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Current Concepts Review: Noninsertional Achilles Tendinopathy

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INTRODUCTION

Achilles tendinopathy is characterized by the clinical triad of pain, limitation in activities, and focal swelling associated with degenerative change in the tendon.[27,45] The histologic change in the area of swelling and degeneration is best defined as Achilles tendinosis. Pathologic findings include areas of disorganized collagen and abnormal neovessels in the absence of inflammatory cells. Often, Achilles tendinopathy is improperly referred to as Achilles tendonitis. The clinical entity of Achilles tendinopathy often occurs in elite and recreational athletes but is also seen in more sedentary populations.[68]

Achilles tendinopathy is the most common tendinopathy associated with running and was diagnosed in 56% of one group of elite middle-aged runners.[36] It can be characterized as insertional (at the calcaneus-Achilles tendon junction) or noninsertional (2 to 6 cm proximal to the insertion of the Achilles tendon into the calcaneus). Each type has its own pathophysiology and treatment strategies. This review will address noninsertional Achilles tendinopathy only.

Considerable controversy surrounds the management of noninsertional Achilles tendinopathy. Rest, eccentric and concentric stretching exercise, nonsteroidal anti-inflammatory medications, noninvasive modalities, injections, and surgery have all been utilized. A 2001 Cochrane Review, however, found little evidence to support the use of any one particular therapy for this condition.[53] The application of cytokines, growth factors, gene therapy, and stem cells for the future management of this disorder are under investigation. This current concepts article will review the etiology, pathophysiology, and the evidence to support the available treatment options for noninsertional Achilles tendinopathy.

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BACKGROUND

Etiology

Several theories exist regarding the etiology of Achilles tendinopathy. These include overuse, poor tissue vascularity, mechanical imbalances of the extremity, and a genetic predisposition. Tendinopathy secondary to overuse is thought to arise from repetitive microtrauma in the region of a vascular watershed. A retrospective case-control study (Level III prognostic evidence) identified several patient factors that were more likely to be associated with Achilles tendinopathy: hypertension, diabetes, obesity, and a previous exposure to steroids or estrogen. Each of these factors decrease the microvascularity of tendons and as such were postulated to play a role in the development of Achilles tendinopathy.[26] Other studies have found advancing age, previous injury, exposure to quinolone antibiotics, and endocrine and metabolic abnormalities to be associated with Achilles tendinopathy (Level IV prognostic evidence).[16,87] From a biomechanical standpoint, Williams et al. found patients with Achilles tendinopathy to have decreased tibial external rotation during running, which was attributed to an imbalance of muscle forces in the transverse-plane of motion that increases the strain on the Achilles tendon.[92] Finally, the gene for matrix metalloprotease-3 (MMP-3) is involved in the homeostasis of the ground substance surrounding tendons. Variants in the gene are potential genetic contributions to the development of tendinopathy.[71]

Pathophysiology

The pathophysiology of Achilles tendinopathy is thought to involve the cellular and molecular response to microscopic tearing of the tendon. The resulting chronic degenerative process that ensues occurs in areas of the tendon with poor vascularity and a poor potential for healing. Histological examination of the affected tissue demonstrates an

Table 1: Level of evidence and grades of recommendation

Level of Evidence
- Level I: high quality prospective randomized clinical trial
- Level II: prospective comparative study
- Level III: retrospective case control study
- Level IV: case series
- Level V: expert opinion

Grades of Recommendation (given to various treatment options based on Level of Evidence supporting that treatment)
- **Grade A** treatment options are supported by strong evidence (consistent with Level I or II studies)
- **Grade B** treatment options are supported by fair evidence (consistent with Level III or IV studies)
- **Grade C** treatment options are supported by either conflicting or poor quality evidence (Level IV studies)
- **Grade I** when insufficient evidence exists to make a recommendation

Table 2: Grades of Recommendations for Treatment Options for Noninsertional Achilles Tendinopathy

Grade A Recommendations: Treatment options are supported by strong evidence (Level I or II studies)
No option meets these criteria

Grade B Recommendations: Treatment options are supported by fair evidence (Level III or IV studies)
Operative Management for Recalcitrant Tendinopathy

Grade C Recommendations: Treatment options are supported by either conflicting or poor quality evidence (Level IV studies)
Eccentric Stretching Exercise
Sclerosing Injections / Prolotherapy
Topical Glyceryl Trinitrate

