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Vibration training intervention to maintain cartilage thickness and serum concentrations of cartilage oligometric matrix protein (COMP) during immobilization

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Summary

Objective: To test the hypotheses that 1) 14-days of immobilization of young healthy subjects using a 6°-"head-down-tilt-bed-rest"-model (6°-HDT) would reduce cartilage thickness in the knee and serum Cartilage oligometric matrix protein (COMP) concentration and 2) isolated whole body vibration training would counteract the bed rest effects.

Method: The study was performed and designed in compliance with the Declaration of Helsinki and is registered as trial DRKS00000140 in the *German Clinical Trial Register* (register.germanctr.de). Eight male healthy subjects (78.0 ± 9.5 kg; 179 ± 0.96 cm, 26 ± 5 years) performed 14 days of 6°-HDT. The study was designed as a cross-over-design with two study phases: a training and a control intervention. During the training intervention, subjects underwent 2 × 5-min whole body vibration training/day (Frequency: 20 Hz; amplitude: 2–4 mm). Magnetic resonance (MR) images (slice thickness: 2 mm; in-plane resolution: 0.35 × 0.35 mm; pixels: 448 × 512) were taken before and after the 6°-HDT periods. Average cartilage thicknesses were calculated for the load bearing regions on the medial and lateral articulating surfaces in the femur and tibia.

Results: While the control intervention resulted in an overall loss in average cartilage thickness of −8% (pre: 3.08 mm ± 0.6 mm post: 2.82 mm ± 0.6 mm) in the weight-bearing regions of the tibia, average cartilage thickness increased by 21.9% (pre: 2.66 mm ± 0.45 mm post: 3.24 mm ± 0.63 mm) with the vibration intervention. No significant differences were found in the weight-bearing regions of the femur. During both interventions, reduced serum COMP concentrations were observed (control intervention: −13.6 ± 8.4%; vibration intervention: −9.9 ± 3.3%).

Conclusion: The results of this study suggest that articular cartilage thickness is sensitive to unloading and that vibration training may be a potent countermeasure against these effects. The sensitivity of cartilage to physical training is of high relevance for training methods in space flight, elite and sport and rehabilitation after illness or injury.

Key words: COMP, Cartilage thickness, Immobilization, Vibration training.

Introduction

While the role of mechano-biological factors for healthy cartilage development and maintenance has received much attention[1–3], the effects of immobilization[4,5] or partial weight bearing after injuries[6] or in patients with degenerative joint diseases and the effects of space flight on cartilage biology and morphology are largely unknown. Maintaining healthy cartilage during space flight especially during a possible flight to Mars with an assumed duration of 2–3 years is challenging. To simulate the mechanical loading experienced during space flight, we used the well established model of bed rest in a 6°-head-down-tilt (HDT) position[7]. This model simulates many of the physiological effects of space flight including a reduced mechanical stimulus of the lower extremity.

Cartilage presumably maintains and responds to the loads placed on joints during activities of daily living. For instance, the loads generated at the knee during walking correlate with cartilage thickness in the weight-bearing regions of the knee[8]. Contrasting results are published on the effect of mechanical unloading on changes in proteoglycan and collagen content in animals[9–11]. The discrepancy of these results may be due to the fact that the type of immobilization plays a role in the potential of the cartilage to recover[12]. Only few studies[4–6,13,14] have investigated the influence of mechanical unloading on articular cartilage in humans and reported cartilage thinning after 7 weeks of partial load bearing[6] and in spinal cord injured patients[4].

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Changes in tibio-femoral cartilage thickness are not dose dependent suggesting that adult human cartilage properties may not be sensitive or enhanced with training[15].

