

# Sclerosing Polidocanol Injections of Small Vessels to Treat the Chronic Painful Tendon

H. Alfredson\* and R. Lorentzon

*Sports Medicine Unit, University of Umeå, 901 87 Umeå, Sweden*

**Abstract:** The chronic painful tendon (tendinopathy, tendinosis) is generally considered difficult to treat, not seldom causing long-term disability and sometimes ending the sports or work career. Most common sites for tendinopathy are the Achilles-, patellar-, extensor carpi radialis brevis (ECRB)-, and supraspinatus tendons. The origin of pain has for many years been unknown, but recently, by using ultrasound (US) + colour Doppler (CD), immunohistochemical analyses of tendon biopsies, and diagnostic injections of local anaesthesia, we found a close relationship between areas with vasculo-neural ingrowth and tendon pain. Sensory nerves (Substance-P-SP and Calcitonin Gene Related Peptide-CGRP) were found inside and outside the vascular wall. In following clinical studies we have demonstrated good short- and mid-term clinical results using treatment with US+CD-guided sclerosing polidocanol injections, targeting the area with neovessels outside the tendon. Two-year follow ups have showed remaining good clinical results, and sonographically signs of remodelling with a significantly thinner tendon with a more normal structure. Whether the effects of polidocanol are mediated through destruction of neovessels, activity on nerves or a combination, is under evaluation.

**Key Words:** Chronic tendon pain, neovessels, nerves, ultrasonography, Doppler, polidocanol.

## GENERAL BACKGROUND

Chronic tendon pain was for many years considered to be an inflammatory condition, secondary to overuse of the tendon [1-5]. However, research using histological examinations of tendon tissue specimens [6, 7], microdialysis [8-10], and gene technology [11], has clearly demonstrated that there is no prostaglandin-mediated intra-tendinous inflammation in the chronic stage of this condition. Instead, during the recent years, researchers have started to study other possible mechanisms for pain in the chronic painful tendon [12-14].

## BASIC BIOLOGY

Intra-tendinous **microdialysis** was first done in 1999, and showed normal prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) levels in chronic painful Achilles tendinosis [8]. The same findings were also later found in chronic painful patellar tendinosis (Jumper's knee) [9], and extensor carpi radialis brevis (ECRB) tendinosis [10]. Also, for the first time, the neurotransmitter glutamate, well known to be an important and potent modulator of pain in the central nervous system [15], was found [8]. The glutamate concentrations were found to be significantly higher in the painful tendinosis tendons, compared to pain-free normal control tendons. In a parallel study glutamate NMDAR-1 receptors were found in close relation to nerve structures in tendon tissue specimens from Achilles tendinosis tissue [16]. The possible importance glutamate had for tendon pain, was evaluated in a prospective study again using microdialysis technique. In chronic painful Achilles tendinosis tendons, it was found that there were no differences in the intra-tendinous glutamate concentrations before

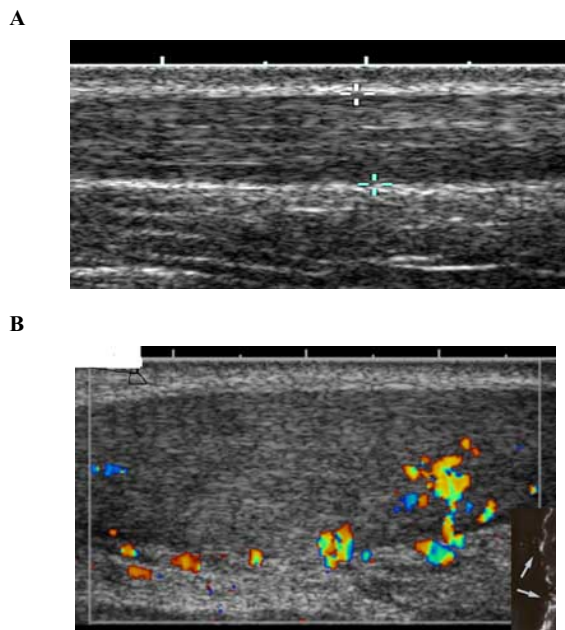
compared to after successful treatment with eccentric training [17]. The importance of the glutamate findings in the chronic painful tendons is under evaluation. Also, significantly higher lactate levels were found in chronic painful Achilles tendinosis tendons, compared to pain-free normal tendons, implying possibly hypoxic conditions, or maybe a high metabolic rate, in tendinosis [18].