Grade I Recommendations: Insufficient evidence exists to make a recommendation
Rest and Activity Modification
Ultrasound
Shock Wave Therapy
Low Level Laser Therapy
Corticosteroid Injections
Platelet-rich Plasma
Aprotinin Injections

increased number of tenocytes, an increased concentration of glycosaminoglycans in the ground substance, disorganization and fragmentation of the collagen, and neovascularization. The tenocytes present at the site of degeneration have an irregular shape and a higher rate of apoptosis.[46,78] Although inflammation occurs around the tendon, biopsies demonstrate no inflammatory cells infiltrating the tendon.[27]

Tendinopathy is understood as a failed healing response within the extracellular matrix that is mediated by a cascade of proinflammatory molecules that include IL-1 B, prostaglandin E2, and nitric oxide. In patients who develop tendinopathy, these mediators induce apoptosis, signal pain responses, and increase the production of matrix metalloproteinases (MMP). This response leads to degeneration of the tendon, rather than signaling a repair process.[1] There is little evidence to suggest that Achilles tendinopathy leads to frank rupture. Nevertheless, the histological evaluation of tissue taken from ruptured Achilles tendons contained more degeneration than those taken from patients with tendinopathy and uninvolved controls.[84] In a large retrospective case-control study, no spontaneous Achilles tendon ruptures were found in patients with healthy tendons (Level III evidence).[30]

Sampling the environment within and around the Achilles tendon with a microcatheter and microdialysis has clarified some aspects of the molecular pathophysiology of tendinopathy. In a series of patients with Achilles tendinopathy a small clinical study utilizing this technique showed no change in the levels of prostaglandin E2, a marker of inflammation, compared to controls. Instead, an increase in concentration of glutamate, a neurotransmitter associated with pain was detected (Level II diagnostic evidence).[7] Scott et al.[77] have demonstrated that vesicular glutamate transporters (VGluT2) are within Achilles fibroblasts in patients with Achilles tendinopathy. These findings suggest that a glutamatergic system mediates pain in the tendon and this pathway is more activated in degenerated tendons due to high levels of glutamate derived from tenocytes. Glutamate may play other roles in the pathophysiology of Achilles tendinopathy. It may regulate a mechanotransmitter pathway that stimulates increased production of collagen in response to loading of the tendon. Glutamate may also be a toxic stimulus to neurons and fibroblasts, inducing necrosis or apoptosis of these cells.[77]

Other studies have demonstrated higher levels of lactate, increased expression of enzymes producing acetylecholine and catecholamines, increased substance P, and increased neurokinin-1 (NK-1) in patients with Achilles tendinopathy (Level III diagnostic evidence).[2,7,13] All of these substances are hypothesized to contribute to the pathophysiology of the disorder. High lactate levels suggest the presence of ischemia or anaerobic conditions within the tendon in Achilles tendinopathy. Acetylcholine has vasoactive, trophic, and pain-modulating effects that could contribute to tendinopathy. Autocrine/parocrine effects between the diseased tenocytes could increase muscularinic receptors on those cells and increase the production of acetylcholine.[13] Substance P has been associated with pain transmission, cell growth, angiogenesis,[8] and the organization of tendon.[76] NK-1 receptors are the preferred receptor for substance P, and

interactions between the two may influence tendon repair through another autocrine/paracine loop.[9] At the present time, the specific contributions of these mechanisms to tendinopathy are not understood completely.

Neovascularization of the tendon is considered an important etiological factor and a pain generator in Achilles tendinopathy. Doppler ultrasound has been used to demonstrate neovascularization in Achilles tendons with tendinopathy (Level II diagnostic evidence).[61] Abnormal vessels have been found in the ventral aspect of the tendon adjacent to Kager's triangle. These vessels are accompanied by proliferating nerves that are hypothesized to be integral in pain transmission.[12,59,61]

PRESENTATION

Clinical manifestations

Khan and Mafulli described the triad of pain, swelling, and impaired performance as the clinical hallmarks of Achilles tendinopathy.[31,45] Patients are often unable to participate in athletic activities or work due to pain that worsens with activity. They usually report painful stiffness in the morning that eases over the course of the day. Athletes should be asked about a change in footwear, exercise surface, or exercise regimen.[66] Other predisposing factors include a history of hypertension, diabetes, obesity, exposure to steroids, estrogens, or quinolone antibiotics.[16,26]