Cartilage oligometric matrix protein (COMP) is a structural protein primarily found in cartilage[16], and the turnover of COMP fragments may be an important mechanism for the regulation of tissue synthesis and degradation[3,17–19]. COMP plays a major role in stabilizing the extracellular matrix through its interaction with collagen fibrils and other matrix components[20,21]. Serum COMP concentrations are elevated in patients with knee osteoarthritis[22] and rheumatoid arthritis[23] but also after a moderate walking exercise in healthy adults[24,25] and after intense running exercise in athletes[26]. Thus, serum COMP concentration appears to be sensitive to physiological loading. Overall, applying controlled mechanical load to cartilage may off-set or reverse some of the biological and morphological changes caused by joint disease, disuse or immobilization.

Vibration training is mechanically and biologically a potential stimulus and a popular training method that is easy to perform and complements regular strength training[27]. Vibration frequencies between 15 Hz and 90 Hz have been used to achieve adaptations in muscle and bone[27–35]. The purpose of this study was to test the hypothesis that a 14 days bed rest immobilization will lead to a reduction in cartilage thickness and serum COMP concentration and that vibration training will reduce or even prevent this response.

Methods

POPULATION

Eight healthy male subjects (average ± 1 standard deviation (SD); age: 26 ± 5 years; mass: 78.1 ± 9.5 kg; height: 179 ± 10 cm) participated in this study after giving their informed consent in accordance with the ethics committee of the Ärztekammer Nordrhein, Düsseldorf, Germany. The study was performed and designed in compliance with the *Declaration of Helsinki* and registered as trial DRKS00000140 in the *German Clinical Trial Register* (register.germanctr.de). All subjects were moderately physically active, that is they exercised three times per week or less on a regular basis. Each subject underwent physical and psychological screening prior to enrolment into the study. All eight subjects who were initially enrolled in the study completed the study, and thus the drop out rate was 0%.

STUDY DESIGN

The study design was a randomized cross-over-design with two study phases, each of which consisted of 23 days where the subjects stayed stationary in the clinical research center of the Institute of Aerospace Medicine, German Aerospace Center (DLR), in Cologne, Germany. The first and second study phases were conducted in August 2004 and in March 2005, respectively, resulting in a recovery phase of 5.5 months between the study phases. Each study phase was divided into three periods: a 4-day adaptation period, a 14-day intervention period with bed-rest in 6°-HDT and a 5-day recovery period (Table I). Both study phases were identical and controlled with respect to environmental conditions, daylight conditions, study protocol and diet. Subjects were allowed to walk around the ward in the adaptation and the recovery period but physical exercise was not allowed. During the intervention period subjects were kept in 6°HDT for 24 h every day and were not allowed to elevate their upper body. All activities, including eating, showering, and weighing, were carried out in the 6°-HDT position.

TRAINING INTERVENTION

During the intervention period, subjects received either whole body vibration training or a control intervention twice daily. Training sessions were scheduled at least 30 min after breakfast and lunch. Subjects walked the distance between their room and the training room each session (~25 steps). Each vibration training unit was composed of five times 60 s of isometric exercise bouts on a vibration platform (Galileo 900, Novotec Medical GmbH, Pforzheim, Germany) in an upright standing position with a knee flexion angle of 30°. Subjects carried an additional load of 15% of their body mass on a diving belt around their pelvis. Between exercise bouts subjects rested for 60 s while sitting on a chair. The vibration platform vibrated at 20 Hz with approximately 3 mm amplitude at the centre of the foot.

Control and vibration intervention were identical except that the vibration platform was switched off during the control intervention. The order of the control and the vibration intervention was randomized, half of the subjects started with the control intervention and half of the subjects started with the vibration intervention.

Because of the length of the period between the two study phases and the randomisation of the order, the order of interventions is presumed to be negligible.

