[Sports Physical Therapy]

CEU

Tendinopathy in Sport

Paul W. Ackermann, MD, PhD,*† and Per Renström, MD, PhD†

Context: Tendinopathy is increasing in prevalence and accounts for a substantial part of all sports injuries and occupational disorders. Despite the magnitude of the disorder, high-quality scientific data on etiology and available treatments have been limited.

Evidence Acquisition: The authors conducted a MEDLINE search on tendinopathy, or "tendonitis" or "tendinosis" or "epicondylitis" or "jumpers knee" from 1980 to 2011. The emphasis was placed on updates on epidemiology, etiology, and recent patient-oriented Level 1 literature.

Results: Repetitive exposure in combination with recently discovered intrinsic factors, such as genetic variants of matrix proteins, and metabolic disorders is a risk factor for the development of tendinopathy. Recent findings demonstrate that tendinosis is characterized by a fibrotic, failed healing response associated with pathological vessel and sensory nerve ingrowth. This aberrant sensory nerve sprouting may partly explain increased pain signaling and partly, by release of neuronal mediators, contribute to the fibrotic alterations observed in tendinopathy. The initial nonoperative treatment should involve eccentric exercise, which should be the cornerstone (basis) of treatment of tendinopathy. Eccentric training combined with extracorporeal shockwave treatment has in some reports shown higher success rates compared to any therapies alone. Injection therapies (cortisone, sclerosing agents, blood products including platelet-rich plasma) may have short-term effects but have no proven long-term treatment effects or meta-analyses to support them. For epicondylitis, cortisone injections have demonstrated poorer long-time results than conservative physiotherapy. Today surgery is less indicated because of successful conservative therapies. New minioperative procedures that, via the endoscope, remove pathologic tissue or abnormal neoinnervation demonstrate promising results but need confirmation by Level 1 studies.

Conclusions: Novel targeted therapies are emerging, but multicenter trials are needed to confirm the results of exercise and mini-invasive treatments.

Keywords: tendon; pain; tendinopathy; tendinosis

Tendinopathy is a clinical syndrome, often but not always implying overuse tendon injuries, characterized by a combination of pain, diffuse or localized swelling, and impaired performance.[39] Tendinopathy can also occur without signs of overuse and is then mostly associated with medical conditions. Midportion and insertional tendinopathy (enthesopathy) should be distinguished as 2 different clinical diagnoses. The tendons most vulnerable to overuse are the Achilles and patellar tendons and, in the upper extremities, the rotator cuff and extensor carpi radialis brevis (tennis elbow) tendons.[80]

The common pathological conditions associated with tendinopathy are tendinosis and peritendinitis. Tendinosis is the histopathological finding of collagen disorganization and fiber separation, increase in mucoid ground substance, hypercellularity, and nerve and vessel ingrowth but mostly without signs of intratendinous inflammation (tendinitis).[54] However, lately, the noninflammatory etiology of tendinopathy has been questioned, as inflammation may play a role in the initial phase of the disease.[9]

Tendinosis is per se not painful. Thus, histopathological alterations associated with degeneration, such as tendinosis, not correlated to pain must be separated from pain generating pathophysiology. Tendinitis, however, which is seen to a much lesser extent (< 3%) is associated with classic inflammation usually observed during the early reparative phase.[53] Peritendinitis is an acute or chronic inflammation of the thin membrane, paratenon, surrounding the tendon, often induced by repetitive exercise and characterized by local swelling and infiltration of inflammatory cells.[53]

The tendon insertion and bursae surrounding the tendon are common sites of classical inflammation, as a response to

From the †Section of Orthopedics and Sports Medicine, Department of Molecular Medicine and Surgery, Stockholm Sports Trauma Research Center, Karolinska Institutet, Stockholm, Sweden

*Address correspondence to Paul W. Ackermann, MD, PhD, Orthopedic Department, Karolinska University Hospital, 171 76 Stockholm, Sweden (e-mail: paul.ackermann@ki.se).

