Effects of long-term immobilization and recovery on human triceps surae and collagen turnover in the Achilles tendon in patients with healing ankle fracture

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IMMobilIZATION IS OFTEN PART of the postoperative treatment for many surgical procedures, including fractures of the lower extremity. It is well known that immobilization leads to muscle atrophy, loss of bone mass, as well as a limited functional level (7, 28, 29). It is therefore important to minimize the length of the immobilization period to reduce atrophy and loss of function and thus to reduce the time required before full recovery of the changes induced by the disuse. A full understanding of the immobilization-induced effects on the components of the muscle-tendon unit is also important to provide optimal treatment and rehabilitation of patients after a period of immobilization (8, 27, 30).

It is currently well known that immobilization affects muscle and bone tissue, but there is still uncertainty about how tendon tissue reacts to immobilization. Most studies trying to consider this issue have been performed in animals (4, 9, 21, 25), and it has been proposed that both tendon ultrastructure, biochemistry and biomechanical properties are altered after a period of immobilization (28). However, not much is known about how tendon tissue responds to immobilization in humans. To our knowledge, only one study has tried to consider this, de Boer et al. (1) found that patellar tendon collagen synthesis rate was decreased after 21 days of immobilization. This is supported by previous studies in animals demonstrating a decrease in the activity of enzymes involved in the biosynthesis of type I collagen (prolyl-4-hydroxylase and galactosylhydroxy-lysyl-glucosyltransferase) in rat tendons in response to immobilization (9). However, other studies using rabbits have found that both collagen synthesis and degradation, measured by stable isotopes, increased in response to a period of immobilization (4). None of these animal studies have been able to find any significant change in the overall concentration of hydroxyproline, a measure for total collagen content in relation to short-term immobilization (1 wk) (9, 25). Nakagawa and colleagues (21) have shown that 5 wk of immobilization of the hindlimbs decreases significantly both the surface area and the diameter of the collagen fibers of the Achilles tendon. This was, however, not confirmed in a recent study by Zhou et al. (35), finding no change in collagen fibril diameter or area in response to 4 or 8 wk of immobilization in rabbits. Even though from the above-mentioned studies it seems that the collagen turnover is affected by changes in mechanical loading, it has not been possible to detect any reduction in tendon size due to immobilization. Thus both 3 wk of immobilization (1) and 90 days of bed rest (24) have shown not to induce any significant changes in human tendon cross-sectional area (CSA).

The aim of this study was to analyze the effect of both a period of immobilization and a following recovery period on the tendon collagen metabolism in vivo in humans. For this...
purposely, patients with unilateral fracture of the ankle joint were used. This was done due to the fact that healthy volunteers ethically only could be immobilized for a short period of time (2 wk), whereas individuals with fractures habitually are immobilized for a longer period and thus provide an opportunity for studying tendon collagen turnover simultaneously with healing of the fracture. The majority of these patients were immobilized for 6–8 wk. For determination of the in vivo tendon concentrations of indirect markers for collagen metabolism the microdialysis technique was used. NH$_2$-terminal propeptide of type I collagen (PINP) is released in a one-to-one manner, making PINP a very good marker for collagen type I synthesis. The removal of this propeptide from the procollagen molecule seems to be necessary for collagen fiber formation (20). COOH-terminal telopeptide of type I collagen (ICTP) and COOH-terminal telopeptide region of type I collagen (ICTP) were the markers used for collagen type I degradation. They are both telopeptides that are cleaved from the collagen molecule during degradation (3). Furthermore, clinical parameters such as muscle strength and CSA of the calf muscle were measured to demonstrate and monitor the changes in load applied on the tendon tissue, and tendon CSA was also measured. Based on the studies mentioned above, it is hypothesized that immobilization would decrease and remobilization increase collagen turnover but that total tendon size would remain unchanged.

