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Hylonome

Case Report Article

Effects of joint unloading and reloading on human cartilage morphology and function, muscle cross-sectional areas, and bone density – a quantitative case report

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Abstract

Recent studies have shown that thinning of human cartilage occurs with unloading, but no data are available on the effect of remobilization (after immobilization) on knee joint cartilage status in humans. We examined a 36-year-old patient after 6 weeks of unilateral immobilization. Knee joint cartilage morphology (patella and tibia), patellar cartilage deformation, and thigh muscle cross-sectional areas were assessed with quantitative MR imaging and bone density with peripheral quantitative computed tomography (pQCT) during 24 months of remobilization. The immobilized limb displayed lower muscle cross-sectional areas (MCSA) of the knee extensors (-36%), lower bone density of the femur and tibia (-12/-6%), lower patellar cartilage thickness (-14%), but no side differences of tibial cartilage thickness. During remobilization, side differences decreased to -4% for knee extensor MCSAs, to -6%/-3% for femoral and tibial BMD, and to -8% for patellar cartilage thickness. No change was observed in tibial cartilage. Patellar deformation decreased from 9% to 4% after 15 months. In conclusion, we observed substantial changes of thigh MCSAs, but little (patella) to no (tibia) change in cartilage thickness during remobilization. These preliminary results indicate that human cartilage macro-morphology may be less adaptive to variations of the mechanical loading than muscle and bone.

Keywords: Articular Cartilage, Bone Mineral Density, Magnetic Resonance Imaging, Muscle Cross-Sectional Areas, Immobilization, Remobilization

Introduction

It has been recognized that functional adaptation of muscle and bone tissue occurs during unloading and during immobilization[1,2]. The impact of unloading and immobilization on articular cartilage has been investigated in animal models[3-11] and has been recently reviewed by Vanwanseele et al.[12]. Previous work in animals either reported no change in cartilage thickness[11], a significant decrease[3,4], a compartment-specific response[10], or differential effects on the calcified and uncalcified cartilage[8]. In particular, Palmoski et al.[3] observed that cartilage thickness decreased in the absence of normal joint loading, despite preservation of a full range of joint motion. Moreover, investigators have described deterioration of biochemical[5,7,11] and mechanical properties[4,11] of the cartilage during immobilization.

Several animal studies have also looked at the effect of remobilization on articular cartilage. The authors[5] found no difference in thickness of the uncalcified cartilage in immobilized animals, but a lower calcified cartilage thickness of the femoral condyles. They interpreted incomplete restoration of uncalcified femoral cartilage thickness as inability of previously unloaded cartilage to withstand the loads occurring during the remobilization process[6]. The results of these

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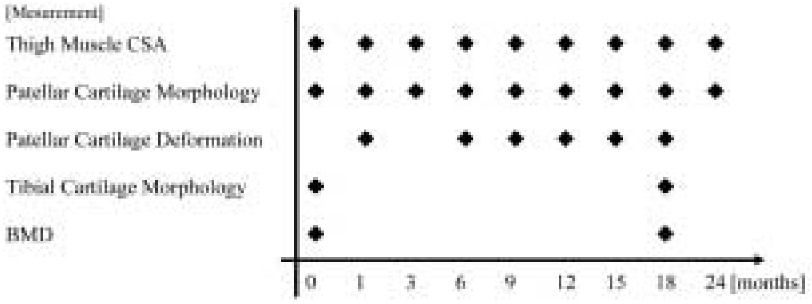

Figure 1. Timeline of data-acquisition. The diamonds display at which point in time during the 24-month remobilization period measurements were taken with the different methods (CSA=cross-sectional areas, BMD=bone mineral density).

studies are partly contradictory, which may be due to the particular type of animal model, degree of maturity of the animals, type of unloading or immobilization, anatomic sites studied, and methodologies employed.

