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ORIGINAL ARTICLE

The effect of acute exercise on collagen turnover in human tendons: influence of prior immobilization period

L. Moerch · J. Pingel · M. Boesen · M. Kjaer · Henning Langberg

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Abstract Mechanical loading of human tendon stimulates collagen synthesis, but the relationship between acute loading responses and training status of the tendon is not clear. We tested the effect of prolonged load deprivation on the acute loading-induced collagen turnover in human tendons, by applying the same absolute load to a relative untrained Achilles tendon (2-week immobilization period prior to acute loading) and a habitually loaded contra-lateral Achilles tendon, respectively, within the same individuals. Eight untrained, healthy males had one lower limb totally immobilized for 2 weeks, whereas the contra-lateral leg was used habitually. Following the procedure both Achilles tendons and calf muscles were loaded with the same absolute load during a 1-h treadmill run. Tissue collagen turnover was measured by microdialysis performed post-immobilization but pre-exercise around both Achilles tendons and compared to values obtained by 72-h post-exercise. Power Doppler was used to monitor alterations in intratendinous blood flow velocity of the Achilles tendon and MRI used to quantitate changes in tendon cross-section area. Acute loading resulted in an increased collagen synthesis 72 h after the run in both Achilles tendons ($p < 0.05$) with no significant difference. No signs of acute tendon overloading were demonstrated by Power Doppler, and tendon cross-section area did not change as a result of immobilization and reloading. The present study indicates that 2 weeks of tendon load deprivation is not sufficient to affect the normal adaptive response to loading determined as increased collagen synthesis of peritendinous Achilles tendon tissue in humans.

Keywords Immobilization · Power Doppler · Blood flow velocity · Procollagen type I N-terminal peptide · Microdialysis

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L. Moerch · J. Pingel · M. Boesen · M. Kjaer · H. Langberg
Institute for Sports Medicine, Bispebjerg Hospital, Copenhagen and Centre for Healthy Aging, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark

H. Langberg
CopenRehab, Institute of Social Medicine, Department of Public Health and Centre for Healthy Ageing, Faculty of Heath Sciences, University of Copenhagen, Copenhagen, Denmark

H. Langberg (✉)
Department of Social Medicine, Institute of Public Health, University of Copenhagen, Copenhagen, Denmark
e-mail: henninglangberg@gmail.com

Introduction

Tendons are metabolic active structures (Langberg et al. 1999a) transferring tensile forces from muscle to bone leading to joint movement. Mechanical stress is known to play an important role in both the development and the adaptation of the tendons (Woo et al. 1980, 1981; Kjaer 2004; Reeves et al. 2005; Sun et al. 2010) leading to changes in the structural composition of the tendons as well as in changed mechanical properties (Kjaer et al. 2006; Couppe et al. 2008). In several studies, it has been shown that the synthesis of collagen I, the major structural component of human tendons, is increased in response to acute exercise (Langberg et al. 1999b; Heinemeier et al. 2003; Miller et al. 2005) as well as after prolonged training (Langberg et al. 2001, 2007). The increased net synthesis of collagen is reflected in the mechanical properties of the tendons with increased tensile strength and enlarged cross-sectional area of tendons in highly trained individuals (Birch et al. 1999; Rosager et al. 2002; Reeves et al. 2003a, b; Kongsgaard et al. 2005; Couppe et al. 2008). Despite the ability to adapt to loading, overuse injuries in tendons represent a major clinical problem. One of the reasons might be the very pure understanding of the dose–response relationship between degrees of mechanical loading and the adaptation of the tissue. We know that increased stress leads to adaptation of tendons and that the opposite—load deprivation—changes the mechanical properties of tendons by decreasing collagen synthesis (de Boer et al. 2007; Sun et al. 2010) or increasing collagen turnover probably resulting in a net loss of collagen (Christensen et al. 2008a), but still our knowledge is very limited.

