Effect of Progressive High-Impact Exercise on Femoral Neck Structural Strength in Postmenopausal Women with Mild Knee Osteoarthritis: A 12-Month RCT

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DISCLOSURES

RA and TJ are the inventors of patent application FI 20090320. Juhani Multanen, Timo Rantalainen, Hannu Kautiainen, Miika T. Nieminen, Eveliina Lammentausta, Arja Häkkinen, Ilkka Kiviranta, and Ari Heinonen declare that they have no conflict of interest.

SUMMARY

It is uncertain whether subjects with mild knee osteoarthritis, and who may be at risk of osteoporosis, can exercise safely with the aim of improving hip bone strength. This RCT showed that participating in a high-impact exercise program improved femoral neck strength without any detrimental effects on knee cartilage composition.

ABSTRACT

Purpose No previous studies have examined whether high-impact exercise can improve bone strength and articular cartilage quality in subjects with mild knee osteoarthritis. In this 12-month RCT we assessed the effects of progressive high-impact exercise on femoral neck structural strength and biochemical composition of knee cartilage in postmenopausal women.

Methods Eighty postmenopausal women with mild knee radiographic osteoarthritis were randomly assigned into the exercise (n=40) or control group (n=40). Femoral neck structural strength was assessed with DXA. The knee cartilage region exposed to exercise loading was measured by the quantitative MRI techniques of T2 mapping and dGEMRIC. Also, an accelerometer-based body movement monitor was used to evaluate the total physical activity loading on the changes of femoral neck strength in all participants. Training effects on the outcome variables were estimated by the bootstrap analysis of covariance.

Results A significant between-group difference in femoral neck bending strength in favor of the trainees was observed after the 12-month intervention (4.4%, $p<0.01$). The change in femoral neck bending strength remained significant after adjusting for baseline value, age, height and body mass (4.0%, $p=0.020$). In all participants, the change in bending strength was associated with the total physical activity loading ($r=0.29$, $p=0.012$). The exercise participation had no effect on knee cartilage composition.

Conclusion The high-impact training increased femoral neck strength without having any harmful effect on knee cartilage in women with mild knee osteoarthritis. These findings imply that progressive high-impact exercise is a feasible method in seeking to prevent hip fractures in postmenopausal women whose articular cartilage may also be frail.

KEYWORDS: RCT; EXERCISE; MENOPAUSE; BONE STRENGTH; CARTILAGE.

1 INTRODUCTION

Osteoarthritis (OA) is debilitating disease, particularly in the weight-bearing joints of the knees. Knee pain and other symptoms often reduce mobility, such as in walking [1,2]. Reduced mobility, in turn, changes the bone loading environment at the affected lower limb. It is well acknowledged that decreased loading decreases bone mineral mass and, more importantly, bone strength in loading-related site-specific fashion [3-5]. There is evidence that in certain populations OA and osteoporosis (OP) are not necessarily mutually exclusive [6,7]. For example, in large epidemiological study among postmenopausal women with fragility fractures, X-rays revealed the presence of hip OA [8]. OA and OP coexist among postmenopausal women more than any other subject group, and it has been suggested that changes in estrogen levels might be a common hormonal link in the development of these diseases [9]. Thus, femoral neck strength is of major clinical importance for fracture prevention in postmenopausal women with knee OA and who may also be at risk of OP. It is important to bear in mind, that hip fractures represent the most serious consequence of bone loss, i.e. decrease in bone strength, from the individual's perspective [10,11] and impose an enormous economic burden on society [12].

Exercise is among the key treatment strategies recommended for preventing and treating OP in postmenopausal women [13-15]. To date, relatively few studies on how exercise affects femoral strength in this population segment have been published. In the few RCTs that have included postmenopausal women [16-18], the effect of exercise on femoral neck strength have been inconsistent, and thus firm conclusions cannot be drawn based on these findings. Likewise, in knee OA, exercise is recommended as one of the most important treatments in current guidelines [19]. Although exercise is effective in relieving pain and improving physical function in the short term [20,21], little is known about the effects of exercise on knee cartilage, a hallmark feature of early pathological change in OA. With reference to subjects with mild OA who are also at risk for OP, the question often arises, can bone and cartilage properties be augmented or maintained through exercise?

In a recent study, we showed that progressive high-impact exercise lowered fall risk by increasing physical function along with femoral neck bone mineral mass in postmenopausal women with mild knee OA [22]. However, since bone mass is only one determinant of bone strength, it is important to examine the response to exercise of other bone strength traits. While a high-impact exercise program had no positive or negative effects on knee cartilage in a detailed subregional analysis [22] no canonical standard procedure exists for defining cartilage regions-of-interest (ROIs) in knee OA, and therefore detection of potential cartilage responses to mechanical loading calls for a more comprehensive approach. The aim of this study was to investigate the effects of exercise on femoral neck structure, and on the biochemical properties of the whole cartilage region exposed to mechanical loading. Thus, we asked whether a 12-month high-impact exercise program would be effective in increasing femoral neck structure and in enhancing cartilage biochemical properties in postmenopausal women with mild knee OA.

2 METHODS & MATERIALS

This study was a comprehensive analysis of a 12-month randomized controlled trial with two experimental groups: a high-impact exercise group and a control group (ISRCTN58314639). Training frequency was three times per week for 12 months. The measurements were performed at baseline and at the end of the 12-month intervention. All the outcome assessors, except for author JM, who performed the knee cartilage segmentation, were blinded to the treatment-group assignment. The study protocol has been described in detail elsewhere [22]; briefly, recruitment was implemented in the the Jyväskylä region in Central Finland through newspaper advertisements, and a total of 298 postmenopausal women indicated interest in participation. Of this group, 80 volunteers met the inclusion criteria as assessed with a telephone interview, a clinical screening examination, radiographs of the tibiofemoral joint and lumbar spine, and femoral neck DXA scanning. The criteria for eligibility were: postmenopausal woman, 50-65 years of age, knee pain on most days, leisure time physical activity equivalent to no more than two sessions of intensive exercise weekly, no contraindications for exercise and no diseases that would limit participation in the exercise program, and Kellgren/Lawrence (K/L) 1-2 radiographic grading of the tibiofemoral joint OA [23]. The exclusion criteria were: osteoporosis, body mass index above 35 kg/m^2, knee surgery or instability, inflammatory joint disease, recent intra-articular steroid injections in the knee, contraindications to MRI or contrast agents. The study was conducted in facilities at the Department of Health Sciences, University of Jyväskylä, where all the study assessments and structured exercise sessions took place. The trial profile is presented in Fig. 1.

