# Chronic tendon pain: no tendinitis, but high levels of glutamate and a vasculoneural ingrowth – implications for a new treatment?

*Håkan Alfredson*[†] *&*
*Lars Öhberg*

[†]*Author for correspondence*
*Umeå University of Sports Medicine, Department of Surgical and Perioperative Science, S-901 87 Umeå, Sweden*
*Tel.: +46 907 853 951*
*Fax: +46 901 356 92*
*hakan.alfredson@idrott.umu.se*

The etiology and pathogenesis of chronic tendon pain is unknown and treatment is notoriously difficult. Despite the fact that tendon biopsies have demonstrated an absence of inflammatory-cell infiltration, anti-inflammatory agents (nonsteroidal anti-inflammatory drugs and corticosteroidal injections) are commonly used. The authors have demonstrated that it is possible to use the microdialysis technique for *in vivo* investigations of human tendons and have found significantly higher concentrations of the neurotransmitter glutamate but not prostaglandin $E_2$ in chronic painful tendinosis tendons compared with pain-free normal control tendons. The findings indicate that glutamate might be involved in chronic tendon pain and that there is no intratendinous prostaglandin $E_2$-mediated inflammation during the chronic stage of these so-called tendinopathies. Using ultrasonography and color Doppler, and immunohistochemical analyses of biopsies, the authors have recently demonstrated a vasculoneural ingrowth in the chronic painful tendinosis tendon, but not in the pain-free normal tendon. A specially designed treatment, using ultrasonography and color Doppler-guided injections of the sclerosing agent polidocanol targeting the neovessels outside the tendon has, in pilot studies, been shown to cure the tendon pain in most patients. A recent, randomized, double-blind study verified the importance of injecting the sclerosing substance polidocanol. This review focusses on the chronic painful tendon in otherwise healthy individuals, and does not include patients with inflammatory conditions, such as rheumatic diseases.

Keywords: chronic pain, glutamate, neovascularization, neuropeptides, prostaglandins, sclerosing injections, tendon, treatment

Chronic tendon pain is relatively common in the Achilles tendon [1–3], patellar tendon [4], and extensor carpi radialis brevis (ECRB)-tendon of the elbow [5]. The etiology and pathogenesis are unknown. There is a wide range of suggested etiological factors; however, the scientific background to most of these is lacking and they are characterized as nonproven theories. An association with overuse from repetitive loading is most often stated as the primary etiologic factor [6]. However, for the Achilles tendon, these conditions are also seen in individuals who are not physically active [7].

For many years, the chronic painful tendon has been treated as an inflammatory condition [8–10]. Even the terminology used – tendinitis – implies the involvement of an inflammation. Interestingly, this treatment is not based on scientific knowledge. On the contrary, histologic examinations of tendon-tissue specimens have repeatedly demonstrated the absence of inflammatory cell infiltrates [11,12]. Even so, corticosteroidal injections and many anti-inflammatory tablets have been used in the treatment of this disorder over time [13,14]. However, during recent years, researchers have started to question this treatment and to study the background to pain in the chronic painful tendon [15–17].

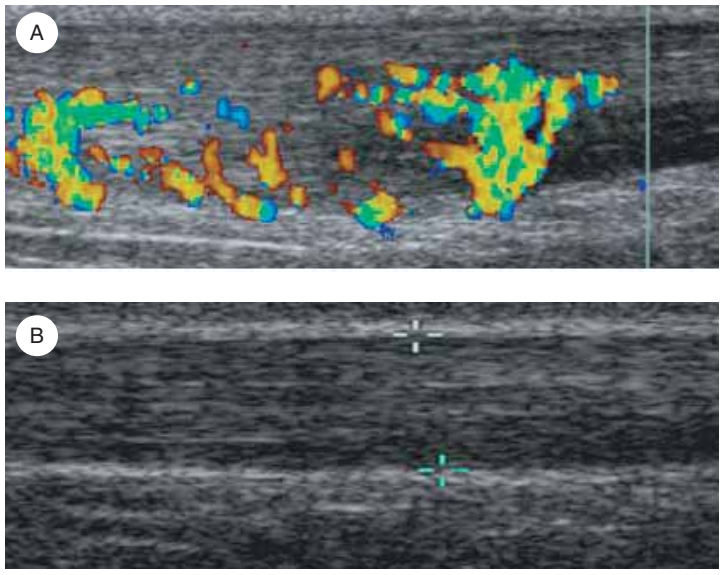
Based on the absence of inflammatory cell infiltrates in biopsies, the terminology has recently been changed to tendinopathy (pain associated with an impaired function of the affected tendon) and tendinosis (where ultrasound, magnetic resonance imaging [MRI] or biopsies show specific changes in the affected tendon) [11,18].

