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Corticosteroid injections, eccentric decline squat training and heavy slow resistance training in patellar tendinopathy

M. Kongsgaard[1], V. Kovanen[2], P. Aagaard[1,3], S. Doessing[1], P. Hansen[1], A. H. Laursen[1], N. C. Kaldau[1], M. Kjaer[1], S. P. Magnusson[1]

[1]Institute of Sports Medicine, Department 8, Bispebjerg Hospital and Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark, [2]Department of Health Sciences, University of Jyväskylä, Jyväskylä, Finland, [3]Institute of Sports Exercise and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark
Corresponding author: Mads Kongsgaard, PhD, MSc, Department 8, Institute of Sports Medicine, Bispebjerg Hospital and Faculty of Health Sciences, University of Copenhagen, 1st Floor, Bispebjerg Bakke 23, 2400 Copenhagen NV, Denmark. Tel: +45-3531 2599, Fax: +45-3531 2733, E-mail: mk11@bbh.regionh.dk

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A randomized-controlled single-blind trial was conducted to investigate the clinical, structural and functional effects of peritendinous corticosteroid injections (CORT), eccentric decline squat training (ECC) and heavy slow resistance training (HSR) in patellar tendinopathy. Thirty-nine male patients were randomized to CORT, ECC or HSR for 12 weeks. We assessed function and symptoms (VISA-p questionnaire), tendon pain during activity (VAS), treatment satisfaction, tendon swelling, tendon vascularization, tendon mechanical properties and collagen crosslink properties. Assessments were made at 0 weeks, 12 weeks and at follow-up (half-year). All groups improved in VISA-p and VAS from 0 to 12 weeks ($P<0.05$). VISA-p and VAS improvements were maintained at follow-up in ECC and HSR but deteriorated in CORT ($P<0.05$). In CORT and HSR, tendon swelling decreased ($-13\pm9\%$ and $-12\pm13\%$, $P<0.05$) and so did vascularization ($-52\pm49\%$ and $-45\pm23\%$, $P<0.01$) at 12 weeks. Tendon mechanical properties were similar in healthy and injured tendons and were unaffected by treatment. HSR yielded an elevated collagen network turnover. At the half-year follow-up, treatment satisfaction differed between groups, with HSR being most satisfied. Conclusively, CORT has good short-term but poor long-term clinical effects, in patellar tendinopathy. HSR has good short- and long-term clinical effects accompanied by pathology improvement and increased collagen turnover.

Patellar tendinopathy is a disabling overload injury of the patellar tendon that may persist for >15 years (Kettunen et al., 2002). It has been reported that jumping athletes and recreational athletes have a prevalence rate of 40% and 14%, respectively (Ferretti, 1986; Lian et al., 2005). Tendinopathy has been associated with pathological extracellular matrix (ECM) changes (Cook et al., 1997), but specific structural, functional and mechanical properties of the tensile-bearing component in tendinopathy remain to be identified.

Patellar tendinopathy lacks an obvious treatment of choice (Cook et al., 1997). Corticosteroid injections are commonly used clinically, but recent histopathological data indicate that tendinopathy is a non-inflammatory condition (Cook et al., 1997; Alfredson et al., 2001). Moreover, studies on tendinous tissue samples suggest that corticosteroids have deleterious effects (Wong et al., 2004; Haraldsson et al., 2006). Yet, studies have reported reduced tendon pain, swelling and vascularization following corticosteroid injections in patellar tendinopathy (Fredberg, 1997; Fredberg et al., 2004). Thus, the effect of corticosteroid injections in patellar tendinopathy remains elusive.

Conservative treatment for patellar tendinopathy in the form of eccentric training performed twice daily has gained popularity, and some (Purdam et al., 2004; Jonsson & Alfredson, 2005), but not all (Visnes et al., 2005), studies report a positive short-term clinical outcome. However, the explanatory mechanisms of eccentric training in tendinopathy remain elusive, and the treatment has seldom been compared with that of other management therapies.

The magnitude of load in exercise-based management of patellar tendinopathy appears to be fundamental (Purdam et al., 2004; Kongsgaard et al., 2006; Frohm et al., 2007). Because heavy resistance training can produce both tendon hypertrophy and augmented tendon mechanical properties (Kongsgaard et al., 2007), we hypothesized that heavy slow resistance training would be advantageous in the treatment of patellar tendinopathy.

Existing clinical studies on tendon overload injuries have more or less exclusively focused on the clinical outcome, which precludes any explanation

for the reported benefits, and therefore limits the possibility of developing new and more effective treatment options.

We investigated, in a single-blind randomized-controlled trial, the clinical, structural and functional effects of peritendinous corticosteroid injections (CORT), eccentric decline squat training (ECC) and heavy slow resistance training (HSR) in patellar tendinopathy. The present study was conducted to compare the three management options in addition to investigating some of the associated underlying mechanisms of these managements.

Materials and methods

Patients and design

From January 2006 through June 2006, 52 recreational male athletes (18–50 years) diagnosed with chronic patellar tendinopathy applied for trial submission (self-selection following advertisement). An experienced physician confirmed the diagnosis based on defined clinical findings. A pain duration of >3 months was required to qualify as a chronic condition (Leadbetter, 1992). The clinical diagnosis required confirmation by ultrasonography: local anterior–posterior (AP) thickening of the tendon of at least 1 mm compared with the mid-tendon level, and a hypo-echoic area and presence of a color Doppler signal within the hypo-echoic area (Cook et al., 2001). A 4-week "wash-out" period from any previous treatment was required. The exclusion criteria were as follows: (1) corticosteroid injections within 12 months, (2) previous knee surgery, (3) arthritis, (4) diabetes or (5) any confounding diagnosis to the knee joint. Thirty-nine subjects fulfilled the inclusion criteria and 13 subjects were randomly allocated to each group (Fig. 1).

A prospective randomized single-blind clinical trial design with a 12-week intervention period and a half-year follow-up period was applied and carried out at the Institute of Sports Medicine, Copenhagen. Following baseline assessments, subjects were allocated to one of the three intervention groups (CORT, ECC or HSR) using a computer-generated minimization randomization procedure (Jensen, 1991). The minimization randomization procedure was performed according to activity level, symptom duration and age.