The study protocol was approved by the Ethics Committee of the Central Finland Health Care District (Dnro1E/2008). The protocol conformed to the principles of the Declaration of Helsinki. Informed consent was obtained from all participants.

A priori statistical power calculations were based on DXA-measured femoral neck bone mineral content, and indicated that 35 participants in each group were required to detect a difference of 0.08 gram (~2%) in change between the intervention and control groups (α=0.05, power=80%), assuming a drop-out rate of approximately 10%. The dropout estimation was based on data from our previous studies [16,17]. The participants were randomly assigned to the exercise group (N = 40) or control group (N = 40) using computerized block randomization. A block size of 10, stratified according to K/L grades 1 and 2, was used. Two participants from the exercise group withdrew immediately after randomization and two more dropped out during the study, while the control group remained intact (Fig. 1).

Exercise intervention

The exercise group participated in three weekly 55-min sessions of supervised high-impact aerobic and step-aerobic exercise for 12 months [22], similar to exercise programs that we have applied previously [16,17,24]. The practical training included high-impact loading (jumping exercises) and rapid change of direction with music. The degree of knee motion during the exercise sessions ranged from 5°, or nearly full extension, to 70° flexion. The loading was gradually increased over the course of the intervention at 3-month intervals by increasing stepping height and the height of the obstacle that the participants were asked to jump over. Mean training compliance, measured as attendance at all the training sessions offered, was 68% and mean training frequency was 2.1 (SD 0.9) sessions per week (including the two dropouts). All training sessions were supervised by exercise instructors recently trained to supervise this specific exercise program. The instructors also kept an attendance record for each of the participants. The exercise program has been described in details elsewhere [22].

Control group

Controls were asked to continue their usual leisure time activities during the 12-month trial. To maintain their interest in the study, they were offered the possibility of participating in a social group meeting every third month. Most took part in these meetings, which included lectures on a healthy lifestyle and relaxation techniques.

Bone strength assessement

Femoral neck was scanned with dual-energy X-ray absorptiometry (DXA, GE Medical Systems, Lunar Prodigy, Madison, WI, USA) in both hips by an external radiographer blinded to the intervention allocation. Subsequently, femoral neck cross-sectional area (CSA, [mm^2], the surface area of bone in the cross section after excluding all trabecular and soft tissue space), section modulus (Z, [mm^3]), an index of bending strength), and subperiosteal width (W, [mm], outer diameter of the bone after correcting for image blur) were calculated with Advanced Hip Analysis (AHA). The coefficient of variation for repeated measurements of the various AHA variables has been reported to be less than 3% [25].

Knee cartilage assessment

Transverse relaxation time (T2) and dGEMRIC index; i.e., spin lattice relaxation time (T1) in the presence of gadolinium, were determined using a Siemens Magnetom Symphony Quantum 1.5 T scanner (Siemens AG, Medical Solutions, Erlangen, Germany); a detailed description has been published elsewhere [22]. Briefly, T2 mapping was performed using a sagittal multislice multiecho fast-spin echo sequence. Two slices, each covering the central region of the medial or lateral femoral condyles, were analyzed. For the dGEMRIC measurements, an intravenous administration of 0.4 ml/kg of Gd-$DTPA^{2-}$ (Magnevist, Schering, Berlin) was followed by active knee motions for 15 min. After a 90-minute post-injection delay, T1 relaxation time measurements were performed by using a single slice inversion recovery fast-spin echo sequence from the same topographical location as the T2 slices. All scans were performed on the side with the higher K/L grade knee.

dGEMRIC and T2 maps were generated using an in-house MATLAB application (Mathworks, Inc. Natick, MA, USA). The dGEMRIC index and T2 are given with results averaged across the sagittal view of the regions-of-interest (ROIs) in the medial and lateral femoral condyles. Both ROIs included full-thickness cartilage entities (hereafter termed bulk cartilage) which were the areas most highly exposed to the exercise loading. ROI was drawn manually from the outer edge of the anterior horn of the meniscus to the midpoint of the posterior femoral cartilage (the posterior femoral cartilage ranges from the outer edge of the posterior horn of the meniscus up to the posterior top corner of the cartilage) (Fig. 2). The dGEMRIC indices were corrected by body mass index [26]. Generally, the dGEMRIC index is reported to decrease with lowered glycosaminoglycan (GAG) content [27].

Correspondingly, T2 is reported to become elevated with degeneration [28,29]. Mean inter-observer error (CV_{RMS}) in our laboratory was 2% for T2 full-thickness ROI and 3% for dGEMRIC.

Physical activity assessment

Daily physical activities were recorded for three consecutive days at four and ten months from intervention start by recording the number and intensity of vertical acceleration peaks (impacts) using accelerometer-based body movement monitors (Newtest, Oulu, Finland) in all participants (intervention training sessions not included). During the three-day measurements, the participants wore the monitors attached to a waist belt while performing normal day-to-day activities. The monitor was taken off at bedtime or in conditions where it might get wet. The participants were also asked to keep a diary on precisely when the monitors were worn, and to list all their daily physical activities lasting at least 15 min at a time. The number of peaks was divided into 32 different acceleration-level bins (0 g to 9.3 g) and the number of impacts in each acceleration-level bin was calculated. A daily impact score was calculated for daily physical activity using the logarithmic relationship (DIS_{Log})[30] between the loading numbers and the magnitude equation as follows:

$$DIS_{Log} = \sum_{i=1}^{32}(a_i + 1)ln(N_i + 1),$$

where a_i = the higher cutoff of the i^{th} acceleration-level bin and N_i = number of acceleration peaks within the i^{th} acceleration-level bin. The value 1 was added to the acceleration measured with the accelerometer-based body movement monitor in the DIS_{Log} calculations, since the accelerometer gives 0 g while standing still, whereas the muscles still have to counteract the 1 g caused by gravitation. Outside the intervention training sessions, given as DIS_{Log}, no difference in average daily physical activity over the 12-month study period was observed between the groups [22].

The aerobic and step-aerobic exercise loading was quantified by recording the number and intensity of acceleration peaks (impacts) with accelerometer-based body movement monitors (Newtest, Oulu, Finland) during one exercise session in every 3-month period. The number of impacts were combined to form five acceleration levels according to Vainionpää et al. [40] to describe the different patterns of exercise loading; 0.3-1.0 g (e.g., walking), 1.1-2.4 g (e.g., stepping), 2.5-3.8 g (e.g., jogging), 3.9-5.3 g (e.g., running, jumping), and 5.4-9.3 g (e.g., jumping, drop-jumping). In addition, a total physical activity loading index, DIS_{Total}, was calculated to describe participants' total physical activity over the study period (i.e. exercise during the intervention training sessions and physical activity outside the intervention training sessions) estimated using the same formula used to calculate daily physical activity in the three-day measurements. For the control participants $DIS_{Total} = DIS_{Log}$, since they were not involved in the exercise intervention.