Physical examination

The diagnosis of Achilles tendinopathy can usually be made clinically based on symptoms and the location of pain and swelling. The area of tenderness, warmth, and swelling should be determined to differentiate insertional from noninsertional disease. A palpable fusiform thickening that moves with ankle dorsiflexion and plantarflexion is a common finding with the latter. The physical examination should also include a complete assessment of the lower extremity to identify the presence of a leg-length inequality, ankle instability, malalignment, generalized ligamentous laxity, and joint stiffness or contractures.[3,92]

Imaging

Plain radiographs may reveal intratendinous calcifications, but otherwise are not helpful in evaluating noninsertional Achilles tendinopathy. Advanced diagnostic imaging is also not necessary establish a diagnosis, but is helpful in determining the extent of the pathology. Currently, magnetic resonance imaging (MRI) is preferred over ultrasound, but both are useful studies and each can be advantageous in certain scenarios.[32] Both can be used before and after treatment to access changes in diseased tendons. MRI visualizes the location and extent of pathology within the tendon and distinguishes intratendinous from paratendinous pathology as well.

In patients with Achilles tendinopathy, MRI will demonstrate thickening and intratendinous signal changes without edema of the tendon.[32] The anterior to posterior diameter of the tendon is increased beyond the normal limit of 6 mm, and altered heterogeneous signals on short tau inversion recovery (STIR) and gadolinium enhanced T1-weighted images are seen.

Ultrasound examination is operator dependent, but has the advantage of better delineation of neovascularization associated with tendinopathy using Doppler techniques.[32,61] Diseased tendons demonstrate hypoechogenic areas due to irregular tendon structure and changes in the patterns of fibrillar collagen and increased cross-sectional and anterior-posterior tendon diameter.[5,41] Abnormal echogenicity of Kager's fat pad, thickening of the paratenon, and subtle micro-tears are also indicative of Achilles tendinopathy.[10,22,23,41] In addition to its diagnostic capabilities, ultrasound can also be used to localize and guide invasive therapeutic procedures.[37,59,85]

NON-INVASIVE TREATMENT

Rest and activity modification

Most patients diagnosed with Achilles tendinopathy are treated initially with a course of relative rest. The spectrum of rest includes complete cessation of all activities, cessation of specific activities such as athletic training or competitive sports, and the use of ankle-foot orthoses, shoe inserts, and casts.[67] Usually, a period of rest lasting between 2 to 6 weeks is prescribed and its effect on symptoms is evaluated before more aggressive or invasive treatments are recommended. There are no studies, however, that demonstrate the efficacy of rest. In fact, one study demonstrated the superiority of eccentric exercise and shock wave therapy over rest in patients with chronic tendinopathy (Level I evidence).[73] Based on the lack of published data, there is insufficient evidence to support the use of this treatment (Grade I recommendation).

Ultrasound

Ultrasound is a common adjuvant to a prescribed program of physical therapy. Although a recent laboratory study in rats suggests that the application of ultrasound may promote healing in the Achilles tendon by inducing tenocyte migration, a meta-analysis performed in 1995 concluded that there were insufficient well-designed studies to support ultrasound as a treatment of tendinopathies.[21,86] Due to a lack of new, high quality data on the effect of ultrasound on noninsertional Achilles tendinopathy, the evidence remains insufficient to support its clinical use (Grade I recommendation).

Low level laser therapy

At the cellular level, low level laser therapy (LLLT) may increase collagen production, down-regulate matrix metalloproteinases (MMP), and decrease the capillary flow of neovascularization. There have been two recent randomized controlled trials (Level I evidence) comparing LLLT

to placebo for Achilles tendinopathy.[11,83] The first trial reported decreased pain at rest, during exercise, and on palpation of the tendons treated with the laser compared to placebo at 12 weeks followup.[83] The second trial showed improved pain threshold immediately (105 min) after LLLT but no long-term followup was performed.[11] Both studies included a small number of patients with brief followup. Given the limited clinical investigation of this technology, the evidence is insufficient to support its use (Grade I recommendation) until larger studies with longer followup are performed.