**Gene technology** using cDNA-arrays and PCR techniques, it was demonstrated that there was no up-regulation of multiple so-called pro-inflammatory cytokines in chronic painful Achilles tendinosis tissue compared with normal pain-free Achilles tendon tissue [11].

**Ultrasound (US)** is an established and reliable method to examine tendons [19, 20]. The thickness and structure of the tendon can be accurately evaluated. **Colour Doppler (CD)** is a method to study flows, and direction of flows, like blood flow [21, 22]. The normal blood flow in tendons has a low flow rate and cannot be visualised with this technique, but vessels with high flows, like neovessels, can be detected. Using US and CD together, a neovascularisation 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 neovascularisation and pain (Fig. (1)) [23]. To further analyse the possible relationship between neovascularisation and pain, small amounts of a local anaesthetic was under US and CD-guidance injected towards the neovessels outside the tendon [14]. 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 from the area with tendinosis and neovascularisation showed nerve structures in close relation to the vessels [14]-the nerves were "travelling with the vessels", and following

\*Address correspondence to this author at Sports Medicine Unit, University of Umeå, 901 87 Umeå, Sweden; Tel: +46 90 7854816; Fax +46 90 135692; Email: hakan.alfredson@idrott.umu.se



**Fig. (1).** Ultrasonography+Colour Doppler examinations-longitudinal views.

**A.** Grey-scale ultrasonography: Normal Achilles tendon—normal thickness (4.5-6mm) and normal structure.

Colour Doppler: No vascular flow can be registered in the tendon.

**B.** Grey-scale ultrasonography: Chronic painful Achilles tendinosis - the tendon is thick, irregular and echo poor.

Colour Doppler: Vascular flow (neovascularisation) is registered inside and outside the ventral part of the tendon (white structures).

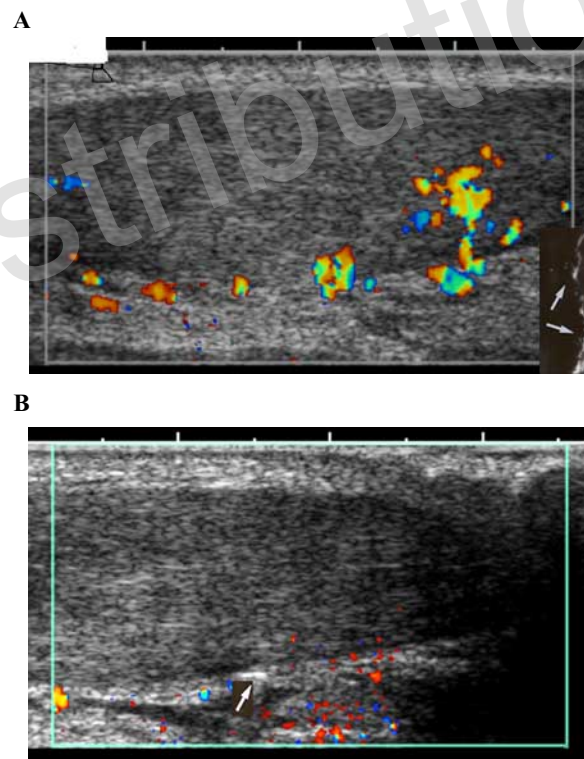
Inserted is a section of a specimen from an area with neovascularisation. The section was processed for the general nerve marker PGP 9.5. There are PGP 9.5-immunoreactive nerve strands in close relation to a blood vessel (arrows in lumen).

studies have shown Substance-P (SP) nerves in the vascular wall, and Calcitonin Gene Related Peptide (CGRP) close to the vascular wall [24, 25]. Also, the Neurokinin-1-receptor (NK-1R), that is known to have a high affinity for SP, has been found in the vascular wall [26]. The findings of neuropeptides indicate that there still might be an inflammation in the tendon, however, not a prostaglandin-mediated inflammation, but instead a so-called neurogenic inflammation mediated *via* neuropeptides like SP. Very recently, in the chronic painful tendon there seems to be an up-regulation of the cholinergic system, and an occurrence of autocrine/paracrine effects [27]. The sympathetic system is under evaluation.