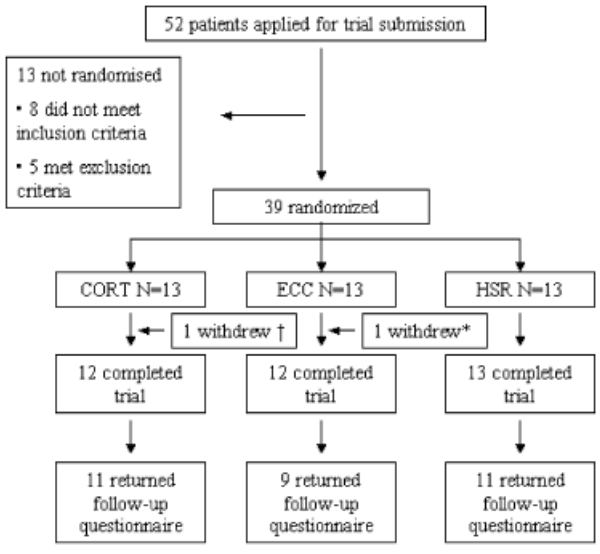

Fig. 1. Trial profile. †One subject withdrew due to holiday. *One subject withdrew due to a sports-related ankle sprain.

Subjects with bilateral symptoms received the same treatment on both sides, but only the tendon with the greatest symptoms was selected for analysis to preclude biased reduction of the variance. Tendons without any clinical symptoms, sonographical hypoechoic abnormalities or detectable color Doppler signal were used as a healthy tendon sub-sample for baseline comparison ($n = 26$). Two subjects (one CORT and one ECC) withdrew from the study. One withdrew due to reasons related to vacation and one withdrew due to an ankle sprain (week 2). The subject characteristics are shown in Table 1.

The study complied with the Declaration of Helsinki, was approved by the local ethics committee for medical research (KF 256131) and was registered at ClinicalTrials.gov (NCT00404469). All subjects gave their written informed consent to participate.

CORT

CORT subjects received ultrasound-guided (gray scale) injections of 1 mL of 40 mg/mL methylprednisolon in 0.5 mL lidocain (1%) into the peritendinous tissue posterior to the hypoechoic area of the patellar tendon. Injections were administered from the medial side of the knee. A second injection was administered 4 weeks later according to normal clinical practice. The same physician administered all the injections. Subjects were instructed to refrain from training and sporting activities the first week after the injections.

ECC

The eccentric exercise program has been described in detail previously (Purdam et al., 2004). Subjects performed three sets of 15 slow repetitions of eccentric unilateral squats on a 25° decline board twice daily (morning and evening) for 12 consecutive weeks (Fig. 2(a)). Subjects were instructed to spend approximately 3 s completing each repetition and to have a 2-min rest period between sets. Subjects with a bilateral condition used the arms and both legs during the concentric phase. To ensure compliance and correct performance of the exercises, a supervised training was conducted once a week. Pain during exercises was acceptable, but pain and discomfort was not to increase following cessation of training. Load was increased using an incrementally loaded backpack as pain diminished.

HSR

Three weekly sessions, including one supervised session, were performed. Each session consisted of three bilateral exercises: squat, leg press and hack squat (Fig. 2(b)–(d)). Subjects completed four sets in each exercises with a 2–3-min rest between sets. The repetitions/loads were: 15 repetition maximum (RM) week 1, 12 RM weeks 2–3, 10 RM weeks 4–5, 8 RM weeks 6–8 and 6 RM weeks 9–12. All exercises were performed from complete extension to 90° of knee flexion and back again. Subjects were instructed to spend three seconds completing each of the eccentric and concentric phases, respectively (i.e. 6 s/repetition). Pain during exercises was acceptable but pain and discomfort was not to increase following cessation of training.

Subjects in all groups were allowed to perform sporting activities throughout the 12-week intervention period if these could be performed with only light discomfort (maximal VAS score of 30). A leisure-time activity pain threshold of 50, on the VAS scale, has previously been applied successfully in the management of Achilles tendinopathy (Silbernagel et al., 2007). However, to reduce the risk of relapse we chose a maximal allowed pain of 30 on the VAS scale. Subsequently,

the mean leisure time activity level during the 12-week intervention period was not different from the baseline level (Table 1) for all three groups. None of the subjects were directly encouraged to maintain treatment nor were they given any further guidelines following intervention termination.

Clinical evaluation

Subjects completed a written VISA-p questionnaire to assess the symptoms, function and the ability to participate in sports (Visentini et al., 1998; Frohm et al., 2004). The VISA-p score was determined *a priori* as the primary outcome measure of this study. Maximal tendon pain during preferred sporting activity was indicated on a 100 mm visual analogue scale (VAS). Subjects completed the VAS and VISA-p questionnaire with no investigator assistance at 0 weeks, 12 weeks and at the half-year follow-up. Their reproducibility was assessed in 10 randomly selected subjects after five days and yielded a typical error percent for duplicate measures of 2.7% and 3.2%, respectively. At the end of the treatment period and at the half-year follow-up, subjects completed a mailed written questionnaire, in which they ticked one of two boxes to indicate whether they were "satisfied" or "not satisfied" with the clinical outcome.

Ultrasonography

Ultrasonography was performed on the injured patellar tendon using a GE Medical Systems, Logiq™ 9 scanner with a 14 MHz linear array transducer (GE Medical Systems, Milwaukee, Wiscounsin, USA). Gray-scale and color Doppler

Table 1. Baseline subject characteristics

	All subjects ($n = 37$)	CORT ($n = 12$)	ECC ($n = 12$)	HSR ($n = 13$)
Age (years)	32.4 ± 8.8 (18–53)	34.3 ± 10.0 (25–53)	31.3 ± 8.3 (18–47)	31.7 ± 8.5 (19–50)
Height (cm)	183 ± 9 (168–204)	181 ± 5 (170–190)	185 ± 11 (168–203)	185 ± 9 (174–204)
Weight (kg)	83.3 ± 11.1 (65.0–107.0)	80.8 ± 9.4 (65–92)	84.1 ± 13.4 (65–105)	84.8 ± 10.7 (68–107)
BMI (kg/m^2)	24.7 ± 2.5 (20.5–34.9)	24.8 ± 2.2 (20.5–27.8)	24.4 ± 2.1 (21.6–27.5)	24.8 ± 3.2 (22.5–34.9)
Symptom period (months)	18.7 ± 12.3 (3–36)	18.3 ± 14.1 (4–36)	18.8 ± 13.0 (3–36)	18.8 ± 10.6 (3–33)
Activity level (h/week)	6.0 ± 3.0 (2–15)	5.8 ± 2.4 (2–10)	6.1 ± 3.3 (2–13)	6.2 ± 3.5 (3–15)
Unilateral/bilateral	26/11	8/4	9/3	9/4
Proximal/distal	31/6	11/1	10/2	10/3

Unilateral/bilateral denotes how many subjects were diagnosed with unilateral and bilateral patellar tendinopathy, respectively. Proximal/distal denotes how many subjects were affected by patellar tendinopathy at the proximal or distal tendon region, respectively. All values are means ± SD. Values in brackets are range. There were no differences between groups for any parameter at baseline.