Eccentric and concentric exercise therapy

Eccentric exercises, a technique of elongating a tendon during a simultaneous voluntary muscle contracture, is a widely used treatment for Achilles tendinopathy. Although the mechanism of action is unknown, it is theorized that eccentric exercise decreases neovascularization within a symptomatic tendon.[34] The tensile force generated within the tendon during the exercise temporarily ceases blood flow through the neovessels. With repetition over time, the neovessels are obliterated, along with their associated pain receptors, which lead to the resolution of symptoms. Doppler ultrasonography has shown a decrease in neovascularization after 12 weeks of eccentric exercise training in patients who reported improvement in their symptoms with this program (Level II evidence).[58] Another study demonstrated that 12 weeks of eccentric exercise did not effect oxygen saturation in the Achilles tendon, but did decrease capillary blood flow and postcapillary venous filling pressure (Level II evidence).[34] The data from these studies suggest that improved pain control in patients with noninsertional tendinopathy occurs after neovascularization decreases within the Achilles tendon.

Structural and compositional changes have been observed in diseased tendons after eccentric exercise. A recent study with nearly 4 years followup demonstrated resolution of structural anomalies and decreased tendon thickness (Level IV evidence).[60] However, the study did not include a control to confirm the effect of exercise by direct comparison. In a small group of elite athletes, eccentric exercise increased the synthesis of type I collagen, but did not change the degradation of collagen with affected tendons (Level II evidence).[38]

Various studies have compared the efficacy of eccentric exercise to concentric exercise.[50,56,74,81] Alfredson et al. used a 12-week protocol[6] that involved unsupervised eccentric exercise performed to the point of pain, with the patient controlling the increase in the force applied to the Achilles tendon (Level IV evidence). This original protocol indicated that an eccentric training program may offer an alternative to surgical treatment, but did not offer convincing, comparative evidence of the program's effects.[6] Four randomized controlled trials have compared this 12-week eccentric training program (or a similar program) to a control of splinting or concentric exercise. In a randomized controlled trial, Mafi et al. compared concentric training to Alfredson's eccentric training regimen and found superior patient reported pain results with eccentric training (Level II evidence).[49] In another randomized controlled trial, Silbernagel et al. (Level I evidence) compared an elaborate 12-week eccentric training regimen to a more basic concentric training program and found that, while significantly more people in the eccentric training group were satisfied at one year, objective comparisons were not significantly different.[48] Roos et al. (Level II evidence) compared eccentric training to night splinting and found no significant differences between the two treatments, or when used in combination.[74] Niesen-Vertommen et al. (Level II evidence) compared eccentric and concentric exercises in a small group of athletes and found similar results in all outcome measures other than pain, which favored eccentric exercise.[56] Problems with the methodology used for blinding and heterogeneity of the subjects may limit the applicability of the studies individually, but when the results are pooled for analysis the four studies indicate that eccentric exercise does not offer a significant decrease in pain compared to concentric exercise. However, there is evidence to suggest that eccentric exercise results in better satisfaction and return to activity at 12 weeks than concentric exercise.[34,74,81,93]

Although there is fair evidence to support the use of eccentric exercise to reduce the pain associated with noninsertional Achilles tendonopathy (Grade B recommendation), the evidence to support its use over other options is conflicting and not of uniformly high quality (Grade C recommendation). Therefore, its specific role in the management of this condition remains unclear.

Shockwave therapy

Shockwave therapy (SWT) is a relatively new option in the management of Achilles tendinopathy. It is believed that high energy SWT alleviates pain by stimulating soft tissue healing, regenerating tendon fibers, and inhibiting pain receptors. The energy transmitted to the tendon through the shock wave produces intracellular damage that results in increased permeability of the cell membranes in the tissue. In the peripheral nerves, this effect is thought to cause nerve depolarization and to block the transmission of pain signals.[57] SWT has also been shown to attract neutrophils to the treated area, to increase cytokine-mediated vascularity,[82] and to enhance angiogenesis.[91] All of these changes stimulate cellular division and tissue regeneration.

There have been three recent randomized controlled trials (Level I evidence) of SWT for chronic noninsertional Achilles tendinopathy.[17,72,73] The studies compared low-energy SWT treatments to various non-operative therapies. Two studies[17,72] found no difference in pain relief between SWT and placebo, although one of these studies[72] reported significantly improved American Orthopaedic Foot

and Ankle Society outcome scores in the SWT group. In the third trial, Rompe et al.[73] found improved self-reported functional outcomes and pain scores in both eccentric loading and SWT groups when compared to a wait-and-see group. While most adverse effects from SWT were minimal (temporary redness and achiness) two traumatic Achilles tendon ruptures occurred after SWT in older patients in one study.[17] These were traumatic ruptures, and were not necessarily related to therapy. All three studies had short (3 month) followup, a small cohort and utilized different low-energy SWT protocols.