Recently, quantitative magnetic resonance imaging (qMRI) has made it possible to determine knee joint cartilage morphology in the human *in vivo* with high accuracy and precision[13] and also patellar cartilage behavior after *in vivo* loading[14,15]. Using this methodology, atrophic changes (thinning) of human articular cartilage has been described for short-term post-operative unloading of the joint[16] and in patients with spinal cord injury[17,18]. However, the effect of remobilization on articular cartilage has thus far not been investigated in human setting. This question is, for instance, of relevance in managing patients post-operatively, and in evaluating the potential consequences of long-term space flight.

The objective of this study was to assess the effects of a 24-month period of remobilization (after 6 weeks of post-operative unloading and partial immobilization) on the morphology and deformational behavior of knee cartilage, the muscle cross-sectional areas (MCSAs), and the bone mineral density (BMD) of the lower limb in a human subject.

Materials and methods

We investigated a 36-year-old male patient after a 6-week period of unloading and partial immobilization of the left knee. No data was obtained prior to the immobilization period, because the event came unexpectedly. Measurements were obtained over 24 months at narrow time intervals, Figure 1 summarizing the time points of measurement. The patient was fully aware of the significance and scientific nature of the study and participated voluntarily after being informed about the nature of the methodology.

The unloading followed an arthroscopic suture of a small tear on the posterior horn of the lateral meniscus. The tear had been asymptomatic and was discovered by chance when removing a partially loose body (partial bunk of the medial collateral ligament with its bony insertion) from the knee, which had caused the knee to occasionally lock at 90° of flexion. Please note that the patient had no impaired knee function and no reduced musculature prior to the incident and after remobilization. The articular cartilages were found to be fully intact at arthroscopy. After the operation, the participant walked on crutches (no weight bearing) and although full range motion was possible post-operatively, it was limited to 0°-30° flexion by a Donjoy brace to protect the meniscal suture from loading. After 6 weeks of unloading and limited movement, the rehabilitation process included restoration of the full range of motion by physical therapy, co-ordinative exercises, and muscle training (weight training) 3 times per week. After approximately one week of remobilization, the volunteer was able to fully weight-bear and walk, after 2 weeks he had regained a range of motion of approximately 90° and was able to train on a bicycle regularly. After 4 weeks, he was able to perform knee bends. Weight training at increasing levels (2 x per week) was performed for approximately 6 months. Measurement of the peak torque (Cybex 6000, Cybex International) revealed side differences of -30% for knee extension and +17% for knee flexion after 8 weeks of rehabilitation, but no relevant side differences were observed after 16 weeks. After 6 months of weight training, the volunteer returned to normal day-to-day activity without performing particular exercises or sports.

Analysis of Muscle Cross-Sectional Areas

To determine the thigh MCSAs, transverse MR images were acquired at 25%, 50% and 75% of the distance between the greater trochanter and the knee joint space using the body-coil of a 1,5 T clinical MRI scanner (Magnetom VISION, Siemens, Erlangen, Germany) using a T1-weighted spin echo sequence [repetition time=532 msec, echo time=15 msec], with an in-plane resolution of 1.1 mm and a section thickness of 10 mm. The knee-extensors, knee-flexors, and hip-adductors were analyzed (Figure 2), excluding bones, vessels, and larger amounts of connective tissue. To minimize the influence of positioning, the MCSAs derived from the three measurement sites of the thigh were added for each muscle group and leg. The precision for these

