J Musculoskelet Neuronal Interact 2014; 14(4):418-424

Hylonome

Original Article

Relationship between lower limb neuromuscular performance and bone strength in postmenopausal women with mild knee osteoarthritis

M. Munukka[1], B. Waller[1], J. Multanen[1,2], T. Rantalainen[3], A. Häkkinen[1,2], M.T. Nieminen[4,5,6], E. Lammentausta[4,6], U.M. Kujala[1], J. Paloneva[7], H. Kautiainen[8,9,10], I. Kiviranta[11], A. Heinonen[1]

[1]Department of Health Sciences, University of Jyväskylä, Jyväskylä, Finland; [2]Department of Physical Medicine and Rehabilitation, Central Finland Central Hospital, Jyväskylä, Finland; [3]Centre for Physical Activity and Nutrition Research, School of Exercise and Nutrition Sciences, Deakin University, Melbourne, Australia; [4]Department of Diagnostic Radiology, Oulu University Hospital, Oulu, Finland; [5]Department of Radiology, University of Oulu, Oulu, Finland; [6]Medical Research Centre, University of Oulu and Oulu University Hospital, Oulu, Finland; [7]Department of Surgery, Central Finland Central Hospital, Jyväskylä, Finland; [8]Unit of Primary Health Care, Helsinki University Central Hospital, Helsinki, Finland; [9]Department of General Practice, University of Helsinki, Helsinki, Finland; [10]Unit of Primary Health Care, Kuopio University Hospital, Kuopio, Finland; [11]Department of Orthopaedics and Traumatology, University of Helsinki, and Helsinki University Hospital, Helsinki, Finland

Abstract

Objectives: To investigate whether neuromuscular performance predicts lower limb bone strength in different lower limb sites in postmenopausal women with mild knee osteoarthritis (OA). **Methods:** Neuromuscular performance of 139 volunteer women aged 50-68 with mild knee OA was measured using maximal counter movement jump test, isometric knee flexion and extension force and figure-of-eight-running test. Femoral neck section modulus (Z, mm^3) was determined by data obtained from dual-energy X-ray absorptiometry. Data obtained using peripheral quantitative computed tomography was used to asses distal tibia compressive (BSI_d, g^2/cm^4) and tibial mid-shaft bending ($SSImax_{mid}$, mm^3) strength indices. **Results:** After adjustment for height, weight and age, counter movement jump peak power production was the strongest independent predictor for Z (β=0.44; p<0.001) and for BSI_d (β=0.32; p=0.003). This was also true in concentric net impulse for Z (β=0.37; p=0.001) and for BSI_d (β=0.40; p<0.001). Additionally, knee extension force (β=0.30; p<0.001) and figure-of-eight-running test (β= -0.32; p<0.001) were among strongest independent predictors for BSI_d after adjustments. For $SSImax_{mid}$, concentric net impulse (β=0.33; p=0.002) remained as the strongest independent predictor after adjustments. **Conclusions:** Neuromuscular performance in postmenopausal women with mild knee OA predicted lower limb bone strength in every measured skeletal site.

Keywords: Bone Strength, Neuromuscular Performance, DXA, pQCT, Osteoarthritis

Introduction

Osteoarthritis (OA) and osteoporosis (OP) are universal age-related musculoskeletal disorders that commonly occur in the same patient population[1-3]. Degenerative changes in cartilage, e.g. in OA can cause pain and loss of muscle mass and thus the decline in associated force production causes mobility limitations and a decrease in daily physical activity[4]. This results in decreased musculoskeletal loading, causing bone loss[5]. Furthermore, it is relatively well known that bone mineral mass[6], bone strength and bone structure associate positively with muscle mass[7]. Also, functional decline is contributed to reduction of lean body mass and an increase of fat mass[8]. Reduced muscle strength together with attenuated bone increases the risk for falls and fragility fractures[9], and represent significant morbidity and healthcare costs[1,10].

It has been previously shown that neuromuscular performance is a better indicator of the bone loading environment than

The authors have no conflict of interest.

Corresponding author: Matti Munukka, MSc, Department of Health Sciences, University of Jyväskylä, P.O. Box 35, 40014 Jyväskylä, Finland
E-mail: matti.munukka@jyu.fi

Edited by: J. Rittweger
Accepted 12 November 2014

body mass in models predicting skeletal rigidity in pre- and postmenopausal women[11]. This notion is supported by previous randomized controlled trials of osteogenic exercise, in which typical osteogenic exercises with high impact loading and fast changes of direction have been shown to have beneficial effects on lower limb bone indices[12-14]. Neuromuscular performance, such as bilateral jumping, is found to be related to tibial strength in young healthy men and women[15]. Furthermore, in female athletes, the strong bone structure was found to be attributable to muscle performance in the weight-bearing lower limbs[16]. However, high-impact loading may not be most optimal form of exercise for postmenopausal women with mild knee osteoarthritis[17]. Thus, it is reasonable and interesting to look at the interplay between neuromuscular characteristics and bone strength to get a better picture how this interaction occurs in postmenopausal women. This interplay should be studied more extensively at several different skeletal sites (femoral neck, tibial mid-shaft and distal tibia) in different population groups, in order to find out new and more relevant information on the potential relationship between exercise related loading and the bone strength. Therefore this study focused on assessing whether neuromuscular performance predicts lower limb bone strength indices in different lower limb sites in postmenopausal women from 50 to 68 years of age with mild knee osteoarthritis.

