Imaging of intratendinous distribution of glucocorticosteroid in the treatment of Achilles tendinopathy. Pilot study of low-field magnetic resonance imaging correlated with ultrasound

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Abstract

Objective

Recently, a positive treatment effect of intratendinous injections of steroid in Achilles tendonitis (AT) has been described. Our aim was to test the localization and distribution of the injected steroid in both healthy (animal) tendons and in diseased human Achilles tendons.

Material and methods

Four pig tendons were injected in vivo *and harvested. The harvested tendons were placed in 0.2 Tesla MRI scanner, in order to select the optimal MRI sequences for tracking and localizing the bolus injection. Three patients with AT were treated with intratendinous steroid injection. Injections were placed in the pathologic areas of the tendon guided by ultrasound (US). MRI and US were performed at baseline and again immediately and 60 minutes after injection. A final follow-up MRI was performed 1 month after the injection.*

Results

In the animal model, significant recoil of the injected substance was seen in all cases. In all three patients the injection was readily distributed within the tendon and no recoil through the injection channel was found. One-month follow-up showed a total regression of hyperaemia on US as well as regression of intratendinous oedema on MRI in all 3 patients.

Conclusion

It is possible to demonstrate the distribution pattern of injected steroid in diseased Achilles tendons by MR-imaging. In contrast to the recoil experienced in the healthy tendon of the animal, the lack of recoil of the injected volume through the injection channel in the sick human tendon may be caused by a derangement of the fibre structure, which allows the extra volume to be distributed within the lesion. This indicates that the effect on AT of intra-tendinous injections of steroid is due to a local intra-tendinous action of the drug.

Key words

Achilles tendon, colour Doppler, injection, glucocorticoid, animal, hyperaemia.

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Introduction

Various treatment strategies of Achilles tendinopathy have been discussed for many years. Many different treatment regimens have been tested including, paratendinous steroid injections (1), eccentric training (2-5), laser (6), shock waves (7), and sclerosing therapy (8, 9). In a recent publication, the treatment effect of intra-tendinous injections of steroid in Achilles tendonitis (AT) was described (10).

The present study was undertaken to demonstrate the localization and distribution of intra-tendinous steroid injections into the healthy tendons of a pig and into diseased human tendons with clinical and ultrasonographic signs of AT.

Material and methods

In vitro *study*

Four common calcaneal pig tendons were included in the study. The pigs were landrace pigs, all female, with a body weight of 36 kg (range 34 – 42 kg). Immediately prior to entering this study, the pigs were used in a local procedure including eye-surgery.

The tendons were injected, guided by ultrasound, in the mid-portion with a mixture of Depo-Medrol 40 mg/ml (0.5 ml), lidocaine 1% (0.25 ml) and methylene blue. The mixture of Depo-Medrol 40 mg/ml and lidocaine 1% was the same as used for injection in patients (10). Methylene blue was used to assure visually that the injected substance was placed correct. Immediately after injection the four pig tendons were dissected and placed in a tray of homogenous material (Butter: Kaergaarden®). Both ends of the tendons were sutured when placed in the butter.

MRI pulse sequences

All MRI examinations for both the *in-vitro* and *in-vivo* study were performed using a 0.2 T musculoskeletal dedicated extremity scanner (E-scan®, Esaote Biomedica, Genoa, Italy). For signal collection the receive-only cylindric solenoid knee coil was used.

In order to obtain the best possible image resolution, simple phantom examinations were performed before final selection of the MR pulse sequence parameters. These examinations included examinations of the above mentioned pig tendons. All standard pulse sequences provided by Esaote® and suited for ankle joint and tendon examination were tested in order to secure minimal chemical shift artefacts and maximum edge detection as well as best possible image contrast between muscle, joint, fat, tendon and bone. Two radiologists evaluated all the pig tendon sample images, by visual comparison. These tests suggested the use of a sagittal Gradient Echo (GE) STIR, sagittal and axial T1 Spin Echo (SE) sequence, and a sagittal and axial TME sequence. To save time the TME (turbo-multi-echo) sequence was chosen giving both T2 and PDW images in the same scan time.