DIET

Subjects received a controlled diet throughout the entire study which was individually tailored according to their respective body mass. Total Energy Expenditure (TEE) was calculated by summing up the basal metabolic rate (BMR) according to the World Health Organization (WHO)-equation[36], plus 40% of BMR for a light physical activity during the adaptation and the recovery periods and 10% of BMR during the bed rest periods. 10% of TEE for thermogenesis was added. Dietary protein, fat and carbohydrate intakes were calculated according to the German Dietary References[37] (protein: 1 g/kg body weight (BW); fat: <30% of TEE; carbohydrate: 55–60% TEE). Sodium intake was 200 m mol (Na)/day and calcium intake was 1000–1150 mg/day). Subject were given 50 ml water *kg/BW^{-1}/d^{-1}. The amount of vitamins and minerals also matched recommended references. Predefinition of the daily menus for each subject was done using PRODI®-software[38]. Subjects received the exact amount of the food that was predefined (precision: 0.1 g) and they were asked to consume their meals completely at the given time. The menu composition and the meal frequency were identical for both study phases for each subject to avoid any impact of nutrition on the outcome of the study.

MR-IMAGING (MRI)

The left knee of each subject was examined using a 1.5 Tesla magnetic resonance imaging (MRI) scanner (Siemens Sonata, Erlangen, Germany) with a special knee coil. MRI data acquisition was performed at the Cardio-MR Praxis, Krankenhaus Porz, Cologne, Germany. During the scan, subjects lay in a supine position with their legs fully extended. Both feet were fixed in a parallel and a moderately plantar-flexed position. Subjects lay for a minimum of 30 min before the imaging of the knee was started. Articular cartilage of the tibio-femoral joint was imaged in the sagittal plane before and after the intervention and control phases. Images were taken on the last day (day-1) of the adaptation period and the first day (R1) in the recovery period. Subjects walked a defined distance to the MR practice, controlled by the activity monitor. Imaging was performed at an in-plane resolution of 0.35 mm × 0.35 mm, slice thickness of 2 mm, and an image matrix of 448 × 512 pixels. After the data acquisition completion of study phase II., all images were segmented by the same investigator. The segmenting investigator was blinded to the order of the image acquisition (pre-HDT, post-HDT) and also to the intervention (vibration training, control intervention).

THREE-DIMENSIONAL (3D) CARTILAGE MODEL

Cartilage in each slice of the MR images was segmented using a B-Spline Snake algorithm[39] with manual correction built in our custom software[40]. Once a user draws an initial boundary, the algorithm moves the boundary close to the edges of cartilage. The MR images do not always have consistent brightness, thus manual correction was required. The cartilage boundaries from all slices in a MR image set were combined to create a 3D cartilage model using a volume rendering technique[40], which fills the space between boundaries obtained from adjacent slices and creates a polygonal surface model. The cartilage model was divided into an articulating surface and cartilage-bone interface surface to calculate cartilage thickness. For each point on the articulating surface, the closest point on the cartilage-bone interface surface was found and the distance between the two points was color coded on the two points. The accuracy of the cartilage thickness measurement using the method had been verified previously[40]. The cartilage model building process was performed by a single observer to increase the reproducibility of the process. The coefficient of variation (=SD/mean × 100) of intra-observer reproducibility in measuring average cartilage thickness of a weight-bearing region over five repetitions was 1.6%.

CARTILAGE THICKNESS MEASUREMENT OF WEIGHT BEARING REGIONS

For the femoral cartilage the tibio-femoral contact areas are varying with the angle of knee flexion. During walking knee is commonly been flexed between 0–30° during stance phase and 0–60° during swing phase, respectively. The tibio-femoral contact areas in the femoral cartilage were divided

Table I
VBR-Study design: Cross-over-design with to different phases − vibration training and control intervention