### CLINICAL RESEARCH

The findings of neovessels and sensory nerves “travelling together” from the soft tissue outside the tendon, into the area with structural changes in the tendon, raised the hypothesis that the area with vasculo-neural ingrowth was responsible for the pain in the tendon. In a following investigation, US and CD-guided injections of small amounts of a local anaesthetic targeting the neovessels outside the tendon, temporarily cured the tendon pain [14]. This finding further

indicated that the area with vasculo-neural ingrowth was closely related to the tendon pain, and focus was placed on finding a method to destroy the vasculo-neural ingrowth. The substance polidocanol that had been in use for many years primarily with the purpose to treat varicose veins and teleangiectasies [28], and had been demonstrated to have very few side-effects [29], was selected. Polidocanol has a sclerosing effect (primarily acting on the intima layer in the vascular wall), and a local anaesthetic effect. The active substance is an aliphatic non-ionised nitrogen-free surface anaesthetic. In a pilot study, US and CD-guided injections of the substance polidocanol, targeting the area with neovessels outside the tendon, was given to patients with chronic painful midportion Achilles tendinosis (Fig. (2)) [30]. In the pilot study, the majority of the patients were pain-free after a mean of 2 treatments (with 6-8 weeks in between), and there was no remaining neovascularisation [30]. The material was extended, and two-year follow-ups of 42 patients showed a reduced tendon thickness, and an ultrasonographically “normalised” structure in the successfully treated patients [31]. These findings indicate a possible remodelling potential in



**Fig. (2).** Grey-scale ultrasonography and colour doppler examination (a longitudinal view) of an Achilles tendon with tendinosis in the mid-portion of the tendon. The affected area of the tendon is thick, irregular and echo poor.

**A.** Before sclerosing injections. There is a neovascularisation 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 neovascularisation. The tip of the injection needle is marked with an arrow.

the tendon. In additional pilot studies using the same type of treatment on patients with similar findings in the Achilles tendon insertion [32], the patellar tendon [33], and the ECRB-tendon [34] the good short term results have been reproduced. Recently, in two randomized double-blind studies (Achilles- and patellar tendon), the effects of injecting Polidocanol was compared with the effects of injecting lidocaine+Adrenaline. The results clearly demonstrated good clinical effects using Polidocanol, but poor effects using lidocaine+Adrenaline [35, 36].

#### **Rationale for Polidocanol Injection Treatment (Umeå Model)**

We started to use Polidocanol in the concentration of 5mg/ml, but since two years we use the concentration 10 mg/ml. The ultrasound- and Doppler-guided injections are given in small fractions, were 0.1-0.2 ml are injected at each site (area with neovessels and nerves outside the tendon). Altogether, a maximum of 2 ml are injected at each treatment. After injection treatment the patients are not allowed to do strenuous tendon activity for 2 weeks. They are allowed short walks and light bicycling. After 2 weeks the patients are allowed to return to their previous (before injury) tendon loading activity. Six to eight weeks after treatment the patient is followed up. If there is still pain, and the Doppler shows neovessels in the area with structural tendon changes and pain, another Polidocanol injection treatment is given. Up to 5 treatments, with the same intervals between the treatments, are given.

All types of complications possibly related to the treatment, are carefully noticed. The polidocanol injection treatment appears to be safe, we have only had three complications, one partial and two total Achilles tendon ruptures. There have been no skin problems or infections. Tendon tissue specimens have been obtained from patients that have been surgically treated because of a poor result with sclerosing polidocanol injections, and analyses have shown that there were no areas with necrosis in the tendon and no large areas with fat tissue atrophy outside the tendon. All patients having had this treatment are routinely followed-up, clinically, and by US and CD, to be able to identify side-effects, and to present the results of mid- and long-term follow-ups.

Altogether, based on the short-term results of these studies, it seems that there is a potential to cure the tendon pain, to decrease the tendon thickness, and to "normalise" the tendon structure, by interfering with the area with neovessels and nerves outside the tendon with Polidocanol injections.

#### **POLIDOCANOL EFFECTS ON CHRONIC TENDON PAIN**

The background to the good effects (decreased tendon pain and tendon thickness, "normalised" tendon structure) achieved with polidocanol injections have not been fully clarified. It might be effects on the neovessels, or the nerves, or a combination.