MATERIALS AND METHODS

Subjects. Twelve patients (8 men and 4 women) with unilateral fracture of the malleolus were recruited through the Emergency and Orthopaedic Department of Bispebjerg Hospital (Copenhagen, Denmark). The patients were immobilized for a period of 6–10 wk with a short leg cast (ROM-walker). Patients were allowed partial weight bearing using the ROM-walker halfway through the immobilization period. None of the subjects (age, 30 ± 2.4 yr; height, 179 ± 4 cm; weight, 84 ± 5 kg; body mass index, 26 ± 1.2 kg/m$^2$) had any history of previous tendon symptoms or injuries (Table 1). In adherence with the Declaration of Helsinki, all patients were informed about the study approved by the local Human subject Ethics Committee of Copenhagen and Frederiksberg ([KF] 01 319605), and they all gave a written informed consent to participate.

Study design. The first examination was acquired at the earliest possible time point following the reconstruction of the ankle joint, on average 4 days (3–7 days) after the fracture. At this time point, both legs were computed tomography (CT) scanned, and microdialysis and the strength test were performed on the control leg only. The patients were immobilized on average for 7 wk (6–10 wk), and were examined again in relation to the removal of the ROM-walker. This was followed by a remobilization period of the same length as the previous immobilization period, and at the end of the remobilization period the patients were examined a third time. The patients were given the same rehabilitation as normally offered by the hospital, consisting of an exercise program to improve balance and strength of the lower leg, and the patients were encouraged to perform these exercises daily.

Strength test. The patients were seated in a rigid steel frame with one knee fully extended and the hip flexed at 90°, and the foot rested in a neutral position (90°) against a steel plate. The position of the heel was adjusted to ensure that the mechanical axis of rotation corresponded to the lateral malleolus. The back of the seat was adjusted to prevent displacement during the test. Plantar flexion force was measured with a strain gauge load cell attached between the footplate and the steel frame. The control leg was at all time points tested first. After warm-up (5 forceful contractions), three force ramp contractions and two maximum isometric plantar flexions were performed. The contractions lasted for ~5 s with a 1-min rest in between. Force signals were sampled at 50 Hz by an analog-to-digital converter, and the data were stored on a computer for subsequent analysis. Data were analyzed for maximum isometric plantar flexion force based on the highest out of the five efforts.

Measurements of muscle and tendon CSA. At all time points, Achilles tendon and triceps surae muscle CSA were measured using a CT scanner (Siemens, 4500 scanner). Axial scans with a slice thickness of 5 mm, matrix 1,024, 120 kV, 200 mA, and 1.0 s). CSA of the calf muscles was measured 10 cm distally to the top of caput fibula (corresponding to the largest CSA) and Achilles tendon CSA was measured at the level of the most distal part of the medial malleolus with the ankle joint at 90° (corresponding to the area where the tendon are most prone to rupture). Because the patients in the present study underwent surgical stabilization (with metal parts) of the ankle joint, it was not possible to determine CSA using the safer MRI scans.

The CSAs of the different regions were measured by the use of the software Web1000. All scans were blindered and randomized. Scans were measured twice on 2 separate days, and the average was used as the CSA. Because of difficulties in separation of the different muscles in the calf and to minimize the measurements error, CSA of the calf muscles was measured by drawing a straight line between the dorsal part of tibia and the dorsal part of fibula and then following the edge of the soleus and gastrocnemius muscles, leading to a small but systematic overestimation of the total CSA of the triceps surae muscle. The mean coefficient of variation (CV) for repeated measurements was 1.6% for muscle CSA and 4.7% for tendon CSA.

Microdialysis. Microdialysis was used to determine collagen turnover and performed in principle as described previously (14, 16). The microdialysis catheter was placed in the peritendinous space ventral and as close to the Achilles tendon as possible. This was done under local anesthesia (lidocaine, 10 mg/ml), leaving the active part of the catheter in the area from 3 to 6 cm proximal to the Achilles tendon insertion on the calcaneus bone. The catheter was perfused at a rate of 2 ml/min with a Ringer-aceatate solution containing radioactively labeled D-[3-H]glucose (specific activity 250 Ci, Perkin-Elmer) by a high-precision syringe pump (CMA 100), in accordance to the internal reference method (26). Radioactively labeled glucose was used because no labeled PINP was commercially available. To evaluate the setup, an in vitro experiment was performed (data not shown). Here it was found that the calculated concentrations of PINP would be slightly underestimated when using labeled glucose as the reference substance. The dialysate was collected every hour for a total of 5 h, weighed to eliminate the possibility of ultra filtration, and immediately frozen to −80°C until analysis was performed. The first hour of collected dialysate was not used for analysis, thereby minimizing the possible effects of the insertion of the microdialysis catheter (13).