## Recent research on basic biology

### *Microdialysis*

Microdialysis is a method used to study concentrations of certain substances in particular tissues over a period of time [19,20]. Intratendinous microdialysis was first carried out in 1999 and demonstrated normal prostaglandin (PG)$E_2$ levels in chronic painful Achilles tendinosis [17]. Normal $PGE_2$ levels were also found when microdialysis was performed in chronic painful patellar tendinosis (jumper's knee) [21], and ECRB tendinosis (tennis elbow) [22]. For the first time, the neurotransmitter glutamate, which is well known as an important and potent modulator of pain in the CNS [23], was found in its free form outside the CNS in humans, and the concentrations were found to be significantly higher in the painful tendinosis tendons than in pain-free control tendons [17,21,22]. A parallel study of biopsies from

**Figure 1. Gray-scale ultrasonography and color Doppler examination (a longitudinal view) of an Achilles tendon with tendinosis in the midportion of the tendon and a normal Achilles tendon.**




**(A)** Tendinosis: the tendon is thick, irregular and echo poor. There are small vessels (neovascularization demonstrated as colored structures) inside and outside the ventral part of the tendon. **(B)** Normal tendon: normal thickness (4.5–6 mm) and normal structure. No vessels are found in the tendon.

Achilles tendinosis tissue-localized glutamate *N*-methyl-D-aspartate receptor (NMDAR)-1 to nerve structures [24]. Theoretically, the high glutamate levels found in the chronic painful tendons could be of importance for the pain suffered from the tendon. In a prospective study using microdialysis in chronic painful Achilles tendinosis in an attempt to evaluate this possible relationship, it was found that there were no differences in the intratendinous glutamate concentrations after succesful treatment with eccentric training [25]. The importance of the glutamate findings in chronic painful tendons is still under scientific evaluation.

### *Gene technological analyses*

Using cDNA-arrays and polymerase chain reaction (PCR) techniques, it was demonstrated that there was no upregulation of multiple so-called proinflammatory cytokines in chronic painful Achilles tendinosis tissue compared with normal, painfree Achilles tendon tissue [26].

### *Gray-scale ultrasonography & color Doppler*

Ultrasonography is an established and reliable method to examine tendon thickness and structure [27,28]. Color Doppler (CD) is used to study flows and direction of flows (i.e., blood flow) [29,30]. The technique is not sufficiently sensitive to register normal circulation in a normal tendon, due to the relatively low level of blood flow in the tendon, but vessels with high flows, such as neovessels, can be registered. Using ultrasonography and CD together, a neovascularization was found inside and outside the area with structural tendon changes in chronic painful Achilles tendinosis tendons, but not in pain-free normal Achilles tendons, suggesting a relationship between neovascularization and pain (Figure 1A&B) [31]. To further analyze the possible relationship between neovascularization and pain, small amounts of a local anesthetic were injected under ultrasonography and CD guidance towards the neovessels outside the tendon [32]. This resulted in temporarily pain-free tendons and indicated that the area with neovessels was of importance for the tendon pain.