Patients

Three patients, 1 male and 2 females (age: 38-, 47- and 52 years; BMI: 21.5, 22.5 and 23.6), with clinical symptoms and signs of AT agreed to participate in the study. The patients were recruited from another treatment study with intratendinous steroid. The duration of AT in the patients were 5, 7 and 9 months, respectively. In two cases the provoking factor was a single episode of overuse by running, and in the last case ill-fitting skiing boots. None of the patients had previously been treated with steroid injections into the tendon or peritendinously. In these patients, all other previous treatment including rest, NSAIDs, and specific eccentric exercises had failed.

Ultrasound

US was performed with an Acuson Sequoia (Mountainview, CA, USA) equipped with a linear array transducer. The centre frequency used was 14 MHz. The colour Doppler was optimised for low flow and the Nyquist limit was ± 0.014 m s^{-1}. The Doppler frequency was 7 MHz and the gain was set just below the level that produced random noise. The Doppler settings were the same for all patients at all visits. The Achilles tendon was scanned in longitudinal and transverse planes (11) with the patient lying prone and the foot relaxed in 90 degree flexion. The

tendon and peritendinous tissues were evaluated with colour Doppler and the presence of intratendinous flow was regarded as a pathological finding (12). A longitudinal image with maximum flow on colour Doppler was obtained to calculate the percentage of colour pixels (Fig. 1A).

The digitally stored images were exported to a computer as a DICOM file. A β-version of DataPro (Noesis, Courtaboeuf, France) was used to calculate the colour fraction. On the longitudinal image with maximum flow, the Achilles tendon was traced inside the colour box whereupon the software reported the total number of pixels inside the trace as well as the number of colour pixels inside the trace. The colour fraction was calculated as colour pixels/total pixels.

Magnetic Resonance Imaging

The *in vivo* MRI protocol was adjusted according to the results from the *in vitro* study. The patients were scanned with the ankle in the knee coil, using the above-mentioned 0.2 T musculoskeletal dedicated extremity scanner (E-scan®, Esaote Biomedica, Genoa, Italy). MR images were post-processed on the E-scan image-processing console.

The MRI protocol used in the present study consisted of a sagittal Gradient Echo (GE) STIR (TR/TE/NEX: 780/25/1, TI:75, FOV: 190x170mm, Matrix:256x256, ST:3mm.), a sagittal T1 Spin Echo (SE) sequence (TR/TE/NEX: 400/26/2, FOV: 160x160, Matrix: 256x192, ST: 4mm), an axial T1 Spin Echo (SE) sequence (TR/TE/NEX: 700/26/2, FOV: 160x160, Matrix: 256x192, ST:4mm), a sagittal TME sequence (TR/TE/NEX: 1620/28+90/1, FOV: 170x170mm, Matrix:256x256, ST:3mm) and an axial TME sequence (TR/TE/NEX: 2800/28+90/1, FOV: 170x170mm, Matrix:256x256, ST:3mm) before and after intratendinous steroid injection. The same protocol was used in the follow-up scans. This imaging protocol and sequence selection is in agreement with international recommendations (13).