The total amount of radioactivity that the patients received through out the study, in relation to microdialysis, was <0.001 mSv, which does not give any considerable risks for injuries. For comparison, the normal radioactivity dose that a person in Denmark receives yearly is 3 mSv.

The microdialysis catheters were custom made in the laboratory, as previously described (13). The catheters were sterilized using ethylene oxide before usage. The interstitial peritendinous concentrations of

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<th>Table 1. Anthropometric data</th>
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<td>No. of subjects</td>
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<td>Range age, yr</td>
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<td>Mean age, yr</td>
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<td>Mean BMI, kg/m²</td>
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Values are means ± SE. BMI, body mass index.
PINP and ICTP were calculated using the internal reference calibration method (26) as previously described (13).

**Blood and urine sampling.** All blood samples were taken in the morning (patients been fasting from midnight, intake of water was allowed). Blood samples were collected by a butterfly needle (Terumo; cannula 0.8 × 19 mm, 18 cm) from the antecubital vein and left on ice for 10–15 min before they were centrifuged for 10 min with 3,800 rpm at 4°C. Blood samples were stored at −80°C for subsequent analysis.

Urine was collected and immediately frozen to −80°C for further analysis of urinary levels of CTx and creatinine. Concentrations of creatinine were measured to evaluate the filtration rate in the kidneys.

**Measurements of collagen fragments.** Both serum and dialysate were analyzed for PINP by a sandwich ELISA as previously described (22). Serum samples were diluted 1:50 before analysis, and dialysate was diluted 1:8. All samples from each subject were always analyzed in the same assay. The detection level was 41 pg/ml, and the intra-assay variation (CV) was 4.7% (at 480 g/l, and the intra-assay variation (CV) was 11.3% at 2.9 μg/l (Orion Diagnostica)).

Concentrations of CTx were measured in the urine with the Urine Crosslaps ELISA assay from Nordic Bioscience. The urine samples were diluted 1:2 before analysis, and the results were corrected for creatinine levels in the same urine sample. The detection level was, according to the manufacturer, 50 μg/l, and the intra-assay variation (CV) was 4.7% (at 480 μg/l).

**Statistics.** In all statistical analysis, the level of significance was set to P < 0.05. All results are expressed as means ± SE. A χ² test was used for analysis of ICTP. To test for differences in serum and urine concentrations of PINP and CTx, a one-way ANOVA was used followed by Tukey’s multiple comparison tests. A two-way ANOVA was used to analyze for differences in muscle and tendon CSA. The two-way ANOVA was followed by a Tukey’s post hoc test. Because of the operation of the fracture no baseline measurements of isometric maximum voluntary contraction and peritendinous concentrations of PINP were available in the intervention leg; thus a one-way ANOVA was used to analyze the control leg, and a Student’s paired t-test was used for analysis of changes in the immobilized leg. Graf Pad Prism and Sigma STAT were used for statistical analysis.

**RESULTS**

**Muscle CSA.** No significant difference in CSA of the calf muscles between the two legs before the immobilization period was found (Fig. 1A). A statistically significant decrease in CSA of the calf muscles in the immobilized leg was detected (P < 0.001) after 7 wk of immobilization, with an average decrease of 15% (from 5,316 ± 306 to 4,517 ± 307 mm²). After the immobilization period, there were a significant difference in the CSA between the immobilized leg and the control leg (P < 0.001). The CSA of the calf muscles in the immobilized leg increased significantly during the 7 wk of recovery by 9% (4,943 ± 285 mm²; P < 0.001). The CSA of the immobilized leg was still significantly lower after the recovery period, compared with before the immobilization period (P < 0.01) as well compared with the control leg (P < 0.001) (Fig. 1A). CSA of the calf muscles in the control leg did not change significantly throughout the study (5,434 ± 239, 5,330 ± 268, and 5,427 ± 261 mm²; P > 0.05).