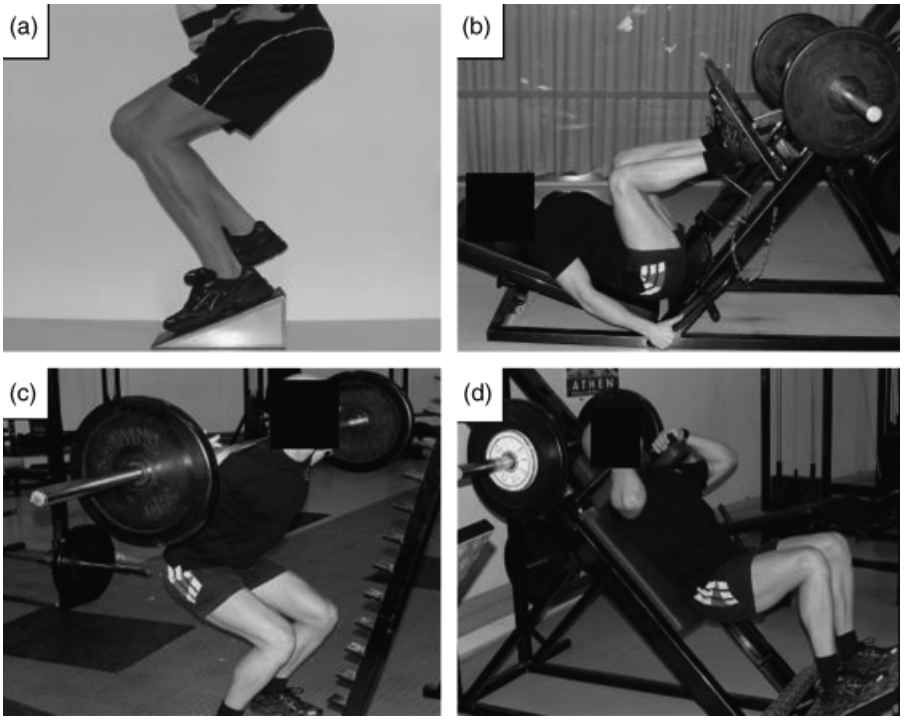

Fig. 2. Depiction of applied exercises: (a) eccentric decline squat, (b) leg press, (c) squat and (d) hack squat. All exercises conducted to a 90° knee angle. (b), (c) and (d) performed bilateral.

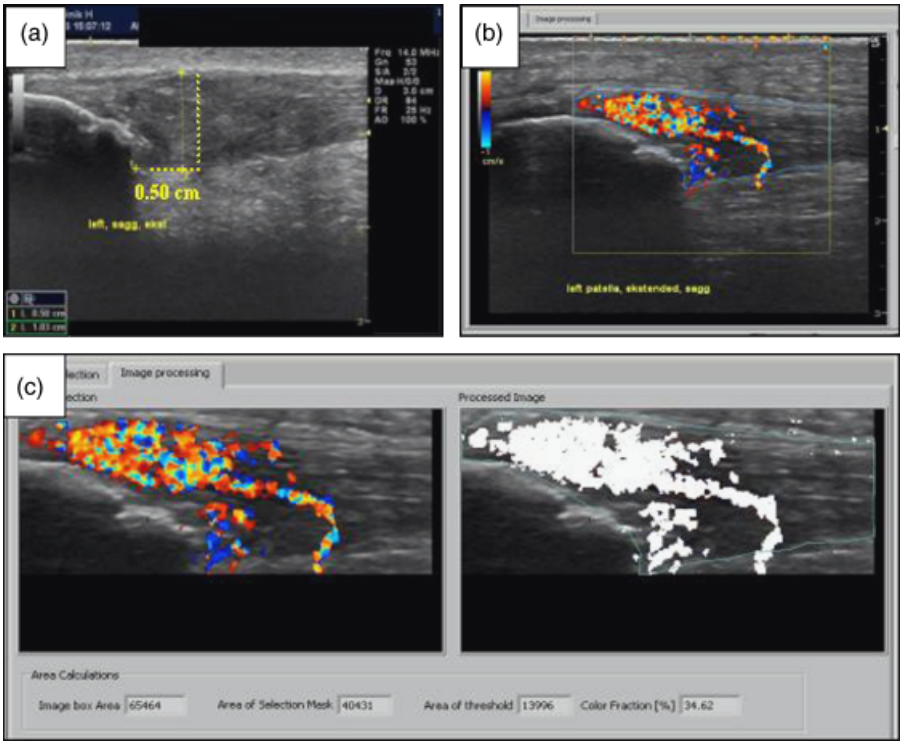

Fig. 3. Ultrasonography assessments. (a) Assessment of anterior–posterior patellar tendon thickness. (b) Color Doppler activity recording and (c) software assessment and calculation of color Doppler area.

(CD) settings were identical for all examinations. Subjects were examined in a supine position with the knees flexed 20° during the gray-scale examination, and with a completely extended and relaxed knee during CD evaluation. Gray-scale examinations were performed with a depth of 3.0 cm, AO = 100%, DR = 84 and gain = 53. AP patellar tendon thickness was measured exactly 0.5 cm distal from the apex of the patella or 0.5 cm proximal from the tibial tuberosity, respectively (Fig. 3(a)). The specific measuring sites were chosen according to typical pathological findings and to ensure standardization and validity (Fredberg et al., 2008). The mean of three AP thickness measurements of each image was used for analysis.

CD settings were optimized for low flow; CD frequency = 7.5 MHz, gain just below random noise level, AO = 100%, PRF = 0.4 kHz and WF = 48 Hz. CD scans were obtained with a visual thin layer of gel between the transducer and the skin. A color box of 2.5 × 2.5 cm was positioned at a standardized position relative to the patella apex or tibial tuberosity, respectively (Fig. 3(b)). CD scans were recorded as 4-s sine-loops in the saggital plane visually displaying the highest CD activity. The sine-loop image displaying the greatest amount of Doppler activity was selected and saved (JPEG-format) for analysis. CD activity was quantified as color area (CA), i.e. as the total number of colored pixels within the region of interest, using the custom-made software program Doppler Flow Image Analyser version 1.01 (http://www.gtech.dk). (Fig. 3(b) and (c)). The mean of three CA measurements was used for analysis.

Analyses of ultrasonography measures were conducted in an investigator-blinded fashion. Re-scanning of 10 random subjects assessed the reproducibility of tendon thickness and CA measurements. The typical error percent for duplicate measures was 2.6% and 6.1% for the AP tendon thickness and CA, respectively.