MRI was performed at baseline and

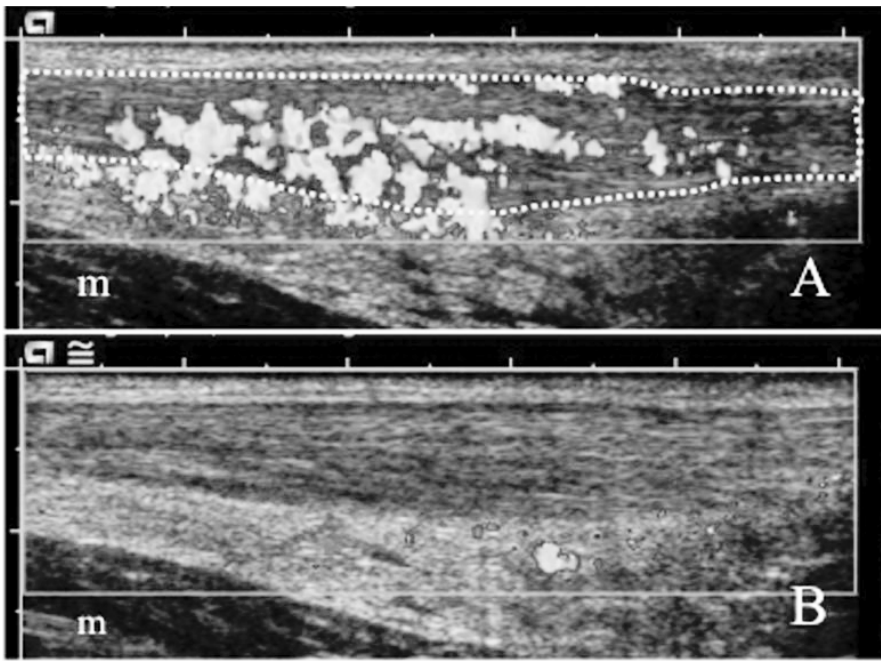
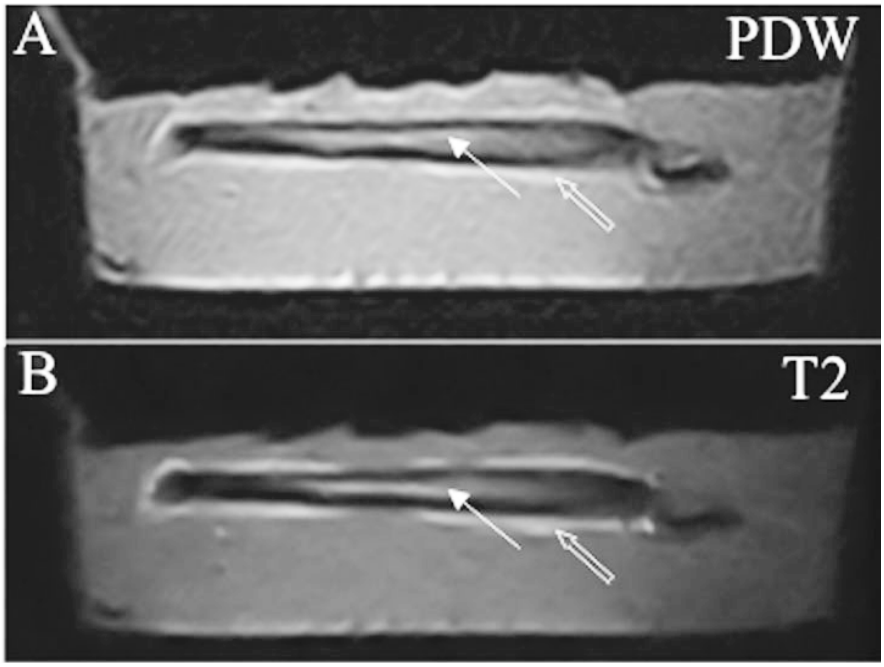


Fig. 1. Longitudinal ultrasound Doppler image of the Achilles tendon before (A) injection and at one month follow up (B).
The Achilles tendon is seen in the top of the image (A) traced by the dotted line. Proximal is oriented left. The flexor hallucis longus muscle (M) is seen anterior (below) to the tendon.
The dotted line indicates the region of interest from where the colour fraction is calculated. The colour fraction is 36%. There is pronounced intratendinous hyperaemia (colour pixels) and classical spindle-shaped thickening of the tendon as well as heterogeneous internal architecture.
Ultrasound Doppler images of the Achilles tendon at one month follow-up is seen in B. The Doppler activity has disappeared, and the tendon is no longer tender on clinical examination. The grey-scale changes (spindle-shaped thickening and heterogeneous architecture) persist.