Questionnaires

Health-related quality of life (HRQoL) was assessed using the Finnish version of the validated RAND 36-item health survey 1.0 questionnaire (RAND-36) [31]. The RAND-36 is a generic questionnaire comprising 8 distinct dimension of health status: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role limitations (emotional), mental health, and role limitations (physical). The scale runs from 0 to 100, with higher scores representing higher HRQoL. Clinically important symptoms of knee pain, stiffness and physical function were measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [32]. We have reported earlier that after the 12-month trial, no intergroup differences were observed in knee pain, stiffness, or physical function [22].

Statistical analysis

Data were analysed using SPSS 20.0.0.2 (IBM Corp., Armonk, NY). All analyses were based on the intention-to-treat principle. Means and standard deviations are given as descriptive statistics. The Epps-Singleton two-sample test was used to examine the equality of distributions for the total physical activity loading index (DIS_{Total}) in both the exercise and control groups. Owing to violation of the distribution assumptions, statistical comparisons of changes in the bone strength indices and quantitative MRI were performed by using the bootstrap analysis of covariance (ANCOVA). Thus, the confidence intervals (95% CI) for the bone and MRI outcome means were obtained by bias-corrected bootstrapping (5000 replications). The baseline value of the variable of interest and baseline height, body mass and age were used as covariates in the ANCOVAs. The association between DIS_{Total} and the changes in the bone and cartilage indices were examined with Pearson's correlation coefficient. The level of statistical significance was set at $\alpha \leq 0.05$.

3 RESULTS

Baseline characteristics of the study groups are given in Table 1. The demographic and clinical characteristics of both groups were similar at baseline (Table 1).

Six medical consultations were required due to musculoskeletal injuries or other symptoms (knee swelling, distension of the hamstring muscles, ankle sprain, low-back pain, Achilles tendon pain, asthma-like symptoms) that arouse during the high-impact exercise sessions. No fall-related injuries occurred during the exercise sessions. All the trainees returned to the exercise regime within 5 to 21 days. Two control subjects required a medical consultation due to a previous meniscal tear injury and cardiac dysrhythmia [22].

In the exercise group, the mean number of exercise program acceleration peaks over the 12-month exercise intervention period was 1713 (SD 337) at the 0.3-1.0 g acceleration level, 401 (33) at the 1.1-2.4 g acceleration level, 76 (5) at the 2.5-3.8 g acceleration level, 41 (7) at the 3.9-5.3 g acceleration level, and 44 (16) at the 5.4-9.3 g acceleration level. The total physical activity loading (DIS_{Total}) was significantly higher (364 [73]) in the exercise group than in the control group (168 [46], $P < 0.01$), indicating that the group difference in impact was due to the exercise program. The percentage distribution of average DIS_{Total} for the exercise and control groups is shown in Fig. 3.

The baseline values and post-treatment bone strength indices are given in Table 2. The adjusted treatment effect (mean [95% CI]) in femoral neck Z was 23 (4 to 42) mm^3 in favor of the exercise group, while no significant differences between the groups were observed in femoral neck CSA or W over the intervention (Table 2). DIS_{Total} was positively associated with change in Z ($r = 0.29$, $p = 0.012$), whilst no significant associations were observed between DIS_{Total} and change in femoral neck CSA or W.

The baseline values and post-treatment cartilage indices are given in Table 2. At 12 months no significant differences between the groups were observed in bulk cartilage values in the medial or lateral condyle in either the T2 or dGEMRIC mapping variables (Table 2). No statistically significant relationships were observed between DIS_{Total} and change in T2 in the medial condyle (r = 0.12, p = 0.30) or lateral condyle (r = 0.05, p = 0.65), or in the dGEMRIC index in the medial (r = 0.15, p = 0.20) or lateral condyle (r = 0.20, p = 0.09).

With respect to the cartilage and bone relationship, an association was found between change in the T2 value in the medial femoral condyle and Z, showing that Z increased with decreasing relaxation time at T2 (r = -0.32, 95% CI: -0.55 to -0.04) (Fig. 4). In addition, an association was found between changes in the dGEMRIC index in the lateral femoral condyle and Z, showing that Z increased with increasing dGEMRIC index values (r = 0.24, 95% CI: 0.02 to 0.46) (Fig. 4).

4 DISCUSSION

The primary finding of this study was that femoral neck strength can be positively modified with high-impact exercise in postmenopausal women with mild knee OA. In addition, the high-impact training applied turned out to be safe for the bulk cartilage area exposed to loading, which is in line with our recent finding [22], obtained with the very same group and intervention, that high-impact loading did not harm load-bearing cartilage subregions. It is also noteworthy, that total physical activity during the study was related to an improvement in femoral neck strength in all participants.

To date, a limited number of randomized controlled exercise intervention trials have evaluated the effects of exercise or overall physical activity on femoral strength in postmenopausal women. In contrast to our study, previous RCTs in early postmenopausal women [16], older postmenopausal women [17] and pre- and postmenopausal women with breast cancer [18], have not consistently demonstrated improvements in femoral neck exercise-induced strength. To some extent, these inconsistent results may be explained by different group characteristics, exercise compliance or training intensities. In the present study, we quantified the actual exercise loading of the trainees throughout the trial by using accelerometer-based body movement monitors. Our finding is also in line with our previous findings in premenopausal women, where we observed a 3% increase in femoral neck section modulus following an 18-month high-impact exercise intervention [33] similar to that utilized in the present study. Further, since improvement in pQCT-derived bone mass and geometry has consistently been found following weight-bearing jumping exercises in both premenopausal [34] and postmenopausal women [35], it is plausible that the high-impact loading regimen in the present study is the primary reason for the positive response observed in femoral neck bending strength.