Muscle and tendon structural properties

The anatomical cross-sectional area of the quadriceps femoris muscle (Q-ACSA) was assessed 20 cm proximal from the tibia plateau by MRI (General Electric, Signa Horizon LX 1.5 Tesla, T1-weighted SE, GE Healthcare Diagnostic Imaging, 2605 Broendby, Denmark) (Kongsgaard et al., 2007). Patellar mid-tendon cross-sectional area (P-CSA) and tendon length were also determined with MRI as described previously (Kongsgaard et al., 2007). Patellar tendon CSA and length were manually outlined using the software program Osiris 4.19 (http://www.sim.hcuge.ch/osiris/). The mean value of three measurements of the same image was used for analysis. Duplicate measures of 10 different images on two separate days showed that the typical error percent of repeated measures of P-CSA was 4.4% for the mid tendon level. The MRI investigator was blinded with regard to subject treatment.

Patellar tendon biopsies

A Bard MAGNUM® Biopsy Instrument (C.R. Bard Inc., Covington, Kentucky, USA), with a disposable core biopsy needle (14 G), was used. Following sterilization the skin was injected with a local anesthetic (lidocaine, 1%) and a 3–5-mm-long incision was created just distal to the patella apex in patients with proximal tendon abnormality, and just proximal to the tibia insertion in patients with distal tendon abnormality. The biopsy needle was inserted onto the tendon surface at a ~ 30° angle and fired, securing a tissue sample of approximately 8 mg. Samples were snap-frozen in liquid nitrogen and stored at –80 °C. Tendon biopsies were taken from both legs at 0 and 12 weeks. Care was taken to avoid obtaining tissue from the previous biopsy site. All biopsy samples were analyzed in an investigator-blinded fashion.

Biochemical analysis of collagen, pyridinoline crosslink and pentosidine concentrations

Freeze-dried tendon samples were hydrolyzed in 6 M HCl (+108 °C, 24 h), evaporated into dryness and dissolved into H_2O. Hydroxyproline (collagen specific) was measured spectrophotometrically (Creemers et al., 1997). Hydroxylysyl pyr-

idinoline (HP), lysyl pyridinoline (LP) and pentosidine (Pent) were separated via a single reversed-phase HPLC (high-performance liquid chromatography) run and detected on the basis of their natural fluorescence (Bank et al., 1997). At 0–16 min the wavelength for HP and LP fluorescence was 400 nm for emission and 295 nm for excitation. The wavelength was varied at 16–60 min to 328/378 nm to measure the pentosidine. For the elution of the crosslinks, a gradient was built up to contain 17% eluent B (75% acetonitrile with 0.13% HFBA) at 0 min and 25% eluent B at 30 min. Eluent A was 0.13% HFBA. The flow rate was 1 mL/min. HP was eluted at 12 min, LP at 13.5 min and pentosidine at 23 min. The calculations of collagen crosslink(s) density are based on the use of pure compounds of HP, LP and pentosidine as external standards in each HPLC run. The HPLC system used included the Quaternary Gradient Pump unit, PU-2089 Plus, Intelligent AutosamplerAS-2057 Plus and Intelligent Fluoresence Detector, FP-2020, by Jasco (Jasco Scandinavia AB, Mölndal, Sweden). Data processing software was Jasco Chrompass. The LiChroCART''® 125-4 column was from Merck Hitachi (Merck KGaA, Darmstadt, Germany).

Patellar tendon mechanical properties

The details and reliability of this method have been reported previously (Hansen et al., 2006). Subjects were tested between 14:00 and 17:00 hours. Synchronized values of patellar tendon elongation (ΔL), obtained from ultrasound recordings, and patellar tendon forces (ΔF) were sampled. Measurements were performed on both legs. All trials were analyzed to a greatest common force for each individual subject. Force–deformation curves were fitted to a second- or third-order polynomial fit that exceeded $R^2 = 0.95$ in all cases. Tendon stiffness ($\Delta F/\Delta L$) and modulus (stress/strain) were calculated in the final 20% of the curves. The mean of the three contractions yielding the greatest force was used for analysis. Analysis was performed in an investigator-blinded fashion.

Half-year follow-up

Six months after the termination of the treatment, each patient received a half-year follow-up letter including the treatment satisfaction, VAS and VISA-p questionnaires. The half-year follow-up questionnaires were completed by 11/12 subjects in CORT, 9/12 subjects in ECC and by 11/13 subjects in HSR (Fig. 1).

Statistical analysis

All data are presented as means ± SD and range. Statistical analyses were performed using GraphPad Prism® Version 4.01 and GPower version 3.0.10. The VISA-p score was defined as the primary outcome measure. A sample size calculation was performed *a priori* based on an expected change of 20 points in the VISA-p score within the ECC group (Frohm et al., 2007). A group size of eight subjects was required in order to detect a significant within-group effect size (Cohen's *d*) of 1.0 with an 80% power ($P < 0.05$). The Mann–Whitney *U*-test was used to analyze for differences between affected and healthy tendon baseline values. The Wilcoxon matched-pairs signed-ranks test was used to analyze for changes within each group. Kruskal–Wallis ANOVA by ranks with Dunns' *post hoc* test was used to test for differences in absolute values and relative change differences globally between groups. For repeated measures of VISA-p and VAS scores, we used the Friedman test, followed by Dunns' *post hoc* test. Categorical data were analyzed using a global 3 × 2 chi-square analysis. All tests were carried out as two-tailed with a chosen α-level of 0.05. Typical error percents for duplicate measures were calculated as $[(SD_{diff}/\sqrt{2})/\text{Mean}] \times 100$ (Hopkins, 2000).

Results

All three groups were similar at baseline. Twenty-six (70%) and 11 (30%) of subjects suffered from unilateral and bilateral patellar tendinopathy, respectively. Sonographical abnormality was proximal to the tibia insertion in six (16%) subjects and distal to the patella insertion in 31 (84%) subjects. There were no obvious differences in the clinical outcome, or other parameters, between patients with proximal and distal tendon abnormality. No appreciable adverse events or side effects occurred in any of the groups during the intervention or the follow-up periods. The mean training session compliance rate for ECC and HSR subjects was 89 ± 8% and 91 ± 5%, respectively, and all subjects fulfilled at least 75% of all prescribed sessions. All CORT subjects complied with both consultations. The mean activity level during the 12-week intervention period was not different from the baseline level for any of the three groups.

