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## CURRENT CONCEPTS REVIEW

# Novel Approaches for the Management of Tendinopathy

By Nicola Maffulli, MD, MS, PhD, FRCS(Orth), Umile Giuseppe Longo, MD, and Vincenzo Denaro, MD

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- Tendinopathy is a failed healing response of the tendon.
- Despite an abundance of therapeutic options, very few randomized prospective, placebo-controlled trials have been carried out to assist physicians in choosing the best evidence-based management.
- Eccentric exercises have been proposed to promote collagen fiber cross-link formation within the tendon, thereby facilitating tendon remodeling. Overall results suggest a trend for a positive effect of eccentric exercises, with no reported adverse effects. Combining eccentric training and shock wave therapy produces higher success rates compared with eccentric loading alone or shock wave therapy alone.
- The use of injectable substances such as platelet-rich plasma, autologous blood, polidocanol, corticosteroids, and aprotinin in and around tendons is popular, but there is minimal clinical evidence to support their use.
- The aim of operative treatment is to excise fibrotic adhesions, remove areas of failed healing, and make multiple longitudinal incisions in the tendon to detect intratendinous lesions and to restore vascularity and possibly stimulate the remaining viable cells to initiate cell matrix response and healing.
- New operative procedures include endoscopy, electrocoagulation, and minimally invasive stripping. The aim of these techniques is to disrupt the abnormal neoinnervation to interfere with the pain sensation caused by tendinopathy.
- Randomized controlled trials are necessary to better clarify the best therapeutic options for the management of tendinopathy.

### **Evolving Concepts in Tendinopathy: New Theories**

Tendinopathies account for a substantial proportion of overuse injuries associated with sports<sup>1</sup> and are a common cause of disability<sup>2,3</sup>. Most major tendons, such as the Achilles, patellar, rotator cuff, and forearm extensor tendons (among others), are vulnerable to overuse, which induces pathological changes in the tendon<sup>4</sup>.

The term “tendinopathy” is a generic descriptor of the clinical conditions (both pain and pathological characteristics) associated with overuse in and around tendons<sup>5</sup>. The histo-

logical descriptive terms “tendinosis” (a degenerative pathological condition with a lack of inflammatory change) and “tendonitis” or “tendinitis” (implying an inflammatory process) should be used only after histopathological confirmation<sup>5</sup>. However, it should be kept in mind that, despite the use of the term “tendinosis,” at histopathological examination the essence of a tendinopathic lesion is a failed healing response, with haphazard proliferation of tenocytes, intracellular abnormalities in tenocytes, disruption of collagen fibers, and a subsequent increase in noncollagenous matrix<sup>6,7</sup>. Tendinopathic tendons

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have an increased rate of matrix remodeling, leading to a mechanically less stable tendon that is probably more susceptible to damage<sup>8</sup>. Histological studies of surgical specimens from patients with established tendinopathy consistently show either absent or minimal inflammation<sup>9-11</sup>. They generally also show hypercellularity, a loss of the tightly bundled collagen fiber appearance, an increase in proteoglycan content, and commonly neovascularization<sup>12,13</sup>. Inflammation seems to play a role only in the initiation, but not in the propagation and progression, of the disease process<sup>14</sup>. Competing theories have been proposed to explain the pathogenesis of tendinopathy at specific stages and presentations of the condition<sup>15-18</sup>. A continuum of tendon pathology from asymptomatic tendons to tendon tears has been proposed<sup>19,20</sup>.

Failed healing and tendinopathic features have been associated with chronic overload, but the same histopathological characteristics also have been described when a tendon is unloaded: stress shielding seems to exert a deleterious effect<sup>9</sup>. Unloading a tendon induces cell and matrix changes similar to those seen in an overloaded state and decreases the mechanical integrity of the tendon<sup>19,20</sup>.

Despite an abundance of therapeutic options, very few randomized prospective, placebo-controlled trials have been conducted to assist physicians in choosing the best evidence-based management<sup>21,22</sup>. Treatments that have been investigated with use of a randomized controlled trial design include nonsteroidal anti-inflammatory medications<sup>23-25</sup>, eccentric exercise<sup>26-30</sup>, glyceryl trinitrate patches<sup>31-33</sup>, sclerosing injections<sup>34</sup>, aprotinin injections<sup>35-37</sup>, ultrasound<sup>38</sup>, and shock wave treatment<sup>39-50</sup>. What may appear clinically as an acute tendinopathy is actually a well-advanced failure of a chronic healing response in which there is neither histological nor biochemical evidence of inflammation<sup>23</sup>. The available literature suggests that, in the absence of an overt inflammatory process, there is no rational basis for the use of nonsteroidal anti-inflammatory drugs in chronic tendinopathy<sup>51</sup>.