In addition to the exercise-induced positive response in femoral neck bending strength, the training maintained, although not statistically significantly, femoral neck CSA, thereby reflecting sustainable strength abilities against compressive force. In contrast, exercise had no effect on the outer diameter (W) of the femoral neck. These findings may indicate that increased loading over the 12-month training period has led to reshaping of the bone cross section and a redistribution of bone minerals from the trabecular to cortical component without any external expansion. Unfortunately, we had no opportunity to verify this assumption by QCT measurement, which enables cortical and trabecular bone to be analyzed separately. However, our result on the response to exposure to mechanical loading of the load-bearing femoral neck is in line with our previous results in sedentary premenopausal women [33], premenopausal female athletes representing high-impact and odd-impact loading sports [36], and national-level female and male triple jumpers [37]. A feature common to femoral neck strengthening studies is exposure of the skeleton to activities involving jumps and versatile movements with relative high ground-reaction forces, varying from 2 to 6 times body weight in pre- and postmenopausal women [22,24] up to 14 to 22 times body weight in triple jumpers [37]. These findings confirm earlier observations that to achieve an osteogenic bone response, the loading-induced mechanical deformation, i.e., strain, needs to be of a high magnitude and produced at a high/fast rate [38,39]. However, it should be noted that a high magnitude and fast rate of exercise may not be appropriate in subjects with severe osteoporosis, owing to an elevated risk of fracture from high-intensity loading. Similarly, high-impact loading cannot be recommended for subjects with severe knee osteoarthritis.

Quantification of study participants' coverall physical activity (i.e. frequency, intensity and duration) over an intervention trial is often challenging due to the somewhat indirect metering of physical activity. In the present study, we described individual daily osteogenic loading by using a previously validated method that provides a single score DIS_{Log} [30]. We found an association between change in femoral neck bending strength change and the total physical activity loading index DIS_{Total}. In other words, the greater the amount, and the higher the intensity, of the impacts included in the subjects' daily physical activity, the greater the increase in their femoral neck bending strength. The present finding is in line with the finding by Ahola et al. [30], who reported an association between the individually specific loading measured by an accelerometer-based body movement monitor, i.e., DIS_{Log}, during a high-impact exercise intervention and the osteogenic response at the trochanter [30]. Unfortunately, there is a relative paucity of literature on the topic, but a previous exercise study by Vainionpää et al. [40] measuring exercise loading at different acceleration levels revealed that, in healthy premenopausal women, physical activity, including accelerations in excess of 3.9 g forces, induced a positive response in femoral neck BMD. Less than 100 accelerations per day were needed to improve hip BMD over the threshold level of 3.9 g [40]. These findings indicate that monitoring the performance technique and consequent loading during the exercise regimen as either DIS_{Log} or absolute values may be useful indicator of the osteogenic potential that can be expected.

Further analyses on cartilage responses to exercise were also carried out in this study in addition to our previously published cartilage results [22]. Our previous results were obtained from the load-bearing cartilage regions, which had been divided into several subregions based on certain anatomical landmarks, whilst in the present study much the similar region in the medial and lateral femoral condyles were analyzed as combined topographical entities. The present cartilage ROI division was based on the functional adaptation premise, in which the femur acts as the bearing surface of several reaction forces in the knee joint. During standing and walking the central part of the femoral cartilage is in contact with the tibia cartilage or meniscus, whereas during knee flexion the reaction forces are transmitted more posteriorly onto the femoral cartilage [41]. Thus, we focused on the femoral cartilage areas, which were the most highly exposed to the exercise loading and therefore the most clinically relevant to OA patients. We have also previously shown that bigger cartilage ROIs are associated with higher measurement accuracy than smaller ROIs [42], and therefore enable more subtle detection of possible cartilage responses. However, the bulk cartilage regions remained unchanged, as was also seen in our previous analyses of several cartilage subregions. However, in the correlation analysis of the present study we found that as femoral neck strength increased, the surrogate for the knee cartilage constituent (T2) decreased in the medial femoral condyle, indicating favorable cartilage collagen integrity and water content [43,44]. Similarly, an association was observed between femoral neck strengthening and elongating of the cartilage dGEMRIC index in the lateral femoral condyle, indicating an increase in GAG content. Although the exercise program per se had no effects on the bulk cartilage areas and the aforementioned bone-cartilage associations remained non-significant, these findings imply that, in this population of women with mild knee OA, osteogenic exercise, and physical activity in general, is likely to have favorable rather than detrimental effects on knee cartilage biochemical composition. Due to the small number of RCTs investigating exercise effects on knee cartilage in OA, further studies are needed to investigate the optimal type and dose of exercise for cartilage health.

As we have previously pointed out [22], this study has several strengths: it is the first RCT conducted with OA subjects to directly investigate the effects of exercise at the knee cartilage level; the study design fulfills all the important quality criteria of a RCT; the intervention was of sufficient duration; training compliance was high; and dropouts were few. The main limitation of the study is that the use of DXA-based AHA analysis to evaluate femoral neck bone structure does not permit the effects of high-impact loading on the redistribution of bone minerals on the trabecular component to be distinguished from those on the cortical component. In addition, bone trait change in the complex three-dimensional hip is not likely to be accurately depicted by data extracted from a two-dimensional DXA scan. These inaccuracies related to imaging techniques, however, were to some extent overcome in this study by use of an appropriately powered study design. One limitation related to the accelerometer-based measurements was that the exercise impact scores required to describe the overall loading level of the exercise regimen were determined from the recording of only one aerobic and step-aerobic training session per trainee per quarter. In addition, in the daily physical activity measurements, three consecutive days of accelerometer-based recording may not be representative of habitual levels of physical activity. Moreover, to describe all the activities engaged in throughout the study, we used a rather coarse total physical activity index that combined the average loadings from the exercise intervention and those of the participants' daily physical activities. Furthermore, since an accelerometer measures gravitational forces only, some daily physical activities may not have been captured due to the meter's inability to gauge static work or activities which do not contain much in the way of acceleration forces, such as in climbing, cycling or skiing. However, the information in the physical activity diaries showed that the groups did not differ in their daily physical activities and that the monitors were not falsely activated, for example while riding bicycles or driving motor vehicles. It is important to remember that although a body movement monitor does not provide more than a crude description of different human activities, it is advantageous in quantifying individual ambulation with osteogenic loading. Finally, the study was limited by the lack of participant blinding, which is an obvious limitation in exercise therapy studies, and by the fact the researcher who segmented the cartilage tissue was not blinded to group allocation.

In conclusion, high-impact exercise can modify femoral neck strength in a positive manner in postmenopausal women. In addition, hip strengthening was associated with total physical activity over the one-year study period: the more impact-containing physical activity assessed using an accelerometer-based body movement monitor, the higher the increase in femoral neck strength. The progressive high-impact training proved to be safe for cartilage health in mild knee OA, since the exercise did not in any way alter the biochemical composition of the cartilage region exposed to loading. These findings in conjunction with our previous results that training improved physical function suggests that high-impact exercise may be feasible in the prevention of hip fractures by increasing femoral neck bone strength and by reducing physical performance-related risk factors, such as falling, in postmenopausal women with mild knee OA.