Beyond these investigations, one retrospective comparative study (Level III evidence) showed significantly better results in the SWT group at 3 and 12 months followup compared to other non-operative treatments.[20] In this study, patients received a single, high-energy dose of SWT as opposed to the low-energy dose utilized in the three randomized, controlled trials.

The most effective dose and duration of SWT is unknown. This, in conjunction with the absence of a consistent, uniform benefit in three high-quality studies indicates that there is insufficient evidence (Grade I recommendation) to support a role for SWT in the treatment of noninsertional Achilles tendinopathy.

Glyceryl trinitrate

It is theorized that glyceryl trinitrate, a prodrug of nitric oxide, may increase fibroblast collagen synthesis in patients with tendinopathy.[73,74] This therapy is administered topically through transdermal patches applied directly over the area of maximal tenderness. Paoloni et al.[69,76] evaluated topical glyceryl trinitrate treatment for chronic noninsertional Achilles tendinopathy in a randomized, prospective double-blind, placebo controlled trial (Level I evidence). The treatment group showed decreased tenderness, night pain, activity pain, and improved functional outcomes after 6 months of treatment.[69] A 3-year followup study demonstrated that the benefits of the treatment were maintained.[70] There have been no microcirculatory studies that demonstrate an increase in collagen synthesis after this therapy to demonstrate why this treatment is effective.

In a randomized controlled trial, a comparison of topical glyceryl trinitrate and placebo patches with both groups performing eccentric exercise (Level I evidence) showed significant improvements in both groups at 6 months followup with no difference between groups in pain or disability as measured on the Ankle Osteoarthritis Scale.[29] Furthermore, histological samples showed no changes in neovascularity, wound fibroblasts, collagen synthesis, or nitric oxide production in tendons that received transdermal glyceryl trinitrate patches compared to placebo controls. Approximately 20% of patients with the transdermal glyceryl trinitrate patches developed headaches and had to discontinue participation in the study. The lack of an Achilles specific instrument or a functional outcome measurement limits interpretation of results. Also no pre-hoc power analysis was performed to determine the appropriate number of subjects in each group needed to avoid an underpowered study and a type II error. Given these limitations, this study does not clarify the therapeutic effect of topical glyceryl trinitrate patches over standard eccentric exercises alone.[29] The evidence from these level I studies is conflicting regarding the efficacy of transdermal topical glyceryl trinitrate and its role in the management of this disease remains uncertain (Grade C recommendation).

INVASIVE MANAGEMENT

Corticosteroid injections

Corticosteroid injections have been used to provide short-term pain relief in Achilles tendinopathy, although several authors have stated that insufficient data exists to weigh the risks against the benefits of this practice.[65,80] A randomized, controlled trial (Level I evidence) reported decreased pain during ambulation and tendon thickness measured by ultrasound after paratendinous injections.[21] A retrospective comparative study (Level III evidence) assessed the safety of low-volume, fluoroscopically-guided, paratendinous injections and reported no serious complications including ruptures at 2-year followup.[24] Intratendinous injection carries a relative contraindication based on its catabolic effect on tendons observed in animal studies.[65,80] A small number of patients followed prospectively after receiving intratendinous steroid injections (Level II evidence) had decreased pain without any major side effects.[37] Overall, the evidence to support the injection of corticosteroid in or around the Achilles tendon is insufficient (Grade I recommendation) and the unquantified risk of iatrogenic rupture inveighs against its use.

Platelet-rich plasma therapy

The introduction of platelet-rich plasma at the site of tendon injury is thought to facilitate healing through the delivery of hyperphysiologic doses of cytokines. A Level III study to determine the effect of platelet rich plasma on healing after the surgical repair of Achilles tendons found moderately enhanced return of range of motion and activity when compared to repair alone.[54,75] At this time, the evidence to support the use of platelet-rich plasma in the management of noninsertional Achilles tendinopathy is insufficient (Grade I recommendation).

