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The chronic painful Achilles and patellar tendon: research on basic biology and treatment

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The etiology and pathogenesis of chronic tendon pain are unknown. Even though tendon biopsies having shown an absence of inflammatory cell infiltration, anti-inflammatory agents (non-steroidal anti-inflammatory drugs, corticosteroidal injections) are commonly used. We have demonstrated that it is possible to use intratendinous microdialysis to investigate human tendons, and found normal prostaglandin E_2 (PGE_2) levels in chronic painful tendinosis (Achilles and patellar) tendons. Furthermore, gene technological analyses of biopsies showed no upregulation of pro-inflammatory cytokines. These findings show that there is no PGE_2-mediated intratendinous inflammation in the chronic stage of these conditions. The neurotransmitter glutamate (a potent modulator of pain in the central nervous system) was, for the first time, found in human tendons. Microdialysis showed significantly higher glutamate levels in chronic painful tendinosis (Achilles and patellar) tendons, compared with pain-free normal control tendons. The importance of this finding is under evaluation. Treatment is considered to be difficult, and not seldom, surgery is needed. However, recent researches on non-surgical methods have shown promising clinical results. Painful eccentric calf-muscle training has been demonstrated to give good clinical short- and mid-term results on patients with chronic painful mid-portion Achilles tendinosis. Good clinical results were associated with decreased tendon thickness and a structurally more normal tendon with no remaining neovessels. Using ultrasonography (US)+color Doppler (CD), and immunhistochemical analyses of biopsies, we have recently demonstrated a vasculo/neural (Substance-P and Calcitonin Gene-Related Peptide nerves) ingrowth in the chronic painful tendinosis tendon, but not in the pain-free normal tendon. A specially designed treatment, using US- and CD-guided injections of the sclerosing agent Polidocanol, targeting the neovessels outside the tendon, has been shown to cure tendon pain in pilot studies, in a majority of the patients. A recent, randomized, double-blind study verified the importance of injecting the sclerosing substance Polidocanol.

Tendons have been demonstrated to be more metabolically active than previously thought, demonstrated as clear circulatory responses and collagen turnover changes related to activity (Langberg et al., 1998, 2001). However, after exercise, it takes 48–72 h for the type-I collagen formation to peak (Langberg et al., 2000).

Chronic painful conditions in the Achilles and patellar tendons, often referred to as tendinopathy, are relatively common, especially among recreational and sports-active individuals (Kvist, 1994; Maffulli et al., 1998). Overuse is considered to induce the condition (Curwin & Stanish, 1984; Archambault et al., 1995; Józsa & Kannus, 1997), but the etiology and pathogenesis have not been scientifically clarified. Interestingly, chronic painful mid-portion Achilles tendinosis has also been demonstrated in physically inactive individuals (Movin, 1998; Alfredson & Lorentzon, 2000). In a study on a large group of patients with chronic Achilles tendinopathy (342 tendons with tendinosis), it was demonstrated that physical activity was not correlated to the histopathology, suggesting that physical activity could be more important in provoking the symptoms than being the cause of the actual lesion (Åström, 1998).

A correct clinical diagnosis can be established by clinical examination, combined with ultrasonography (US) (Åström et al., 1996; Paavola et al., 1998), magnetic resonance imaging (MRI) (Neuhold et al., 1992; Paavola et al., 1998), or biopsy (Movin et al., 1997). Most often, the clinical examination reveals an area in the tendon with tenderness and pain during tendon-loading activity. It is of importance to exclude differential diagnoses, such as, for the Achilles tendon, os trigonum syndrome, tenosynovitis or dislocation of the peroneal tendons, tenosynovitis of the plantar flexors, an accessory soleus muscle, tumors of the Achilles tendon (xanthomas), neuroma of the suralis nerve, and especially femuro–patellar cartilage lesions for the patellar tendon. Hypoechoic areas seen on ultrasound, and areas with increased

signal intensity seen on MRI, have been shown to correspond to areas of altered collagen fiber structure and increased interfibrillar ground substance (hydrophilic glycosamino-glycans) (Movin, 1998).