The intention of the present study is to compare the effect of two different relative workloads on the adaptive response of collagen synthesis to exercise in tendons. This is done by immobilizing one leg for 2 weeks prior to loading, and by determination of collagen turnover using microdialysis in the peritendinous tissue and measuring Procollagen propeptides release. Both tendons are in the present experiment loaded with the same absolute load during a subsequent 1-h run, but the relative load applied to the two tendons is expected to be different due to the preceding one-legged immobilization procedure previously shown to result in a drop in calf muscle strength of 9 % (Pingel et al. 2009). The concentration of Procollagen type 1 N-propeptide (PINP) is used as a marker for collagen synthesis (Miyahara et al. 1982) and the concentration of type 1 collagen c-terminal telopeptide (ICTP) as a marker for collagen degradation (Garnero et al. 2003). We hypothesized that the Achilles tendon in the immobilized leg will have a higher collagen synthesis than the control tendon as a response to acute relative overload of the tendon. The markers of collagen turnover (PINP and ICTP, respectively) were measured in serum and dialysate representing systemic and peritendinous collagen turnover, respectively. In addition, the potential mechanical overload and vascular reaction to the exercise were determined in the Achilles tendons by Power Doppler.

Materials and methods

Subjects

Eight healthy male volunteers (23 ± 2 years; BMI 24 ± 3) were included in this quasi-experimental study approved by the Ethical Committee of Region Copenhagen (H-KF-319605) after obtaining oral and written acceptance from participants. Six of the volunteers were involved in recreational sports (self reported training: 5 ± 3 h/week). None of the subjects had any history of Achilles tendons symptoms or injuries, nor did they take any medications or were smoking.

Study design

A white plaster of Paris was applied to the lower leg on one leg from below the knee to the toes, randomly (envelope) on the dominant/non-dominant leg. The casted leg was left immobilized for 2 weeks (Immob; $n = 8$) with no weight bearing allowed at any time during the 2 weeks. The other leg served as a control with no restriction in loading or physical activity (Control; $n = 8$). This design made it possible to compare the influence of immobilisation (comparing "the immob leg before exercise" with "the control leg before exercise") and the effect of loading on a loaded leg (control leg post-running) and in a load-deprived leg (Immob leg post-running).

At the end of the 2 weeks of immobilization, the cast was checked for signs of load bearing (any marks on the white plaster of Paris resulted in exclusion). The plaster of Paris was then removed and microdialysis catheters were positioned ventrally to the Achilles tendon on both legs. Immediately after removal of the microdialysis catheters, the subjects were remobilized on a treadmill running at an individual pace for 1 h. The subjects were told to keep running at all times and if possible above 75 % of maximum heart rate, but were allowed to lower the pace, if they felt it was too uncomfortable. During the run, the subjects' heart rate were monitored. The microdialysis procedures were repeated 72-h post-exercise. MRI scans were performed before the immobilisation, following the run and 72 h after the exercise.

Microdialysis

Microdialysis was performed immediately following the immobilization as well as 72-h post-exercise and used to determine collagen turnover as previously described (Langberg et al. 1999a, b). The subjects arrived in the lab in the morning after an overnight fast. After removal of the cast, the skin was anaesthetised (Lidokain, 0.5 ml, 10 mg/ml) the custom-made microdialysis catheters (Langberg et al. 1999a) were placed in the peritendinous tissue ventral to the Achilles tendon under ultrasound guidance as close to the tendons as possible. The active part of membrane of the catheters covered the area 3–6 cm proximal to the Achilles tendon insertion on the calcaneus. The placement of the catheters was recorded and the second insertion 72-h post-exercise was placed 3 cm apart from the first insertion. The microdialysis catheters were placed in both legs and perfused with a Ringer-Acetate solution containing radioactive-labeled glucose for recovery determination (Scheller and Kolb 1991) at a rate of 2 µl/min by a syringe pump

(CMA 100). Dialysate was collected for a total of 4.5 h with the first 30 min of sampling discharged to minimize the risk of influence from the insertion of the catheters.

Doppler US

The ultrasound was performed using a GE Logic 9 scanner with a 15 MHz linear transducer type, M12L. The settings were standardized for all exams and the same experienced investigator (MB) performed all the scanning. The patients were examined in a prone position with the ankle in a relaxed position to insure that no passive or active tension was applied on the tendons. The Achilles tendons (both Immob and Control) were scanned in a longitudinal and transversal plan at the insertion, at the muscolotendinous border, and in a longitudinal plan at the midportion of the tendon. The tendons and peritendinous tissue were evaluated with gray scale US and color Doppler. The results from the Doppler examination were evaluated based on the presence, amount and distribution of Doppler activity as previously described in Boesen et al. (2006a). The tendons were graded according to the amount of color Doppler present in the region of interests (ROI) which were defined as the insertional area, midtendon area and muscolotendinous border in order to the obtained pictures. The grading system was identical to the one previously used (Boesen et al. 2006a) with 5 grades, where 0, no Doppler flow; 1, 1 or 2 tiny color inside ROI; 2, up to 50 % color inside ROI; 3, 50 to 90 % color inside ROI; 4, 90 to 100 % color inside ROI. Grade 0–1 is defined as normal flow. In each subdivided area, we stored the image with the highest amount of Doppler activity. We then used these images for post-procession and graded them according to ROI and Doppler activity. The tendons were divided into immobilized and control legs on the pre-, post- and 72-h post-exercise scans and blinded before the pictures of the Doppler activity were evaluated.