Study period	Adaptation				Intervention							Recovery				
Study days	−4	−3	−2	−1	1	2	3	…	12	13	14	R1	R2	R3	R4	R5
Study phase																
A	normal physical activity (4 days)				bed rest + vibration training (14 days)							normal physical activity (6 days)				
B	normal physical activity (4 days)				bed rest + control intervention (14 days)							normal physical activity (6 days)				

into three functional weight-bearing regions for each condyle based on the knee flexion angle during walking[40]. The flexion angle can be less than 0° in the case of knee hyper-extension. Thus we defined the weight-bearing regions on the medial and lateral femur condyle as the regions that matches the tibio-femoral contact regions from −30° to 0°, 0° to 30° and 30−° to 60° of knee flexion angles, respectively (Fig. 1). Average thickness was calculated for the load bearing regions of the medial and lateral femur condyles and the entire medial and lateral articulating surfaces of the tibia, respectively. Average thickness of the medial and lateral weight-bearing regions of the femur and tibia were used for further analysis.

BLOOD

Fasting blood samples were drawn at 7 am on days −3 and −1 in the adaptation period, days 2, 6, 8, 11, 13, 14 of the intervention period and on day R2, R3 and R5 of the recovery period (Table I). Blood was drawn by medical doctors using a short catheter in serum monovettes (Sarstedt, Germany) from the antecubital vein. 150 µl Serum was aliquoted into Eppendorf tubes and frozen at −80°C until analysis. Serum COMP concentration was analyzed using a commercial enzyme-linked immunosorbent assay (COMP® ELISA; AnaMar Medical AB, Lund Sweden). Analysis was performed in duplicate. All samples of any subject of both study phases were analyzed on plates from the same batch of COMP® ELISAs. In addition all samples of any subjects were analyzed on the same plate to avoid differences in serum COMP concentration due to inter-assay variation.

STATISTICAL ANALYSIS

Statistical analyses were performed using STATISTICA software, Version 7.0 (StatSoft, Inc., Tulsa, USA). All results are shown as means ± 1 SD. Separate analysis of variance (ANOVAs) were used for the detection of significant differences in cartilage thickness and serum COMP concentration between region, intervention and time points. Bonferroni adjustments were made to account for multiplicity effects for changes in cartilage thickness at the femur and tibia. Mixed factor ANOVAs for repeated measures were used with region (medial vs lateral), intervention (control vs vibration) and time (pre- vs post-intervention) as factors. Differences in serum COMP concentrations between days and phases were detected using a mixed factor ANOVA for repeated measures ANOVA) with time and intervention (control vs vibration) as factors. Similarly, differences in cartilage thickness before and after intervention and between phases were detected using repeated measures ANOVA with time and intervention as within-subject factors.

Results

CARTILAGE THICKNESS

There was a substantial and significant decrease in the tibial cartilage thickness for both average (−8.3%, $P = 0.025$) and maximum (−14.57%, $P = 0.015$) thicknesses after 14 days of 6°−HDT bed-rest (Table II). The opposite result was observed for the vibration training condition. Average and maximum thicknesses in the tibial cartilage increased significantly by 21.9% and 26.6%, respectively. The percentage change in average and maximum cartilage thicknesses did not differ between the medial and the lateral compartments of the tibia for both study phases. Cartilage thickness in the lateral and the medial compartments of the femoral cartilage did not show significant changes due to the bed rest or to the training intervention (Table II).

SERUM COMP CONCENTRATION

On adaptation day -3 mean serum COMP concentration was 7.02 ± 1.12 U/l for the control phase (CON) and 7.23 ± 1.15 U/L for the intervention phase (VIB) (Fig. 2). With serum COMP concentrations of 6.80 ± 1.41 U/L (CON) and 6.90 ± 0.95 U/L (VIB) at day -1 prior to bed rest data were stable for the baseline measurements. Serum COMP concentration was in the range of normal distribution for healthy subjects[41].The first blood samples after 24 h of 6°-HDT intervention showed a significant decrease in serum COMP levels (CON: 5.80 ± 0.84 U/L; VIB: 6.20 ± 0.75 U/L; $P = 0.022$) (Fig. 2). Values decreased on average by 14.8% when subjects received the control condition and by 10.1% for the vibration training condition. No statistical difference in the change in serum COMP concentration during bed rest was observed between the control and the