VISA-p and VAS improved significantly ($P < 0.05$) and similarly in all groups from baseline to 12 weeks. The VISA-p and VAS scores decreased in CORT ($P < 0.05$) and were unchanged in ECC and HSR from week 12 to the half-year follow-up (Fig. 4). The relative VISA-p improvement from baseline to the

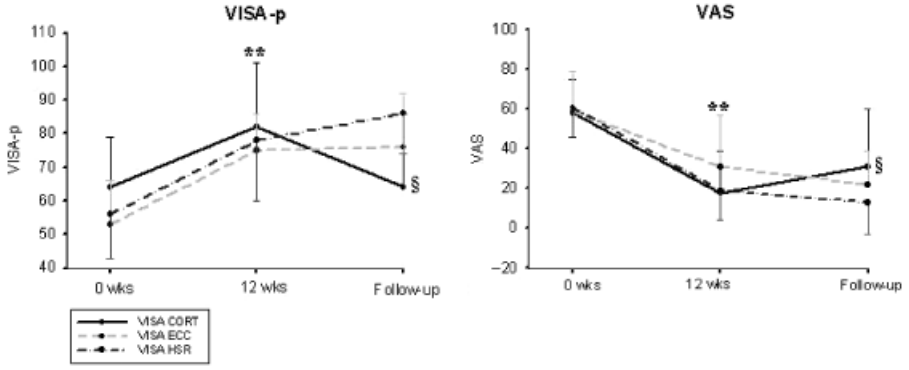

Fig. 4. VISA-p and VAS score at baseline (0 weeks), after the treatment intervention (12 weeks) and at the half-year follow-up (follow-up) for the three intervention groups. Values are means ± SD. **Significantly different from 0 weeks, $P < 0.01$. §Significantly different from 12 weeks, $P < 0.05$.

Table 2. Clinical and sonographical assessments

	CORT ($n=12$)	ECC ($n=12$)	HSR ($n=13$)
VISA-p – 0W	64 ± 14 (40–80)	53 ± 13 (29–78)	56 ± 13 (29–73)
VISA-p – 12W	82 ± 19** (34–100)	75 ± 3** (59–92)	78 ± 18** (29–95)
VISA-p – 1/2 year	64 ± 22§ (35–100)	76 ± 16 (45–98)	86 ± 12 (62–98)
VISA-p Δ0W – 1/2 year (%)	13 ± 33 (−44 to 78)	54 ± 57£ (22–203)	65 ± 71£ (4–238)
VAS – 0W	58 ± 17 (25–83)	59 ± 20 (32–80)	61 ± 15 (29–82)
VAS – 12W	18 ± 21** (0–68)	31 ± 26** (0–73)	19 ± 15** (0–42)
VAS – 1/2 year	31 ± 29§ (0–82)	22 ± 17 (0–55)	13 ± 16 (0–55)
VAS Δ0W – 1/2 year (%)	−47 ± 54 (−97 to 63)	−55 ± 53 (−100 to 72)	−70 ± 31£ (−97 to −17)
T-thickness – 0W (mm)	7.3 ± 2.0 (5.2–12.5)	7.3 ± 1.3 (5.5–9.5)	8.3 ± 2.2 (5.1–11.7)
T-thickness – 12W (mm)	6.3 ± 1.8** (4.2–10.3)	6.6 ± 1.3 (5.1–8.6)	7.1 ± 1.7** (4.9–10.1)
Δ T-thickness (%)	−13 ± 9† (−32 to 2)	−8 ± 19 (−35 to 39)	−12 ± 14† (−44 to 2)
CA – 0W (# pixels)	11 089 ± 10 433 (1609–35 244)	11 186 ± 6607 (1022–21 654)	15 116 ± 8749 (3331–30 806)
CA – 12W (# pixels)	6534 ± 8497** (234–21 586)	8939 ± 6276 (321–22 133)	9069 ± 6447** (901–21 234)
Δ CA (%)	−52 ± 49†† (−97 to 70)	−23 ± 29 (−97 to 105)	−45 ± 23†† (−83 to −11)

Values are means ± SD.

Values in brackets are range.

**Significantly different from 0 week ($P<0.01$).

§Significantly different from 12 weeks, $P<0.05$.

£Significantly different from steroid group ($P<0.05$).

†,††Significantly different from eccentric group ($P<0.05$) ($P<0.01$).

T-thickness, tendon thickness; 0W, 0 weeks/baseline; 12W, 12 weeks/post-intervention; Δ, relative change in time interval; CA, color area.

half-year follow-up was higher in HSR and ECC than CORT ($P<0.05$). The relative improvement in VAS from baseline to the half-year follow-up was significantly greater in HSR compared with CORT ($P<0.05$) (Fig. 4 and Table 2).

At 12 weeks, nine CORT (75%), five ECC (42%) and nine HSR subjects (70%) were satisfied with their clinical outcome. Four CORT (36% of responders), two ECC (22% of responders) and eight HSR subjects (73% of responders) were satisfied at the half-year follow-up. This distribution differed between groups ($P<0.05$), with HSR being the most satisfied.

Tendon thickness decreased significantly from 0 to 12 weeks in CORT (13 ± 9%) and HSR (12 ± 14%) ($P<0.01$) but not in ECC (Table 2). The CA decreased significantly from 0 to 12 weeks in CORT (52 ± 49%) and HSR (45 ± 23%) ($P<0.01$), but not in ECC.

Baseline values of structural, mechanical and crosslink properties for the 37 affected and the 26 healthy tendons are reported in Table 3. MVC (peak knee extension moment) and maximal tendon force were greater for healthy compared with affected legs at baseline ($P<0.05$). There were no differences in quadriceps anatomical cross-sectional area, tendon stiffness or modulus between healthy and affected tendons at baseline. There were no differences between affected and healthy tendons in the collagen concentration, HP/LP ratio or pentosidine concentrations (Table 3). The HP concentration tended to be higher in affected compared with healthy tendons ($P=0.08$). The LP concentration was significantly higher in affected vs healthy tendons ($P<0.05$) (Table 3).

P-CSA increased in ECC from 0 to 12 weeks ($P<0.05$) (Table 5). Q-ACSA was not different between groups at baseline and increased from 0 to 12 weeks for ECC and HSR ($P<0.01$) (Table 5). The relative increase in Q-ACSA was greater for ECC (7 ± 6%) and HSR (7 ± 3%) than CORT (1 ± 4%) ($P<0.01$).

The collagen concentration remained unchanged from 0 to 12 weeks in all three groups but tended to decrease in CORT ($P=0.10$) and to increase in HSR ($P=0.19$) (Table 4). The HP/LP ratio was unchanged from 0 to 12 weeks in CORT and ECC

Table 3. Baseline structural and mechanical properties

	Affected knees ($n = 37$)	Healthy knees ($n = 26$)
Q-ACSA (mm^2)	8322 ± 1126 (6721–10 015)	8329 ± 824 (6253–12 168)
MVC (N m)	164 ± 42† (116–274)	188 ± 52 (112–301)
PTF (N)	5681 ± 1376† (3459–9554)	6387 ± 1869 (3878–10 439)
Stiffness (N/mm)	3252 ± 787 (1714–4739)	3364 ± 1064 (1595–5328)
Modulus (GPa)	1.7 ± 0.5 (0.8–2.7)	1.9 ± 0.6 (0.8–3.2)
Coll con (mg/mg DW)	0.625 ± 0.17 (0.276–0.900)	0.695 ± 0.17 (0.344–0.972)
HP/LP ratio	39 ± 13 (12–70)	44 ± 23 (14–93)
HP con (mmol/mol coll)	768 ± 268 (397–1572)	659 ± 167 (359–1021)
LP con (mmol/mol coll)	24 ± 12† (11–74)	18 ± 10 (6–44)
Pent con (mmol/mol coll)	17 ± 10 (4–46)	17 ± 10 (6–41)