Figs. 2A and B. MRI of steroid distribution post-injection in a healthy pig tendon.
Sagittal (longitudinal) Turbo multiecco sequence giving both proton density weighted (PDW) (A) and T2 weighted (B) MR-images of a pig tendon specimen after intratendinous injection of steroid. The steroid is placed both intratendinously (filled arrows) and peritendinously (open arrows) as seen in both images and the intratendinous distribution is along the fibres in a fan-like fashion. The peritendinous steroid (open arrows) was due to recoil of steroid through the injection canal.

again immediately after and 60 minutes after injection. The final MRI was performed 1 month after the injection in the 3 patients.

Treatment

All patients were treated with an intratendinous injection of Depo-Medrol® 40 mg/ml (1 ml) and lidocaine 1% (0.5 ml) into the pathologic areas identified by US as described by Koenig *et al*. (10).

Both the diagnosis and follow-up in this study were made by clinical examination and imaging by colour Doppler ultrasound (US). The patients were instructed to avoid major stress of the tendons for 4-6 weeks (i.e. sport, running) and a follow-up US scan was performed after one month.

Ethics

The Study was approved by the local Ethical Committee of Copenhagen (KF 01-133/03). All patients consented to participate in the investigation.

Results

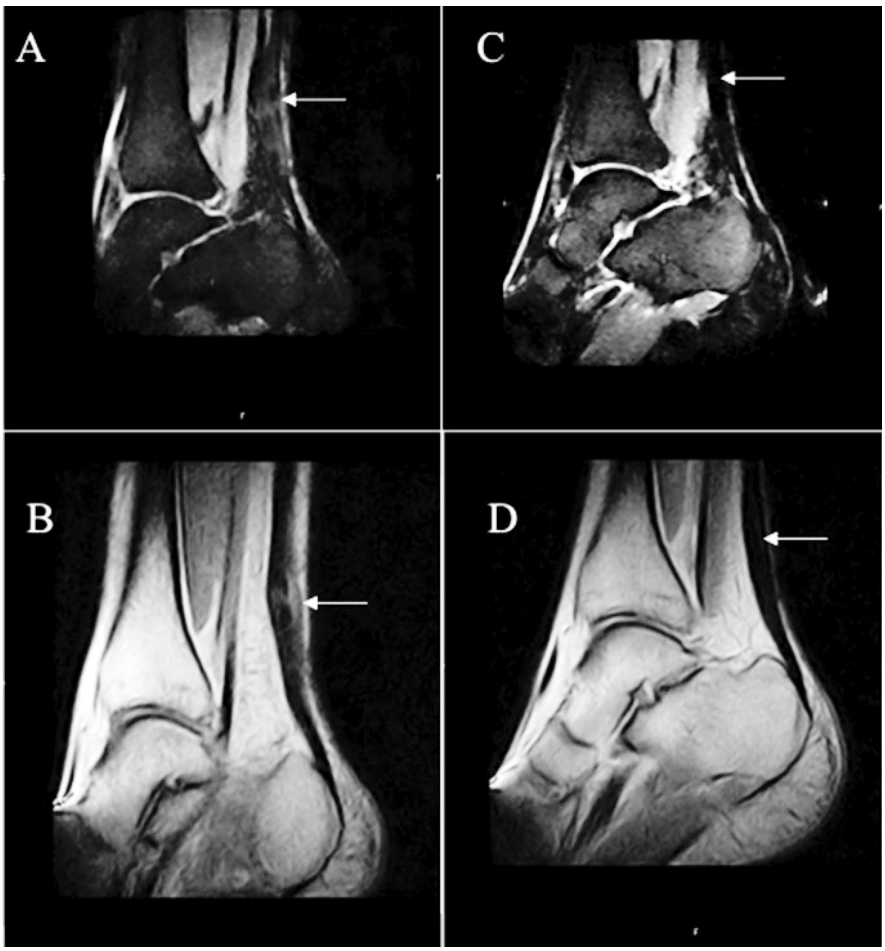
In vitro *study*

In all four tendons tested, the injected substance was distributed both within and outside the tendon. A backflow into the peritendinous area could be demonstrated real-time on ultrasound, and was due to recoil through the injection channel. On MRI the distribution of the injected volume was verified (Figs. 2A and B).