The nomenclature around the chronic painful tendon has been confusing. The chronic painful Achilles and patellar tendons have been considered to include an inflammatory component, and the terms tendinitis and tendonitis have often been used. However, histological evaluation of biopsies, and, recently, intratendinous microdialysis (Alfredson et al., 1999, 2001) and gene technological analyses of biopsies (Alfredson et al., 2003), have shown that there are no signs of a prostaglandin-mediated inflammation in chronic painful Achilles- and patellar tendons. Consequently, using the terms tendinitis and tendonitis for this condition cannot be justified. It is now a common opinion that for chronic pain symptoms from a tender area of the tendon, the term tendinopathy should be used (Maffulli et al., 1998). The combination of chronic pain symptoms from a tender area in the tendon, and where images show corresponding changes in the tendon, is commonly named tendinosis (Movin, 1998; Khan et al., 1999).

Research-basic biology

Intratendinous microdialysis

In vivo investigations of metabolic events inside human tendons are difficult to perform. Consequently, there is relatively sparse knowledge about the normal and injured tendon. *In situ* microdialysis has been shown to be a useful technique to study the metabolism of substances in different types of human tissue (Darimont et al., 1994; Thorsen et al., 1996; Langberg et al., 1998), and it was of interest to investigate whether the microdialysis technique could also be used to study certain metabolic events inside tendons. We found that intratendinous (Achilles and patellar tendons) microdialysis could be performed under resting conditions, without any complications (Alfredson et al., 1999, 2001). However, the technique could not be used under "working" conditions (tendon-loading activity), because the cathether membrane was not strong enough to resist the intratendinous forces.

Using the microdialysis technique, we decided to study the concentrations of prostaglandin E_2 (PGE_2), which is well known to be involved in the so-called chemical inflammation, in tendinosis and normal Achilles and patellar tendons. In patients with chronic painful conditions in the Achilles and patellar tendons, it has, despite the absence of inflammatory cell infiltration in tendon biopsies, been a common opinion that there is involvement of a chemical inflammation (Kvist, 1994; Leadbetter, 1995; Schrier et al., 1996). Prostaglandins are well known to play a central role in inflammation (Solomon et al., 1968), and medical treatment with prostaglandin antagonists is often used. However, the role of prostaglandin-mediated inflammation in this condition has been questioned, and in a randomized, double-blind, placebo-controlled study consisting of 70 patients with chronic painful Achilles tendinopathy, it was demonstrated that oral medication with piroxicam gave similar results as the placebo (Åström & Westlin, 1992). We also decided to investigate whether the excitatory neurotransmitter glutamate, known to be a potent and very important pain modulator in the central nervous system (Dickenson et al., 1997), but never identified in human tendons, could be found in the Achilles tendon. Recently, for the first time, glutamate receptors have been found in human peripheral tissue (bone) (Chenu et al., 1998).

A microdialysis catheter (CMA 60 CMA/Microdialysis AB, Stockholm, Sweden) with a diameter of 1.4 mm, and a length of the membranous covered active part of 30 mm, was under visual control introduced into the tendon through a small skin incision, and placed longitudinally and parallel to the tendon fibers into the area of tendon changes/tendinosis, and in the controls into the central part of the tendon (Fig. 1a, b). The microdialysis pump had a fixed infusion rate of 0.3 μL/min (Ringer solution), and samples were taken every 15 min during a 4 h period. PGE_2 was analyzed using the RIA technique and glutamate was analyzed with the HPLC technique. The results showed that there were no significant

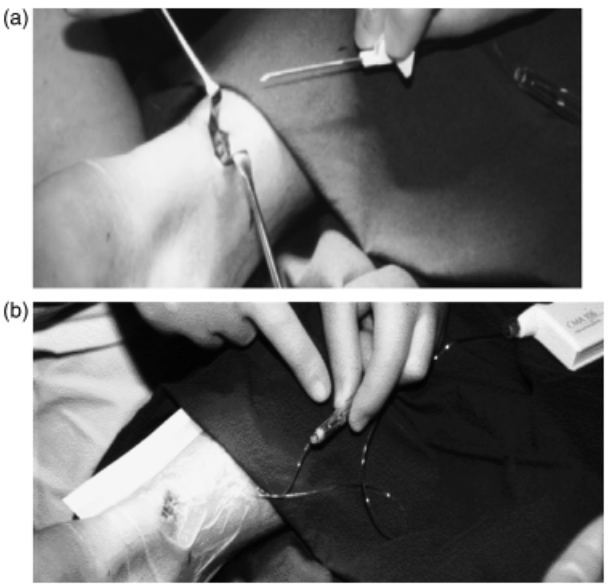

Fig. 1. (a, b) Intratendinous microdialysis. Through a small skin incision, the microdialysis catheter, is under visual control, inserted into the mid-portion of an Achilles tendon (a). The catheter is connected to the pump and the system is securely fixed (b).