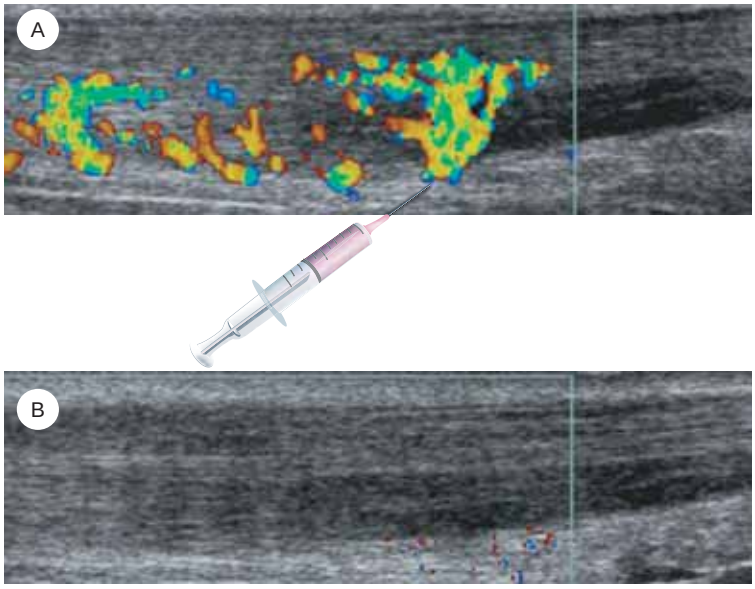
### *Immunohistochemical analyses of tendon tissue specimens*

Biopsies taken from the area with tendinosis and neovascularization showed nerve structures in close relation to the vessels [33], and subsequent studies have shown substance P (SP) nerves in the vascular wall, and calcitonin gene-related peptide (CGRP) nerves close to the vascular wall [33–35]. Also, the neurokinin-1 receptor (NK-1R), which is known to have a high affinity for SP, has been found in the vascular wall [36]. The neuropeptide findings indicate that there may still be an inflammation in the tendon not, however, a chemical inflammation ($PGE_2$-mediated) but, instead, a neurogenic inflammation. Peripheral local noxious stimulation makes peptidergic (SP- and CGRP-containing) Group IV fibers release peptides from their terminals, starting various pathophysiologic processes contributing to neurogenic inflammation.

### *Clinical research*

In previous research projects, the authors have shown good clinical results in approximately 80% of patients, using a specially designed eccentric calf muscle-training regimen on patients with chronic painful midportion Achilles tendinosis [37–39]. Also, ultrasonography follow-ups demonstrated that, in successfully treated cases, the tendon thickness was significantly decreased and the structure was ultrasonographically 'more normal' [40]. The authors have not been able to explain the background behind the good results achieved using

**Figure 2. Gray-scale ultrasonography and colour Doppler examination (a longitudinal view) of an Achilles tendon with tendinosis in the midportion of the tendon. The affected area of the tendon is thick, irregular and echo poor.**