In vivo *study*

Ultrasound

On colour Doppler all patients initially had intratendinous hyperaemia. No peritendinous hyperaemia was found. Prior to the injection, the median colour fraction was 20 % [range 9-36%] and decreased to 0.5 % [0-1%] at follow-up one month later (Fig. 1B). In all three cases, the tendons on grey-scale US were spindle-shaped with a heterogeneous internal echo pattern. These US grey-scale findings did not change during follow-up although the clinical condition improved and the hyperaemia disappeared. The injected bolus of steroid was observed at baseline. At one month follow-up, no signs of the injected volume or any adverse effects e.g. partial rupture was observed.



Figs. 3 A-D. MRI before injection and at follow-up.
Sagittal pre-steroid injection STIR (A) (short inversion time inversion recovery) image and sagittal pre-steroid injection PDW (B) images both showing a typical Achilles tendonitis with spindle-shaped tendon with hyperintense (whiter) signal due to oedema in the thickened tendon (arrow). The fibre structure is deranged on PDW(B).
Sagittal STIR (C) and PDW (D) at 1 month follow up examination showing normalized tendon shape and thickness and no tendon oedema (arrow).

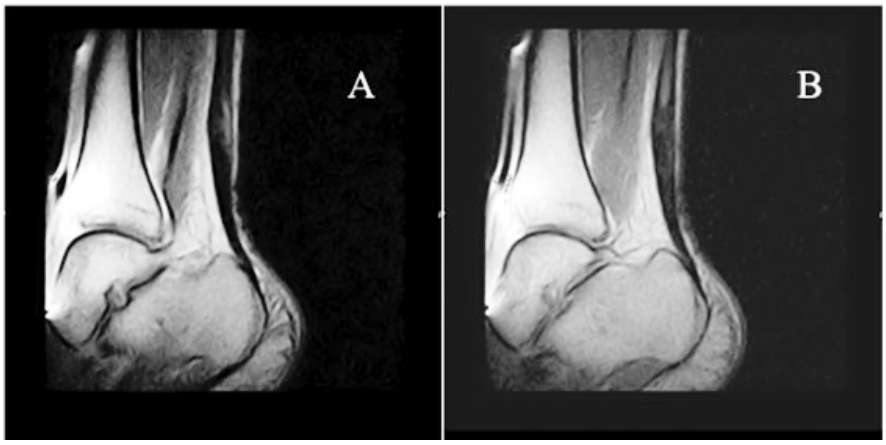
Magnetic resonance

All patients showed pathological high signal changes in the thickened area of the tendon on the STIR and TME sequences while none had bone marrow oedema (Figs 3A and B). The injected substance was visualized with MRI intratendinously, both inside and proximal to the pathological area in all patients on the TME sequences (Figs. 4A and B), and the signal due to the injected steroid persisted on the follow-up scan approximately 60 minutes post-injection (Fig. 4B). No sign of peritendinous recoil of the injected substance was observed on the axial or on the perpendicular sagittal scan planes. One-month follow-up showed a total regression of pathological high signal on both the STIR and the TME-sequences in all patients (Figs. 3C and D). MRI revealed no signs of adverse effects from the injection e.g. partial or full thickness rupture.

Discussion

This preliminary study was performed in order to demonstrate the intratendinous distribution of steroid by use of both MRI as well as US. The aim was not to evaluate the treatment response or advocate for the intra-tendineous approach, which require future controlled studies.