differences in the mean concentrations of PGE_2 between tendons with tendinosis and normal tendons (Alfredson et al., 1999, 2001). Surprisingly, glutamate was found in the tendons and there were significantly higher concentrations of glutamate in tendons with tendinosis compared with normal tendons. There were no significant changes of the glutamate concentration over the time of investigation. The finding of the excitatory neurotransmitter glutamate in a human tendon has never been reported before. In recent years, the importance of glutamate as a mediator of pain in the human central nervous system has been emphasized (Dickenson et al., 1997), and, from animal studies, it is known that glutamate receptors, including the ionotrophic glutamate receptor *N*-methyl-D-aspartate (NMDA), are present in unmyelinated and myelinated sensory axons (Coggeshall & Carlton, 1998).

To find out if the glutamate levels could by affected by treatment, a prospective study using the microdialysis technique evaluated the effects of treatment with eccentric training. The results showed that although the patients were pain free after the treatment, the high intratendinous glutamate levels were unchanged (Alfredson & Lorentzon, 2003). Theoretically, the unchanged glutamate levels could possibly be explained by a decreased sensitivity to glutamate on receptor level.

Recently, the microdialysis technique was used to study the concentrations of lactate in chronic painful mid-portion Achilles tendinosis and in normal pain-free tendons. The results showed significantly higher concentrations of lactate in the tendinosis tendons compared with the normal tendons (Alfredson et al., 2002). The findings possibly indicate that there are anaerobic conditions, expressed as higher lactate levels, in tendons with painful tendinosis. However, whether ischemia precedes the start of tendinosis, or whether the tendinotic tendon changes in itself is causing ischemia, is yet to be investigated. Another possibilty is that the high lactate levels reflect a high metabolic rate in the tendinosis tendon. Of course, there may be other explanations to the higher lactate levels found in the tendinosis tendons.

Gray-scale US and color Doppler (CD)

Gray-scale US is considered a good method to study tendon structure (Åström et al., 1996). When combining gray-scale US with CD there is also information about flows, such as blood flow. On 28 consecutive patients with chronic painful mid-portion Achilles tendinosis, but not in any of the normal pain-free tendons, we found a neovascularization inside and outside the area with structural tendon changes (Öhberg et al., 2001) (Fig. 2). The findings might possibly be of importance for the pathogenesis of chronic mid-portion Achilles tendinosis, and/or the pain symptoms that most often are associated with this condition.

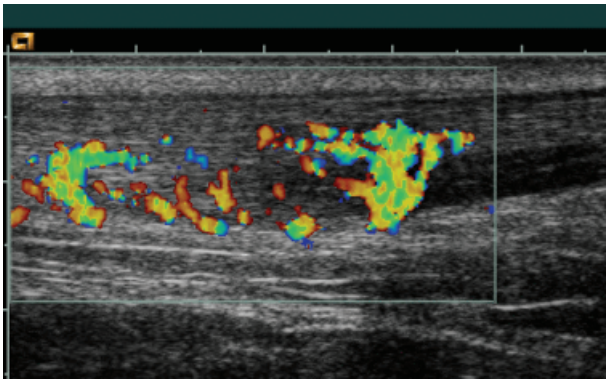

Fig. 2. Neovascularization. Gray-scale ultrasonography and color doppler examination (a longitudinal view) of an Achilles tendon with tendinosis located at the 2–6 cm level in the tendon. The coloration represents a neovascularization, located outside and inside the ventral part of the area with structural tendon changes.