Cross-sectional area

MRI obtained axial plane images of the Achilles tendon with the ankle joint at 90°. Cross-sectional area (CSA) of the Achilles tendon was measured at 8 cut-points using a lower extremity coil [General Electric Sigma Horizon LX, 1.5 T, (T1)-weighed spin echo]. The scanning protocol for the Achilles tendon was: repetition time to echo time 625:15, field of view 16; matrix 256 × 256; slice thickness 3 mm; spacing 3 mm. To avoid differences in scanning procedure, one person scanned all images using a standardized protocol. CSA from triceps surae muscle was manually outlined using the software (http://www.sim.hcuge.ch/osiris; National Institutes of Health color scale mode). To account for the superimposed magnetic gradient field, the software program Osiris 4.19 was used to adjust the color intensity of each image (Coupe et al. 2008). The intensity was increased until the first pixel turned white in the calcaneus bone, before the images were shifted back to the gray scale image display for analyzing CSA (Coupe et al. 2008). All images were analyzed three times manually and single-blinded and the mean of the three measurements calculated.

Blood samples

Blood samples were taken from an anterocubital vein. The samples were used for measurements of the systemic levels of PINP and ICTP. Blood was collected via a butterfly (Vacuette, cannula 0.8 × 19 mm, 19 cm) and left on ice for 5–10 min or immediately centrifuged for 10 min with 3,800 rpm at 4 °C. The samples were stored at −80 °C for further analysis.

Analysis

The peritendinous concentration of Procollagen type 1 N-propeptide (PINP) was analysed and calculated as previously described (Langberg et al. 1999a). Collagen synthesis was measured by analysing the samples for PINP by a sandwich Elisa as previously described (Christensen et al. 2008b). The dialysate samples were diluted: 1:9, 1:10 or 1:20 before the analysis, based on previous analysis on the sample. Serum samples were not diluted before analysis. The detection level was 41 pg/ml and the intra-assay variation (coefficient of variation) of 4.9 % at 4.2 ng/ml. All the samples from the same subject were analysed on the same plate.

Collagen degradation was measured by analysing serum samples for concentration of type 1 collagen c-terminal telopeptide (ICTP) by the ICTP EIA assay (Orion Diagnostica; cat. no. 05892) as previously described (Christensen et al. 2008b). The serum samples were not diluted before analysis and all the samples from the same subject were analysed in the same assay. The detection level was in accordance to the manufacturer 0.3 ng/ml ICTP and intra-assay variation (coefficient of variation) 11.3 % at 2.9 ng/ml (Orion Diagnostica).

Statistical methods

In all statistical analysis, the level of significance was set to $p = 0.05$. All results are expressed as mean ± SD, unless otherwise stated. To test for difference in peritendinous levels of PINP, tendon CSA and Power Doppler changes a two-way ANOVA was used. A one-way ANOVA was used to test for differences in serum concentrations of PINP and ICTP. Graf Pad Prism 4.0 was used for all statistical analysis.

Results

All subjects completed the 2 weeks of immobilization without loading the immobilized leg. After removal of the plaster and the microdialysis catheters, the subject performed the 1-h exercise on the treadmill (all subjects ran for 60 min; HR: mean 90 % ± 7). The estimated maximal heart rate was calculated as 220 bpm minus age. The average speed was 9.5 km/h ± 1.1 km/h. The activity diaries of the subjects showed that the general activity level was very low before as well as during the immobilization period (results not shown).

Collagen metabolism

No effect of the load deprivation could be detected on the collagen synthesis of the immobilised Achilles tendons comparing the level of PINP in the peritendinous space of the two tendons following the immobilisation (Fig. 1). Furthermore, the concentration of PINP increased significantly around both Achilles tendons as a result of the 1-h run when determined 72 h later ($p = 0.006$) (Fig. 1). No significant difference could be detected in collagen synthesis in the response to exercise ($p = 0.56$).