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repetitive stress, because of their greater density of blood vessels and nerves. The tendon proper meanwhile is mostly aneuronal and avascular and does not under normal conditions exhibit classical inflammatory responses.[3,54]

EPIDEMIOLOGY

Sports

The incidence of tendinopathy is rising in the developed world because of increased participation in recreational sports.[53,80] Around 30% of all runners exhibit Achilles tendinopathy, with an annual incidence of 7% to 9%.[51] Repetitive exposure seems to be associated with increased risk of injury. Long-distance runners compared with age-matched controls exhibit an increased incidence of tendinopathy, with an adjusted odds ratio of 31.2.[46]

Patellar tendinopathy is common in volleyball (14%), team handball (13%), basketball (12%), and track and field (7%) and is a fairly common condition in football/soccer (2.5%).[104] Among top-level football/soccer players, high total exposure hours has been identified as a significant risk factor for patellar tendinopathy.[30] Former male athletes participating in maximal overhead maneuvers such as the tennis serve or a baseball pitcher's throw show 4 times increased risk (odds ratio) of shoulder tendinopathy before the age of 45 years compared with controls.[38]

Diseases

Although sports activity is the most common source of tendinopathy, 1 of 3 patients with Achilles tendinopathy is not active in sports. In the upper extremities of nonsports participants, tendinopathy is even more common and mostly work related. However, some patients may develop tendinopathies without being exposed to repetitive tendon loading. Recently, metabolic disorders such as disturbed glucose metabolism and atherosclerosis have been identified as underlying factors in tendinopathy.[77] Thus, obesity, hypertension, diabetes mellitus, hypercholesterolemia, and other metabolic factors have been clearly associated with increased incidence of tendinopathy.[1,10,26,43,77] The consequences of metabolic factors in healthy and pathologic tendons are currently an area of investigation.

Furthermore, in Achilles tendinopathy, approximately 2% of the disorders can be attributed to inflammatory joint disorders, such as rheumatoid arthritis.[36] Notably, in diabetes mellitus and inflammatory disorders, the peripheral nervous system has been identified as a common cause of connective tissue healing malfunction and homeostasis.[13,71,74]

Drugs

Certain drugs should be avoided, especially among active sports participants. Drug treatment for hypercholesterolemia with statins[56] and quinolone antibiotics[58,94] have been reported to increase the risk for tendinopathy. Low molecular weight heparin and immunosuppressive drugs such as cortisone (especially intratendinous) and cyclosporine may exert detrimental effects on tendon metabolism and repair and should be used cautiously.[42,98]

Genetics

A study of twins revealed a heritability of 40% for tendinopathy at the lateral epicondyle.[31] Recently, the genetic sequence variants that encode for several tendon extracellular matrix proteins associated with tendinopathy have been identified. Gene variants within the tenascin-C, collagen type I, alpha 1 chain (COL5A1) and matrix metalloproteinase-3 genes correlate to tendinopathy.[63,64,76] Patients with this syndrome are prone to multiple problems, including rotator cuff, epicondylalgia, carpal tunnel syndrome, and trigger finger.[79] The precise role of these genes in the development of tendinopathy is still unclear.[17]

ETIOLOGY: PATHOPHYSIOLOGY

Mechanical loading of tendon tissue is anabolic by upregulating collagen gene expression and increasing synthesis of collagen proteins. This peaks around 24 hours after exercise and remains elevated for up to 70 to 80 hours.[32,62] However, exercise also results in degradation of collagen proteins, although the timing of this catabolic peak occurs earlier than the anabolic peak. This results in a net loss of collagen around the first 24 to 36 hours after training, followed by a net gain in collagen.[54] Thus, a certain restitution time interval in between exercise bouts is critical for the tissue to adapt and to avoid a net catabolic situation (Figure 1).

The tendon is able to adapt to load linked with the specific function of anatomic structures in and around the tendon—that is, the tendon cells, tenocytes, extracellular matrix, and nerve-ending receptors.