cDNA arrays and real-time PCR

The rapidly growing area of gene technology has created possibilities to study the expression of genes involved in pathological and normal conditions in different tissues. The cDNA-array technique allows for studies of a large amount of gene expressions, and by using the real-time PCR technique more precise measurements of mRNA expression levels can be done. Recently, a down regulation of matrix metalloproteinase-3 (MMP-3) and an up regulation of type I and type III collagen were found in tendons from patients with chronic Achilles tendinopathy (Ireland et al., 2001). Very recently, our research group found an up regulation of MMP-2 (enzyme involved in degrading processes), FNRB (fibronectin receptor involved in healing processes), and vascular endothelial growth factor (VEGF), in painful tendinosis tissue (Alfredson et al., 2003). These findings are interesting and potentially important, but many more genes, and interactions between certain genes, need to be studied before any conclusions can be drawn. Interestingly, in our study, there was no major regulation of the genes for a variety of different cytokines known to be involved in inflammatory processes. This finding further supports the view that there is no prostaglandin-mediated inflammation inside the chronic painful Achilles tendon.

Immunohistochemical analyses of tendon biopsies

The microdialysis and US+CD findings initiated further analyses of tendon biopsies. Immunohisto-

chemical analyses of tendon biopsies revealed glutamate NMDAR1 receptors in tendinosis and normal Achilles tendon tissue (Alfredson et al., 2001). The NMDAR1 immunoreaction was confined to acetylcholinesterase-positive structures, implying that the receptors were localized in association with nerves. Studies on biopsies taken from the area with tendinosis and neovascularization have shown nerve structures in close relation to vessels (Bjur et al., 2005). Furthermore, Substance-P (SP) nerves and the Neurokinin-1 receptor (NK-1R) (known to have a high affinity for SP) were found in the vascular wall, and calcitonin gene related peptide (CGRP) nerves were found close to the vascular wall (Forsgren et al., 2005). The findings of neuropeptides indicate that there still might be an inflammation in the tendon; however, not the so-called chemical inflammation (PGE_2 mediated), but instead the so-called neurogenic inflammation mediated via neuropeptides such as SP.

Research on treatment methods

Chronic painful conditions in tendons are associated with a huge variety of proposed treatment regimens, but it is important to know that there is sparse scientific evidence for most of the conservative and surgical treatments proposed and used. The few scientific prospective studies, and the absence of studies comparing different types of conservative and surgical treatment regimens in a randomized manner, are major disadvantages when evaluating the effects of specific treatment regimens.

A non-operative (conservative) treatment regimen is recommended as the initial strategy by most authors (Kvist, 1994; Józsa & Kannus, 1997; Sandmeier & Renström, 1997). This strategy includes identification and correction of possible etiological factors, and also a symptom-related approach. Most commonly the initial treatment consists of a multi-oriented approach, including combined rehabilitation models. There are many different designs of combined rehabilitation models, most often they include a combination of rest (complete or modified), medication with non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, orthotic treatment (heel lift), change of shoes, corrections of malalignments, stretching, and strength training.

If the non-operative treatment is not successful, surgical treatment is instituted. It has been a general opinion that in about 25% of patients with chronic painful conditions located in the Achilles tendon, non-surgical treatment is not successful and surgical treatment is needed. For the Achilles tendon, frequency of surgery has been shown to increase with patient age, duration of symptoms, and occurrence of tendinopathic changes (Kvist, 1994).

