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ORIGINAL ARTICLE

Strategies in treatment of tendon overuse injury. The chronic painful tendon

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Abstract

The etiology and pathogenesis to chronic tendon pain is unknown, and treatment is known to be difficult. Treatment is often based on opinions and not findings in scientific studies.

Recent research, using the intra-tendinous microdialysis technique, has shown that in chronic painful Achilles-, patellar-, and extensor carpi radialis brevis (ECRB) tendons, there were no signs (normal Prostaglandin-2 levels) of a so-called chemical inflammation. Furthermore, in biopsies from chronic painful Achilles tendons, pro-inflammatory cytokines were not up-regulated, again showing the absence of an intra-tendinous inflammation. Consequently, if the purpose is to treat a chemical inflammation, there is no science backing up for treatment of these conditions with anti-inflammatory agents (NSAIDs, corticosteroidal injections). Interestingly, Substance-P (SP) and Calcitonin Gene Regulated Peptide (CGRP) nerves have been demonstrated in close relation to vessels in biopsies from these chronic painful tendons, indicating the existence of a possible so-called neurogenic inflammation.

Using ultrasonography (US) + color Doppler (CD), and immunohistochemical analyses of biopsies, a vasculo/neural(SP- and CGRP-nerves) ingrowth in the chronic painful tendinosis tendon, but not in the pain-free normal tendon, has recently been found. A specially designed treatment, using US- and CD-guided injections of the sclerosing agent Polidocanol, targeting the neovessels outside the tendon, has in pilot studies on chronic painful Achilles-, and patellar tendons been shown to cure the tendon pain in the majority of patients. A recent randomized double-blind study, verified the importance of injecting the sclerosing substance Polidocanol.

Background

Chronic tendon pain is relatively common in the Achilles tendon (Kvist, 1994; Åström, 1997; Movin, 1998), patellar tendon (Khan et al., 1996), and ECRB-tendon of the elbow (Kraushaar & Nirschl, 1999). The etiology and pathogenesis are unknown. There is a wide range of suggested etiological factors, but the scientific background to most of these suggestions is lacking, and they are to be characterized as non-proven theories. An association with overuse from repetitive loading is most often stated as being the etiologic factor (Józsa & Kannus, 1997). However, for the Achilles tendon, these conditions are also seen in not physically active individuals (Åström, 1998).

For many years, the chronic painful tendon has been treated as an inflammatory condition (Nelen, Martens, & Burssens, 1989; Leadbetter, Mooar, & Lane, 1992; Myerson & McGarvey, 1998). Even the terminology used, tendinitis, implies involvement of an inflammation. Interestingly, this treatment has

not been based on scientific knowledge, on the contrary, histological examinations of tendon tissue specimens have repeatedly shown the absence of inflammatory cell-infiltrates (Movin, Gad, & Reinholt, 1997; Khan, Cook, Bonar, Harcourt, & Åström, 1999). Still, corticosteroidal injections, and tons of anti-inflammatory tablets, have been used in the treatment (Weiler, 1992; Leadbetter, 1995). However, during recent years, researchers have started to question this treatment, and studied the background to pain in the chronic painful tendon (Schrier, Matheson, & Kohl, 1996; Khan, Cook, Maffulli, & Kannus, 2000; Alfredson, Thorsen, & Lorentzon, 1999).

Based on the absence of inflammatory cell-infiltrates in biopsies, the terminology has recently been changed to tendinopathy (pain and impaired function of the affected tendon) and tendinosis (where ultrasound, MRI, or biopsies, show specific changes in the affected tendon) (Movin et al., 1997; Maffulli, Khan, & Puddu, 1998).

Recent research on basic biology

Microdialysis

Microdialysis is a method to study concentrations of certain substances, in certain tissues, over a period of time (Darimont, Vassaux, Gaillard, Ailhaud, & Négrel, 1994; Thorsen, Kristoffersson, Lerner, & Lorentzon, 1996). Intra-tendinous microdialysis was first done in 1999, and showed normal prostaglandin E₂ (PGE₂) levels in chronic painful Achilles tendinosis (Alfredson et al., 1999). Normal PGE₂ levels, were also found when microdialysis was performed in chronic painful patellar tendinosis (Jumper's knee) [Alfredson, Forsgren, Thorsen, & Lorentzon, 2001], and extensor carpi radialis brevis (ECRB) tendinosis (Tennis elbow) [Alfredson, Ljung, Thorsen, & Lorentzon, 2000a]. For the first time, the neurotransmitter glutamate that is well known to be an important and potent modulator of pain in the central nervous system (Dickenson, Chapman, & Green, 1997), was found in its free form outside the central nervous system in humans, and the concentrations were found to be significantly higher in the painful tendinosis tendons, compared to pain-free normal control tendons (Alfredson et al., 1999; Alfredson et al., 2001; Alfredson et al., 2000a). A parallel study on biopsies from Achilles tendinosis tissue, localized glutamate NMDAR-1 receptors to nerve structures (Alfredson et al., 2000b). To try to evaluate the possible importance glutamate had for tendon pain, in a prospective study using microdialysis in chronic painful Achilles tendinosis, it was found that there were no differences in the intra-tendinous glutamate concentrations after successful treatment with eccentric training (Alfredson & Lorentzon, 2003a). The importance of the glutamate findings in the chronic painful tendons is still under scientific evaluation.