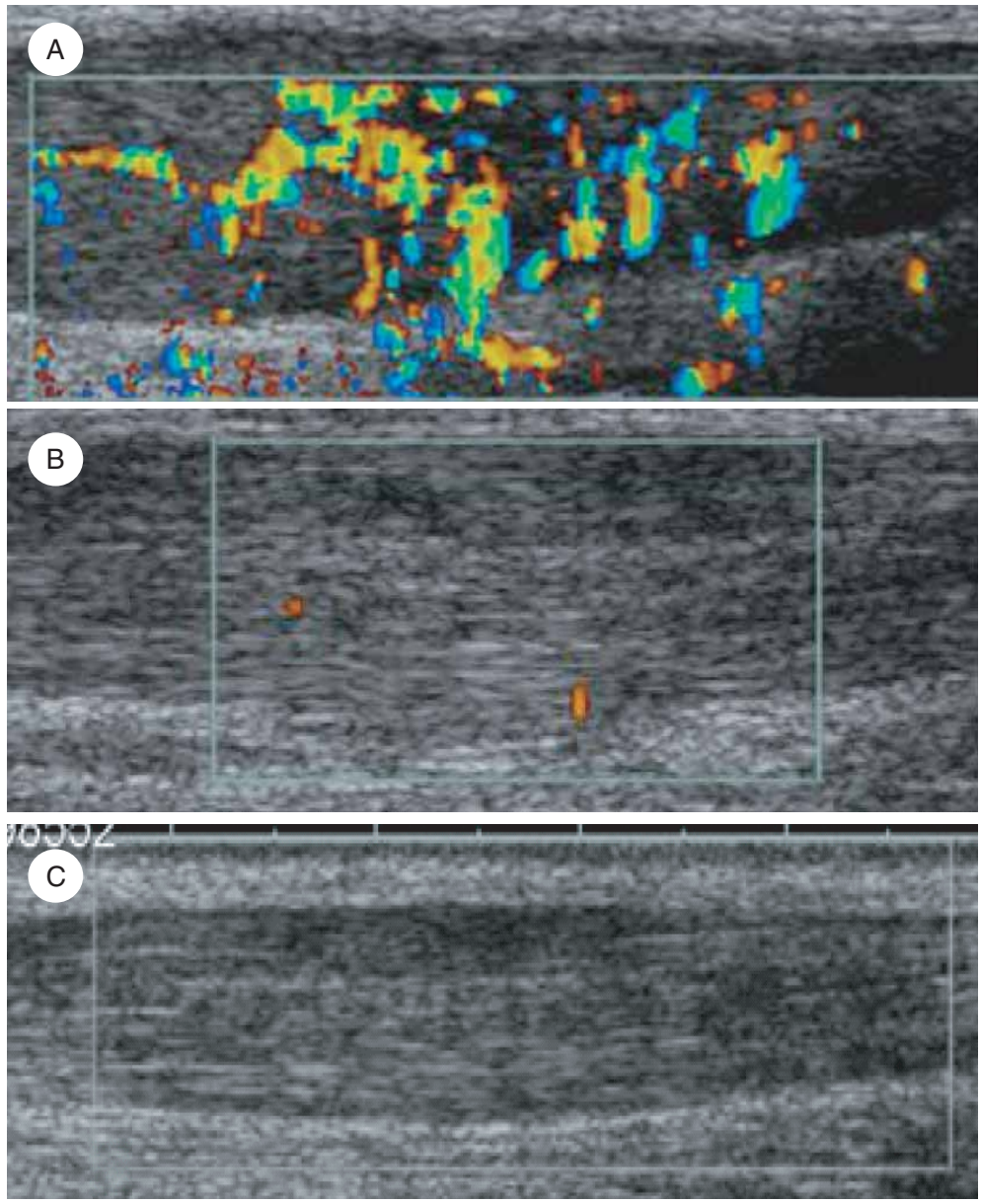



**(A)** Before sclerosing injections. There is a neovascularization outside and inside the area with tendon changes. During injection, the needle is placed close to or inside the vessels outside the ventral part of tendon. **(B)** Immediately after sclerosing injections. There is no remaining neovascularization.

this treatment, but the follow-ups using both ultrasonography and CD showed that there was no remaining neovascularization in the cases with a good clinical result and remaining neovessels in the cases with a poor clinical result. This indicates a possible effect on the area with neovascularization [41]. By performing dynamic ultrasonography + CD examinations, it was possible to demonstrate that the flow in the neovessels stopped during dorsiflexion of the ankle joint and came back in the neutral ankle joint position [41]. During the eccentric training regimen, the ankle joint is in the loaded dorsiflexion 180 repetitions/day and, possibly, in this position, the vessels and nerves could be injured or destroyed? This is the only mechanism that the authors have been able to objectively visualize, which could possibly explain how the eccentric training regimen works.