Repetitive strain causes tenocytes to produce inflammatory molecules and microruptures of collagen fibrils. Increased levels of inflammatory mediators (eg, prostaglandin E2 [PGE2]) are found in tendons after repetitive mechanical loading.[100] Intratendinous injections of PGE2 cause intense degenerative changes, and peritendinous injections of PGE1 result in a histological pattern of tendinopathy.[40,91] Today, several studies confirm a partly inflammatory background to tendinopathy with granulation alterations of capillary vessels and a significant inflammatory infiltrate consisting of macrophages, mast cells, B and T lymphocytes.[60,86] These findings suggest a role for intrinsic immune pathways in the events that mediate early tendinopathy. Presumably, the inflammatory cells activate a cascade of proinflammatory cytokines (eg, IL-18, IL-15, and IL-6) found in tendinopathy.[61]

Tendon cells and fibroblasts, subjected to repetitive mechanical stress in combination with proinflammatory cytokines and transforming growth factor β (TGF-β) stimulation, can transform into myofibroblasts.[93] Myofibroblasts are important cells for tendon healing, possibly also for tissue adaptation. After the healing process is completed and the mechanical stress is released on the myofibroblasts, these cells undergo programmed cell death (apoptosis).[93]

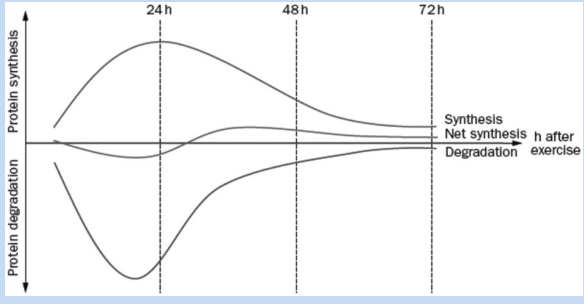

Figure 1. Diagram depicting collagen synthesis and degradation after acute exercise in humans. The first 24 to 36 hours after exercise results in a net loss of collagen. However, 36 to 72 hours after exercise, a net synthesis of collagen follows. Hence, repetitive training without enough resting time in between may result in a net catabolic situation with degradation of the matrix and lead to tendinopathy. Reproduced with permission from Magnusson et al.[54]

If this mechanism fails, the myofibroblasts will propagate a hyperproliferative process, fibrosis, seen as a prominent histological feature of tendinopathy (Figure 2).

Another factor that may cause fibroblast hyperproliferation is hypoxia,[23] which can upregulate matrix metalloproteinases, leading to altered material properties of the tendon.[75] Hypoxia upregulates vascular endothelial growth factor, which increases microvessel ingrowth (angiogenesis) into the tendon—a major finding in tendinopathy.[75]

Angiogenesis has been speculated to be a causative factor for pain since sclerotherapy relieves pain in tendinopathy.[69] However, Blood vessels per se are not painful, but ingrowth of sensory nerve fibers alongside of blood vessels can be painful (Figure 3).[2,47,86] Healthy nonpainful tendons are almost aneuronal within the tendon proper.[2,47] Chronic painful tendons, however, show ingrowth of sensory nerves from the paratenon with release of nociceptive substances. Restricting pathological nerve ingrowth by denervation (eg, mini-invasive surgery or release of the paratenon) can cause pain relief.[97]

Interestingly, sensory nerve ingrowth in the tendon can be a reaction to repetitive loading and also a response to injury.[59] In normal tendon repair, sensory nerve ingrowth is correlated with increased nociception, followed by autonomic nerve ingrowth, coinciding with decreased nociception and subsequent nerve retraction.[2,3] In tendinopathy, the ingrown sensory nerves do not retract, as in normal healing. Thus, neuronal dysregulation in tendinopathy, characterized by aberrant sensory nerve sprouting may reflect a failed healing response (Figure 3), leading to increased pain signaling and possibly to the hyperproliferative changes associated with tendinopathy.[47]