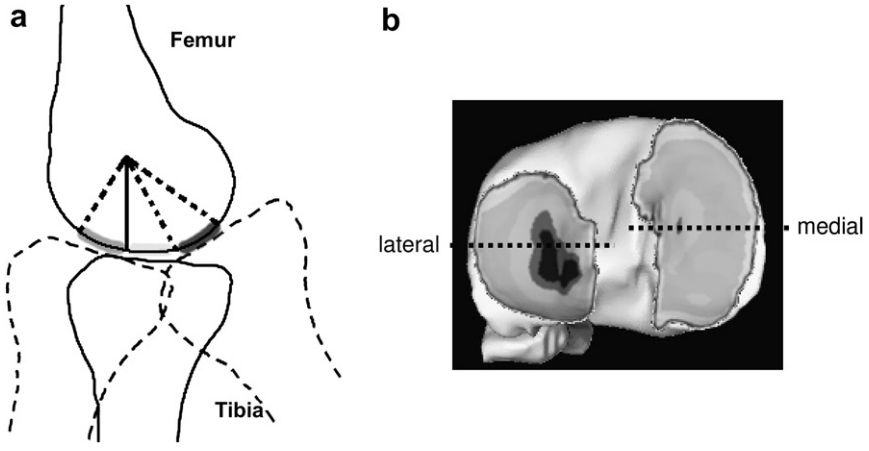

Fig. 1. Three functional weight-bearing regions on each condyle were defined based on flexion angle during normal walking. (a) lateral view, (b) selected cartilage regions of the tibia: regions framed with the grey line were included into the analysis.

Table II
Changes in mean and maximum thickness (±SD) of articular cartilage in the knee due and 14 days of HDT-bed rest (n = 8)

Compartment	Maximum thickness [mm]		Mean thickness [mm]	
	Control	Vibration	Control	Vibration
Tibia				
Pre-HDT (d−1)	5.02 ± 1.18	4.18 ± 1.03	3.08 ± 0.60	2.66 ± 0.45
Post-HDT (d R1)	4.29 ± 1.25	5.25 ± 1.21	2.82 ± 0.60	3.24 ± 0.63
% change	−14.57*	26.61*	−8.3*	21.91*
Lateral femur				
Pre-HDT (d −1)	3.70 ± 0.50	3.91 ± 0.52	2.37 ± 0.40	2.50 ± 0.24
Post-HDT (d R1)	3.90 ± 0.74	3.97 ± 0.46	2.41 ± 0.30	2.52 ± 0.25
% Change	5.32	1.58	−2.16	−5.90
Medial femur				
Pre-HDT (d−1)	3.73 ± 0.51	3.50 ± 0.86	2.36 ± 0.43	2.28 ± 0.22
Post-HDT (d R1)	3.84 ± 0.50	3.40 ± 0.58	2.44 ± 0.32	2.30 ± 0.23
% Change	2.70	−2.50	3.70	−2.51

Values are the mean ± SD. *$P < 0.05$ vs (d−1).

vibration training protocol. During the intervention period the values stayed stable at lower levels for both groups. No difference in the adaptation of the serum COMP concentration due to the training intervention could be observed throughout the period of bed rest. Serum COMP concentration for both protocols returned to baseline levels after subjects were mobile again (CON: 6.78 ± 0.91 U/L (+28.6%), VIB: 6.96 ± 0.94 U/L (+26%); $P < 0.001$) and stayed stable at higher levels during the recovery period.

Discussion

The results of this study demonstrated that immobilization during bed rest leads to a significant loss in cartilage thickness in the tibia and a significant reduction in systemic serum COMP concentration. Vibration training prevented partially the loss of cartilage thickness in the tibia but not the reduction in serum COMP concentration.