- The immediate effects of the polidocanol injections have been studied using US+CD. Immediately after injection the flow in the neovessels cannot be visualised, but the

first day after the injection treatment there is instead an increased intra-tendinous vascular flow [37]. This can possibly be explained as a secondary intra-tendinous vasodilatation, induced by the injection of polidocanol outside the tendon? Maybe, this is a part of the healing response. This increased intra-tendinous vascular flow seems to remain for weeks, but it appears to be varying in different individuals. In patients that are successfully treated (no remaining tendon pain) there are usually no remaining neovessels at follow-up 8 weeks after treatment.

- Sclerosing the neovessels might possibly destroy the vascular supply to the sensory nerves and cause nerve death?
- There might possibly be direct nerve effects caused by the polidocanol injections?
- The effect might be a result of a later induced increased blood flow containing growth factors and other remodeling substances.

#### **CLINICAL EXPERIENCES**

Since this method was invented in 2001, there are now longer clinical and US+CD follow-ups, showing stable good clinical results and a more normal tendon thickness and structure after treatment with sclerosing polidocanol injections [31]. The results show that for the Achilles midportion around 90% of the patients are satisfied, whereas around 65-70% with chronic pain in the Achilles insertion and patellar tendon are satisfied with the result of the treatment. The method seems safe, we have treated more than 700 tendons at our clinic, mainly Achilles- and patellar tendons, but also ECRB-tendons, and there are very few complications. The group of patients is a mixture, ranging from relatively non-active individuals to Olympic level athletes, and it appears that it is possible to achieve a good clinical result in patients on different activity levels.

#### **PERSPECTIVES**

- We have very recently investigated the sensory nervous system and the cholinergic system in the human tendon, and there is on-going research investigating the sympathetic system. These systems might modulate blood flow to the tendon. From a vascular point of view, the findings of an up-regulation of the cholinergic system in the chronic painful tendon is interesting. Is this a primary or secondary phenomenon? When there is information also about the sympathetic system, new approaches for treatment might be considered. Studies evaluating the effects of using pharmacological agents are being considered.
- There are on-going projects evaluating other chronic painful tendons, such as; the supraspinatus tendon in the shoulder. Preliminary results, using US+CD, show neovessels also in this tendon, and in a pilot study, the clinical results of US+CD-guided injections of polidocanol, targeting the neovessels, are promising.

We intend to introduce the method internationally, and we have introduced the method to groups in several countries such as; Norway, Finland, Denmark, Australia, Netherlands, England and Spain.