In the serum, no significant change could be detected in the levels of PINP ($p = 0.62$; Fig. 2a), or in ICTP concentrations ($p = 0.07$: Fig. 2b).

Ultrasonography Doppler

There was a tendency toward an increased flow within the Achilles tendons as a result of the load deprivation or following the run, determined as increased color Doppler activity [($p = 0.05$); Fig. 3)], but there was no difference

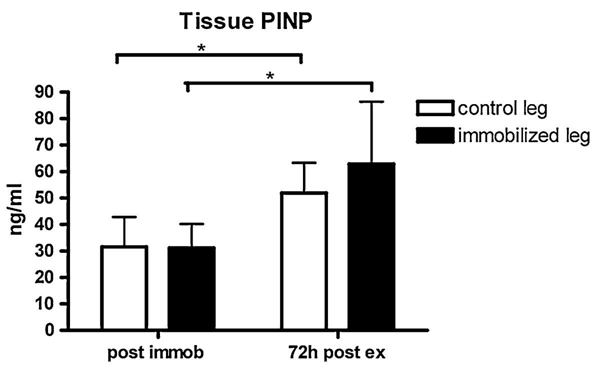

Fig. 1 Interstitial concentrations of Procollagen type I N-terminal propeptide (PINP) in the peritendinous tissue around the Achilles tendon measured immediately after and 72 h after 1 h of running in the previously immobilized leg (immob) or control leg (control). Values are corrected for relative recovery. *Error bars* represent SD. *$p < 0.05$

between the control leg and the immobilized leg ($p = 1.00$). In all the images taken throughout the study, the presence of Doppler activity was limited to grade 0–1 defined as below pathological flow, and with only a few measurements on grade 2.

Cross-sectional area

As previously reported, results on muscle cross-sectional area (reduced by 6 %) and calf muscle strength of the calf muscle (reduced by 9 %) confirmed that the immobilization had an effect on the muscular tissue (Pingel et al. 2009). With respect to the CSA of the Achilles tendon, no significant difference between the immobilized and control Achilles tendons was observed in any of the eight cuts

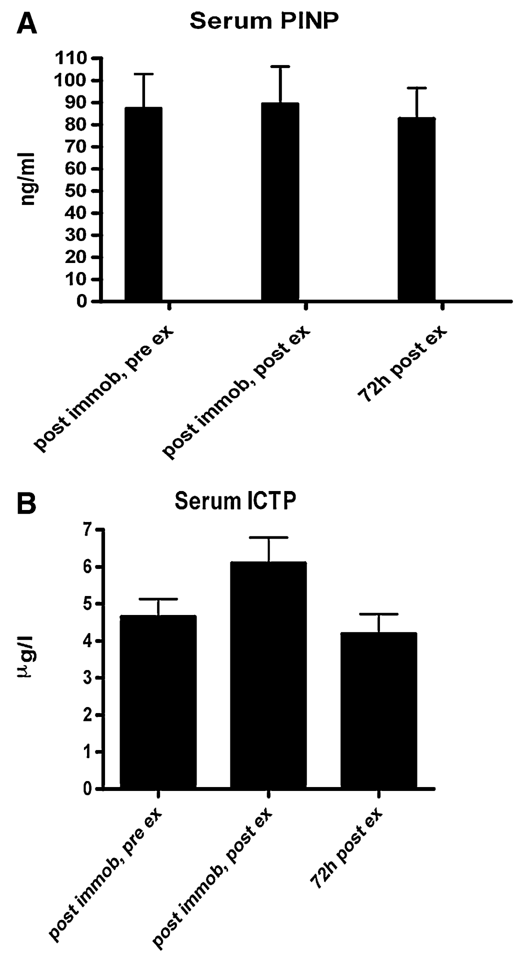

Fig. 2 **a** Serum concentrations of Procollagen type I N-terminal propeptid (PINP) measured following the immobilization period, respectively, before, after and 72 h after the 1-h run. *Error bars* represent SD. **b** Serum concentrations of C-terminal telopeptide of type I collagen (ICTP) measured following the immobilization period, respectively, before, after and 72 h after the 1-h run. *Error bars* represent SD