Methods

Study design and participants

This study was a cross-sectional trial using combined baseline data from two RCTs datasets conducted at Department of Health Sciences in University of Jyväskylä: LuRu (n=52)[12] (ISRCTN58314639) and AquaRehab (n=87)[18] (ISRCTN65346593). In both datasets, postmenopausal women from the Jyväskylä region in Central Finland (total n=621) were recruited on a voluntary basis through local newspaper advertisements. After eligibility was assessed by structured telephone interview, weight bearing radiographs were taken from tibiofemoral joints, dual-energy X-ray absorptiometry (DXA) were taken from both proximal femurs and lumbar spine and clinical examinations were obtained, 139 subjects met the inclusion criteria. According to aforementioned projects, the criteria for eligibility were: volunteer postmenopausal women, between the ages of 50-68 year-old, knee pain on most days, no more than twice a week regular intensive exercise, no illnesses that would limit participation in the exercise interventions or contraindicate exercise, mild tibiofemoral joint OA of grade 1 (possible osteophytes) or 2 (definite osteophytes, possible joint space narrowing) on the radiographic Kellgren/Lawrence (K/L) grading and peripheral quantitative computed tomography (pQCT) measured from the affected knee side (i.e. higher knee K/L side). The criteria for exclusion were: femoral neck bone mineral density (BMD, g/cm^2) T-score lower than -2,5 (indicates osteoporosis), body mass index (BMI) ≥35 kg/m^2, surgery of the knee due to trauma or knee instability, inflammatory joint disease, intra-articular steroid injections in the knee during the previous 12 months, contraindications to MRI and allergies to radiological contrast agents or renal insufficiency. Inclusion criteria in these two RCTs were otherwise similar except for age (LuRu age range: 50-66 years, AquaRehab: 60-68 years) and for BMI (LuRu: ≤35 kg/m^2, AquaRehab: ≤34 kg/m^2). Measurement protocols were similar in both studies, and description of participant recruitments and outcome measures can be found in detail elsewhere[12,18].

Both LuRu –research study protocol (Dnro1E/2008) and AquaRehab –research study protocol (Dnro 19U/2011) were approved by the Ethics Committee of the Central Finland Health Care District. Written informed consent in both studies was obtained from all participants prior to enrolment.

Lower limb bone and body composition measurements

Dual-energy X-ray absorptiometry (DXA). DXA (Lunar Prodigy; GE Lunar Healthcare, Madison, WI, USA) was used to assess rigidity of femoral necks and whole body composition. Proximal femur was scanned with DXA at the narrowest neck section. Femoral neck section modulus (Z, [mm^3], an index of bending strength) was calculated with advanced hip structural analysis (AHA) as per manufacturer's software. The femoral neck section modulus (Z) is equal to the cross-sectional moment of inertia (CSMI) divided by the distance from the center of mass to the superior neck margin (y). Coefficient of variation (CV) of femoral neck section modulus (Z) has been assessed to be 5.1% in our laboratory. Total body fat mass and lean mass were analyzed using enCORE software (enCORE 2011, version 13.60.033) for those subjects in AquaRehab study (n=87). *In vivo* precision of these measurements have been reported to be CV of 1.3-2.2%[19].

Peripheral quantitative computed tomography (pQCT). pQCT (XCT 2000, Stratec Medizintechnik GmbH, Pforzheim, Germany) was used to assess the rigidity of the distal and mid-shaft of the tibia from the affected side leg at 5% and 55% of the length of the tibia from the distal end to the mid-shaft of the tibia. A 30 mm planar scout view of the distal tibia was used to define the distal end of tibia. Distal tibia compressive (BSI_d, g^2/cm^4) and tibial mid-shaft bending ($SSImax_{mid}$, mm^3) strength indices were calculated from the data obtained using pQCT. The BSI_d was calculated as:

$$BSI_d = TtD_{d^2} * TtAr_d$$

where $TtD_d{}^2$ is the apparent bone density of the total bone cross-section and $TtAr_d$ the total cross-sectional area of the distal tibia. The $SSImax_{mid}$ was calculated as:

$$SSImax_{mid} = \sum_{i=1}^{n} \frac{y^2 * D_i * ar}{1200 * ymax_{mid}}$$

where i= index of voxel, D_i= Density of the i:th voxel (in mg/cm^3), ar= area of voxel, y_i= distance of the i:th voxel from the bending axis corresponding to the maximal cross-sectional moment of inertia and $ymax_{mid}$= the distance of the most anterior point from the bending axis corresponding to the maximal cross-sectional moment of inertia[11].