The findings that ultrasonography- and CD-guided injections of small amounts of a local anesthetic targeting the neovessels outside the tendon temporarily cured tendon pain raised the hypothesis that destroying the area with neovessels and nerves outside the tendon would affect tendon pain. In a pilot study, ultrasonography- and CD-guided injections of the sclerosing substance polidocanol targeting the area with neovessels outside the tendon, was given to patients with chronic painful Achilles tendinosis (Figure 2A–B)[41]. Polidocanol (an aliphatic nonionized nitrogen-free substance with a sclerosing and anesthetic effect) has been in use for many years, primarily with the purpose of treating varicose veins and teleangiectasies [42,43], and has been demonstrated to have very few side effects. In the pilot study, most patients were pain free after a mean of two treatments, with 6 to 8 weeks in between [41]. Follow-up at 2 years has shown a reduced tendon thickness, no remaining neovessels, and an ultrasonographically 'normalized' structure in the successfully treated patients (Figure 3)[Unpublished observations]. In pilot studies using the same type of treatment on patients with similar findings in the Achilles tendon insertion [44] and in the patellar tendon [45], the good short-term results have been reproduced. Recently, in a randomized double-blind study, the effects of injecting polidocanol were compared with the effects of injecting lidocaine + adrenaline. The results clearly demonstrated good clinical effects using polidocanol, but not using lidocaine plus adrenaline [46]. The patients treated at the authors' clinic are on different tendon-loading activity levels, ranging from relatively nonactive individuals to olympic-level athletes. Based on the short-term results, the method appears to be safe. The authors have treated 400 tendons and only experienced two complications (one partial and one total Achilles tendon rupture). In one patient who had previously been treated with four intratendinous cortisone injections, and who refused to follow the instructions after injection, there was a partial rupture during limbo dancing. In another patient, who had been treated in the tendon insertion, there was a total rupture in the proxiamal part of the tendon at the end of an 800 m running race 6 weeks after treatment. All patients having had this treatment are routinely followed-up, clinically, and by ultrasonography and CD, in order to identify side effects, and to present the results of mid- and long-term follow-up in the future. Altogether, based on the short-term results of these studies, it seems that there is a potential to cure the pain, and also possibly to decrease the thickness and normalize the structure of the tendon, by 'destroying' the area with neovessels and nerves outside the tendon with polidocanol injections.

**Figure 3. Follow-up after treatment with sclerosing injections.**




**(A)** Before treatment. **(B)** 6 months after treatment. **(C)** 24 months after treatment. The tendon is thinner, and the structure looks more 'normal'.

## Expert opinion

There is no scientific evidence for ongoing prostaglandin-mediated inflammation inside the chronic painful Achilles-, patellar-, and ECRB-tendon. However, there could be a neurogenic inflammation, mediated via neuropeptides such as SP and CGRP. High concentrations of the neurotransmitter glutamate have been demonstrated in these chronic painful tendons, but the importance of these findings have not yet been clarified.

The neovascularization (vessels and nerves) that can be visualized in the chronic painful tendons using ultrasonography and CD, is probably the source of pain, and treatment focusing on destroying this area by ultrasonography- and CD-guided injections of the sclerosing substance polidocanol, targeting the neovessels, has been demonstrated to have the potential to cure the pain and allow for most patients to go back to full tendon-loading activity in short-term studies. In conclusion, the

findings might also be of significance in the understanding and treatment of other chronic painful tendons.

**Highlights**

- Intratendinous inflammation is not prostaglandin mediated.
- However, there may be neurogenic (neuropeptides such as substance P [SP] and calcitonin gene-related peptide [CGRP]) mediated inflammation in the chronic painful Achilles, patellar and extensor carpi radialis brevis tendons.
- Vasculoneural growth occurs in the chronic painful tendon.
- Treatment with sclerosing injections targeting the area with neovessels and nerves outside the tendon has the potential to cure tendon pain and to allow for heavy tendon-loading activity.

## Outlook

This new knowledge of where pain associated with chronic painful tendon originates will probably have implications on both nonsurgical and surgical treatment options for these conditions. Despite early full tendon-loading activity, there seems to be a very low risk for tendon rupture after treatment with sclerosing injections, indicating that the tendinosis tendon might be a strong tendon. Within the next 5 to 10 years, follow-ups using clinical examination, ultrasound and CD will show the fate of these tendons. It is possible that the tendinosis tendon, previously thought to be weak and degenerative, could in fact be a strong tendon with the capacity to regenerate.

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## Affiliations


*Håkan Alfredson, MD, PhD*
*University of Umeå, Umeå University*
*Sports Medicine, Department of Surgical and Perioperative Science,*
*S-901 87 Umeå, Sweden*
*Tel.: +46 907 853 951*
*Fax: +46 901 356 92*
*hakan.alfredson@idrott.umu.se*

*Lars Öhberg, MD, PhD*
*University of Umeå,*
*Department of Radiation Sciences,*
*Diagnostic Radiology, 901 87 Umeå, Sweden*