Non-operative treatment methods

Eccentric calf-muscle training

Curwin and Stanish (1984) stressed the importance of eccentric training as a part of the rehabilitation of tendon injuries. Influenced by their theories, we designed a special type of eccentric calf-muscle-training regimen to be used on a well-defined diagnosis. We decided to study patients with chronic painful mid-portion Achilles tendinosis, though the mid-portion of the Achilles tendon is an area that can be examined clinically and visualized with ultrasound or MRI relatively easily. In our model with eccentric training, the patients were told to do the exercises despite having pain in the tendon, and when there was no pain, they were told to increase the load to reach a new level of painful training. First, we reported good clinical short-term results in a prospective pilot study on recreational athletes (Alfredson et al., 1998). All 15 patients in that study had localized changes in the tendon (at the 2–6 cm level from the insertion into the calcaneus) corresponding to the painful area (verified with US). In all patients the conventional treatment (rest, NSAIDs, change of shoes, orthoses, physical therapy, ordinary training programs) had been tried without any effect on the Achilles tendon pain, and all patients were on the waiting list for surgical treatment. The patients performed their eccentric exercises (Fig. 3(a), (b)) 3×15 repetitions, two times daily, 7 days/week, for 12 weeks. The results showed that after the 12-week training regimen, all 15 patients were satisfied and back to their previous (before injury) activity level. No patient was operated. The pain score (VAS scale) during activity (running) decreased from an average of 81.2 before the eccentric training regimen, to 4.8 after training. Follow-ups of this group of patients (non-published data) have shown that in only one patient surgical treatment has been needed because of the re-occurrence of Achilles tendon pain. All the other 14 patients are still satisfied with the result of treatment. At our clinic we have continued to use this method, and in a larger material good clinical results were reported in 90/101 tendons (Fahlström et al., 2003). From that study it was also demonstrated that in patients with chronic insertional Achilles tendon pain, good clinical results were achieved in only 10/31 tendons. Consequently, it seems that treatment with this type of eccentric training is not successful on insertional Achilles tendon pain.

To try to find out if treatment with painful concentric calf-muscle training could give a good clinical result also, a randomized prospective multi-center study was performed, where patients with painful chronic Achilles tendinosis at the 2–6 cm level in the tendon were randomized to either concentric or eccentric training (Mafi et al., 2001). The eccentric

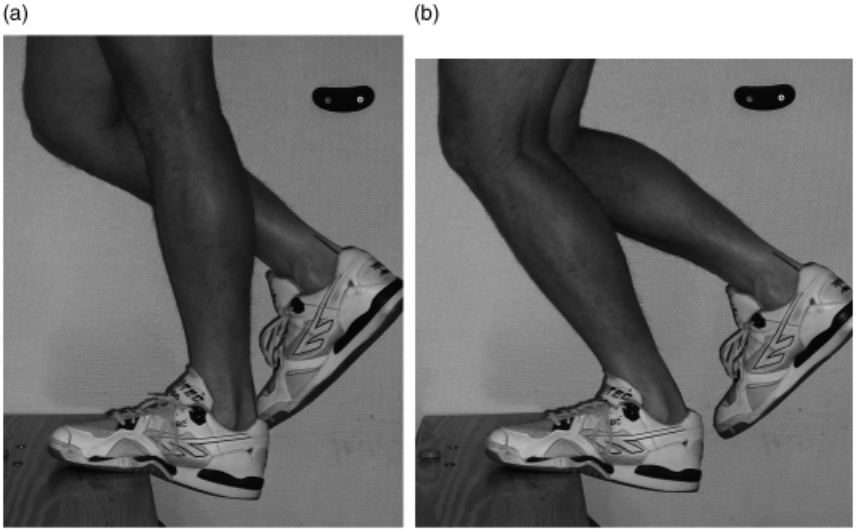

Fig. 3. (a, b) Eccentric calf-muscle training. From an upright body position and standing with all body weight on the ventral half-part of the foot, with the ankle joint in plantar flexion lifted by the non-injured leg, the calf muscle is loaded eccentrically by having the patient to lower the heel beneath the lever. Eccentric calf muscle loading with the knee straight (a) and to maximize the activation of the soleus muscle, eccentric calf-muscle loading with the knee bent (b). When the exercises can be done without experiencing pain in the tendon, the load can be increased to reach a new level of "painful training", by using a backpack that is gradually filled with weights, or by using a weight machine.

training program was the same as previously described, while the concentric training program was designed to include exercises containing mainly concentric calf-muscle action. For both types of programs, training was encouraged despite experiencing pain or discomfort in the tendon. The results showed that the eccentric training regimen (81% of patients satisfied and back to previous activity level) produced significantly better clinical results than the concentric training regimen (38% satisfied patients).

In a clinical and ultrasonographic (gray-scale ultrasound) follow-up (mean 3.8 years) of patients treated with eccentric training, the majority of the patients were satisfied and back to the previous tendon-loading activity level, and interestingly, the tendon thickness had decreased significantly and the tendon structure looked ultrasonographically more normal (Öhberg et al., 2003).