Authors' roles

AHeinonen, AHäkkinen, IK, MTN, TJ and JM designed the research; JM, AHeinonen, MTN, EL and TJ conducted the research; JM, TR and RA collected the data; HK, AHeinonen, JM and TR analyzed the data and performed the statistical analysis; JM, AHeinonen, TR MTN, HK, AHäkkinen and IK interpreted the data; JM and TR drafted the manuscript; JM, TR, AHeinonen and AHäkkinen revised the manuscript content; all authors approved the final version of the manuscript; JM and AHeinonen take responsibility for the integrity of the data analysis.

REFERENCES

1. Childs, JD, Sparto, PJ, Fitzgerald, GK, Bizzini, M, Irrgang, JJ 2004 Alterations in lower extremity movement and muscle activation patterns in individuals with knee osteoarthritis. Clin Biomech (Bristol, Avon) **19**:44-49.

2. Winter, CC, Brandes, M, Muller, C, Schubert, T, Ringling, M, Hillmann, A, Rosenbaum, D, Schulte, TL 2010 Walking ability during daily life in patients with osteoarthritis of the knee or the hip and lumbar spinal stenosis: a cross sectional study. BMC Musculoskelet Disord **11**:233-2474-11-233.

3. Soininvaara, TA, Miettinen, HJ, Jurvelin, JS, Alhava, EM, Kröger, HP 2004 Bone mineral density in the proximal femur and contralateral knee after total knee arthroplasty. J Clin Densitom **7**:424-431.

4. Rittweger, J, Frost, HM, Schiessl, H, Ohshima, H, Alkner, B, Tesch, P, Felsenberg, D 2005 Muscle atrophy and bone loss after 90 days' bed rest and the effects of flywheel resistive exercise and pamidronate: results from the LTBR study. Bone **36**:1019-1029.

5. Ward, KA, Caulton, JM, Adams, JE, Mughal, MZ 2006 Perspective: cerebral palsy as a model of bone development in the absence of postnatal mechanical factors. J Musculoskelet Neuronal Interact **6**:154-159.

6. El Miedany, YM, Mehanna, AN, El Baddini, MA 2000 Altered bone mineral metabolism in patients with osteoarthritis. Joint Bone Spine **67**:521-527.

7. Antoniades, L, MacGregor, AJ, Matson, M, Spector, TD 2000 A cotwin control study of the relationship between hip osteoarthritis and bone mineral density. Arthritis and Rheumatism **43**:1450-1455.

8. Nevitt, MC, Cummings, SR, Lane, NE, Hochberg, MC, Scott, JC, Pressman, AR, Genant, HK, Cauley, JA 1996 Association of estrogen replacement therapy with the risk of osteoarthritis of the hip in elderly white women. Study of Osteoporotic Fractures Research Group. Arch Intern Med **156**:2073-2080.

9. Stevenson, JC 2011 A woman's journey through the reproductive, transitional and postmenopausal periods of life: impact on cardiovascular and musculo-skeletal risk and the role of estrogen replacement. Maturitas **70**:197-205.

10. Greendale, GA, Barrett-Connor, E, Ingles, S, Haile, R 1995 Late physical and functional effects of osteoporotic fracture in women: the Rancho Bernardo Study. J Am Geriatr Soc **43**:955-961.

11. Magaziner, J, Fredman, L, Hawkes, W, Hebel, JR, Zimmerman, S, Orwig, DL, Wehren, L 2003 Changes in functional status attributable to hip fracture: a comparison of hip fracture patients to community-dwelling aged. Am J Epidemiol **157**:1023-1031.

12. Hernlund, E, Svedbom, A, Ivergard, M, Compston, J, Cooper, C, Stenmark, J, McCloskey, EV, Jonsson, B, Kanis, JA 2013 Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos **8**:136-013-0136-1. Epub 2013 Oct 11.

13. Bonaiuti, D, Shea, B, Iovine, R, Negrini, S, Robinson, V, Kemper, HC, Wells, G, Tugwell, P, Cranney, A 2002 Exercise for preventing and treating osteoporosis in postmenopausal women. Cochrane Database Syst Rev **(3)**:CD000333.

14. Kanis, JA, Burlet, N, Cooper, C, Delmas, PD, Reginster, JY, Borgstrom, F, Rizzoli, R, European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) 2008 European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int **19**:399-428.

15. Karinkanta, S, Piirtola, M, Sievänen, H, Uusi-Rasi, K, Kannus, P 2010 Physical therapy approaches to reduce fall and fracture risk among older adults. Nat Rev Endocrinol **6**:396-407.

16. Uusi-Rasi, K, Kannus, P, Cheng, S, Sievänen, H, Pasanen, M, Heinonen, A, Nenonen, A, Halleen, J, Fuerst, T, Genant, H, Vuori, I 2003 Effect of alendronate and exercise on bone and physical performance of postmenopausal women: a randomized controlled trial. Bone **33**:132-143.

17. Karinkanta, S, Heinonen, A, Sievänen, H, Uusi-Rasi, K, Pasanen, M, Ojala, K, Fogelholm, M, Kannus, P 2007 A multi-component exercise regimen to prevent functional decline and bone fragility in home-dwelling elderly women: randomized, controlled trial. Osteoporos Int **18**:453-462.

18. Nikander, R, Sievänen, H, Ojala, K, Kellokumpu-Lehtinen, PL, Palva, T, Blomqvist, C, Luoto, R, Saarto, T 2012 Effect of exercise on bone structural traits, physical performance and body composition in breast cancer patients--a 12-month RCT. J Musculoskelet Neuronal Interact **12**:127-135.

19. Zhang, W, Moskowitz, RW, Nuki, G, Abramson, S, Altman, RD, Arden, N, Bierma-Zeinstra, S, Brandt, KD, Croft, P, Doherty, M, Dougados, M, Hochberg, M, Hunter, DJ, Kwoh, K, Lohmander, LS, Tugwell, P 2008 OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage **16**:137-162.

20. Fransen, M, McConnell, S 2008 Exercise for osteoarthritis of the knee. Cochrane Database Syst Rev **(4)**:CD004376.

21. Juhl, C, Christensen, R, Roos, EM, Zhang, W, Lund, H 2014 Impact of exercise type and dose on pain and disability in knee osteoarthritis: a systematic review and meta-regression analysis of randomized controlled trials. Arthritis Rheumatol **66**:622-636.