Gene technological analyses

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 (Alfredson, Lorentzon, Bäckman, Bäckman, & Lerner, 2003b).

Grey-scale ultrasonography and color doppler

Grey-scale ultrasonography (US) is an established and reliable method to examine tendon thickness and structure (Åström et al., 1996; Paavola et al., 1998). Color doppler (CD) is a method to study flows, and direction of flows, like blood flow (Terslev et al., 2001; Weinberg, Adams, & Hollenberg,

1998). The technique is not sensible enough for registration of the normal circulation in a normal tendon, because of the relatively low blood flow in the tendon, but vessels with high flows, like neovessels, can be registered. Using US 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 (Öhberg, Lorentzon, & Alfredson, 2001). To further analyze the possible relationship between neovascularization and pain, small amounts of a local anesthetic was under US and CD-guidance injected towards the neovessels outside the tendon (Alfredson, Öhberg, & Forsgren, 2003c). 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 (Bjur, Alfredson, & Forsgren, 2004), and following studies have shown Substance-P (SP)-nerves in the vascular wall, and Calcitonin Gene Related Peptide (CGRP)-nerves close to the vascular wall (Bjur et al., 2004; Ljung, Forsgren, & Fridén, 1999; Ljung, Alfredson, & Forsgren, 2004). Also, the Neurokinin-1-receptor (NK-1R), that is known to have a high affinity for SP, has been found in the vascular wall (Forsgren, Danielsson, & Alfredson, 2004). The findings of neuropeptides indicate that there still might be an inflammation in the tendon, however, not a so-called chemical inflammation (PGE₂-mediated), but instead a so-called neurogenic inflammation mediated via neuropeptides such as SP.

Clinical research

We have in previous research projects, using a specially designed eccentric calf muscle training regimen, to be used on patients with chronic painful mid-portion Achilles tendinosis, shown good clinical results in about 80% of the patients (Alfredson, Pietilä, Jonsson, & Lorentzon, 1998; Mafi, Lorentzon, & Alfredson, 2001; Fahlström, Jonsson, Lorentzon, & Alfredson, 2003). Also, US follow-ups showed that in the successfully treated cases the tendon thickness was significantly decreased, and the structure was ultrasonographically "more normal" (Öhberg, Lorentzon, & Alfredson, 2004). We have not been able to explain the background to the good results with this treatment, but the follow-ups using both US and CD, showed that there was no

remaining neovascularization in the cases with a good clinical result, but remaining neovessels in the cases with a poor clinical result. This indicates a possible effect on the area with neovascularization (Öhberg & Alfredson, 2002). By performing dynamic US+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 (Öhberg & Alfredson, 2002). During the eccentric training regimen, the ankle joint is in loaded dorsiflexion 180 repetitions/day, and possibly, in this position the vessels and nerves could be injured/destroyed? This is the only mechanism we have been able to objectively visualize, that possibly could explain how the eccentric training regimen works.

The findings that US and CD-guided injections of small amounts of a local anesthetic targeting the neovessels outside the tendon, temporarily cured the tendon pain, raised the hypothesis that destroying the area with neovessels and nerves outside the tendon would affect the tendon pain. In a pilot study, US 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 (Öhberg & Alfredson, 2003). Polidocanol (an aliphatic non-ionized nitrogen-free substance with a sclerosing and anesthetic effect) has been in use for many years primarily with the purpose to treat varicose veins and tele-angiectasies (Conrad, Malouf, & Stacey, 1995), and has been demonstrated to have very few side effects (Guex, 1993). In the pilot study, the majority of the patients were pain-free after a mean of two treatments, with 6–8 weeks in between. Two-year follow-ups of these patients have shown a reduced tendon thickness, no remaining neovessels, and an ultrasonographically 'normalized' structure in the successfully treated patients (non-published material). In pilot studies using the same type of treatment on patients with similar findings in the Achilles tendon insertion (Alfredson & Öhberg, 2004a), and in the patellar tendon (Alfredson & Öhberg, 2004b), 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+Adrenaline [47]. The patients treated at our clinic are on different tendon-loading activity levels, ranging from relatively non-active individuals to Olympic-level athletes. Based on the short-term results, the method seems safe. We have treated 400 tendons and only had two complications (a partial and a total Achilles tendon rupture). In one patient that previously had been treated with 4 intra-tendinous cortisone

injections, and who refused to follow the instructions after injection, there was a partial rupture during limbo-dancing. In another patient, that had been treated in the tendon insertion, there was a total rupture in the proximal part of the tendon at the finish of an 800-m running race, 6 weeks after treatment. 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 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 possibly also 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.

Conclusions

There is no scientific evidence for an on-going prostaglandin-mediated inflammation inside the chronic painful Achilles-, patellar-, and ECRB-tendon. However, there might well be a neurogenic inflammation, mediated via neuropeptides like SP and CGRP.

The area with vascularity (vessels and nerves) that can be visualized in the chronic painful tendons using US and CD, is most likely the source of pain, and treatment focusing on destroying this area by US and CD-guided injections of the sclerosing substance Polidocanol, targeting the neovessels, has in pilot studies with short-term follow-ups been demonstrated to have a potential to cure the pain and allow for the majority of the patients to go back to full tendon-loading activity.

Altogether, the findings might be of significance for the understanding and treatment of also other chronic painful tendons.

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