In this Current Concepts Review, we report the best available evidence for the management of tendinopathy and provide a comprehensive and up-to-date review of the development of future modalities for treatment.

## Nonoperative Management Options

### *Eccentric Exercises*

Eccentric exercises have been proposed to promote collagen fiber cross-link formation within the tendon, thereby facilitating tendon remodeling (see Appendix)<sup>52</sup>. Evidence of histological changes following a program of eccentric exercise is lacking, and the mechanisms by which eccentric exercises may help to relieve the pain of tendinopathy remain unclear.

Eccentric exercises have been proposed to counteract the failed healing response that underlies tendinopathy by promoting collagen fiber cross-linkage within the tendon, thereby facilitating tendon remodeling<sup>50</sup>. The concept of eccentric exercises is based on the structural adaptation of the musculotendinous units to protect them from increased stresses and thus prevent reinjury.

The basic principles in an eccentric loading regimen are unknown, although it has been speculated that forces generated during eccentric loading are of a greater magnitude than those in concentric exercises<sup>53</sup>. It is possible that eccentric exercises do not just exert a beneficial mechanical effect, but also act on pain mediators, decreasing their presence in tendinopathic tendons. Although microdialysis has shown raised intratendinous glutamate levels<sup>54</sup> and substance P and neurokinin-1 receptor<sup>55</sup> to be significantly higher in Achilles tendons with painful tendinopathy than in normal, pain-free tendons, and treatment with eccentric training has shown good clinical results with diminished tendon pain during activity, in vivo results have shown that successful treatment with eccentric training is not associated with lowered intratendinous glutamate levels<sup>54</sup>. Also, as the exercise regimen is supposed to produce pain and if the patient does not experience pain load is added to produce pain during the exercise, it is possible that progressive habituation to painful stimuli occurs<sup>52,56-58</sup>. Color Doppler sonography demonstrated decreased neovascularization following eccentric training intervention<sup>59</sup>.

Excellent clinical results have been reported both in athletic and sedentary patients<sup>26,60</sup>, although these results were not reproduced by other study groups<sup>26,61</sup>. In general, the overall trend suggests a positive effect of eccentric exercises, with no reported adverse effects<sup>52</sup>. In one study, the combination of eccentric training and shock wave therapy produced success rates that were higher than those with eccentric loading alone or shock wave therapy alone<sup>30</sup>.

### *Extracorporeal Shock Wave Therapy*

Extracorporeal shock wave therapy to address the failed healing response of a tendon is becoming more widely used among the medical community (see Appendix)<sup>50</sup>. Typical characteristics are high peak-pressure amplitudes (500 bar) with rise times of <10 ns, a short life cycle (10 ms), and a frequency spectrum (16 to 20 MHz) ranging from the audible to the far ultrasonic level<sup>62</sup>. This rapid rise is followed by periods of pressure dissipation and negative pressure before a gradual return to the ambient pressure. The shock wave entering the tissue may be reflected or dissipated, depending on the properties of the tissue. The energy of the shock wave may act through mechanical forces generated directly or indirectly via cavitation<sup>63</sup>. The rationale for the clinical use of extracorporeal shock wave therapy is stimulation of soft-tissue healing and inhibition of pain receptors.

There is no consensus on the use of repetitive low-energy extracorporeal shock wave therapy, which does not require local anesthesia, versus the use of high-energy extracorporeal shock wave therapy, which requires local or regional anesthesia<sup>63</sup>. In several well-conducted randomized controlled trials, low-energy extracorporeal shock wave therapy was administered once a week for three or four consecutive weeks, with final assessment undertaken twelve weeks after the last shock wave therapy session<sup>30,50</sup>. At the time of a four-month follow-up, eccentric loading and low-energy shock wave therapy showed comparable results<sup>62</sup>, whereas eccentric loading alone

was less effective than the combination of eccentric loading and repetitive low-energy shock wave treatment<sup>30</sup>.

When used, high-energy extracorporeal shock wave therapy is administered only one time.

Low-energy shock wave therapy has been proposed for tendinopathy to stimulate soft-tissue healing and inhibit pain receptors<sup>30,63-65</sup>. Low-energy shock wave therapy or eccentric training for the management of Achilles tendinopathy produced comparable results in a randomized controlled trial<sup>50</sup>, and both management modalities showed outcomes superior to those of no intervention<sup>50</sup>. However, the results of low-energy shock wave therapy were disappointing in another study<sup>66</sup>.