22. Multanen, J, Nieminen, MT, Häkkinen, A, Kujala, UM, Jämsä, T, Kautiainen, H, Lammentausta, E, Ahola, R, Selänne, H, Ojala, R, Kiviranta, I, Heinonen, A 2014 Effects of high-impact training on bone and articular cartilage: 12-month randomized controlled quantitative MRI study. J Bone Miner Res **29**:192-201.

23. Kellgren, JH, Lawrence, JS 1957 Radiological assessment of osteo-arthrosis. Ann Rheum Dis **16**:494-502.

24. Heinonen, A, Kannus, P, Sievänen, H, Oja, P, Pasanen, M, Rinne, M, Uusi-Rasi, K, Vuori, I 1996 Randomised controlled trial of effect of high-impact exercise on selected risk factors for osteoporotic fractures. Lancet **348**:1343-1347.

25. Khoo, BC, Beck, TJ, Qiao, QH, Parakh, P, Semanick, L, Prince, RL, Singer, KP, Price, RI 2005 In vivo short-term precision of hip structure analysis variables in comparison with bone mineral density using paired dual-energy X-ray absorptiometry scans from multi-center clinical trials. Bone **37**:112-121.

26. Tiderius, C, Hori, M, Williams, A, Sharma, L, Prasad, PV, Finnell, M, McKenzie, C, Burstein, D 2006 dGEMRIC as a function of BMI. Osteoarthritis Cartilage **14**:1091-1097.

27. Watanabe, A, Wada, Y, Obata, T, Ueda, T, Tamura, M, Ikehira, H, Moriya, H 2006 Delayed gadolinium-enhanced MR to determine glycosaminoglycan concentration in reparative cartilage after autologous chondrocyte implantation: preliminary results. Radiology **239**:201-208.

28. Nissi, MJ, Töyräs, J, Laasanen, MS, Rieppo, J, Saarakkala, S, Lappalainen, R, Jurvelin, JS, Nieminen, MT 2004 Proteoglycan and collagen sensitive MRI evaluation of normal and degenerated articular cartilage. J Orthop Res **22**:557-564.

29. David-Vaudey, E, Ghosh, S, Ries, M, Majumdar, S 2004 T2 relaxation time measurements in osteoarthritis. Magn Reson Imaging **22**:673-682.

30. Ahola, R, Korpelainen, R, Vainionpää, A, Jämsä, T 2010 Daily impact score in long-term acceleration measurements of exercise. J Biomech **43**:1960-1964.

31. Hays, RD, Sherbourne, CD, Mazel, RM 1993 The RAND 36-Item Health Survey 1.0. Health Econ **2**:217-227.

32. Bellamy, N, Buchanan, WW, Goldsmith, CH, Campbell, J, Stitt, LW 1988 Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol **15**:1833-1840.

33. Heinonen, A, Mäntynen, J, Kannus, P, Uusi-Rasi, K, Nikander, R, Kontulainen, S, Sievänen, H 2012 Effects of high-impact training and detraining on femoral neck structure in premenopausal women: a hip structural analysis of an 18-month randomized controlled exercise intervention with 3.5-year follow-up. Physiother Can **64**:98-105.

34. Vainionpää, A, Korpelainen, R, Sievänen, H, Vihriälä, E, Leppäluoto, J, Jämsä, T 2007 Effect of impact exercise and its intensity on bone geometry at weight-bearing tibia and femur. Bone **40**:604-611.

35. Hamilton, CJ, Swan, VJ, Jamal, SA 2010 The effects of exercise and physical activity participation on bone mass and geometry in postmenopausal women: a systematic review of pQCT studies. Osteoporos Int **21**:11-23.

36. Nikander, R, Sievänen, H, Heinonen, A, Kannus, P 2005 Femoral neck structure in adult female athletes subjected to different loading modalities. J Bone Miner Res **20**:520-528.

37. Heinonen, A, Sievänen, H, Kyröläinen, H, Perttunen, J, Kannus, P 2001 Mineral mass, size, and estimated mechanical strength of triple jumpers' lower limb. Bone **29**:279-285.

38. Rubin, CT, Lanyon, LE 1985 Regulation of bone mass by mechanical strain magnitude. Calcif Tissue Int **37**:411-417.

39. Mosley, JR, Lanyon, LE 1998 Strain rate as a controlling influence on adaptive modeling in response to dynamic loading of the ulna in growing male rats. Bone **23**:313-318.

40. Vainionpää, A, Korpelainen, R, Vihriälä, E, Rinta-Paavola, A, Leppäluoto, J, Jämsä, T 2006 Intensity of exercise is associated with bone density change in premenopausal women. Osteoporos Int **17**:455-463.

41. Eckstein, F, Ateshian, G, Burgkart, R, Burstein, D, Cicuttini, F, Dardzinski, B, Gray, M, Link, TM, Majumdar, S, Mosher, T, Peterfy, C, Totterman, S, Waterton, J, Winalski, CS, Felson, D 2006 Proposal for a nomenclature for magnetic resonance imaging based measures of articular cartilage in osteoarthritis. OsteoarthritisCartilage **14**:974-983.

42. Multanen, J, Rauvala, E, Lammentausta, E, Ojala, R, Kiviranta, I, Häkkinen, A, Nieminen, MT, Heinonen, A 2009 Reproducibility of imaging human knee cartilage by delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) at 1.5 Tesla. Osteoarthritis Cartilage **17**:559-564.

43. Dardzinski, BJ, Mosher, TJ, Li, S, Van Slyke, MA, Smith, MB 1997 Spatial variation of T2 in human articular cartilage. Radiology **205**:546-550.

44. Nieminen, MT, Töyräs, J, Rieppo, J, Hakumäki, JM, Silvennoinen, J, Helminen, HJ, Jurvelin, JS 2000 Quantitative MR microscopy of enzymatically degraded articular cartilage. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine **43**:676-681.

FIGURE AND TABLE LEGENDS

Figure 1. Trial profile.

Figure 2. Cartilage region-of-interest (ROI) in a single sagittal slice from the center of the medial femoral condyle. The ROI is confined to full-thickness cartilage from the outer edge of the anterior horn of the meniscus to the midpoint of posterior femoral cartilage, as outlined by the dashed lines. In delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), high values correspond to high glycosaminoglycan (GAG) content and low values to reduced GAG content.

Figure 3. Percentage distribution of the total physical activity loading index (DIS_{Total}) for the control group and the exercise group over the 12-month study period. In the controls, DIS_{Total} is same as the average daily impact score (DIS_{Log}), while in the exercisers it includes DIS_{Log} and the average impact loading of the exercise intervention.