In addition to pain transmission, peripheral nerve fibers react to mechanical stimuli and release several chemical substances,

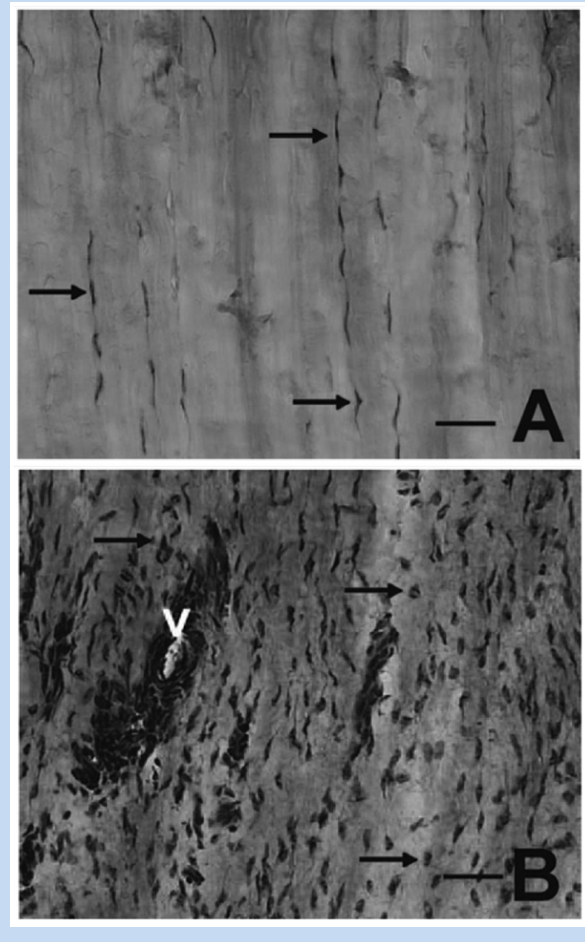

Figure 2. Patellar tendon of healthy control (A) and painful tendinopathy (B) after hematoxylin and eosin staining. Arrows denote tenocytes. The healthy tendon has homogeneous, organized parallel collagen structure and thin, elongated tenocytes (A). Tendinopathy, in contrast, is characterized by collagen disorganization, increased cell count, transformed tenocytes, and vascular ingrowth (V) in the tendon proper (B). Bar, 50 µm. Reproduced with permission from Lian et al.[47]

which are normally involved in healing and homeostasis but cause fibrosis during prolonged release.[3] The presence of essential neuromediators in tendon was established more than 10 years ago[3]; recent studies have verified a diverse group of nerve mediators and receptors in tendon.[3,87] Tendinopathic tendons exhibit increased sensory neuropeptide, substance P (SP),[2,47,86] which may in addition to its role in nociception, reflect proinflammatory and trophic actions (Figure 3).[3] SP regulates vasodilation, plasma extravasation, and release of cytokines by binding to its receptor, neurokinin 1, found in tendon and upregulated by loading.[3,8,15,33,48,83] SP stimulates proliferation of fibroblasts and endothelial cells and possibly also transforms fibroblasts into myofibroblasts by