Values are means ± SD. Values in brackets are range.
†Significantly different from healthy ($P < 0.05$).
Q-CSA, quadriceps anatomical cross-sectional area; MVC, peak knee extension moment; PTF, peak tendon force; con, concentration; coll, collagen; DW, dry weight; HP, hydroxylysyl pyridinoline; LP, lysyl pyridinoline; pent, pentosidine.

but increased significantly in HSR ($P < 0.05$). HP and LP concentrations were unchanged from 0 to 12 weeks in all three groups and there were no differences in the relative changes between groups. The pentosidine concentration was unchanged from 0 to 12 weeks in CORT and ECC but decreased in HSR ($P < 0.05$) (Table 4). The relative changes in the collagen concentration, HP/LP ratio and pentosidine concentration were significantly different between CORT and HSR (Table 4).

MVC (peak knee extension moment) and peak tendon force (PTF) increased from 0 to 12 weeks in ECC ($P < 0.05$) and HSR ($P < 0.05$), but remained unchanged for CORT (Table 5). All the other patellar tendon mechanical properties remained unchanged in all groups.

Table 4. Collagen and crosslink properties (affected tendons)

	CORT ($n = 12$)			ECC ($n = 12$)			HSR ($n = 13$)		
	0W	12W	Δ (%)	0W	12W	Δ (%)	0W	12W	Δ (%)
Coll con (mg/mg DW)	0.670 ± 0.10 (0.565–0.900)	0.566 ± 0.15 (0.333–0.731)	−16 ± 22 (−41 to 16)	0.552 ± 0.22 (0.270–0.816)	0.499 ± 0.16 (0.288–0.684)	−1 ± 38 (−65 to 45)	0.626 ± 0.21 (0.190–0.865)	0.676 ± 0.13 (0.418–0.879)	+14 ± 47£ (−51 to 262)
HP/LP (ratio)	40 ± 15 (21–62)	35 ± 11 (19–48)	−11 ± 25 (−42 to 20)	32 ± 13 (12–70)	35 ± 17 (14–55)	+9 ± 43 (−55 to 55)	40 ± 11 (16–55)	47 ± 15* (23–73)	+19 ± 44£ (−40 to 86)
HP con (mmol/mol coll)	893 ± 389 (461–1571)	792 ± 203 (466–1641)	−10 ± 40 (−40 to 63)	847 ± 345 (397–1282)	886 ± 230 (531–1156)	+16 ± 55 (−20 to 126)	734 ± 165 (501–1004)	783 ± 175 (579–1103)	+13 ± 43 (−37 to 120)
LP con (mmol/mol coll)	23 ± 13 (15–45)	24 ± 10 (17–52)	+9 ± 17 (−13 to 40)	27 ± 17 (12–74)	30 ± 20 (12–67)	+16 ± 52 (−47 to 81)	19 ± 7 (11–37)	19 ± 6 (9–31)	+10 ± 53 (−39 to 100)
Pent con (mmol/mol coll)	17 ± 15 (6–46)	16 ± 12 (7–39)	+14 ± 79 (−59 to 167)	21 ± 18 (4–45)	15 ± 4 (10–21)	−15 ± 40 (−53 to 58)	15 ± 6 (6–27)	10 ± 6* (2–19)	−23 ± 42£ (−84 to 43)

Values are means ± SD. Values in brackets are range.
*Significantly different from 0W ($P < 0.05$).
£Significantly different from steroid group ($P < 0.05$).
0W, 0 weeks/baseline; 12W, 12 weeks/post-intervention; Δ (%), relative change in time interval; coll, collagen; con, concentration; DW, dry weight; LP, lysyl pyridinoline; HP, hydroxylysyl pyridinoline; pent, pentosidine.

Discussion

The main findings of the present study were that the different treatment regimes had similar short-term clinical effects and clinical patient satisfaction, but these parameters differed on a long-term basis. Specifically, ECC and HSR maintained their clinical improvements whereas they deteriorated in CORT at the half-year follow-up. Additionally, the good clinical effects of HSR were accompanied by reductions of tendon abnormality and changes in the ECM composition, indicating an increased turnover and

Table 5. Mechanical and structural properties (affected tendons)

	CORT ($n=12$)			ECC ($n=12$)			HSR ($n=13$)		
	0W	12W	Δ (%)	0W	12W	Δ (%)	0W	12W	Δ (%)
P-CSA (mm^2)	109 ± 24 (71–145)	114 ± 23 (90–167)	+7 ± 16 (−16 to 39)	107 ± 15 (87–129)	124 ± 18* (99–151)	+17 ± 12£ (−3 to 38)	106 ± 19 (78–140)	114 ± 25 (76–166)	+10 ± 18 (−8 to 42)
Q-ACSA (mm^2)	8173 ± 1019 (6845–10 435)	8103 ± 1157 (6596–10 263)	−1 ± 4 (−6 to 6)	8511 ± 767 (7134–9975)	9125 ± 1130** (7517–11 078)	+7 ± 6££ (0–20)	8282 ± 1530 (6253–12 168)	8967 ± 1560** (6990–12 945)	+7 ± 3££ (2–13)
MVC (N m)	168 ± 57 (117–274)	189 ± 49 (116–272)	+11 ± 19 (−18 to 35)	156 ± 28 (116–215)	170 ± 30* (106–223)	+8 ± 12 (−16 to 27)	174 ± 28 (127–228)	191 ± 44** (90–244)	+11 ± 9 (−2 to 30)
PTF (N)	6021 ± 1817 (4154–9554)	6354 ± 1659 (3998–9353)	+8 ± 19 (−9 to 44)	5361 ± 888 (3961–6945)	5750 ± 1006* (3890–8186)	+9 ± 14 (−14 to 36)	5593 ± 1191 (3459–7636)	6396 ± 1699** (2970–8371)	+19 ± 24 (−20 to 63)
Stress (MPa)	45 ± 15 (26–86)	45 ± 16 (22–87)	−1 ± 7 (−14 to 10)	40 ± 9 (22–56)	41 ± 9 (23–58)	+1 ± 7 (−12 to 12)	47 ± 15 (28–78)	44 ± 18 (27–79)	−1 ± 4 (−4 to 11)
Strain (%)	5.4 ± 0.9 (3.9–7.0)	5.4 ± 1.2 (2.9–6.8)	+3 ± 32 (−50 to 48)	4.5 ± 1.1 (2.4–6.1)	5.0 ± 1.4 (2.5–7.1)	+14 ± 21 (−24 to 41)	5.1 ± 1.4 (2.3–6.9)	4.9 ± 1.7 (2.8–8.8)	−4 ± 29 (−43 to 45)
Stiffness (N/mm)	2921 ± 895 (1714–4347)	3033 ± 989 (1536–4889)	+9 ± 42 (−43 to 114)	3448 ± 758 (2225–4502)	3211 ± 984 (2161–5542)	−6 ± 23 (−39 to 28)	3387 ± 644 (2545–4739)	2941 ± 734 (1817–4217)	−11 ± 24 (−45 to 33)
Modulus (GPa)	1.5 ± 0.4 (0.9–2.2)	1.6 ± 0.6 (0.8–2.7)	+9 ± 40 (−41 to 105)	1.8 ± 0.4 (1.4–2.5)	1.6 ± 0.4 (1.2–2.2)	−6 ± 23 (−39 to 28)	1.9 ± 0.6 (0.8–2.7)	1.7 ± 0.5 (0.9–2.4)	−5 ± 54 (−53 to 137)

