changes of tendinopathy, we believe that tendinopathy can be divided into 4 simple and distinct grades of disease, as described above (Figure 1 and Table 1).

No single type of nonoperative therapy has outstanding clinical results, and we would argue that this is at least in part due to no trials having stratified patients according to grade of disease, other than to exclude patients with large tendon tears. Having considered the mechanisms of action and clinical results of the various nonoperative treatments available, we propose a treatment algorithm specifically targeting the 4 grades of tendinopathy (Table 1). In grade 1 disease, the tight array of collagen fibers start to become loose and wavy in appearance, with minimal cellular or vascular changes. Thus, early treatment may focus on relative rest and activity modification to avoid reinjury. Grade 2 disease displays the typical features of tendinosis with cellular hyperplasia, rounding of nuclei, loss of parallel

TABLE 1
Proposed Treatment Algorithm Based on 4 Distinct Grades of Tendinopathy[a]

Grade	Pathoanatomy	Treatment Principle	Treatment Option
1	Wave-like pattern of collagen fibers	Rest, activity modification	Rest, physical therapy
2	Angiofibroblastic hyperplasia; cell hyperplasia, rounding of nuclei, disorganized collagen fibers, neovascularity	Mechanical induction of intrinsic repair, replenish cytokines necessary for tendon healing	Physical therapy (eccentric load), PRP/autologous blood
3	Cell depletion and matrix breakdown, collagen discontinuity, small partial tears	Replenish tendon progenitor cells for tendon repair	Autologous cell therapy
4	Macroscopic tears (bone tendon separation)	Surgical repair	Surgery

[a]PRP, platelet-rich plasma.

configuration of fibers, and immature vascular hyperplasia. Controlled physical therapy may provide the necessary mechanical stimulus to the tenocytes to induce remodeling. Where there is immature vascularity or differentiated cells, PRP or autologous blood injections may be beneficial in providing growth factors that promote collagen production. As the disease progresses to grade 3, apoptosis and autophagy result in cell depletion. Here, autologous cell therapy may be indicated to replenish the missing cells. Autologous tenocytes can synthesize type 1 collagen and may repair defects where there is discontinuity in the collagen matrix. Ultimately, the tissue breakdown apparent in grades 2 and 3 are indicative of biologic intervention. In cases of matrix and collagen breakdown with complete mechanical failure, as present in grade 4, surgical repair may be necessary.

An obvious weakness in our proposition is the current inability to easily and reliably grade the disease without invasive tissue biopsy. Recent studies have used ultrasound or MRI as a proxy for histological staging, but emerging microscopic imaging techniques such as optical coherence tomography[75] may provide better visualization of cells and matrix organization and prove to be critical research or clinical tools for the future. It is noted that some imaging modalities and treatments discussed may not be readily available or cost effective for all patients with LET.

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