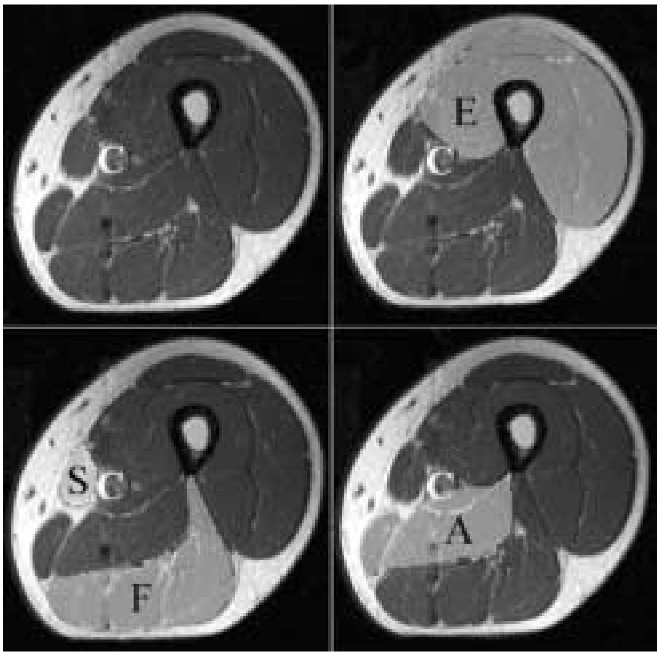

Figure 2. Transverse MR images of the left thigh. Acquired midway between the knee joint space and the greater trochanter with a T1-weighted spin echo sequence (in-plane resolution 1.1 mm, slice thickness 10 mm). The different muscle groups (E=extensors, F=flexors, S=sartorius, A=adductors) are segmented light gray. C=canalis adductorius (not segmented).

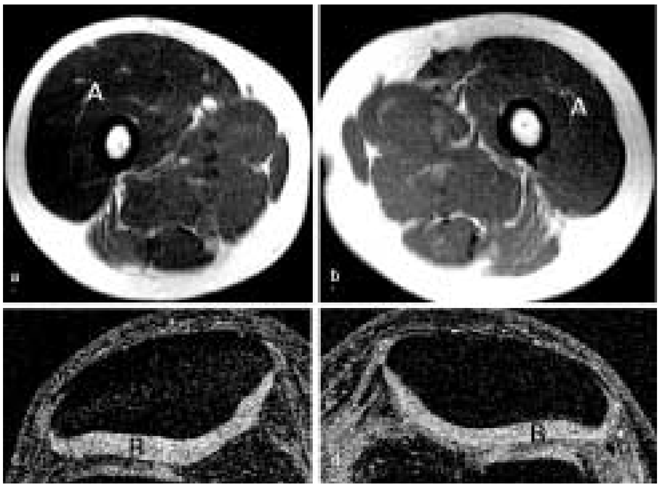

Figure 3. Transverse MR images of the thigh musculature (a, b) and of the patella (c, d) after 6 weeks of unilateral immobilization of the left limb (b, d). The images show in the immobilized limb a substantial reduction of thigh musculature cross-sectional area (particularly the quadriceps, A) and a lower patellar cartilage thickness (B), compared to the non-immobilized side (a, c). The thigh images were acquired at 25% between the greater trochanter and the knee joint space. The patellar images show corresponding sections of the patella.

measurements have been reported previously[19] and were 2.4% for the total MCSAs of the thigh, 1.7% for the quadriceps, 3.4% for the flexors, and 9.9% for the adductors.

Analysis of Bone Density

To assess the bone status, the total bone mineral density (BMD) of the distal femoral and proximal tibial metaphysis, peripheral quantitative computed tomography (pQCT, XCT-2000, Norland-Stratec, Pforzheim, Germany) was employed 3 cm proximal and 3 cm distal of the knee joint space. The section thickness was 2.2 mm, and the in-plane resolution 0.5 x 0.5 mm^2. The precision in our hands has been reported to be 4.7% for femoral BMD and 3.7% for tibial BMD[20].

Analysis of Cartilage Morphology

MR imaging was performed with the same MRI scanner mentioned above and a circularly polarized transmit-receive knee-coil. A previously validated gradient echo sequence (fast low angle shot, FLASH-3D) with selective water excitation[21] (repetition time=17.2 msec, echo time=6.6 msec, flip angle=20°) was used to acquire two coronal datasets of tibial cartilage, and two axial datasets of patellar cartilage (in-plane resolution=0.31 x 0.31 mm^2, section thickness=1.5 mm, acquisition time 6 min 48 sec, and 3 min 45 sec, respectively). Patellar datasets were obtained at 0, 1, 3, 6, 9, 12, 15, 18 and 24 months of remobilization, because a relevant side difference was observed at the baseline measurement. The tibial cartilages, in contrast, were only measured directly at the beginning and after 18 months, because no relevant side differences were observed at baseline. To study patellar cartilage deformational behavior[14,15], the volunteer performed 30 deep knee bends after imaging (flexion angle approximately 120°), and an additional axial dataset of the left patella was acquired immediately (90 to 360 s) after the exercise[14,15]. This exercise was only possible after 1 month of remobilization (because of the inability of the participant to perform knee bends), but not directly at the beginning of the remobilization period.