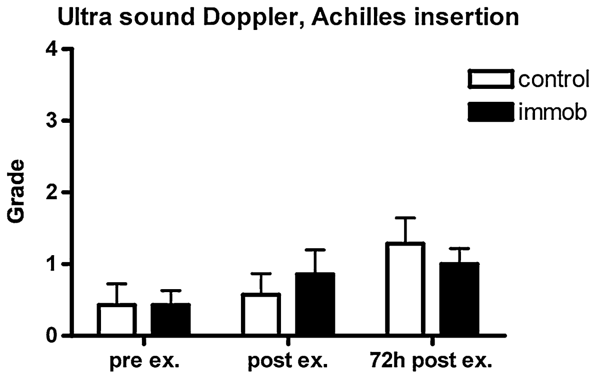

Fig. 3 Data from Power Doppler registration of Achilles tendon insertion, evaluated based on the presence, amount and distribution of Doppler activity. The grading system had 5 grades (*0* no Doppler flow, *1* 1 or 2 tiny color foci, *2* up to 50 % color inside ROI, *3* 50 to 90 % color inside ROI, *4* 90 to 100 % color inside ROI). The data are given as mean for immobilized and control legs divided into pre-, post- and 72-h post-exercise. *Error bars* represent SD

throughout the length of the Achilles tendon ($p = 0.10$; Fig. 4). When comparing the CSA pre- and post-immobilization, no significant difference could be detected over time or as a result of the immobilization ($p = 0.39$).

Discussion

The present study shows that immobilization of the human Achilles tendon for 2 weeks has no significant effect on the collagen synthesis in the tendon (Fig. 1). These data are in line with previous findings from other studies on the effect of stress deprivation of tendons measured in both human Achilles tendon (Christensen et al. 2008a, b; Shin et al. 2008) as well as in animal tendons (Vailas et al. 1988; Loitz et al. 1989; Eliasson et al. 2007, 2009; Heinemeier et al. 2009; Sun et al. 2010). The length of the immobilization however may influence the collagen synthesis as it was not changed after immobilization for 2 weeks (Christensen et al. 2008b), but did after immobilization for longer (Christensen et al. 2008a; Sun et al. 2010).

As a response to loading, previous studies have shown an acute effect on collagen synthesis (Olesen et al. 2007) that in humans was maintained up to 72 h after a long run (Langberg et al. 1999b; Heinemeier et al. 2003). There seems to be a dose–response relationship between load and collagen response (Magnusson et al. 2010) as one study was unable to demonstrate effect of low dose activities on collagen turnover (Doessing et al. 2010). The findings from most earlier studies fit with the present results showing an exercise-induced response with increased levels of PINP 72 h after exercise [from 29.0 ± 27.3 ng/ml (basal) to 60.2 ± 51.4 ng/ml (72-h post-exercise)]. In another study

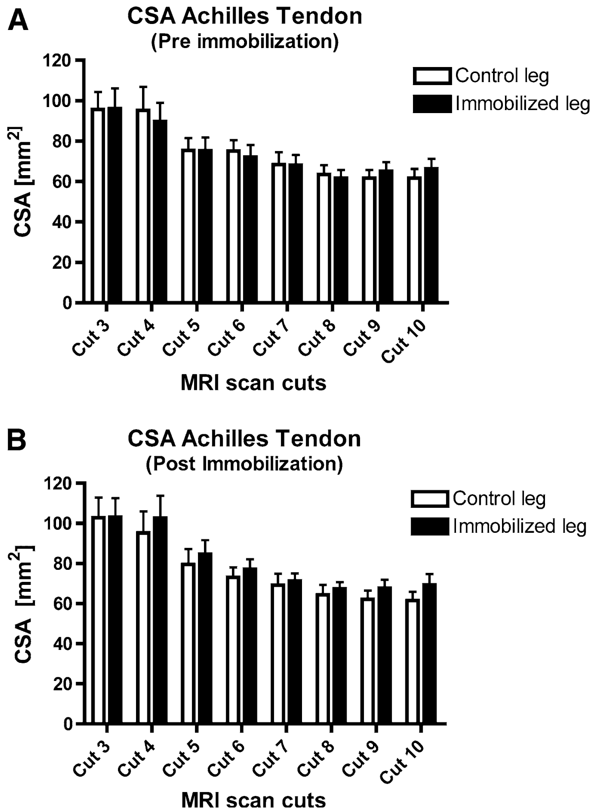

Fig. 4 Axial plane images of the Achilles tendon with the ankle joint at 90° were obtained by MRI. Cross-sectional area (CSA) of the Achilles tendon was measured at eight cut-points with a slice thickness of 3 mm. All images are analyzed three times manually and single-blinded and the mean of the three measurements calculated