Sclerosing injections/prolotherapy

Polidocanol is a sclerosing agent used to treat varicose veins. It selectively targets the vascular intima and causes thrombosis of the vessel. Polidocanol also works extravascularly, to destroy local nerves adjacent to neovessels.[12] The effects of prolotherapy with Polidocanol on the neovascularization associated with diseased Achilles tendinopathy have been investigated.[59,61] Polidocanol injected at multiple

sites around the tendon and neovessels initiates a local inflammatory response.[61] The response induces a proliferation of fibroblasts and synthesis of collagen which is intended to produce a stronger, more organized tendon.[41]

Clinically, a double-blind randomized controlled trial (Level I evidence) found improved results after injections with Polidocanol injections compared to injections with lidocaine or adrenalin in patients with Achilles tendinopathy.[4] The majority of patients were satisfied after therapy and the mean pain score significantly decreased. The patients who received Polidocanol were retrospectively evaluated 2 years later (Level IV evidence) and were found to have maintained subjective improvements in satisfaction, ability to participate in sports, and reduction in pain. Ultrasound studies were obtained on all subjects. Thinner, more normal appearing tendons were found, suggesting a remodeling effect in the tendons after prolotherapy.[41] A pilot study (Level IV evidence), conducted before the trial by the same authors observed significantly improved pain scores in a subset of patients who had received Polidocanol injections and had no neovessels present on followup ultrasound examinations after prolotherapy compared to patients who had neovessels present on ultrasound followup at 6 months.[59] The authors concluded that their findings supported the theory that neovessels and the adjacent nerve bundles are a pain generator in this condition.

Another RCT comparing prolotherapy with Polidocanol to surgery (Level I evidence)[4] found that all ten patients in the operative group were satisfied with their results at 6 months and returned to sport sooner than the prolotherapy group.[4] The authors concluded that operative management improves outcomes more reliably and quickly than patients treated with prolotherapy.[4] It is important to note that this study and the previous study had small cohorts which were recruited from the practice of a single surgeon.

Willberg et al.[91] observed equivalent results in a double-blinded, randomized controlled trial (Level I evidence) comparing 5 mg/mL or 10 mg/mL injections of Polidocanol for noninsertional Achilles tendinopathy. No significant difference was found in number of treatments, total volume injected, or pain scores with activity before or after treatments. There were no adverse events in either group. The authors reported good results and a return to full activity after two to three injections.[91]

Another prolotherapy agent available for clinical use is a 25% Dextrose solution. The injection of this solution is hypothesized to dehydrate cells by causing local tissue trauma and an influx of inflammatory cells which then stimulates tendon healing. In a pilot study (Level IV evidence), the mean pain scores at rest, during normal activity, and during sporting activity all made significant improvements after injections. Most patients remained asymptomatic to mildly symptomatic at one year without any adverse events reported.[52]

Due to the conflicting results with level I studies and more positive results with level IV studies, there is poor quality evidence (Grade C recommendation) to make a recommendation for prolotherapy with Polidocanol or 25% dextrose solution.

Aprotinin injections

Samples from tendons with tendinopathy have shown increased concentrations of matrix metalloproteinases (MMPs), particularly collagenases (MMP-1, MMP-8, MMP-13) and gelatinases (MMP-2 and MMP-9). The activation of these enzymes, which break down collagen and other constituents of the ground substance, are considered to be contributing factors to the delayed healing observed in tendinopathies. Aprotinin is a collagenase inhibitor that is used for preventing blood loss during surgery and promoting soft tissue healing post-surgery.[64] Capasso et al.[15] investigated the role of Aprotinin versus distilled water injections for the management of Achilles tendinopathy (paratendinitis, insertional tendinitis, bursitis) in a small, non-randomized study (Level II evidence). They found improved subjective complaints and resumption of sport in the Aprotinin group with no side effects or allergic reactions reported. Recently, a larger retrospective case study (Level IV evidence) reported on 155 cases treated with Aprotinin injections and followed for an average of nine months. The authors found a 69% improvement rate on a non-validated, subjective questionnaire reporting improvement in symptoms, side effects, other treatments used for tendinopathy, and the perceived value of Aprotinin injections. There was a 6% rate of systemic allergic reaction[63] which led to a change in protocol and an increase in the time interval between injections.[64] In a larger followup study by the same authors (Level IV evidence), 438 injections were performed on a variety of diseased tendons with the Achilles being the most common site. The same non-validated questionnaire revealed that 76% of patients were subjectively improved, 22% had no change, and 2% were worse than before the injections. Patients with noninsertional Achilles tendinopathy had statistically better improvements compared to the patellar tendinopathy group. This study also demonstrated improved outcomes with Aprotinin injections over corticosteroid injections.[62] None of these studies had a control group; therefore, the contribution of a placebo effect from injection alone or the natural history of the disease cannot be distinguished from the treatment effect. Also, Aprotinin was not compared to other agents currently used for prolotherapy. The authors concluded that the potential for a serious side effect limits the use of Aprotinin and this agent should not be used as a first line therapy for tendinopathies. However, due to the superior effect when compared to injections with corticosteroid, they concluded that Aprotinin was preferred over corticosteroid for injecting Achilles, patellar and hamstring tendinopathy.[62]