Tendon mechanics calculated on baseline mid tendon CSA and common force.

Values are means ± SD. Values in brackets are range.

*,**Significantly different from 0W ($P<0.05$) ($P<0.01$).

£,£££Significantly different from steroid group ($P<0.05$) ($P<0.01$).

0W, 0 weeks/baseline; 12W, 12 weeks/post-intervention; Δ(%), relative change in time interval; P-CSA, patellar tendon cross-sectional area; Q-CSA, quadriceps anatomical cross-sectional area; MVC, peak knee extension moment; PTF, peak tendon force.

de novo synthesis of the collagen network. Somewhat surprisingly, the functional biomechanical properties did not differ between affected and healthy tendons and were unaffected by the treatment.

Clinical effects

The baseline VISA-p and VAS scores herein correspond with previous reports (Purdam et al., 2004; Visnes et al., 2005), and the VISA-p improvement of ~ 20 points from 0 to 12 weeks in all groups agrees with previous findings on ECC in patellar tendinopathy (Purdam et al., 2004; Jonsson & Alfredson, 2005; Frohm et al., 2007). The exact mechanisms of the pain reduction cannot be established as it remains unknown how management affects the secretion of the chemical agents associated with pain in tendinopathy i.e. substance P, glutamate and calcitonin gene-related peptide (Danielson et al., 2007).

Currently, exercise-based managements are almost exclusively based on eccentric contractions (Visnes & Bahr, 2007), but HSR is clearly a feasible and promising alternative. The strain pattern of the patellar tendon will certainly be unaffected by the contraction mode *per se*, and the importance of the contraction mode is therefore questionable (Cannell et al., 2001; Jonsson & Alfredson, 2005). However, eccentric contractions may reduce peak loads and prolong loading time due to a lower voluntary contraction velocity (Andersen et al., 2006). In the present study, HSR was performed slowly and included both eccentric and concentric movements, and ultimately resulted in somewhat more favorable adaptations. Combined eccentric and concentric exercises have previously been shown to be clinically effective in Achilles tendinopathy (Silbernagel et al., 2001). Therefore, there does not appear to be an obvious reason for avoiding concentric movements in the management of patellar tendinopathy if movement velocity is restricted.

HSR proved more effective than ECC with regard to tendon tissue normalization and collagen turnover/production, and tended to improve the clinical outcomes more than ECC. It is possible that the frequency and magnitude of loading may explain the advantageous effects of HSR. HSR was only performed three times per week, thus entailing a longer restitution period between loading sessions. It has been shown that collagen synthesis response to exercise is rather slow (Langberg et al., 1999), and that good clinical improvements are possible with only two weekly high-magnitude loading sessions (Frohm et al., 2007). Loading magnitude was considerable in HSR, and tenocyte loading magnitude appears to be positively related to anabolic gene expression and inversely related to catabolic gene expression (Lavagnino et al., 2003; Arnoczky et al., 2007). Collectively, although the number of subjects in this study is limited, our data may suggest that therapeutic tendon loading should be of high magnitude and only performed every other or third day. However, future studies are needed in order to make any conclusions regarding optimal loading magnitude and loading frequency. Also, it cannot be ruled out that possible differences in muscle activation/coordination pattern between the bilateral knee extension in HSR and the unilateral knee extensions in ECC might influence the patellar tendon loading pattern and the subsequent adaptive response. Finally, although ECC appeared to be inferior to HSR in some aspects, ECC have unquestionable advantages in that this treatment regime can be performed by the patients at home and has very low treatment costs.

Studies have reported good short-term clinical effects following corticosteroid injections in tendinopathy, while positive long-term clinical effects are scarce (Shrier et al., 1996; Koenig et al., 2004). The present data show that CORT yielded good short-term clinical effects with a reduction in pain, vascularization and tendon swelling. However, the clinical improvement faded from 12 weeks to the half-year follow-up, which is in agreement with that observed in lateral epicondylitis (Smidt et al., 2002). Albeit speculative, the poor long-term clinical effect of CORT might be related to the immediate pain relief and conceivable early initiation of intense sport activity. Also, the present collagen and crosslink data indicate an impaired collagen synthesis in CORT. Because corticosteroids reportedly inhibit angiogenesis, tenocyte proliferation and ECM synthesis (Wong et al., 2004), it is possible that corticosteroids might reduce tendon abnormality, but may not increase tendon load tolerance.

In this present study, subjects were allowed to continue sporting activities during the intervention period if these could be completed with only minimal pain (VAS <30). The mean weakly hours of leisure time activity during the intervention period were not different from the baseline value in all three groups. Previously, conservative management of patellar tendinopathy has been reported to be unsuccessful when applied in active competing athletes (Visnes et al., 2005). However, in accordance with earlier findings on Achilles tendinopathy (Silbernagel et al., 2007), our results support that continued sporting activity *per se* does not impair clinical improvement if pain during activity is somewhat restricted. However, it cannot be ruled out that the clinical improvements may have been greater if sporting activity had been disallowed.

Ultrasonography

The mean AP tendon thickness has been reported to be ~ 8 mm in patellar tendinopathy and ~ 4 mm in

healthy tendons (Cook et al., 1997), which is in agreement with the present data. Also, tendinopathy-associated neovascularization is related to the areas of tissue degeneration, and nerve structures in the vicinity of these blood vessels seem to be responsible for pain (Alfredson & Ohberg, 2005). Subsequently, a good clinical outcome in tendinopathy has generally been associated with normalization of the tendon structure and vascularity (Koenig et al., 2004; Ohberg et al., 2004). In the present study, clinical improvements were indeed accompanied by a normalization of the ECM, including its vascular supply, supporting an association between ECM normalization and clinical improvements.