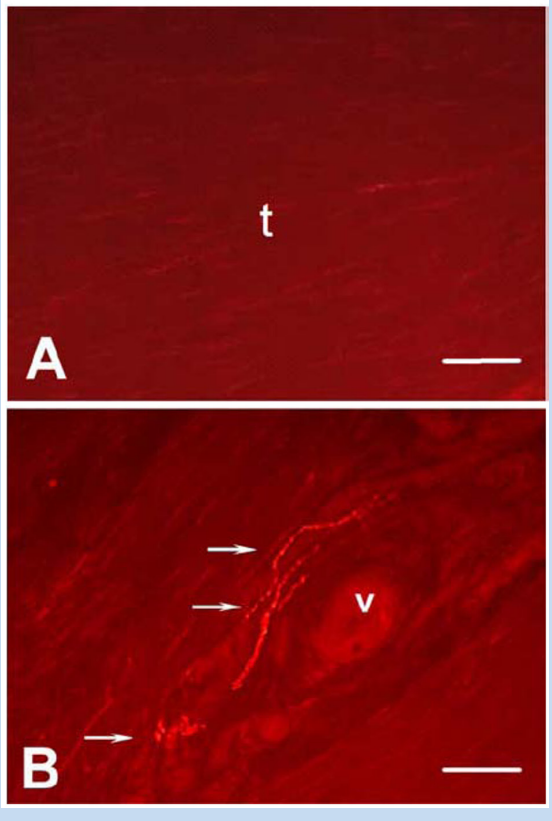

Figure 3. Achilles tendon of healthy control (A) and painful tendinopathy (B) after immunostaining for substance P (SP); picture taken with immunofluorescence microscopy. Arrows denote free nerve endings. The micrograph illustrates SP-positive nerve fibers in close vicinity to a proliferated vessel (B). v = blood vessel. Bar = 50 µm. Reproduced with permission from Ackermann et al.[3]

increasing the production of TGF-β in fibroblasts.[3,33] Hence, abnormal upregulation of SP may contribute to tendinosis (fibrosis), tenocyte transformation, hypercellularity, and hypervascularization observed in tendinopathic patients.

Other neuronal factors, highly upregulated in tendinopathy, are the neurotransmitter glutamate and its receptor, NMDAR1, which are implicated in various painful diseases.[5,65,84] Furthermore, the localization of the increased glutamate signaling has just lately been established in tendinopathic patients, suggesting a pathological role.[84] Thus, upregulated glutamate/NMDAR1 is observed in morphologically transformed tenocytes, in the endothelial and adventitial layers of neovessel walls, and in ingrown sprouting nerve fibers.[84] Activated NMDA is seen in the tendon proper of tendinopathic biopsies but not in controls, suggesting a role in pathologic tenocyte transformation, neovessel formation, and pain signaling. These may be hypothetically mitigated by blocking of NMDAR1. Systematic investigation of the pathophysiological processes in tendinopathy may lead to novel and targeted therapies.

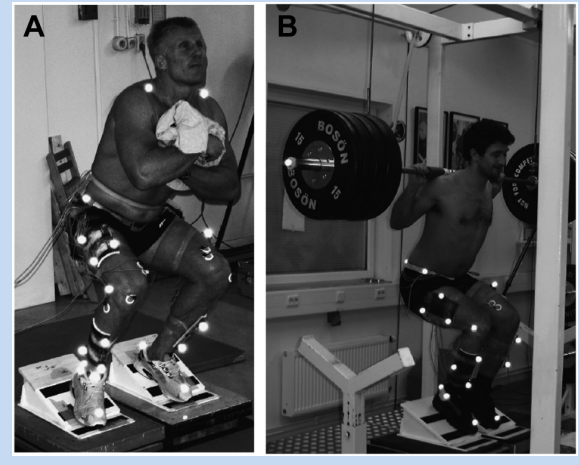

Figure 4. Eccentric squats exercises for the patellar tendon in an experimental setup for (A) free weight, decline board and (B) overload, decline board experiments. Reproduced with permission from Frohm et al.[24-25]

NONOPERATIVE TREATMENT

The optimal management for tendinopathy is still debated. Nonoperative treatment is often effective and, compared with operative management, less costly and involving no risk of perioperative and postoperative complications. It is therefore still the first line of treatment.

Exercises

The conservative treatment with the best documentation for successful management of tendinopathy is eccentric exercises (Figure 4). In a prospective study of 200 patients with a 6-week once-daily eccentric loading regime, Stanish et al found that 44% of patients had complete relief of pain and 43% reported a marked improvement.[89]

Several clinical studies investigating Achilles and patellar tendinopathy have verified a 40% to 60% good outcome after a home-based, twice-daily, 12-week regime of mainly eccentric training.[7,28,41,44,50,99] Favorable outcomes after eccentric training are emerging on other tendinopathic locations, such as elbow and shoulder.[11,55] Overall, the trend indicates positive effects of eccentric exercises without reported adverse effects.