#### *Use of Injectable Substances*

A wide variety of substances have been injected and are routinely injected in and around tendons.

#### **High-Volume Injections: Normal Saline Solution, Corticosteroids, and Anesthetics**

Neovascularization is a characteristic feature of Achilles and patellar tendinopathy; it is generally accompanied by nerve ingrowth and normally is not present in patients without tendon pathology<sup>67,68</sup>. The ingrowth of new blood vessels and associated nerves from the peritendinous tissues may be a source of pain<sup>69</sup>. Histopathological studies showed immunoreactions for neurokinin-1 receptor and alpha-1-adrenoreceptor in biopsy specimens from the ventral area of tendinopathic Achilles<sup>70</sup> and patellar<sup>71</sup> tendons as well as elevated levels of the neurotransmitter glutamate and the presence of its receptor, N-methyl-d-aspartate receptor type 1<sup>71-73</sup>.

The hypothesized rationale behind this management modality was that high-volume injections of normal saline solution, corticosteroids, or anesthetics would produce local mechanical effects causing new blood vessels to stretch, break, or occlude. Occluding and possibly breaking these vessels would lead to the accompanying nerve supply also being damaged by either trauma or ischemia, therefore decreasing the pain in patients with resistant Achilles tendinopathy.

Preliminary studies showed that high-volume injection of normal saline solution, corticosteroids, or anesthetics reduces pain and improves short and long-term function in patients with Achilles<sup>74</sup> or patellar<sup>75</sup> tendinopathy, regardless of their symptoms (see Appendix). High-volume injection is safe and relatively inexpensive, with the potential to offer an alternative to operative treatment, resulting in a quicker return to sports<sup>76</sup>.

Hydrocortisone acetate is used in the high-volume injections, primarily to prevent an acute mechanical inflammatory reaction produced by the large amount of fluid injected in the proximity of the tendon. The injection is performed under ultrasound guidance, so that corticosteroids have no direct action on the tendon itself. The role of corticosteroids in the management of tendinopathy is still debated. Meta-analysis of the effects of corticosteroids has shown that published data are insufficient to determine the risk of rupture following corticosteroid injections<sup>77</sup>, and we do not advocate their intratendinous injection<sup>76</sup>.

#### **Platelet-Rich Plasma**

Platelet-rich plasma is a bioactive component of whole blood, which is now being widely tested in different fields of medicine for its possibilities in aiding the regeneration of tissue with poor healing potential<sup>78-82</sup>.

The use of platelet-rich plasma to help wound-healing has been proposed since the early 1980s<sup>83</sup>. Its use in orthopaedic surgery, especially for augmentation of bone-grafting, began during the present decade, although to date there is no definitive evidence that it improves bone healing<sup>84</sup>. The use of platelet-rich plasma to improve tendon healing has been advocated only recently<sup>85-87</sup>. In general, the concentration of platelets in platelet-rich plasma is higher than that in blood<sup>88,89</sup>.

Dense granules may play a role in tissue modulation and regeneration by releasing their content of adenosine, serotonin, histamine, and calcium. The alpha granules release transforming growth factor- $\beta$ , platelet-derived growth factor, and vascular endothelial growth factor, with concentrations increasing linearly with increasing platelet concentration. The released cytokines bind to transmembrane receptors on the surface of local or circulating cells and induce intracellular signaling. This may result in the production of proteins responsible for cellular chemotaxis, matrix synthesis, and proliferation<sup>86</sup>.

Tendon healing occurs through three overlapping phases (inflammation, proliferation, and remodeling), which are controlled by a variety of growth factors<sup>86,90-92</sup>. The rationale for the use of platelet-rich plasma to promote tendon healing is the high content of these cytokines and cells in hyperphysiologic doses of platelet-rich plasma. Several studies on the application of platelet-rich plasma to promote tendon healing are ongoing worldwide, although the exact mechanisms by which platelet-rich plasma promotes tendon healing are still not clear (see Appendix). One of the main advantages is that platelet-rich plasma is autologous and is prepared at the time of treatment (point of care) and therefore has an excellent safety profile. De Vos et al.<sup>93</sup> performed a stratified, block-randomized, double-blind, placebo-controlled trial of fifty-four patients with Achilles tendinopathy treated, at a single center, with exercises (usual care) as well as injection of either platelet-rich plasma or saline solution (the placebo group). The authors concluded that, compared with the saline-solution injection, the platelet-rich-plasma injection did not result in greater pain relief or improvement in activity.