In this study, cartilage thinning was only observed in the tibia but not in the femur. This result is similar to previous reports[5,6] of more pronounced changes of articular cartilage thickness in the tibia compared to the femur after unloading. Further it has been suggested that altered contact mechanics in the knee may lead to altered local degenerative changes of articular cartilage[8,42]. Thus, under these conditions, immobilization appears to affect only selected areas of knee cartilage. This result has important implications for specific immobilizations such as the position of the joint during immobilization with a cast and for the selection of potential countermeasures for effects of immobilization on cartilage health such as static or dynamic activities.

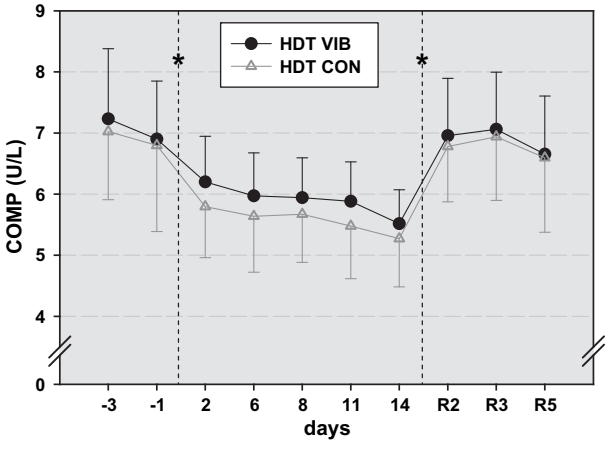

Fig. 2. Average changes in serum COMP concentration in response to 6°-HDT bed rest and vibration training ($n = 8$). Serum COMP concentration decreased significantly ($P = 0.022$) after 24 h of bed rest and returned to baseline levels after subjects were mobile again ($P = 0.001$).

In contrast to previous studies[5,6], cartilage thinning was similar for the medial and lateral tibial compartments. It is possible that 14 days of bed rest may not be sufficient to cause changes in all cartilage compartments of the knee joint. In addition, the tibia may be more sensitive to altered loading conditions because of the smaller load bearing region on the tibia compared to that on the femur as the femur rolls and slides on the tibia. Hence, the accumulated load on a given area is greater in the tibia which may result in a stronger response of the tibia to unloading. This phenomenon can be compared with the response of bone mineral content to unloading. Loss in bone mineral content due to unloading is more pronounced in bones that are usually exposed to mechanical loading[43]. Similarly, for articular cartilage a greater response to unloading in cartilage regions that are loaded during normal joint motions than in normally unloaded regions may be expected. If usually loaded regions are more sensitive to unloading, then this may explain the greater range of change in mean cartilage thickness in our study compared to previous studies[5,6].

The measured decrease in cartilage thickness for the control condition and the increase for the vibration training intervention may not necessarily reflect a loss in cartilage tissue but a change in the mechanical properties of cartilage due to an altered hydrostatic pressure, for instance in such as decreased compressibility of cartilage. In addition, it has also been shown previously, that unloading cartilage changes proteoglycan synthesis[44] resulting in altered mechanical properties of the tissue. Proteoglycans are negatively charged and thus exert a large swelling pressure that causes tensile stress on the surrounding collagen network[45]. If unloading of a joint can lead to changes in proteoglycan content this may result in different hydration of cartilage. This mechanism is also a possible explanation for the increased cartilage thickness after the vibration training if the mechanical stimulus increases proteoglycan content of cartilage.

An alternative explanation for our results is that the participants developed more vulnerable cartilage during the immobilization period. Subsequently, the vibration training may have caused early cartilage degeneration with cartilage swelling or hypertrophy similarly to that observed in patients following anterior cruciate ligament (ACL) injury[46]. This change would not be a healthy adaptation or recovery process. However, the subjects in this study did not experience the effusion associated with trauma that is common to ACL injury.

To understand the relevance of the current results of this study the next logical step is to perform a study investigating cartilage thickness during vibration training in the absence of bed rest which was not within the scope of this study.