Eccentric training produces around 20% more load on the tendon compared with concentric training.[78] During eccentric work, the mean and peak patellar tendon force and angle at peak force were greater (25%-30%) for squats on a decline board compared with horizontal surface with free weight (Figure 4).[24] Heavy slow eccentric overload strength training without decline board has also shown to be effective for patellar tendinopathy.[25] A recent study also showed that eccentric training and static stretching exercises combined are superior to eccentric training alone to reduce pain and

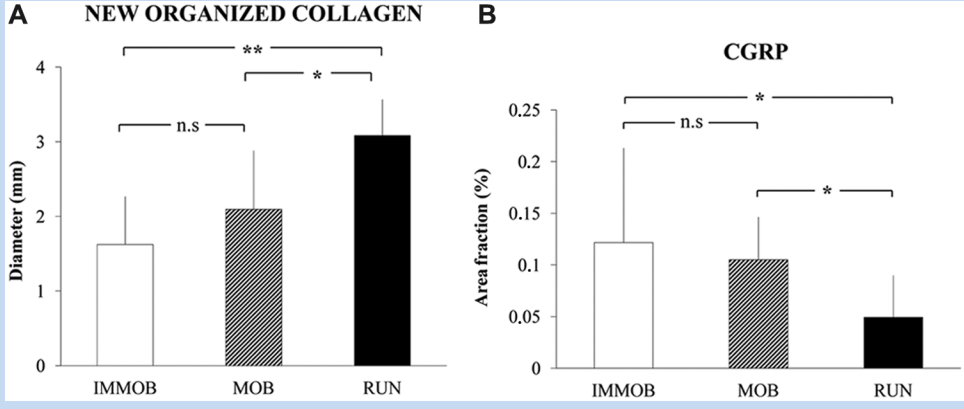

Figure 5. Achilles tendon subjected to 3 levels of physical activity during 4 weeks postrupture. Rats were post Achilles tendon rupture treated with a plaster cast (IMMOB), freely mobilized (MOB), or wheel-running (RUN). (A) Midtendon mediolateral diameter of new organized collagen in the healing area. (B) Area occupied by nerve fibers (%) immunoreactive to a sensory nerve marker, calcitonin gene related peptide (CGRP) in relation to total area, of the Achilles tendon proper. Increased physical activity seems to accelerate sensory nerve retraction from the tendon proper. Mean + SD. $^{*}P < 0.05$; ns, $P > 0.05$. Reproduced with permission from Bring et al.[14]

improve function in patients with patellar tendinopathy.[21] Moreover, color Doppler sonography demonstrated decreased neovascularization following eccentric training intervention.[68]

Tendon loading, especially eccentrically, promotes collagen synthesis and collagen fiber cross-linking, thereby facilitating tendon remodeling (Figure 5A).[28,54] Although the underlying mechanisms of successful eccentric exercises are not clear, the duration of such an exercise program is usually 3 months,[99] the same time needed for the tendon to form new fibroblasts. Presumably, exercise stimulates the formation of new tendon cells, fibroblasts that are adapted to load.