As shown in the present study, an injected substance in healthy (animal) tendon tissue will recoil peritendinous-



Figs. 4A and B. MRI of steroid distribution post-injection.
PDW images, 60 minutes after ultrasound guided steroid injection showing the steroid inside the tendon in two different image planes. The injected steroid has changed the shape and signal intensity in the pathological area (A) compared to the pre-injection image (3B). In the adjacent image slice (B) the steroid have been distributed proximal to the pathological area giving a high signal intensity (white) in the lower intensity (dark) tendinous tissue, which was not present on the pre-injection images. By toggling between the images on the image console the two adjacent images (A+B) show continuity of the injected steroid.

ly, presumably due to the tight nature of the tissue. This may correspond to the clinical impression of resistance to injections into tendons, e.g. treatment of tennis elbows using steroid injections into the extensor origin at the elbow. Significant side effects may be provoked due this procedure from recoiled steroid in the subcutaneous tissue (14, 15).

In contrast to the tight tendinous tissue, the experience with intratendinous injections in AT has been that this tissue readily holds an injected substance of 1.5 to 2 ml. A possible explanation could be that pathological changes in Achilles tendonitis lead to a derangement of the normal fibre structure allowing the fibres to separate as the volume is injected thus creating room for the injected volume in situ.

Both ultrasound with colour Doppler and low field MRI may be important for diagnosis, location, follow-up on and evaluation of treatment of AT (13, 16, 17). Our data indicate that low field MRI is well suited for tracking and localizing the intratendinously injected treatment bolus.

There is an ongoing debate, whether AT is an inflammatory or a degenerative condition. This is reflected in the terminology where AT and Achilles tendinosis describe the same condition and reflect different opinions upon aetiology (18, 19). The use of imaging in treatment studies may provide new objective data for clarification of this very important clinical problem.

The amount of colour pixels in a region reflects the amount of flowing blood in the investigated area (20), which makes it possible to obtain an estimate of the blood flow in a particular area as an estimate of disease activity (21-23). There is a good correlation between Doppler activity and tendon disorders (12, 24). Some groups have shown similar results and conclude that the colour/power Doppler technique is a good way to visualize soft-tissue hyperaemia as a sign of tendinopathy (22, 25, 26) and that the technique may be used to quantify disease activity in treatment. In this study we chose images of the Achilles tendons with maximum intratendinous Doppler activity. Hereby we were not subject to bias – no judgment *per se* was involved. We believe that this procedure is the best way to report on intratendinous Doppler activity in Achilles tendons. However, we acknowledge that the single scan plane cannot describe the volume of flow present in the entire tendon. The single scan plane does however describe a worst-case scenario and when a reduction is found as a treatment response, it is valid. In our case, all three patients had an almost total reduction in all locations of the tendon at follow-up.

With future development in US machines, modalities such as 3-Dimensional (3D) US (Filippucci, 2006 2782 /id), (Downey, 2000 2783 /id) or dynamic US (Koski, 2006 2781 /id) may be an even better indicator of intratendinous Doppler activity. However, the Doppler signal is very sensitive to movement and 3D US images can only be obtained by moving the probe over the area of interests with inherent risk of movement artefacts. Therefore, we believe that these modalities still need some development.

Both US and MRI findings seem to support the notion of an inflammatory component in the pathogenesis and show fluid accumulation in the diseased area on the STIR and TME sequences where presence of intratendinous colour Doppler pixels indicate hyperaemia. Furthermore, the MRI changes regressed after steroid application.

Using high-end US equipment with a very sensitive Doppler, flow is seen in muscles and subcutaneous tissues, occasionally in normal joints but not in normal tendons (26) and accordingly the presence of colour pixels inside the tendon may be taken as sign of hyperaemia. Similarly, with regard to MRI, fluid accumulation is not found inside normal tendons (27). Colour Doppler furthermore provided the location used to guide the injection, which was performed centrally in the area with maximum flow.