This study focused on the tibial-femoral regions of the cartilage surface that are more frequently in contact during activities of daily living. Most likely regions that are more often exposed to mechanical loading in every day life are more sensitive to unloading than regions that are generally not exposed to loading. This phenomenon can be compared with the response of bone mineral content to unloading. Loss in bone mineral content due to unloading is more pronounced in bones that are usually exposed to mechanical loading[43]. Similarly, for articular cartilage a greater response to unloading in cartilage regions that are loaded during normal joint motions than in normally unloaded regions may be expected. If usually loaded regions are more sensitive to unloading, then this may explain the greater range of change in mean cartilage thickness in our study compared to previous studies[5,6].

The results of this study show that a short term bed-rest at 6°-HDT results in a reduction in serum COMP concentration within less than 2 days indicating that COMP is sensitive to unloading. One possible explanation for this reduction in serum COMP concentration is a decreased diffusion of COMP molecules from the cartilage into serum due to a lack of exposure of the joint to cyclic movement and loading. This possibility is supported by the fact that serum COMP concentrations returned to baseline within 24 h following bed-rest. Previous studies also found the sensitivity of COMP to mechanical loading[3,24,26,47]. Our results are consistent with studies in marathon runners[26] and healthy subjects after walking exercise[24] that reported increases in serum COMP concentration in healthy subjects after exercise and concluded that COMP concentration is sensitive to mechanical loading. This would lead to the hypothesis that unloading should also affect serum COMP concentration. The results of this study that show deceases of serum COMP in the absence of joint loading support this hypothesis.

Another potential explanation for the reduction in serum COMP concentration during bed-rest is a change in cartilage metabolism in response to the lack of mechanical stimulus during this period. Wong *et al.*[3] earlier reported that cyclic compression *in vitro* results in an up-regulation of protein synthesis. They stated that chondrocytes have the ability to sense stress or strain in the extracellular environment which then results in an alteration of the expression of matrix proteins. The immobilization in our study presumably led to a reduction of mechanical forces acting in the knee joint which was possibly leading to a slower metabolism and thus to reduce turnover of COMP or the decrease in serum COMP concentration may reflect a decreased metabolic activity of cartilage.

There was no difference in serum COMP concentration between the control and the intervention phase. Despite its benefits for general physical conditioning[30], the used vibration training intervention with the goal to avoid the effects of prolonged bed rest may not have been sufficient in magnitude and/or duration to cause any significant changes in serum COMP concentration compared to the control intervention. It is possible that the serum concentration levels of COMP require motion as well as load. The lack of motion might also influence the amount of cartilage that is affected by bed rest compared to articular cartilage that is affected by the vibration training. Thus maybe only a more demanding training protocol that includes motion would lead to changes in serum COMP concentrations systemically measured in blood. It is possible, that the decrease in serum COMP concentration was caused by reduced diffusion of COMP molecules into the blood due to lack of joint movement. Different biological tissues, including cartilage, bone, muscle, ligaments, and tendons, may respond differently to the various combinations of vibration frequency, amplitude, training duration, and number of vibration bouts, and thus a training regime that is beneficial to muscle may not affect COMP turnover.

In summary, the results of this study suggest that articular cartilage thickness is sensitive to unloading, and that vibration training may be a potent countermeasure against these effects. Understanding and quantifying the mechanical response of articular cartilage in healthy subjects to its physical environment may help to develop countermeasures to reduce or even prevent cartilage thinning after prolonged unloading or immobilization due to illness, surgery or space flight. Until countermeasures have been developed, cartilage health should be considered when patients start to load their joints again after mid-term or long-term bed rest and for astronauts upon their return to earth after a prolonged space flight.

Conflict of interest

We hereby declare that none of the authors has any conflict of interest concerning this study.

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Supplementary material

Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.joca.2009.07.007.

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