We cannot explain the background to the good clinical results achieved with painful eccentric calf-muscle training. Theoretically, there are several possible explanations. It can be effects of loading-induced hypertrophy and increased tensile strength in the tendon, or maybe an effect of stretching, with a "lengthening" of the muscle–tendon unit and consequently less strain during ankle joint motion. Also, the eccentric training regimen is painful to perform, and maybe this type of painful loading is associated with some kind of alteration of the pain perception from the tendon. As previously mentioned, we have in a study using US and CD, demonstrated that in Achilles tendons with chronic painful tendinosis, but not in normal pain-free tendons, there is a neovascularization outside and inside the ventral part of the area with tendon changes (Öhberg et al., 2001). Also, studies on tendon biopsies have shown nerve structures in close relation to the vessels (Alfredson et al., 2000, 2003). By using US and CD during eccentric calf-muscle contraction we observed that the flow in the neovessels disappeared in the position with the ankle joint in dorsi-flexion, and re-occurred when the ankle joint was in the neutral position. These observations raised the question whether the good clinical effects demonstrated with eccentric training could be because of the action on the neovessels and accompanying nerves. Theoretically, the vessels and nerves could be traumatically damaged during the eccentric training regimen (180 repetitions/day), when travelling from the soft tissue outside the tendon into the the dense tendinosis tissue. Very recent results of a prospective study, evaluating the US and CD findings, showed that in the majority of the patients that were satisfied with the result of the eccentric training regimen there were no remaining neovessels, and in all patients with a poor clinical result the neovessels remained (Öhberg & Alfredson, 2004).

Sclerosing injections

In a following experiment, to evalute the possible importance the neovessels and accompanying nerves have for the pain symptoms, we injected local anesthesia in the area with neovessels outside the tendon (Alfredson et al., 2003). This resulted in a pain-free tendon; the patients could load their Achilles tendon without experiencing any pain from the tendon. These findings raised the hypothesis that the neovessels and accompanying nerves were responsible for the pain in the area with tendinosis. To try this hypothesis, in a non-controlled pilot study, we injected small volumes of a sclerosing agent (Polidocanol) in the area with neovessels outside (ventral) the tendon (Fig. 4 (a), (b)). The short-term (6 months) results were very promising, and 8/10 patients were pain free and satisfied with treatment after a mean of two treatments, with 6–8 weeks in between (Öhberg & Alfredson, 2002). At the 6

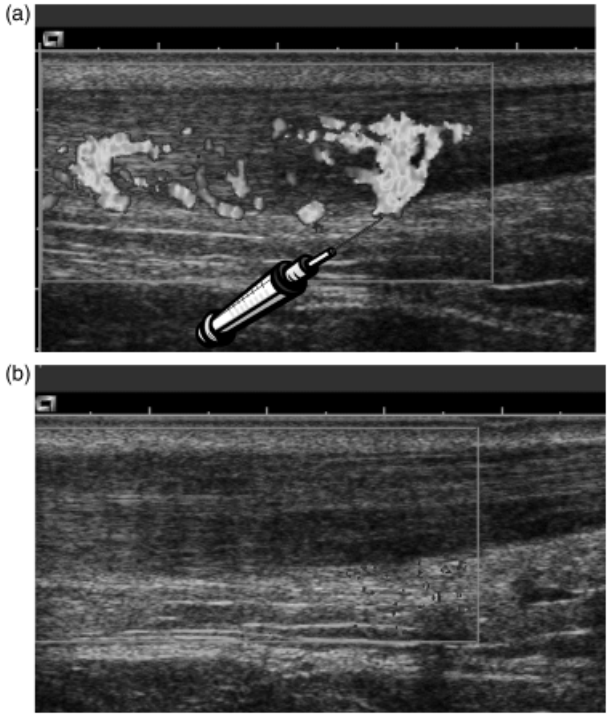

Fig. 4. (a, b) Sclerosing injection. Gray-scale ultrasonography and color doppler examination (a longitudinal view) of an Achilles tendon with tendinosis located at the 2–6 cm level in the tendon. The affected area of the tendon is thick, irregular and echo poor. There is a neovascularization outside and inside the ventral part of the area with tendon changes. (a) Before injection of the sclerosing substance. Note the position of the needle close to the neovessels outside the anterior part of the tendon. (b) After injection. Note that there are no remaining neovessels.

months follow-up, in the successfully treated patients there were no neovessels outside or inside the tendon, but in the two non-successfully treated patients there were neovessels. A 2-year follow-up (non-published data) of these patients showed that the same eight patients were still satisfied and pain free, and there were no remaining neovessels in the tendon. Interestingly, the tendon thickness had decreased, and ultrasonographically the tendon structure looked more normal. The results of this new type of treatment are promising, but longer follow-ups of clinical status and sonographic findings are needed. Very recently, in a double-blind randomized-controlled study comparing the effects of injections of a sclerosing and a non-sclerosing substance, the importance of injecting the sclerosing substance was clearly demonstrated (Alfredson & Öhberg, 2005b).