Finally, colour Doppler and MRI were of value in follow-up with measurements of a decreasing amount of colour pixels inside the tendon on US and a total regression of fluid signal inside the tendon on MRI, paralleled by a normalisation in tendon signal and tendon appearance on (both US) and MRI.

Limitations

We are aware of some limitations in this study. The aim of the report is not to discuss the appropriateness of this approach but only to report on the distribution of injected steroid. In this study we only reported on the Doppler findings and not the grey scale findings.

With only one month follow-up and a very limited case material, it is not possible to draw any conclusion on the clinical and ultrasonographical long-term effect. On short term, the hyperaemia disappeared but no effect was observed on the grey scale images (data not shown).

Since this study is only a pilot study of the distribution and not about the treatment itself we did not include controls. A more widely use of this approach would indeed require a RCT

In conclusion, our preliminary results seem to indicate recoil of injected substances in healthy animal tendons. In contrast to these findings, in a diseased human tendon with AT, the ultrasound guided injection stayed inside and proximal to the pathological tendon area, as visualized by low-field MRI.

References

1. FREDBERG, U: Local Corticosteroid Injection in Sport: Review of literature and guidelines for treatment. *Scand J Med Sci Sports* 1997; 7: 131-9.
2. ALFREDSON H, NORDSTROM P, PIETILA T, LORENTZON R: Bone mass in the calcaneus after heavy loaded eccentric calf-muscle training in recreational athletes with chronic achilles tendinosis. *Calcif Tissue Int* 1999; 64: 450-5.
3. ALFREDSON H, PIETILA T, JONSSON P, LORENTZON R: Heavy-load eccentric calf muscle training for the treatment of chronic achilles tendinosis. *Am J Sports Med* 1998; 26: 360-6.
4. FAHLSTROM M, JONSSON P, LORENTZON R, ALFREDSON H: Chronic achilles tendon pain treated with eccentric calf-muscle training. *Knee Surg Sports Traumatol Arthrosc* 2003; 11: 327-33.
5. OHBERG L, LORENTZON R, ALFREDSON H: Eccentric training in patients with chronic achilles tendinosis: normalised tendon structure and decreased thickness at follow up. *Br J Sports Med* 2004; 38: 8-11.
6. SIEBERT W, SEICHERT N, SIEBERT B, WIRTH CJ: What is the efficacy of "soft" and "mid" lasers in therapy of tendinopathies? A double-blind study. *Arch Orthop Trauma Surg* 1987; 106: 358-63.
7. CHEN YJ, WANG CJ, YANG KD *et al*.: Extracorporeal shock waves promote healing of collagenase-induced achilles tendinitis and increase TGF-beta1 and IGF-I expression. *J Orthop Res* 2004; 22: 854-61.
8. OHBERG L, ALFREDSON H: Sclerosing therapy in chronic achilles tendon insertional pain-results of a pilot study. *Knee Surg Sports Traumatol Arthrosc* 2003; 11: 339-43.
9. OHBERG, L, ALFREDSON H: Ultrasound Guided Sclerosis of Neovessels in Painful Chronic Achilles Tendinosis: Pilot Study of a New Treatment. *Br J Sports Med* 2002; 36: 173-5.
10. KOENIG MJ, TORP-PEDERSEN S, QVISTGAARD E, TERSLEV L, BLIDDAL H: Preliminary results of colour doppler-guided intratendinous glucocorticoid injection for achilles tendonitis in five patients. *Scand J Med Sci Sports* 2004; 14: 100-6.