#### **Autologous Blood Injection**

An injection of autologous blood for the management of tendinopathy has been reported<sup>94</sup>. The aim of this treatment is to provide cellular and humoral mediators to induce healing in areas where the healing response has failed (see Appendix). The use of autologous blood injection is thought to lead to tendon healing through collagen regeneration and the stimulation of a well-ordered angiogenic response<sup>89</sup>. It has been hypothesized that transforming growth factor- $\beta$  and basic fibroblast growth factor carried in the blood will act as humoral mediators to induce the healing cascade<sup>95,96</sup>. Although the results of laboratory studies are encouraging, such studies have always involved

healthy tendons or surgically induced lesions, given the lack of a good experimental model for tendinopathy. At present, it is unclear whether these results can be extrapolated to tendinopathic tendons<sup>89</sup>. So-called needling of the tendon has been described in conjunction with the use of autologous blood. However, it could be difficult to distinguish between the effect of needling and the effect of autologous blood injection<sup>96</sup>.

### **Polidocanol**

In patients with chronic painful Achilles tendinopathy, there is neovascularization outside and inside the ventral part of the tendinopathic area<sup>97,98</sup>. Local anesthetic injected in the area of neovascularization outside the tendon may result in a pain-free tendon, indicating that this area is involved in pain generation. These are the bases for the injection of the sclerosing substance polidocanol (Aetoxisclerol; Kreussler Pharma, Wiesbaden, Germany) under ultrasonography and color Doppler guidance in the area with neovessels outside the tendon<sup>99-104</sup>.

Injections with polidocanol in a randomized controlled trial showed the potential to reduce tendon pain during activity in patients with chronic painful midportion Achilles tendinopathy (see Appendix)<sup>102</sup>.

In Achilles and patellar tendinopathy, there is evidence of neural ingrowth in conjunction with neovascularization. Injections of polidocanol close to the tendon seem to be remarkably safe.

Of 150 patients in whom Achilles tendinopathy had been managed with polidocanol, two experienced a complication<sup>105</sup>. One patient who had insertional Achilles tendinopathy sustained a total rupture in the proximal part of the tendon at the end of an 800-m running race, and the other patient sustained a partial rupture in the midportion of the tendon, where he previously had received four intratendinous corticosteroid injections.

### **Intratendinous Injections of Corticosteroids**

The use of corticosteroid injections is highly controversial<sup>14,106-110</sup>. There is a lack of good-quality research data to support the widespread use of these drugs. There are numerous case reports of tendon rupture after corticosteroid injections in patients<sup>111,112</sup>. Animal studies have suggested that local corticosteroid injections may lead to a reduction in tendon strength<sup>113</sup>, but this finding is not universal<sup>114</sup>.

At present, there is insufficient evidence from which to draw firm conclusions on the utility of local corticosteroid treatments for Achilles tendinopathy (see Appendix). Three randomized controlled trials<sup>115-117</sup> showed different results in terms of the effects of local corticosteroids on healing, with two studies demonstrating some benefit<sup>115,116</sup> and the other showing none<sup>117</sup>. A meta-analysis of the effects of corticosteroid injections showed little benefit<sup>77</sup>. The safety of corticosteroid injections can be enhanced with the use of ultrasound imaging needle guidance. With the high-volume-injection technique, the needle is kept extratendinous and outside the peritendinous space<sup>118</sup>, so that the fluid is injected only in the Kager triangle (for the Achilles tendon) or in the Hoffa body (for the patellar tendon).

### **Operative Treatment**

The objectives of operative treatment are to excise fibrotic adhesions, remove or debride areas of failed healing, restore vascularity, and possibly stimulate viable cells to initiate protein synthesis and to promote healing<sup>13,119</sup>. Recent studies have shown that multiple longitudinal tenotomies trigger neoangiogenesis in the Achilles tendon, with increased blood flow<sup>120</sup>. This would result in improved nutrition and a more favorable environment for healing.

Multiple percutaneous longitudinal tenotomies can be performed when conservative management has failed in patients who have isolated tendinopathy with no involvement of the paratenon and a well-defined nodular lesion <2.5 cm long<sup>121</sup>. This procedure may be ultrasound guided to confirm the precise location of the area of tendinopathy<sup>121-123</sup>. It is a simple procedure and can be performed in an ambulatory setting with the use of local anesthesia and without a tourniquet.