Figure 4. Associations between change in the femoral neck section modulus and change in the T2 (panels A and B in the upper row) and dGEMRIC indices (panels C and D in the lower row) for the bulk femoral cartilage.

Table 1. Descriptive and clinical characteristics (mean, SD) at baseline in the exercise group and control group.

Table 2. Baseline, follow-up, and treatment values of the DXA-derived Advanced Hip Analysis (AHA) variables and the dGEMRIC Index and T2 from the medial and lateral weight-bearing bulk femoral cartilage.

Table 1

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Characteristics	Exercise N = 38	Control N = 40
Age [years]	57.9 (4.2)	58.8 (4.2)
Body mass [kg]	73.4 (9.4)	69.4 (11.7)
Height [cm]	165 (6)	161 (5)
Body mass index [kg/m^2]	27.1 (3.1)	26.7 (4.2)
Kellgren Lawrence grade, n [%]		
Grade 1	12 (32)	13 (32)
Grade 2	26 (68)	27 (68)
RAND-36[a] Item		
General health	74.1 (11.0)	73.6 (14.0)
Physical functioning	89.9 (9.1)	90.6 (10.3)
Emotional well-being	83.9 (11.2)	83.3 (12.9)
Social functioning	88.9 (17.9)	94.7 (11.3)
Energy	70.4 (16.2)	75.4 (14.2)
Pain	80.5 (12.7)	83.1 (14.7)
Role physical	88.5 (21.7)	91.3 (22.3)
Role emotional	84.7 (27.9)	89.2 (30.6)

[a]RAND 36 item health survey questionnaire

Table 2 Click here to download Table Table 2.docx

Variable	Baseline, Mean (SD)		Follow-up Mean (SD)		Treatment effect		p-value	
	Exercise (n=36)	Control (n=40)	Exercise (n=36)	Control (n=40)	Crude mean (95% CI)	Adjusted[a] mean (95% CI)	Crude	Adjusted[a]
DXA AHA								
Z [mm^3]	640 (146)	609 (109)	658 (148)	600 (110)	28 (11 to 47)	23 (5 to 41)	0.003	0.020
CSA [mm^2]	153 (24)	143 (20)	153 (23)	141 (19)	2 (-0 to 5)	3 (-0 to 5)	0.079	0.096
W [mm]	49.2 (4.2)	48.9 (4.8)	48.7 (4.1)	48.8 (4.7)	-0.3 (-1.2 to 0.6)	-0.4 (-1.4 to 0.7)	0.48	0.49
quantitative MRI								
dGEMRIC [ms]								
Medial	453 (54)	469 (53)	457 (67)	459 (64)	10 (-15 to 36)	10 (-15 to 36)[b]	0.47	0.45[b]
Lateral	458 (57)	466 (46)	460 (44)	468 (52)	-5 (-24 to 15)	-8 (-26 to 12)[b]	0.61	0.44[b]
T2 [ms]								
Medial	51.2 (3.7)	50.0 (4.6)	51.5 (5.2)	49.4 (3.9)	1.1 (-0.3 to 2.5)	1.3 (-0.1 to 2.7)	0.12	0.088
Lateral	49.4 (4.2)	49.9 (3.5)	50.0 (5.1)	50.4 (3.6)	-0.4 (-2.5 to 1.6)	-0.6 (-2.6 to 1.3)	0.69	0.54

[a]Adjusted by baseline value, age, height and body mass, [b]Adjusted by baseline value and age only.