Brown et al.[14] performed the only RCT (Level I evidence) evaluating injections with Aprotinin for Achilles tendinopathy.

Their results showed a trend towards improved results with Aprotinin, but the difference was not significant from placebo injections. This study only enrolled a small number of participants and may have been underpowered to assess the effect of Aprotinin.

Considering the results from these studies, the evidence is insufficient (Grade I recommendation) to support the use of Aprotinin for the treatment of noninsertional Achilles tendinopathy.

Operative management

Operative management is typically reserved for recalcitrant Achilles tendinopathy, which in some case series can occur in 25% to 50% of patients with this condition.[28,67] The goal of surgery is to resect degenerative tissue, stimulate tendon healing by means of controlled, low-grade trauma, and/or augment the Achilles tendon with a well-vascularized graft. It has been suggested that noninvasive treatment be tried for at least 4 months prior to operative interventions.[28,85]

One of the least invasive procedures currently available is percutaneous longitudinal tenotomy, which is indicated for mild to moderate focal noninsertional Achilles tendinopathy.[79,85] Longitudinal tenotomies are percutaneously made to the areas of tendon with degeneration and swelling. Success rates have been reported between 67% to 97% with good results shown in athletic patients (Level IV evidence)[47] and worse outcomes in patients with extensive tendinopathies, multinodular tendons, and paratendinopathies (Level IV evidence).[85]

Minimally invasive stripping of the tendon is another less invasive operative intervention.[42] In this procedure, large diameter sutures are passed through stab incisions and slid anterior to the Achilles tendon to free adhesions in Kager's triangle. Minimally invasive stripping can be performed in conjunction with longitudinal tenotomies. One group has suggested that this offers a safe, less-invasive precursor or alternative to open procedures (Level IV evidence).[42] Currently, there is not a controlled trial to demonstrate the effectiveness of the procedure.

For moderate to severe tendinopathy, an open procedure with or without tenosynovectomy can be performed.[43] Adhesions that would otherwise be difficult to break up with percutaneous procedures can be easily removed with the more extensive open procedure. During this procedure, degenerative tendon tissue should be excised. This operation has produced good results (success rates greater than 80%)[28,39] that are better when the duration of patient symptoms is shorter (Level IV evidence).[28,43]

Visual inspection of the tendon during the open procedure can confirm if greater than 50% of the cross sectional area of the tendon is healthy. If so, a simple debridement with or without tubularization of the tendon can be performed. If greater than 50% of the cross sectional area of the tendon is diseased, a tendon augmentation by transfer of the flexor hallucis longus (FHL) muscle, as originally described by Wapner et al.,[89] can be performed (Level IV evidence). The muscle belly of the FHL is well vascularized and can theoretically help augment the avascular area present in Achilles tendinopathies. The FHL is also a strong plantar flexor with an axis similar to the Achilles tendon.[89]

The results of FHL augmentation for chronic Achilles tendinopathy have been promising, though limited. In a recent study by Martin et al.,[51] patients treated with excision of the entire degenerative Achilles tendon had improved pain, improved functional outcomes, and improved patient satisfaction (Level IV evidence). Patients undergoing this operation had decreased strength and plantarflexion on the operative side, but most patients were still able to perform a single leg heel raise.[51] Other studies also found good outcomes (Level IV evidence)[90] with few patients losing hallux push-off strength (Level IV evidence).[18]

Long-term results of operative interventions are promising but limited in scope. A recent study examined 2-year postoperative data on 13 patients with degenerative Achilles tendinopathies who failed 3 months of nonoperative treatment and were ultimately treated with debridement plus FHL transfer (Level IV evidence). Clinical exam and patient questionnaires showed improvement in pain and strength. Postoperative MRI showed resolution of inflammation around the Achilles tendon and homogenous incorporation of the FHL into the Achilles tendon.[25] In contrast, Alfredson et al.[8] found a persistence of ultrasound abnormalities at a mean of 8 years after midsubstance operations in 14 patients, despite improvements on clinical exam and subjective questioning (Level IV evidence).