## REFERENCES

- [1] Schepesis, A.A.; Leach, R.E. *Am. J. Sports Med.*, **1987**, *15*, 308.
- [2] Nelen, G.; Martens, M.; Burssens, A. *Am. J. Sports Med.*, **1989**, *17*(6), 754.
- [3] Leadbetter, W.B.; Moar, P.A.; Lane, G.J. *Clin. Sports Med.*, **1992**, *11*(4), 679.
- [4] Kvist, M. *Sports Med.*, **1994**, *18*(3), 173.
- [5] Myerson, M.S.; McGarvey, W. *J. Bone Joint Surg.*, **1998**, *80-A*(12), 1814.
- [6] Movin, T.; Gad, A.; Reinholt, F.P. *Acta Orthop. Scand.*, **1997**, *68*(2), 170.
- [7] Khan, K.M.; Cook, J.L.; Bonar, F.; Harcourt, P.; Åström, M. *Sports Med.*, **1999**, *27*(6), 393.
- [8] Alfredson, H.; Thorsen, K.; Lorentzon, R. *Knee Surg. Sports Traumatol. Arthrosc.*, **1999**, *7*, 378.
- [9] Alfredson, H.; Ljung, B.O.; Thorsen, K.; Lorentzon, R. *Acta Orthop. Scand.*, **2000**, *71*(5), 475.
- [10] Alfredson, H.; Forsgren, S.; Thorsen, K.; Lorentzon, R. *J. Orthop. Res.*, **2001**, *19*, 881.
- [11] Alfredson, H.; Lorentzon, M.; Bäckman, S.; Bäckman, A.; Lerner, U. *J. Orthop. Res.*, **2003**, *21*, 970.
- [12] Schrier, I.; Matheson, G.O.; Kohl, III H.W. *Clin. J. Sport Med.*, **1996**, *6*(4), 245.
- [13] Khan, K.M.; Cook, J.L.; Maffuli, N.; Kannus, P. *Br. J. Sports Med.*, **2000**, *34*(2), 81.
- [14] Alfredson, H.; Öhberg, L.; Forsgren, S. *Knee Surg. Sports Traumatol. Arthrosc.*, **2003**, *11*, 334.
- [15] Dickenson, A.H.; Chapman, V.; Green, G.M. *Gen. Pharmac.*, **1997**, *28*(5), 633.
- [16] Alfredson, H.; Forsgren, S.; Thorsen, K.; Fahlström, M.; Johansson, H.; Lorentzon, R. *Knee Surg. Sports Traumatol. Arthrosc.*, **2000**, *9*, 123.
- [17] Alfredson, H.; Lorentzon, R. *Knee Surg. Sports Traumatol. Arthrosc.*, **2003**, *11*, 196.
- [18] Alfredson, H.; Bjur, D.; Thorsen, K.; Lorentzon, R. *J. Orthop. Res.*, **2002**, *20*, 934.
- [19] Åström, M.; Gentz, C.F.; Nilsson, P.; Rausing, A.; Sjöberg, S.; Westlin, N. *Skeletal Radiol.*, **1996**, *25*, 615.
- [20] Paavola, M.; Paakkala, T.; Kannus, P.; Jarvinen, M. *Acta Radiol.*, **1998**, *39*, 612.
- [21] Terslev, L.; Qvistgaard, E.; Torp-Pedersen, S.; Laetgaard, J.; Daneskiold-Samsøe, B.; Bliddal, H. *Eur. J. Ultrasound*, **2001**, *13*, 183.
- [22] Weinberg, E.P.; Adams, M.J.; Hollenberg, G.M. *AJR*, **1998**, *171*(3), 743.
- [23] Öhberg, L.; Lorentzon, R.; Alfredson, H. *Knee Surg. Sports Traumatol. Arthrosc.*, **2001**, *9*, 233.
- [24] Bjur, D.; Alfredson, H.; Forsgren, S. *Cell Tiss. Res.*, **2005**, *320*, 201.
- [25] Ljung, B.O.; Forsgren, S.; Fridén, J. *J. Orthop. Res.*, **1999**, *17*(4), 554.
- [26] Forsgren, S.; Danielsson, P.; Alfredson, H. *Regul. Pept.*, **2005**, *126*, 173.
- [27] Danielsson, P.; Alfredson, H.; Forsgren, S. *Microsc. Res. Tech.*, **2006**, *69*, 808.
- [28] Guex, J.J. *J. Dermatol. Surg. Oncol.*, **1993**, *19*(10), 959.
- [29] Conrad, P.; Malouf, G.M.; Stacey, M.C. *Dermatol. Surg.*, **1995**, *21*(4), 334.
- [30] Öhberg, L.; Alfredson, H. *Br. J. Sports Med.*, **2002**, *36*, 173.
- [31] Lind, B.; Öhberg, L.; Alfredson, H. *Knee Surg. Sports Traumatol. Arthrosc.*, **2006**, *14*, 1327.
- [32] Öhberg, L.; Alfredson, H. *Knee Surg. Sports Traumatol. Arthrosc.*, **2003**, *11*, 339.
- [33] Alfredson, H.; Öhberg, L. *Knee Surg. Sports Traumatol. Arthrosc.*, **2005**, *13*, 74.
- [34] Zeisig, E.; Öhberg, L.; Alfredson, H. *Knee Surg. Sports Traumatol. Arthrosc.*, **2006**, *14*, 1218.
- [35] Alfredson, H.; Öhberg, L. *Knee Surg. Sports Traumatol. Arthrosc.*, **2005**, *13*, 338.
- [36] Hoksrud, A.; Öhberg, L.; Alfredson, H.; Bahr, R. *Am. J. Sports Med.*, **2006**, *34*(11), 1738.
- [37] Alfredson, H.; Öhberg, L. *Knee Surg. Sports Traumatol. Arthrosc.*, **2006**, *14*, 399.