The digital 3-D-post-processing was performed as described previously[13,22], to assess the mean cartilage thickness (ThC) and articular surface areas (AC). The image data obtained at baseline was analyzed by three observers and that during the remobilization process by the first author. Although the precision errors for the given protocol have been published in previous works[13,15], we determined the precision errors under the given experimental conditions. The short-term precision error (RMS CV%) for the patella was determined from the two axial datasets acquired for each knee at each point in time (18 data pairs, Figure 1). The RMS average was 1.8% for ThC and 1.0% for the AC.

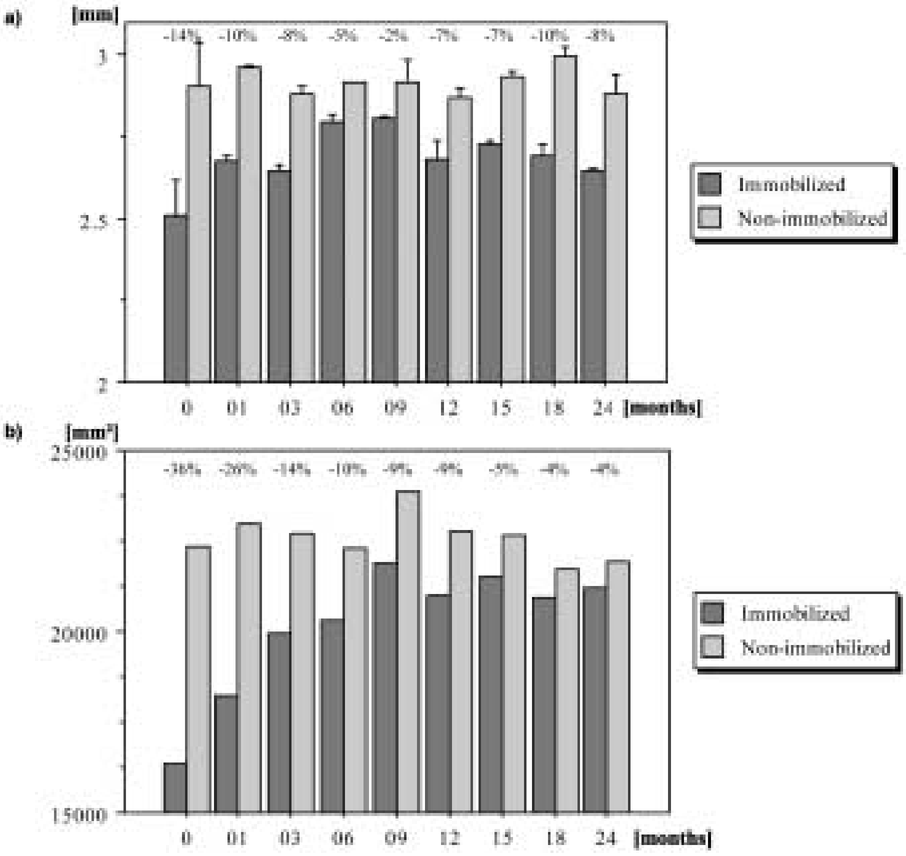

Figure 4. Bar graphs showing the absolute values for the mean thickness of the patellar cartilage (a) and the size of the MCSAs of the extensors (b) during the remobilization process in both limbs. Note that the values of the MCSAs are summations acquired at three different heights of the thigh, and standard deviations are not available.

The long-term precision for the patella was analyzed by using the datasets of the loaded knee from the 3rd to 9th measurement. This was found to be 1.3% for ThC and 0.9% for AC.