Percutaneous longitudinal ultrasound-guided internal tenotomy of the Achilles tendon can be also performed on an outpatient basis. However, it requires the use of high-resolution ultrasound to properly locate the tendinopathic area and to place the initial stab incision<sup>121-123</sup>. Complications (with wound-healing) are minimal and lead to no long-term morbidity. The technique is not as effective in patients with pantendinopathy.

### **Radiofrequency Microtenotomy**

Radiofrequency microtenotomy is a safe and effective procedure for managing patients with chronic tendinopathy (see Appendix). It is a technically simple procedure to perform and has been proposed to produce a rapid and uncomplicated recovery<sup>124-127</sup>. It is hypothesized that the mechanism of action may be to induce acute degeneration and/or ablation of sensory nerve fibers. Early degeneration followed by later regeneration of nerve fibers after bipolar radiofrequency treatment may explain long-term postoperative pain relief<sup>124-127</sup>.

### **Neovessel Destruction**

Pathological nerve ingrowth accompanies pathological neovascularization in the tendinopathic tendon, and it has been considered as a possible cause of the pain. Some authors have attempted to disrupt the abnormal neoinnervation to interfere with the pain sensation caused by tendinopathy. Endoscopy<sup>128-133</sup>, electrocoagulation<sup>134</sup>, and minimally invasive stripping<sup>135-138</sup> have been proposed to achieve this aim. Endoscopy allows direct visualization of the area of tendinopathy and allows use of a motorized shaver or diathermy to destroy neovessels.

### **Endoscopy-Assisted Treatment**

Tendoscopy may allow endoscopic access to several tendons, including the posterior tibial tendon<sup>129</sup>, the peroneal tendons<sup>128,139</sup> and the Achilles tendon<sup>131,132,140,141</sup> (see Appendix). This operative technique provides access to the posterior aspect of the ankle and subtalar joints. Also, extra-articular structures of the hindfoot such as the os trigonum, the flexor hallucis longus, and the deep portion of the deltoid ligament can be accessed<sup>130</sup>.

Thermann et al.<sup>132</sup> described a different technique of endoscopic debridement of the ventral neovascularized area, the peritenon, and the Achilles tendon and reported good short-term clinical results in eight patients.

### Best Modalities for Management of Tendinopathy

In general, it would be reasonable to treat a patient with tendinopathy with physical therapy involving a program of eccentric exercises, to be performed for twelve weeks. If the condition does not respond to this intervention, shock wave therapy or a nitric oxide patch might be considered, although data on their efficacy are limited. If the condition does not respond to those interventions, injections could be considered. The use of operative treatment should be discussed with the patient after at least three to six months of nonoperative management. Moreover, patients should understand that symptoms may recur with either conservative or operative approaches.

### The Future and Conclusions

In the last few decades, biomaterials have become critical components in the development of effective new medical therapies for wound care<sup>142,143</sup>. Many new tissue-engineered materials have been introduced, including artificial polymers, biodegradable films, and biomaterials derived from animal or human tissues<sup>143,144</sup>.


Biological scaffolds are protein-based extracellular matrices, usually derived from human or animal connective tissues<sup>145</sup>. Advantages of biological scaffolds include a well-defined three-dimensional microstructure (allowing host cell integration) and natural porosity (which provides a much larger space for host cell attachment, proliferation, and migration and assists gas and metabolite diffusion). These properties allow biological scaffolds to quickly interact with host tissue and induce new tissue formation faster than synthetic scaffolds. Limitations of biological scaffolds are their poor mechanical properties, undefined rate of degradation, variation in biocompatibility, propensity to induce an inflammatory response, and potential for implant rejection<sup>145</sup>.

On the other hand, synthetic scaffolds are manufactured from chemical compounds<sup>145</sup>, which permit better control of

the chemical and physical properties, leading to stronger mechanical strength and consistency in quality. However, the biocompatibility of synthetic scaffolds is very poor, as they can never be absorbed or integrated into host tissue. High incidences of postoperative infection, and chronic immune responses, have been reported with the use of such materials<sup>145</sup>.

A genetic component has been implicated in tendinopathies, but investigations into the genetic factors involved in their etiology are still in their infancy<sup>146-148</sup>. An enhanced understanding of these factors holds the promise of new approaches to the prevention and management of these common conditions. Additional randomized controlled trials are necessary to better clarify the best therapeutic options for the management of tendinopathy.

### Appendix

 Tables summarizing the studies on the various treatments of tendinopathy are available with the electronic version of this article on our web site at [jbjs.org](http://jbjs.org) (go to the article citation and click on "Supporting Data"). ■

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