Exercises exert mechanical effects on cells on nerve fibers and their receptors. Increased tendon training accelerates nerve retraction from the tendon proper, decreases load-induced pain, and modulates the expression of neuronal substances (Figure 5B).[14,15] Thus, nerves may alter the chemical milieu in response to load, either by increased production and delivery of antinociceptive substances (eg, opioids) and their receptors or by decreased production of nociceptive substances (eg, substance P) and their receptors.[3]

Biophysical Procedures

In failed tendon healing (ie, tendinopathy), there is a lack of essential substances to initiate the repair process. There is a rationale to establish a new trauma to restart the healing process. Biophysical procedures, such as extracorporeal shockwave treatment (SWT) and low-intensity pulsed ultrasound (LIPUS), initiate tendon and tendon-to-bone healing.[52] Thus, SWT and LIPUS have both demonstrated positive experimental effects on tendon healing; SWT selectively denervates sensory unmyelinated nerve fibers without affecting larger motor neurons.[66] In symptomatic calcific tendinitis of the shoulder, LIPUS has helped resolve calcifications, followed by a short-term clinical improvement.[22] However, in a double-blind study on patellar tendinopathy, LIPUS did not provide any additional benefit over placebo.[101] SWT has shown encouraging clinical effects on tendinopathy.[95] However, during the volleyball season players with jumper's knee did not improve after SWT.[105] A randomized clinical trial combining eccentric training and SWT demonstrated higher success rates for midportion Achilles tendinopathy, compared with eccentric loading or SWT alone.[81,82] Thus, there are discrepancies in results of SWT for different tendons indicating that the proper indications for SWT are not yet fully known.

Glyceryl Trinitrate Patches

Two recent meta-analyses of 7 randomized clinical trials concluded that topical nitroglycerin exerts short-term relief (maximum, 6 months) of pain in activities of daily living in chronic or acute tendinopathies.[27,29] Side effects are common, including dizziness and headaches through vasodilation-induced hypotension. Longer term results show no benefit over placebo for lateral epicondylalgia with positive results in Achilles tendinopathy.[57,72]

Injection Therapies

Several local injection formulas have been tested to address the pathology and promote a healing response. Overall, there are no Level 1 studies or high-quality studies to support any of these therapies.

Corticosteroids

Corticosteroid injections are still used extensively in athletes but remain controversial.[52,67,70,88] Reviews of corticosteroid injections in tendons showed little benefit.[70,88] Moreover, there

is good clinical evidence that cortisone produces a small positive short-term effect but also a long-term negative effect.[70] Animal studies show that local corticosteroid injections reduce tendon strength. There are numerous case reports of tendon rupture after corticosteroid injections into humans.[52,67]

Sclerotherapy

In randomized controlled trial, sclerosing substances (Aethoxysclerol) have, under ultrasonography and color Doppler guidance, produced successful results in the peritendinous neovessel area.[68,69] Presumably, the pathological nerve ingrowth in close proximity to the neovessels is reduced by this treatment.[6,34,35,102] However, at 2 years follow-up, one-third of the patients seek additional treatment, and at 3 to 5 years follow-up, around 50% of the patients have received supplementary therapies.[34,96] There is a need for large-scale randomized control studies with appropriate follow-up to determine the efficacy of injection therapies in tendinopathy.[35] A comparative study of patients who received arthroscopic shaving of the neovessels and presumably nerves showed less pain than in those receiving sclerotherapy.[102]

Blood Products

Blood injections provide deficient healing areas devoid of bleeding (tendinopathies) with new growth factors. Autologous blood injections have been reported successful for different tendinopathies, although well-performed studies display less promising results.[18,19,37]

A recent popular development with autologous blood is to spin down the blood and inject the platelet-rich plasma. Platelets release a variety of growth factors (eg, PDGF, VEGF, IGF-1, TGF-β, FGF) that promote repair in various soft tissue models. In the only available randomized controlled study on Achilles tendinopathy, platelet-rich plasma treatment was not more effective than saline injections.[19,20,37]

OPERATIVE TREATMENT

The aims of operative treatment are to excise areas of failed healing, fibrosis, and pathological nerve ingrowth, initiate bleeding and a healing process, and thereby restore vascularity to initiate stem cell ingrowth and protein synthesis. The operative approach can be open, percutaneous, or endoscopic.[52] The technique should be chosen as to best target the pain generating pathology. Targeting the pathological nerve and vessel ingrowth with ultrasound and color doppler-guided abrasion has shown good short-term results for midportion Achilles tendinosis.[4] Arthroscopic surgery for patellar tendinopathy, refractory to nonoperative management, appears to provide significant improvements in symptoms and function maintained for at least 3 years.[73] Endoscopy can access several tendons, such as the posterior tibial and peroneals, otherwise not easily visualized.[16,85]