Results

Unloading

The muscle cross-sectional areas (MCSAs) of the extensors were 36% lower at the unloaded leg after the 6 week immobilization period, those of the adductors were 7% lower, and those of the flexors were, surprisingly, 10% higher (Figure 4). The bone mineral density (BMD) of the unloaded leg, was 12% lower in the femoral, and 6% lower in the tibial metaphysis compared to the loaded side (Table 1). The patellar cartilage displayed an 14% lower mean ThC in the unloaded leg (assessed by the first author; mean of the three observers: 11%, range 8% to 14%), whereas the AC displayed no relevant side differences (range -1% to +1%) (Figure 3). There were no obvious side differences in the tibial cartilage morphology (Table 1).

Remobilization

The MCSAs of the extensors of the unloaded leg increased during remobilization, so that the side differences reduced to -4% after 24 months. The flexors displayed the opposite trend, with a decrease of the side difference from +10% (immobilized vs. contralateral side) to +2% after 24 months. Side differences of the MCSA of the adductors fluctuated during remobilization from -7% to +6%, with no clear trend being observed (Table 1).

The BMD increased in the remobilized leg and decreased in the loaded leg, with a final difference of 6% in the femur and 3% in the tibia (Table 1).

In the remobilized leg the mean thickness of the patellar cartilage increased during remobilization, with the maximum being reached around 6-9 months, where the side differences were only -2% to -5%, respectively (Figure 4). After 24 months of remobilization the thickness of the immobilized patellar cartilage was -8% in comparison to the loaded limb (Table 1, Figure 4). The patellar cartilage volume followed the same pattern, as AC did not change during the study. The tibial cartilage plates displayed no side differ-

Parameters months	0	1	3	6	9	12	15	18	24
Muscle Cross-Sectional Area									
MCSA Extensors	-36%	-26%	-14%	-10%	-9%	-7%	-5%	-4%	-4%
MCSA Flexors	+10%	+4%	+6%	+7%	+6%	±0%	+2%	±0%	+2%
MCSA Adductors	-7%	-4%	+2%	+5%	+6%	-5%	-1%	+3%	+1%
Bone Mineral Density									
Femur BMD	-12%							-6%	
Tibia BMD	-6%							-3%	
Cartilage Morphology									
Patellar Cartilage Thickness	-14%	-10%	-8%	-5%	-2%	-7%	-7%	-10%	-8%
Patellar Cartilage JSA	±0%	-3%	-3%	-4%	-4%	-2%	±0%	+1%	-1%
Patellar Cartilage Volume	-17%	-12%	-12%	-10%	-7%	-10%	-8%	-10%	-11%
Medial Tibial Cartilage Thickness	+1%							-1%	
Medial Tibial Cartilage JSA	+2%							±0%	
Medial Tibial Cartilage Volume	+2%							-2%	
Lateral Tibial Cartilage Thickness	+1%							-2%	
Lateral Tibial Cartilage JSA	-2%							-1%	
Lateral Tibial Cartilage Volume	±0%							-1%	
Cartilage Deformation									
Patellar Cartilage Deformation		-9%		-4%	-6%	-1%	-4%	-4%	

MCSA=Muscle Cross-Sectional Area, BMD=Bone Mineral Density, JSA=Joint Surface Area

Table 1. Percentage differences of cartilage volume, cartilage thickness, joint surface area, muscle cross-sectional area and bone mineral density of the left vs. right limb during the 24-month rehabilitation. The contralateral right leg is used as reference for the immobilized left limb, except for the patellar deformation.

ences at the end of the remobilization period, similar to the situation at baseline.

The magnitude of patellar cartilage deformation in the immobilized leg decreased during remobilization, starting at 9% (after 1 month of remobilization) with values of 1 to 6% at 6 to 18 months of remobilization) (Table 1).

Discussion

In this quantitative case report, we have investigated the effects of 24 months of remobilization, after 6 weeks of unloading with partial immobilization, simultaneously on knee cartilage morphology, deformational behavior of the patellar cartilage, lower limb muscle cross-sectional areas (MCSAs), and lower limb bone mineral density (BMD) in one human subject.