We have used US combined with CD to also investigate the chronic painful Achilles tendon insertion. In the area of the tendon insertion the tendon, bursae, and bone, alone, or together, might be responsible for the pain. Also in this condition we found a local neovascularization. The vessels were localized anterior to and inside the distal tendon. Sometimes the vessels were seen in close relation to the walls of the retrocalcaneal bursa. In a pilot study, we have evaluated the short-term effects of sclerosing injections also on this condition (Öhberg & Alfredson, 2003). The results showed that 8/11 patients were satisfied with the treatment and back to previous tendon-loading activity level. In 7/8 satisfied patients there was no remaining neovascularization. Two out of three patients with a poor result had severe bone pathology (spurs, fragments). Again, the results are promising, but large materials, on patients in different activity levels and with different sonography findings, are needed before any conclusions can be drawn. However, patients that have severe bone pathology causing mechanical problems, are, most likely, less suitable for this type of treatment.

For the chronic painful condition in the patellar tendon, patellar tendinosis-Jumper's knee, there are similar sonographic findings (structural tendon changes and a local neo-vascularization). In a recently finished pilot study (sclerosing injections targeting the neovessels outside the dorsal part of the proximal tendon), 12/15 patients had good short-term clinical results (Alfredson & Öhberg, 2005a). Also in this tendon the results are promising, but as previously stated, long-term follow-ups on large materials are needed.

The rehabilitation after sclerosing injection treatment includes a period of rest (1–3 days), then gradually increased tendon-loading activity but no maximum loading (jumping, fast runs, heavy strength training) during the first 2 weeks. After 2 weeks maximum tendon loading is allowed.

After treatment of 150 Achilles tendons and 70 patellar tendons, we have had two complications that possibly might be related to the treatment. One patient who was treated in the Achilles tendon insertion sustained a total rupture in the proximal part of the tendon at the end of an 800 m running race 8 weeks after treatment. Another patient who was treated in the mid-portion sustained a partial rupture in an area (mid-portion) where he previously had got four intra-tendinous corticosteroid injections. There have been no other complications.

Perspectives

It is well known that the chronic painful Achilles- and patellar tendons are difficult to treat and there is a lack of scientific knowledge about the pain mechanisms associated with these conditions. By using methods like microdialysis, cDNA arrays and PCR, US combined with CD and immunohistochemical analyses of biopsies there is now new and potentially important information about the chronic painful and normal Achilles- and patellar tendons.

The high levels of the neurotransmitter glutamate found in the chronic painful tendons are interesting and should be in focus for further evaluations and studies. Why and how is glutamate, that is a well known and very potent modulator of pain in the central nervous system, involved in chronic tendon pain?

The findings of a local vasculo-neural ingrowth in the chronic painful tendons have led to ideas around new treatment models, and pilot studies where sclerosing injections target the area with neovessels and nerves outside the tendon have shown promising short-term clinical results. Painful eccentric calf-muscle training has scientifically been shown to give good short-to-mid-term clinical results in patients with chronic painful mid-portion Achilles tendinosis, and a good clinical result seems to be associated with a decreased tendon thickness and a more normal tendon structure. But how does it work? There are indications that the eccentric training regimen might work by interference with the vasculo-neural ingrowth, an interference that is also performed by the sclerosing injections. If this vasculo-neural ingrowth is of major importance for the pathogenesis in the so-called degenerated tendon, maybe a destruction (by eccentric training or sclerosing injections) could start a remodelling process in the tendon. These and similar questions can hopefully be answered in future research.

Key words: chronic pain, eccentric training, microdialysis, sclerosing injections, tendons, US+CD.

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