The exact mechanism(s) of reduced vascularization and tendon swelling following loading-based treatments have not been established. Tendinopathy was recently characterized as an exaggerated repair process possibly resulting from a failure to regulate matrix metalloproteinase (MMP) activity (de Mos et al., 2007) and tenocyte production of ECM components (Cook et al., 2004; Scott et al., 2008a). Tensile loading influences tenocyte production of collagen, proteoglycans, glycosaminoglycans, growth factors, MMPs and collagen incorporation (Lavagnino et al., 2003; Arnoczky et al., 2007; Langberg et al., 2007; Wang et al., 2007). Therefore, mechanical loading might reverse degenerative processes and produce a more organized and normal ECM. Additionally, the vascular endothelial growth factor (VEGF) has been shown to be substantially elevated in tendinopathic and degenerated tendinous tissue (Pufe et al., 2005; Scott et al., 2008b) and might therefore be involved in the neovascularization process occurring with tendinopathy. Therefore, although purely speculative, therapeutic loading might reduce the hypervascularization by reducing the tenocyte expression of VEGF (Scott et al., 2008b). Also, corticosteroids induce a direct vasoconstrictor effect on smooth muscle cells, suppress the production of vasodilators (e.g. nitric oxide) (Suzuki et al., 2003), and affect phagocytic activity and tenocyte production of various ECM components (Wong et al., 2004). Thus, corticosteroids may potentially influence the ECM composition in ways that may reduce tendon abnormality as observed with CORT.

Crosslinks and collagen concentration

The mature intermolecular covalent crosslinks HP and LP are important for tendon function and biomechanical properties (Bailey, 2001; Avery & Bailey, 2005). The present study is the first to quantify collagen crosslinks in human patellar tendons. Despite the unique anatomy and considerable loading demand, the crosslinks of the healthy patellar tendons in this study correspond to values reported in other human tendons (Bank et al., 1999; de Mos et al., 2007). Chronically elevated HP and LP are believed to represent an early stage of tissue healing or an impaired remodeling process (Bank et al., 1999), and increases in pyridinolines in the affected tendons of this study suggest a poorly regulated repair process (de Mos et al., 2007; Scott et al., 2008a)

The collagen content of the affected and healthy tendons of this study was similar. Previous studies have reported a slightly lower collagen content in affected tendons (Riley et al., 1994; Bank et al., 1999), although preceding corticosteroid injections complicate the interpretation (de Mos et al., 2007). Although extensive efforts were made to obtain tissue from the abnormal tendon regions in this study, we cannot rule out the possibility that healthy tissue was occasionally sampled from the affected tendons. However, the different pyridinoline concentrations in the affected vs healthy tendons suggest that the biopsy came from abnormal tissue. The collagen concentration actually tended to decrease from 0 to 12 weeks in CORT ($-16 \pm 22\%$, $P = 0.10$), which seems to corroborate earlier reports of lower collagen concentrations after corticosteroid injections. Thus, it remains to be established whether the collagen concentration of tendinous tissue in tendinopathy is different from that of healthy tendinous tissue remains to be established.

Advanced glycation end-products (AGEs), including pentosidine, are used as biomarkers of collagen network age (Bailey, 2001; Avery & Bailey, 2005). In contrast to others (Bank et al., 1999; de Mos et al., 2007), we did not demonstrate lower pentosidine concentrations in affected compared with healthy tendons (Table 3). Also, in contrast to previous findings (Bank et al., 1999; de Mos et al., 2007), the HP/LP ratio, a marker of hydroxylation and collagen turnover, did not differ between affected and healthy tendons. Thus, notwithstanding the limitations of the biopsy procedure, our data do not indicate a significantly higher collagen turnover or a more immature collagen network in affected vs healthy tendons.

Collagen crosslink properties have not been investigated previously in human interventional studies. In the present study, HSR alone displayed changes in the crosslink profile as indicated by the increased HP/LP ratio and decreased pentosidine concentration over 12 weeks while the collagen concentration tended to increase. Collectively, these findings indicate an elevated tendon collagen synthesis in HSR compared with CORT and ECC. In CORT, albeit not statistically significant, the collagen concentration and HP/LP ratio numerically decreased and the pentosidine concentration increased, which suggests a reduced collagen turnover and impaired collagen

synthesis. HP and LP concentrations did not change in any of the groups, implying that these crosslink properties are quite static.

Tendon mechanical properties

The mechanical properties of tendinopathy tendons have not been investigated previously and, to our surprise, were unaffected by the tendinopathy. The stiffness and modulus of the affected tendons are similar to those of healthy young men (Hansen et al., 2006; Kongsgaard et al., 2007). Further, the mechanical properties were unaltered as a result of the treatment in the present study. Tendinopathy is a painful condition, but the collagen and crosslink concentrations and mechanical properties' results collectively indicate that the pathological changes associated with tendinopathy affect the ground substance more than the load-bearing collagen network itself.

This study is the first human *in vivo* study to investigate tendon mechanical properties following corticosteroid injections. Corticosteroids reportedly affect tenocyte proliferation and viability, collagen production and deposition, scar formation, and synthesis of ECM components (Wong et al., 2004), and subsequently reduce tendinous tissue strength (Hugate et al., 2004; Haraldsson et al., 2006). Tendon mechanical properties were unaffected in this study and the absence of deleterious effects with corticosteroids may be related to the fact that the injections were given peritendinously and in moderate concentrations (Kapetanos, 1982). Indeed, increasing concentrations of corticosteroids progressively reduce tissue strength, tenocyte viability and collagen synthesis (Wong et al., 2004; Haraldsson et al., 2006).

Study limitations

The relatively small number of subjects in the present study is a limitation and does not allow any solid conclusions with regard to the differences between ECC and HSR. However, the study design, the elaborate data collection and invasive nature of the biopsy technique precluded a larger sample size. In our opinion, the mechanistic and comparative design of this study significantly increases its scientific value because such studies are rare and are needed to better understand tendinopathy and the management thereof. We encourage future studies with larger samples to firmly establish our clinical findings. With respect to the biopsy technique, it is important to consider the issue of the sampling site within the given tendon.

Perspectives

Presently, no consensus on optimal management of tendinopathy has been established (Cook et al., 1997). The lack of management consensus is mainly due to the absence of comparative randomized clinical trials in the area. Also, existing clinical studies on tendinopathy have more or less exclusively focused on clinical outcomes and have not provided a mechanistic perspective, thus limiting the possibility of developing new and more effective treatment options. The present study has compared three different management options in addition to investigating some of the underlying mechanisms of successful patellar tendinopathy management. We believe that this manuscript offers a number of novel findings that are likely to change the clinical practice and to influence future research on this clinical condition. Questions regarding the optimal type, magnitude and frequency of therapeutic loading in tendinopathy have been addressed by this manuscript but require further investigations.

Key words: tendon mechanical properties, jumper's knee, patellar tendon, collagen crosslinks.

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