The surgeon should address the pathological nerve ingrowth accompanied by pathological neovessels, to mitigate pain. The neonerves that follow the neovessels can be eliminated with electrocoagulation or mini-invasive stripping with color Doppler US visualization.[12,49,92] A motorized shaver, diathermy, or radiofrequency can destroy neovessels and possibly the pathological pain-generating ingrown nerves.

SUMMARY

The recommended treatment strategies for tendinopathy vary. Exercise enhances tendon repair and nerve withdrawal from the tendon proper. Eccentric loading may result in the tendon resistance to injury. Heavy, slow strength training, specifically eccentric, is effective for Achilles and patellar tendinopathy, with encouraging results for epicondylalgia. Physical therapy supervision increases compliance and quality since management of tendinopathy is difficult and time-consuming and may lead to frustration and reinjury. Exercise should be the cornerstone of tendinopathy treatment.

Adjuvant biophysical procedures, such as extracorporeal SWT, may initiate healing of the failed tendon repair by selective denervation of sensory nerves. Injection therapies with blood products, sclerosing agents, and cortisone may have good short-term effects, but all have limited long-term results. There are no Level 1 or high-quality studies to support any of the injection therapies. Thus, there is a limited role for injection treatments in the management of tendinopathy.

Surgery may occasionally be indicated in recalcitrant cases and may allow 60% to 85% of patients to return to preinjury activity levels. Rehabilitation after surgery, however, may take quite some time.[73] Mini-invasive surgery addressing the pathological nerve and vessel ingrowth in tendinopathy shows good initial results.

New techniques addressing tendon repair, such as tissue engineering and regeneration, seem promising. These methods include molecular approaches by which genetically modified cells, including stem cells, synthesize growth factors or other mediators needed for healing. However, molecular procedures are not yet ready for routine clinical use. Novel mini-invasive procedures that target underlying pathology, such as abnormal neoinnervation, are being developed and are initially promising but necessitate high-quality randomized controlled trials before these can be recommended.

Clinical Recommendations

SORT: Strength of Recommendation Taxonomy
A: consistent, good-quality patient-oriented evidence
B: inconsistent or limited-quality patient-oriented evidence
C: consensus, disease-oriented evidence, usual practice, expert opinion, or case series

Clinical Recommendation	SORT Evidence Rating
Strength training with daily eccentric exercises for at least 12 weeks improves pain and function and may reverse tendinosis changes in patients with tendinopathy of the Achilles, patellar, rotator cuff, and elbow extensor tendons.[28,45,70,99,103]	B
Sports activities involving tendon overload should be avoided during the eccentric rehabilitation period and during extracorporeal shockwave treatment.[99,105]	B
Extracorporeal shockwave treatment alone has a midterm effect on pain for tendinopathy of the Achilles, patellar, and rotator cuff tendons, whereas it has little or no effect on tendinopathy of elbow extensor tendons. Extracorporeal shockwave treatment has, in addition to eccentric training of the Achilles tendon, potentiated treatment effects.[81,82,90,95,105]	B
Topical nitroglycerin has short-term effect on pain for tendinopathy of the Achilles, rotator cuff, and elbow extensor tendons.[27,29]	B
Injection therapies with corticosteroids, sclerosing agents, autologous blood, and platelet-rich plasma may have short-term effects, yet they have no proven long-term treatment effects. Reports even show long-term adverse effects of corticosteroids.[19,34,37,70,96]	B
In patients where conservative therapy fails after 3 to 6 months, new minioperative procedures that remove tendinosis tissue and/or abnormal neoinnervation demonstrate promising results.[73,92,102]	C

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