11. RASMUSSEN OS: Sonography of tendons. *Scand J Med Sci Sports* 2000; 10: 360-4.
12. WEINBERG EP, ADAMS MJ, HOLLENBERG GM: Color Doppler sonography of patellar tendinosis. *AJR Am J Roentgenol* 1998; 171: 743-4.
13. SHALABI A: Magnetic resonance imaging in chronic Achilles tendinopathy. *Acta Radiol* 2004; (Suppl.):1-45.
14. ANDERSON B, KAYE S: Treatment of flexor tenosynovitis of the hand ('trigger finger') with corticosteroids. A prospective study of the response to local injection. *Arch Intern Med* 1991; 151: 153-6.
15. LOUIS DS, HANKIN FM, ECKENRODE JF: Cutaneous atrophy after corticosteroid injection. *Am Fam Physician* 1986; 33: 183-6.
16. OHBERG L, ALFREDSON H: Effects on neovascularisation behind the good results with eccentric training in chronic mid-portion Achilles tendinosis? *Knee Surg Sports Traumatol Arthrosc* 2004; 12: 465-70.
17. SHALABI A, KRISTOFFERSEN-WIBERG M, ASPELIN P, MOVIN T: Immediate Achilles Tendon Response After Strength Training Evaluated by MRI. *Med Sci Sports Exerc* 2004; 36: 1841-6.
18. ALMEKINDERS LC, TEMPLE JD: Etiology, Diagnosis, and Treatment of Tendonitis: an Analysis of the Literature. *Med Sci Sports Exerc* 1998; 30: 1183-90.
19. PAAVOLA M, PAAKKALA T, KANNUS P, JARVINEN M: Ultrasonography in the Differential Diagnosis of Achilles Tendon Injuries and Related Disorders. A Comparison Between Pre-Operative Ultrasonography and Surgical Findings. *Acta Radiol* 1998; 39: 612-9.
20. RUBIN JM, BUDE RO, FOWLKES JB, SPRATT RS, CARSON PL, ADLER RS: Normalizing Fractional Moving Blood Volume Estimates With Power Doppler US: Defining a Stable Intravascular Point With the Cumulative Power Distribution Function. *Radiology* 1997; 205: 757-65.
21. QVISTGAARD E, ROGIND H, TORP-PEDERSEN S, TERSLEV L, DANNESKIOLD-SAMSOE B, BLIDDAL H: Quantitative Ultrasonography in Rheumatoid Arthritis: Evaluation of Inflammation by Doppler Technique. *Ann Rheum Dis* 2001; 60: 690-3.
22. TERSLEV L, QVISTGAARD E, TORP-PEDERSEN S, LAETGAARD J, DANNESKIOLD-SAMSOE B, BLIDDAL H: Ultrasound and Power Doppler Findings in Jumper's Knee - Preliminary Observations. *Eur J Ultrasound* 2001; 13: 183-9.
23. TERSLEV L, TORP-PEDERSEN S, SAVNIK A *et al*.: Doppler Ultrasound and Magnetic Resonance Imaging of Synovial Inflammation of the Hand in Rheumatoid Arthritis: a Comparative Study. *Arthritis Rheum* 2003; 48: 2434-41.
24. TORP-PEDERSEN T, TORP-PEDERSEN S, BLIDDAL H: Diagnostic Value of Ultrasonography in Epicondylitis. *Ann Intern Med* 21-5-2002; 136: 781-2.
25. ALFREDSON H, OHBERG L, FORSGREN S: Is Vasculo-Neural Ingrowth the Cause of Pain in Chronic Achilles Tendinosis? An Investigation Using Ultrasonography and Colour Doppler, Immunohistochemistry, and Diagnostic Injections. *Knee Surg Sports Traumatol Arthrosc* 2003; 11: 334-8.
26. OHBERG L, LORENTZON R, ALFREDSON H: Neovascularisation in Achilles Tendons With Painful Tendinosis but Not in Normal Tendons: an Ultrasonographic Investigation. Knee *Surg Sports Traumatol Arthrosc* 2001; 9: 233-8.
27. QUINN SF, MURRAY WT, CLARK RA, COCHRAN CF: Achilles Tendon: MR Imaging at 1.5 T. *Radiology* 1987; 164: 767-70.