**Muscle strength.** Preimmobilization strength of the calf muscles was only measured in the control leg, and it was used for comparison with the immobilized leg. Maximum isometric strength decreased significantly after ~7 wk of immobilization (P < 0.0001) in the immobilized leg, with a total loss in strength of 54% (from 238.7 ± 21.3 to 110.4 ± 16.7 N·m). The strength of the immobilized leg was also significantly decreased compared with the control leg after the immobilization period (P < 0.0001). The strength of the immobilized leg increased significantly in response to the ~7 wk of recovery by 37% (175.9 ± 14.4 N·m; P < 0.001). The strength of the immobilized leg after the remobilization period was, however, still significantly lower than the strength of the control leg at the same time point (P < 0.05), as well as significantly lower than the strength of the control leg before the immobilization period (P < 0.01) (Fig. 1B). No significant change in the strength of the control leg was observed (238.7 ± 21.3, 223.3 ± 21.2, and 224.8 ± 26.4 N·m; P > 0.05).

**Achilles tendon CSA.** The CSA of the Achilles tendon was measured 3–7 days after the patients had fractured their ankle. At this time point, a statistically significant difference in the CSA of the Achilles tendon was found when comparing the control leg with the immobilized leg (P < 0.001), with the CSA of the Achilles tendon of the immobilized leg being 16% (75.2 ± 3.2 and 89.4 ± 7.4 mm²) larger. All other measurements of tendon CSA both after the immobilization period and the remobilization period resembled the measured area of the control leg at baseline (Table 2). This resulted in no significant change in CSA of the Achilles tendon, when comparing the immobilized leg after the immobilization period and after the remobilization period with the control leg before the immobi-
Table 2. Cross-sectional area of the Achilles tendon before immobilization, after immobilization, and after recovery

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<th>Control Leg</th>
<th>Immobilized Leg</th>
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<tr>
<td>Preimmobilization, mm²</td>
<td>75.2±3.2</td>
<td>89.4±7.3*</td>
</tr>
<tr>
<td>Postimmobilization, mm²</td>
<td>72.9±4.5</td>
<td>75.8±4.3</td>
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<tr>
<td>Postrecovery, mm²</td>
<td>70.8±3.3</td>
<td>74.2±4.5</td>
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Values are means ± SE for 12 subjects. *P < 0.01.

...immobilization period (for further explanation, see DISCUSSION). In addition, no change in CSA was found in the control leg or between the experimental days (P > 0.05).

Collagen metabolism. The increase in serum PINP from baseline to after the immobilization period was significant (from 65.8 ± 8.1 to 86.5 ± 6.7 ng/ml; P < 0.01). The serum concentrations of PINP was also statistically increased after the remobilization period compared with before the immobilization period (95.0 ± 8.4 ng/ml; P < 0.001) (Fig. 2A). Peritendinous concentrations of PINP were only measured in the control leg before immobilization, and thus these data are used for comparison to the immobilized leg. The concentration of PINP in the dialysate increased significantly in the immobilized leg after the 7 wk of immobilization compared with the control leg before immobilization (from 21.4 ± 11.5 to 256.5 ± 44.5 ng/ml; P < 0.001), with a 12-fold increase. This led to a significant difference between the two legs after the immobilization period (55.8 ± 18.3 and 256.5 ± 44.5 ng/ml; P < 0.01). Peritendinous concentrations in PINP decreased significantly in relation to remobilization in the immobilized leg (103.0 ± 14.9 ng/ml; P < 0.01). No significant difference was found in the measured concentrations of PINP in the control leg (21.4 ± 11.5, 55.8 ± 18.3, and 44.3 ± 14.9 ng/ml; P > 0.05) (Fig. 2B).

There was no significant change in urine concentrations of CTx corrected for the level of creatinine throughout the study period (286.2 ± 56.5, 269.0 ± 22.5, and 353.8 ± 79.6 μg/mmol; P > 0.05) (Fig. 2C). ICTP concentrations were significantly different between the two legs after the immobilization period, with the peritendinous concentrations of ICTP being higher in the immobilized leg than the control leg (9.8 ± 2.1 and 2.1 ± 0.5 μg/l; P < 0.01). There was no difference in concentrations between the two legs after the remobilization period (4.2 ± 1.3 and 1.9 ± 0.7 μg/l; P > 0.05) (Fig. 2D).