A fundamental limitation of this study is that only one subject was investigated. However, this question has been addressed for the first time in a human setting, and a multitude of innovative techniques and longitudinal measurements were obtained at relatively narrow time intervals. Moreover, all relevant connective tissues were examined simultaneously, and the precision of the given techniques has been shown to be sufficient to reliably pick up small differences, even in only one subject. A second limitation is that no data were available prior to the immobilization period, because the event came unexpectedly. It was also not possible to scan the volunteer immediately after the operation, because of the presence of joint effusion. In a recent study on side differences of cartilage morphology in 15 volunteers[23] with a dominance of one lower extremity, it was found that the mean patellar cartilage thickness displayed no significant side difference (3.8±3.1%, n.s.). In light of these data, the side difference observed in the patella (14%) unlikely represents a physiological state that has existed preoperatively. However, because no pre-operative data were available, the main focus of interpretation is on the longitudinal changes during the remobilization process.

It is interesting to note that, in contrast to the patella, the tibial cartilages displayed no relevant side differences at all after unloading. Site-specific responses of articular cartilage to decreased levels of mechanical loading have also been observed in animals studies[4,8,10]. These results are, however, difficult to compare with ours, because of the differences in methods and in the biomechanics between animals and man. Hinterwimmer et al.[16], found only a 2.9% reduction in patellar cartilage thickness after 7 weeks of partial unloading, but in contrast to the participant in our study, the range of motion of the patients was not limited to 30°. Moreover, the patients in Hinterwimmer's study only displayed a reduction of 11% in the cross-sectional area of the quadriceps, whereas the participant in our study displayed side differences of

36% that vanished during the immobilization period.

While the substantial side difference in extensor MCSA vanished almost completely during the 24-month remobilization process, the side differences in patellar cartilage thickness changed only little during this period, and the thickness of the tibial cartilages did not change at all. The data at 9 months remobilization indicated that the side difference in patellar cartilage thickness had become considerably smaller, potentially because of the weight training performed by the participant. At this point in time, the participant displayed the largest quadriceps cross-sectional area, both in the formerly immobilized and in the contralateral limb. Interestingly, at the end of the observation period, there was a trend to increased asymmetry, although there was no indication of asymmetric limb usage and joint loading during the period of 9 to 24 months. It is of note that physiotherapy and weight training were stopped at month 7 of the remobilization period and that the quadriceps cross-sectional area became less after month 9 in both limbs. Some of the fluctuation of the side differences and thickness values are probably due to precision errors. However, the precision errors for patellar cartilage thickness measurements have been shown to be <2% in this and previous work[15], and it should be noted that in all cases two data sets were obtained and averaged throughout the study. The final asymmetry of patellar cartilage thickness may be explained by the observation of Haapala et al.[10], who found that immobilization caused a decrease in glycosaminoglycan concentration in the knee of beagles, which was not completely restored after remobilization.

Whereas findings on cartilage morphology during unloading/immobilization and remobilization in animal studies have been inconsistent, most studies have reported a deterioration of biochemical and biomechanical properties during non-use of the joint. The magnitude of patellar cartilage deformation returned to levels below 6% during the remobilization process, which is the average reported in young and healthy volunteers[15]. These observations are consistent with the finding of animal models that the biochemical and biomechanical changes are at least partially restored by remobilization.

The preliminary observations presented here provide an insight, for the first time, into the adaptational responses of articular cartilage to remobilization in a human setting. Future longitudinal studies will have to establish whether the morphology and functional competence of human articular cartilage displays relevant changes during unloading, whether these are site (compartment) -specific, and whether a certain time period is required for the tissue to recover and to regain tolerance to physiological load magnitudes.

In conclusion, the current observations indicate that human cartilage macro-morphology may be less adaptive to variations of the mechanical loading than muscle and bone. Quantitative magnetic resonance imaging (qMRI) permits us to longitudinally investigate subtle changes in cartilage macro-morphology in humans during substantial changes in loading history.

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