Figure 1

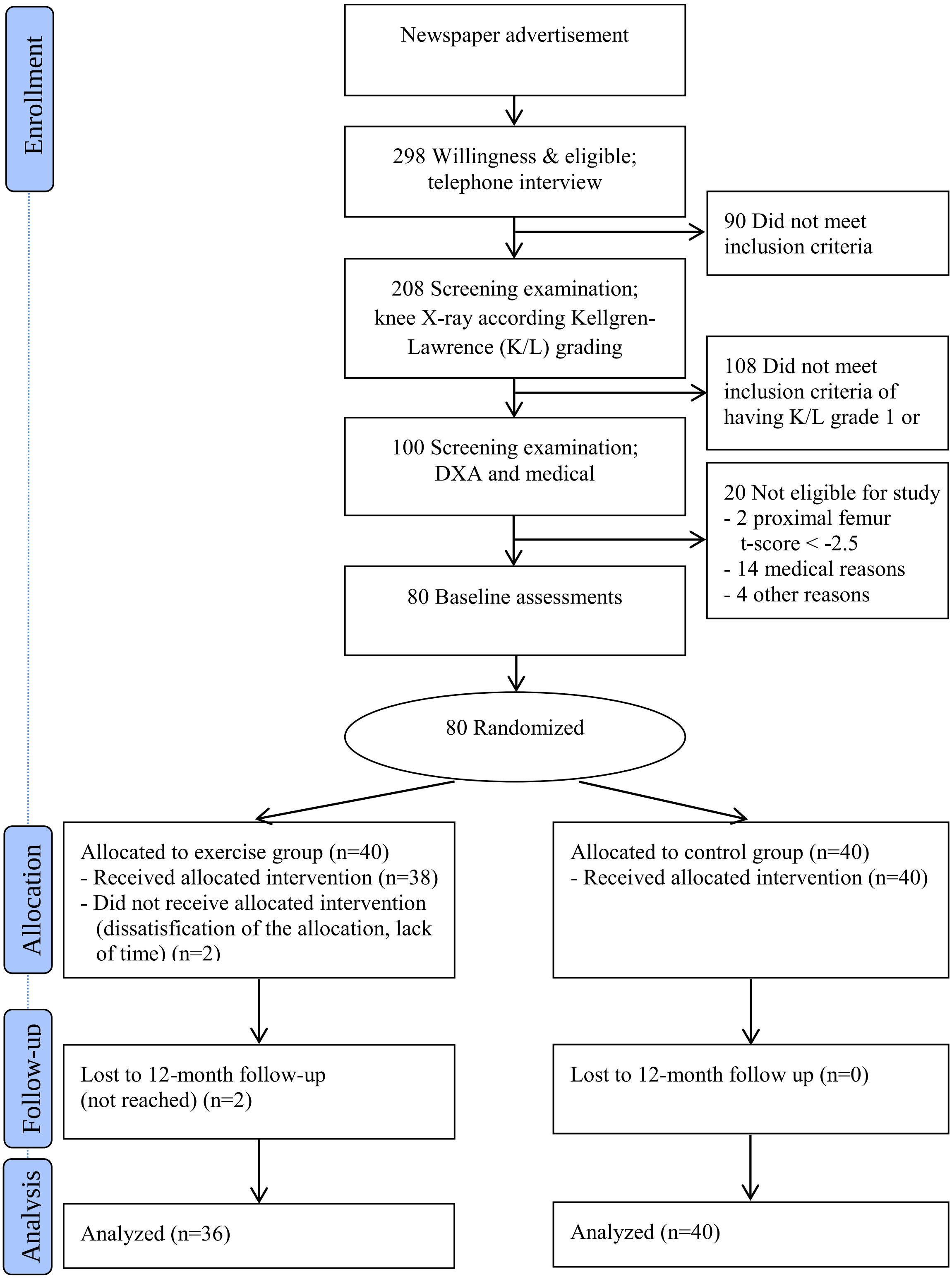

Enrollment
Newspaper advertisement
298 Willingness & eligible; telephone interview
90 Did not meet inclusion criteria
208 Screening examination; knee X-ray according Kellgren-Lawrence (K/L) grading
108 Did not meet inclusion criteria of having K/L grade 1 or
100 Screening examination; DXA and medical
20 Not eligible for study
- 2 proximal femur t-score < -2.5
- 14 medical reasons
- 4 other reasons
80 Baseline assessments
80 Randomized
Allocation
Allocated to exercise group (n=40)
- Received allocated intervention (n=38)
- Did not receive allocated intervention (dissatisfication of the allocation, lack of time) (n=2)
Allocated to control group (n=40)
- Received allocated intervention (n=40)
Follow-up
Lost to 12-month follow-up (not reached) (n=2)
Lost to 12-month follow up (n=0)
Analysis
Analyzed (n=36)
Analyzed (n=40)

Figure 2

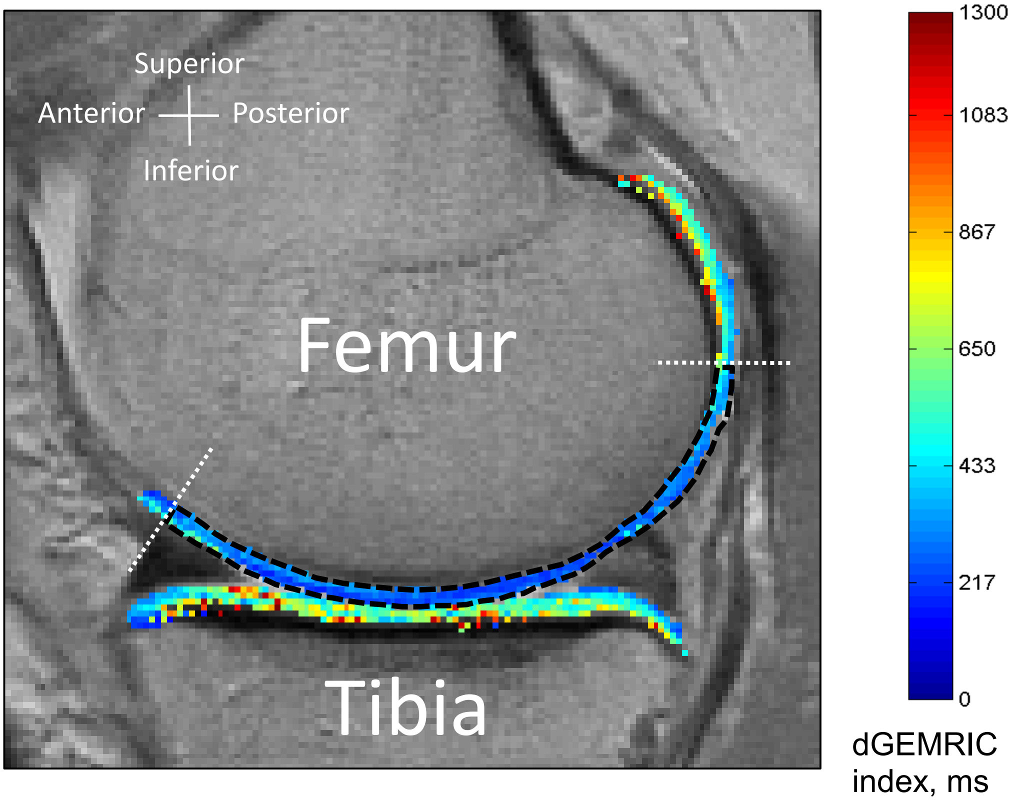
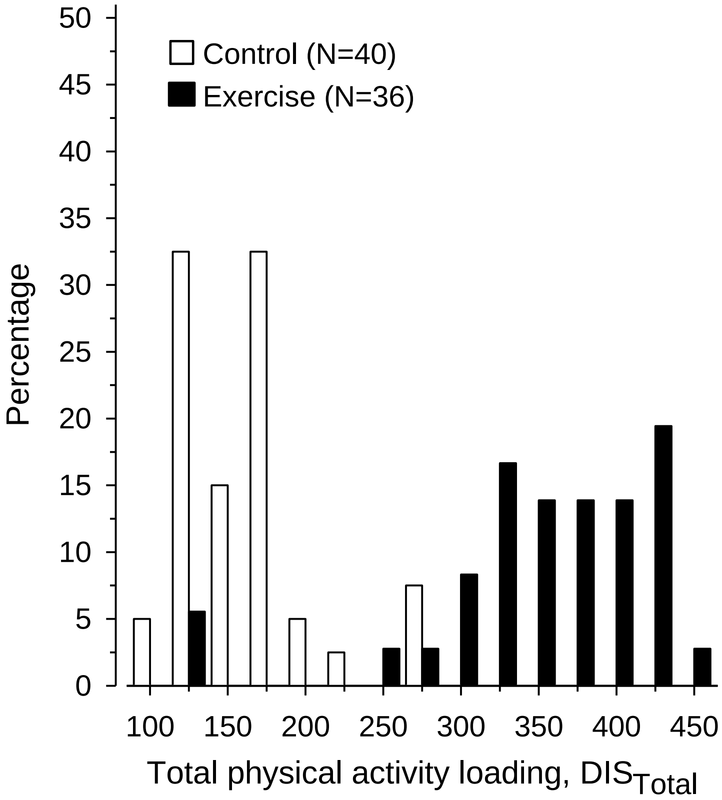

Superior
Anterior
Posterior
Inferior
Femur
Tibia
1300
1083
867
650
433
217
0
dGEMRIC index, ms

Figure 3



Control (N=40)
Exercise (N=36)
Percentage
50
45
40
35
30
25
20
15
10
5
0
100
150
200
250
300
350
400
450
Total physical activity loading, DIS Total

Figure 4

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