DISCUSSION

It is well known that tendon tissue is able to respond to altered levels of physical activity, both acutely and in response to longer periods of training (6, 12, 14, 19). To date, only one study have tried to clarify the effects of immobilization on collagen turnover in human tendon tissue (1), but to our knowledge no previous studies have analyzed collagen turnover after a period of remobilization. The present study was performed to investigate the effects of immobilization and subsequent recovery on the turnover of collagen tissue in human tendons. The main findings were that Achilles tendon CSA seems not to change, with even several weeks of immobilization, and that a longer period of immobilization, due to an ankle fracture, resulted in both an increase in markers for collagen synthesis and degradation in the peritendinous space. However, these markers most likely derive from an increased bone turnover in relation to the ankle fracture and not from an increased turnover of tendon tissue.

Muscle CSA and strength. In accordance with previous studies (5, 15, 23, 29, 30, 32), we found a significant decrease in muscle CSA and strength in response to immobilization. Previous long-term studies (6–8 wk) have shown a somewhat larger decrease in strength of ~75% in response to immobilization (23, 29), whereas others have shown a similar decrease of ~50% in peak torque in response to a longer period of immobilization (6–20 wk) (27, 30, 32, 34). Similarly, previous...
studies have also found a slightly larger decrease in calf muscle CSA in response to immobilization of the ankle joint (5, 23, 29, 30, 32). In the present study, CSA and strength increased in response to 7 wk of remobilization, but they did not reach baseline values. The results from the present study support earlier studies pinpointing that the period needed for full recovery of the tissue and strength is often longer than the length of the immobilization period (23, 29, 30, 32). This further emphasizes the importance of a good and functionally rehabilitation program to ensure a faster recovery.

Tendon CSA. Even though there was a clear unloading of the tendon tissue, measured by a decrease in muscle CSA and strength, this did not result in changes in the CSA of the tendon, measured by CT scanning. However, a significantly increased CSA of the Achilles tendon was found in the immobilized leg preimmobilization compared with the control leg before the immobilization period (Table 2). In a study on the effects of 2 wk of immobilization on the Achilles tendon using a similar setup as the present we showed that the variation between the dominant and the nondominant leg in Achilles tendon CSA is neglectable (B. Christensen, unpublished data). This indicates that the difference between injured and the control Achilles tendon in the present study probably is a result of the fracture. It is well known that a fracture of the ankle is accompanied by a swelling of the tissue around the ankle joint, and hence in the peritendinous tissue of the Achilles tendon and the tendon itself (2). The reason for the swelling of the Achilles tendon in the present study is unknown, and unfortunately it was not possible from the present CT scans to correct the CSA of the tendon for increased water content. The increase in volume of the ankle joint, in response to the fracture, resembles the difference in CSA found between the immobilized leg and the control leg. We therefore decided to use the control leg before immobilization as a reference, and this leg did not show any difference in CSA of the Achilles tendon throughout the study.

Previous studies have similarly found that tendon CSA did not change with immobilization. Recently de Boer et al. (1) found no change in patellar tendon CSA after 21 days of lower leg suspension, and in a study by Reeves et al. (24) tendon CSA was unchanged after 90 days of bed rest. These results are supported by animal studies, where 4 or 8 wk of immobilization in rabbits did not result in any changes in tendon size (18, 35). However, studies are currently debating whether a chronic total unloading of the tendon is capable of reducing the CSA of tendons. Maganaris et al. (17) showed a mean 17% decrease in patella tendon CSA, in response to paralysis, compared with able-bodied subjects. Interestingly, Nakagawa et al. (21) have shown that 5 wk of immobilization in rats resulted in a 43% reduction in the surface area of collagen fibers from the Achilles tendon in the immobilized animals compared with control animals, as well as a 20% decrease in fiber diameter. However, the decrease in fiber area was not confirmed in a recent study by Zhou et al. (35) where neither 4 nor 8 wk of immobilization of rabbits resulted in any change in collagen fiber or fibril diameter.