using a similar protocol with 1-h run on a treadmill, changes in collagen type I turnover after exercise were determined as changed PICP levels (COOH-terminal propeptide of type I collagen) (Heinemeier et al. 2003). In that study, the PICP levels 72 h after exercise were 52 ± 12.6 ng/ml (Heinemeier et al. 2003) and these data correlate well with the levels found in the current study. Following a 3-h run, the PICP level was found to increase to 165 ng/ml after exercise and was accompanied by a rise in PICP plasma values (Langberg et al. 1999b) indicating a dose–response relationship.

We expected to be able to detect an increased exercise-induced response in the collagen turnover in the Achilles tendon of the previously immobilised leg as we expected this tendon to be subjected to a higher relative workload than the control Achilles tendon due to the drop in muscle strength in the immobilised calf (Pingel et al. 2009). However, this was not the case. The running exercise resulted in a significant increase in collagen synthesis and no significant difference in exercise-induced responses between immobilized and control tendon could be detected

(Fig. 1). Furthermore, no sign of overuse of the either of the tendons in response to the acute exercise could be detected as evaluated by Power Doppler. All together these data indicate that a 2-week period of stress deprivation has no significant influence on the ability of the human Achilles tendon to increase the collagen synthesis following exposure to a 1-h run. One limitation of the present study is the lack of a non-running control leg. However, as previously shown there seems to be no acute effect of a 2-week immobilisation on cross-sectional area of the tendon, a grouse measure of collagen turnover in the tendons (Christensen et al. 2008a, b). In the present study, we found no difference in collagen turnover as a response to load deprivation (Fig. 1). This could be due to a systemic change in the collagen turnover in the body as a response to the one leg being immobilised. However, the serum data does not indicate such a systemic change (Fig. 2a, b). The immobilisation of the one leg could have resulted in a general decrease in physical activity thus reducing the load on the control leg. The subjects wrote an activity diary both 3 days before the immobilization period and during the 2 weeks of immobilisation, and these diaries indicate that the activity level of the subjects was very low before as well as during the immobilization. Unfortunately, we do not have numerical data to test this. Additionally, it cannot be ruled out that workloads higher than used in the present study could have provided a different response and potentially demonstrated differences between the two legs, but based on the response from the subjects it was not realistic to use higher workloads.

All subjects were completely exhausted after the exercise, indicating relative work intensity close to 90 % VO_2 max, and could in our view not have been pushed any further.

The Power Doppler images support the notion that the combination of 2 weeks of stress deprivation and a 1-h run is not sufficient to produce any altered tendon vascular response to exercise. Intratendinous Doppler activity is known to be elevated in tendons of patients with chronic Achilles tendinopathy (Cook et al. 2005; Boesen et al. 2006a, b; Koenig et al. 2010). In the present study, no significant increase of intratendinous blood flow velocity was detected either as an immediate acute effect of exercise or 72-h post-running (Fig. 3). None of the subjects developed any sign of overloading of the Achilles tendons due to the present procedure. When interviewed following the 1-h run, none of the subjects complained about sore or painful tendons, however most of them reported sore calf muscles.

The CSA of the Achilles tendons was not influenced by the stress deprivation for 2 weeks at any distance from the bony insertion on the calcaneus bone to the musculotendinous junction indicating that the gross dimensions of the tendon was not largely affected by 2 weeks of immobilization (Fig. 4). This is supported by data showing that human tendon reacts slowly to loading stimuli and is very resistant to shorter periods of unloading (Hansen et al. 2003; Christensen et al. 2008a).

In conclusion, the present study indicates that a 2-week period of stress deprivation is not sufficient to significantly affect the adaptive response to an acute bout of exercise on collagen turnover in human Achilles tendons in vivo.