Some evidence exists to suggest that males may be better operative candidates than females. A retrospective case control study (Level III prognostic evidence) by Maffulli et al.[48] examined the effect of gender on the results of surgery for chronic Achilles tendinopathy. The female patients were found to have worse outcomes, longer recovery time, more complications, and increased incidence of reoperation.[48]

Other, less common operative procedures include open lysis of adhesions and paratenosynovectomy for isolated paratendinopathy or associated tendinopathy. Some surgeons have suggested endoscopic debridement of the Achilles tendon.[50] Additional reconstructive procedures include Achilles turndown and VY advancement.

The variability of clinical data and the paucity of head-to-head comparisons prevents the recommendation of one treatment over another, but all procedures are supported by fair evidence (Grade B recommendation) in the management of noninsertional Achilles tendinopathy.

OPERATIVE COMPLICATIONS

In a large series of patients who underwent surgery for Achilles tendinopathy, 11% had postoperative complications but at one year followup most patients were satisfied with

their outcomes and had returned to previous level of activity (Level IV evidence).[68] The operative complications included skin edge necrosis, superficial and deep infections, seroma or hematoma formations, sural neuritis, new partial ruptures, deep venous thromboses, and sensitive or hypertrophic scars.[47,55,68] Wound healing and skin complications may be more common in poorly controlled diabetics and smokers.[79] There may be an increased risk of tendon ruptures after debridement or percutaneous operations,[25] although it may be difficult to distinguish between trauma related ruptures and postoperative complications. Specific to the FHL transfer, persistent great toe cock up deformity has been reported.[25] More common adverse events after operations are the risks of persistent pain, inability to return to sport, and weakness of plantarflexion.[25]

SUMMARY

1. Achilles tendinopathy is a clinical triad of pain, swelling, and limitation in activities. Achilles tendinopathy can be anatomically classified by location Insertional tendinopathy is located at the tendinous insertion to the calcaneus and noninsertional tendinopathy is located two to six centimeters proximal to that insertion.
2. The etiology of Achilles tendinopathy may include: overuse leading to repetitive microtrauma, poor vascularity of the tissue, mechanical imbalances of the extremity, a genetic predisposition or some combination of these elements.
3. Histological examination of the affected tissue demonstrates an increased number of tenocytes, an increased concentration of glycosaminoglycans in the ground substance, disorganization and fragmentation of the collagen, and neovascularization. The tenocytes present at the site of degeneration have an irregular shape and a higher rate of apoptosis. Although inflammation occurs around the tendon, biopsies demonstrate no inflammatory cells infiltrating the tendon.
4. Bioochemical analyses of the diseased tendon and its environment have shown: elevated glutamate levels that may mediate the pain response, elevated lactate levels demonstrating tissue ischemia; acetylecholine and catecholamine enzymes that are vasoactive and pain-modulating, and substance P that is associated with pain transmission, cell growth, angiogenesis, and the organization of tendons.
5. There is some evidence to support 12 weeks of eccentric exercise to reduce pain and decrease neovascularization. However, there is some conflicting evidence and poor quality studies therefore, the specific role of eccentric exercise in management of this condition is unclear (Grade C recommendation).
6. There is insufficient evidence to support the use of several other modalities that have been used for treating Achilles tendinopathy including: ultrasound, low level laser therapy, shock wave therapy, corticosteroid injections, platelet-rich plasma therapy, and aprotinin injections (Grade I recommendation).
7. There is poor quality of evidence to support transdermal glyceryl trinitrate and prolotherapy with Polidocanol or dextrose (Grade C recommendation).
8. Several operative treatments include percutaneous longitudinal tenotomies, minimally invasive tendon stripping, open tenosynovectomies, open debridement and tubularization, and tendon augmentation with FHL. All are supported by fair evidence to recommend these procedures for recalcitrant Achilles tendinopathies (Grade B recommendation).

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