Immobilization and tendon collagen turnover. To our knowledge, local measurements of concentrations of the markers for collagen type I synthesis and degradation used in the present study (PINP and ICTP) have not previously been performed in relation to immobilization. The hypothesis of the present study is that tendon collagen synthesis decreases in relation to a period of immobilization; however, this could not be confirmed in the present study (Fig. 2B). The local concentrations of PINP increased significantly (12-fold) in the immobilized leg after the immobilization period (Fig. 2B). The systemic concentrations of PINP increased too (Fig. 2A) but not to the same extent as in the dialysate (1.3- vs. 12-fold), supporting the notion that the peritendinous increase in PINP was due to local changes in collagen synthesis. One explanation for the 12-fold increase in PINP after the 7 wk of immobilization could be that the peritendinous space is also close to the malleolus bone, and thus to the place of the fracture, and that the measured increase in PINP partly reflects an increased bone synthesis (callus) in response to bone healing. In fact, 90% of the new mature bone matrix is made up by type I collagen. Resorption and the formation of new bone are coupled, but resorption is much faster than formation, which, however, increases more significantly (7, 31, 33). This fits well with the observed increase in serum PINP and that no change in urinary CTx could be detected after the 7 wk of immobilization in the present study. In accordance with the present study, serum PINP has been shown to peak after 6 wk of immobilization due to ankle fracture (7). The measured increase in peritendinous PINP in the present study is much higher than has been found in relation to a rather large acute bout of exercise (36 km of running) (14), further supporting the assumption that the measured increase in PINP is a combined result of an increase in bone formation and thus type I collagen synthesis and a reduced formation of collagen type I in the tendons in response to immobilization. The relative contribution of the two responses to the overall increase in collagen synthesis cannot be concluded from the present study, thus emphasizing the importance of combing the findings with studies on immobilization of healthy subjects. Even though a previous study has confirmed that the peritendinous concentrations of a variety of different substances resembles the concentrations inside the tendon (11), is it not clear to what extend the peritendinous measurements are affected by changes in the tissue surrounding the tendon (e.g., in relation to a fracture). It was hypothesized that peritendinous concentrations of ICTP would increase in response to immobilization. Data in the present study support the hypothesis because the peritendinous concentrations of ICTP during immobilization were significantly increased compared with the control leg (Fig. 2D). The systemic concentration of CTx was not changed in relation to immobilization (Fig. 2C), indicating that the increased degradation found in the peritendinous space was due to locally increased collagen degradation, either due to increased bone resorption or tendon collagen tissue breakdown. Thus both collagen synthesis and collagen degradation increased in response to 7 wk of immobilization.

Remobilization and tendon collagen turnover. The concentrations of PINP in the immobilized leg decreased again after the remobilization period, and there were no significant differences between the two legs at the end of the study (Fig. 2B). We would have expected to find an increase in response to recovery, because training studies have shown increased local levels of PINP (12). This could reflect that the remobilization has not been intense enough to induce a training effect. Another possible explanation could be that the real effect of training was observed earlier and that, after the 7 wk of
remobilization, the tendon tissue was already fully recovered. The decreased level of PINP most likely reflects the notion that the bone was close to complete healing.

We did not find any significant difference in peritendinous concentrations of ICTP between the two legs after the remobilization period (Fig. 2D). Systemic concentrations of CTx did not change either (Fig. 2C). This is in accordance with a training study (military) by Langberg et al. (12) where it was found that peritendinous concentrations of ICTP increased after 4 wk of training but returned to baseline levels after 11 wk of training. The same group could not detect a change in ICTP concentrations after 12 wk of eccentric training (10). Thus both peritendinous concentrations of ICTP and PINP follow the same pattern in response to recovery.

**Conclusion.** A longer period of immobilization induces a decrease in muscle CSA and strength. Even though tendon CSA was unchanged, there was an increase in both collagen synthesis and degradation, which could reflect a modulation of the tissue due to the changes in loading pattern. Most likely, however, the local measurements reflect bone healing in response to the fracture. Remobilization resulted in a significant increase in muscle CSA and strength, but without the muscle CSA reaching baseline levels, indicating that the effect of the immobilization is not fully overcome after a remobilization period of the same length as the immobilization. These data have great importance for clinical practice, emphasizing that rehabilitation of muscles after immobilization is very important. Tendon CSA did not change as a result of immobilization, indicating that tendons are more robust toward changes during periods of immobilization and thus more protected against overuse in the remobilization period.

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**REFERENCES**