References

Birch HL, McLaughlin L, Smith RK, Goodship AE (1999) Treadmill exercise-induced tendon hypertrophy: assessment of tendons with different mechanical functions. Equine Vet J Suppl 30:222–226

Boesen MI, Koenig MJ, Torp-Pedersen S, Bliddal H, Langberg H (2006a) Tendinopathy and Doppler activity: the vascular response of the achilles tendon to exercise. Scand J Med Sci Sports 16:463–469

Boesen MI, Torp-Pedersen S, Koenig MJ, Christensen R, Langberg H, Holmich P, Nielsen MB, Bliddal H (2006b) Ultrasound guided electrocoagulation in patients with chronic non-insertional Achilles tendinopathy: a pilot study. Br J Sports Med 40:761–766

Christensen B, Dyrberg E, Aagaard P, Enehjelm S, Krogsgaard M, Kjaer M, Langberg H (2008a) Effects of long-term immobilization and recovery on human triceps surae and collagen turnover in the Achilles tendon in patients with healing ankle fracture. J Appl Physiol 105:420–426

Christensen B, Dyrberg E, Aagaard P, Kjaer M, Langberg H (2008b) Short-term immobilization and recovery affect skeletal muscle but not collagen tissue turnover in humans. J Appl Physiol 105:1845–1851

Cook JL, Kiss ZS, Ptasznik R, Malliaras P (2005) Is vascularity more evident after exercise? Implications for tendon imaging. AJR 185:1138–1140

Couppe C, Kongsgaard M, Aagaard P, Hansen P, Bojsen-Moller J, Kjaer M, Magnusson SP (2008) Habitual loading results in tendon hypertrophy and increased stiffness of the human patellar tendon. J Appl Physiol 105:805–810

de Boer MD, Selby A, Atherton P, Smith K, Seynnes OR, Maganaris CN, Maffulli N, Movin T, Narici MV, Rennie MJ (2007) The temporal responses of protein synthesis, gene expression and cell signalling in human quadriceps muscle and patellar tendon to disuse. J Physiol 585:241–251

Doessing S, Heinemeier KM, Holm L, Mackey AL, Schjerling P, Rennie M, Smith K, Reitelseder S, Kappelgaard AM, Rasmussen MH, Flyvbjerg A, Kjaer M (2010) Growth hormone stimulates the collagen synthesis in human tendon and skeletal muscle without affecting myofibrillar protein synthesis. J Physiol 588:341–351

Eliasson P, Andersson T, Aspenberg P (2009) Rat Achilles tendon healing: mechanical loading and gene expression. J Appl Physiol 107:399–407

Eliasson P, Fahlgren A, Pasternak B, Aspenberg P (2007) Unloaded rat Achilles tendons continue to grow, but lose viscoelasticity. J Appl Physiol 103:459–463

Garnero P, Ferreras M, Karsdal MA, Nicamhlaoibh R, Risteli J, Borel O, Qvist P, Delmas PD, Foged NT, Delaisse JM (2003) The type I collagen fragments ICTP and CTX reveal distinct enzymatic pathways of bone collagen degradation. J Bone Miner Res 18:859–867

Hansen P, Aagaard P, Kjaer M, Larsson B, Magnusson SP (2003) Effect of habitual running on human Achilles tendon load-deformation properties and cross-sectional area. J Appl Physiol 95:2375–2380

Heinemeier K, Langberg H, Olesen JL, Kjaer M (2003) Role of TGF-beta1 in relation to exercise-induced type I collagen synthesis in human tendinous tissue. J Appl Physiol 95:2390–2397

Heinemeier KMOJ, Haddad F, Schjerling P, Baldwin KM, Kjaer M (2009) Effect of unloading followed by reloading on expression of collagen and related growth factors in rat tendon and muscle. J Appl Physiol 106:178–186

Kjaer M (2004) Role of extracellular matrix in adaptation of tendon and skeletal muscle to mechanical loading. Physiol Rev 84:649–698

Kjaer M, Magnusson P, Krogsgaard M, Boysen Moller J, Olesen J, Heinemeier K, Hansen M, Haraldsson B, Koskinen S, Esmarck B, Langberg H (2006) Extracellular matrix adaptation of tendon and skeletal muscle to exercise. J Anat 208:445–450

Koenig MJ, Torp-Pedersen S, Boesen MI, Holm CC, Bliddal H (2010) Doppler ultrasonography of the anterior knee tendons in elite badminton players: colour fraction before and after match. Br J Sports Med 44:134–139

Kongsgaard M, Aagaard P, Kjaer M, Magnusson SP (2005) Structural Achilles tendon properties in athletes subjected to different exercise modes and in Achilles tendon rupture patients. J Appl Physiol 99:1965–1971

Langberg H, Ellingsgaard H, Madsen T, Jansson J, Magnusson SP, Aagaard P, Kjaer M (2007) Eccentric rehabilitation exercise increases peritendinous type i collagen synthesis in humans with Achilles tendinosis. Scand J Med Sci Sports 17:61–66

Langberg H, Rosendal L, Kjaer M (2001) Training-induced changes in peritendinous type I collagen turnover determined by microdialysis in humans. J Physiol 534:297–302

Langberg H, Skovgaard D, Karamouzis M, Bulow J, Kjaer M (1999a) Metabolism and inflammatory mediators in the peritendinous space measured by microdialysis during intermittent isometric exercise in humans. J Physiol 515(Pt 3):919–927

Langberg H, Skovgaard D, Petersen LJ, Bulow J, Kjaer M (1999b) Type I collagen synthesis and degradation in peritendinous tissue after exercise determined by microdialysis in humans. J Physiol 521(Pt 1):299–306

Loitz BJ, Zernicke RF, Vailas AC, Kody MH, Meals RA (1989) Effects of short-term immobilization versus continuous passive motion on the biomechanical and biochemical properties of the rabbit tendon. Clin Orthop Relat Res 265–271

Magnusson SP, Langberg H, Kjaer M (2010) The pathogenesis of tendinopathy: balancing the response to loading. Nat Rev Rheumatol 6:262–268

Miller BF, Olesen JL, Hansen M, Dossing S, Crameri RM, Welling RJ, Langberg H, Flyvbjerg A, Kjaer M, Babraj JA, Smith K, Rennie MJ (2005) Coordinated collagen and muscle protein synthesis in human patella tendon and quadriceps muscle after exercise. J Physiol 567:1021–1033

Miyahara M, Njieha FK, Prockop DJ (1982) Formation of collagen fibrils in vitro by cleavage of procollagen with procollagen proteinases. J Biol Chem 257:8442–8448

Olesen JL, Heinemeier KM, Gemmer C, Kjaer M, Flyvbjerg A, Langberg H (2007) Exercise-dependent IGF-I, IGFBPS, and type I collagen changes in human peritendinous connective tissue determined by microdialysis. J Appl Physiol 102:214–220

Pingel J, Moerch L, Kjaer M, Langberg H (2009) The influence of training status on the drop in muscle strength after acute exercise. Eur J Appl Physiol 106:605–611

Reeves ND, Maganaris CN, Ferretti G, Narici MV (2005) Influence of 90-day simulated microgravity on human tendon mechanical properties and the effect of resistive countermeasures. J Appl Physiol 98:2278–2286

Reeves ND, Maganaris CN, Narici MV (2003a) Effect of strength training on human patella tendon mechanical properties of older individuals. J Physiol 548:971–981

Reeves ND, Narici MV, Maganaris CN (2003b) Strength training alters the viscoelastic properties of tendons in elderly humans. Muscle Nerve 28:74–81

Rosager S, Aagaard P, Dyhre-Poulsen P, Neergaard K, Kjaer M, Magnusson SP (2002) Load-displacement properties of the human triceps surae aponeurosis and tendon in runners and non-runners. Scand J Med Sci Sports 12:90–98

Scheller D, Kolb J (1991) The internal reference technique in microdialysis: a practical approach to monitoring dialysis efficiency and to calculating tissue concentration from dialysate samples. J Neurosci Methods 40:31–38

Shin D, Finni T, Ahn S, Hodgson JA, Lee HD, Edgerton VR, Sinha S (2008) Effect of chronic unloading and rehabilitation on human Achilles tendon properties: a velocity-encoded phase-contrast MRI study. J Appl Physiol 105:1179–1186

Sun YL, Thoreson AR, Cha SS, Zhao C, An KN, Amadio PC (2010) Temporal response of canine flexor tendon to limb suspension. J Appl Physiol 109:1762–1768

Vailas AC, Deluna DM, Lewis LL, Curwin SL, Roy RR, Alford EK (1988) Adaptation of bone and tendon to prolonged hindlimb suspension in rats. J Appl Physiol 65:373–376

Woo SL, Gomez MA, Amiel D, Ritter MA, Gelberman RH, Akeson WH (1981) The effects of exercise on the biomechanical and biochemical properties of swine digital flexor tendons. J Biomech Eng 103:51–56

Woo SL, Ritter MA, Amiel D, Sanders TM, Gomez MA, Kuei SC, Garfin SR, Akeson WH (1980) The biomechanical and biochemical properties of swine tendons—long term effects of exercise on the digital extensors. Connect Tissue Res 7:177–183