pQCT bone strength indices predict robustly bone failure in compression at the distal tibia and bending strength at the tibial diaphysis[20]. CV for the reported pQCT variables has been measured to range from 0.4 to 1.6% in our laboratory[15]. DXA and pQCT were measured from the higher K/L grade knee side.

Neuromuscular performance

Counter movement jump test (CMJ). Dynamic maximal muscle power of lower limbs was examined by measuring ground reaction forces in newtons (GRFs, N), peak instantaneous power production during the takeoff phase in watts (W) and concentric net impulse in newton seconds (Ns) with a force platform during counter movement jump test. Subjects were asked to perform a counter movement jump with hands on hips and were instructed to jump as high as possible with the preferred counter movement depth and velocity. The weight of the subject was subtracted from the recorded vertical ground reaction force and then divided by the body mass of the subject to produce vertical acceleration[11]. A custom made force plate (University of Jyväskylä, Jyväskylä, Finland) was used to assess maximal power traits from the counter movement jump test. Results were analyzed from the vertical ground reaction force using a custom made Matlab script. Maximal power traits were extracted following methodology from our previous study[11]. Coefficients of variation of 2.5% for jump height[21] and 3.6% for power[22] have been reported in counter movement jump.

Maximal isometric force. Knee extension and flexion force of the affected side leg was measured using an adjustable dynamometer chair (Good strength; Metitur Ltd, Jyväskylä Finland) and recorded in newtons (N). The precision of the tests in our laboratory is 6.3% for the knee extension force and 8.5% for knee flexion force[23].

Figure-of-8-running test. Standardized figure-of-8-running test consisted of two laps around two cones placed 10 meters apart in a figure of eight. Photocells were used to measure time (in seconds) taken to complete the task. The test has been shown to be sensitive (73.5%) and specific (86.1%) for measuring agility and to be effective at detecting decreased motor performance (area under curve 0.86)[24].

Health status, general health and mean habitual physical activity (the metabolic equivalent of task, MET hours per week) were assessed by a questionnaire devised by the research group. Self-reported pain, stiffness and physical functional difficulty were assessed by Western Ontario and McMaster University Osteoarthritis Index (WOMAC) questionnaire in the range from 0 to 100 mm in the visual analogue scale (VAS)[25].

Statistical analyses

The data are presented as means with standard deviations (SD) or as counts with percentages. Linear regression analyses were used to identify the appropriate predictors of the bone strength indices using unadjusted and adjusted (height, weight and age) standardized regression coefficients Beta (β). The Beta value is a measure of how strongly each predictor variable influences the criterion (dependent) variable. The beta is measured in units of standard deviation. Cohen's standard for Beta values above 0.10, 0.30 and 0.50 represent small, moderate and large relationships, respectively. Hochberg's procedure was used to correct type I error. Statistical comparisons between neuromuscular performance and bone strength indices were made by using t-test or analysis of variance (ANOVA). The bootstrap method was used when the theoretical distribution of the test statistics were unknown or in the case of violation of the assumptions (e.g. non-normality). Correlation coefficients between bone strength indices and body composition were calculated by the Pearson method, using Sidak adjusted probabilities. Stata 13.1, StataCorp LP (College Station, TX, USA) statistical package was used for the analyses.

	Mean (SD)
Age (years)	62 (4)
Height (cm)	162 (5)
Body mass (kg)	71 (11)
Body mass index (kg/m^2)	27 (4)
Clinical characteristics	
Kellgren Lawrence grading I/II, n	64/75
Time from menopause (years)	12 (6)
Use of pain killers, n (%)	46 (33)
Glucosamine use occasionally, n (%)	36 (26)
Knee pain during last week (VAS 0-100 mm)	17 (20)
Habitual physical activity (METh/week)	22 (20)
WOMAC pain (VAS 0-100 mm)	11 (11)
WOMAC stiffness (VAS 0-100 mm)	16 (18)
WOMAC physical function (VAS 0-100 mm)	8 (9)
Neuromuscular performance traits	
GRF[a] (N)	135 (24)
Power[a] (W)	1731 (341)
Concentric net impulse[a] (Ns)	108 (19)
Knee extension force (N)	365 (82)
Knee flexion force (N)	174 (50)
Figure-of-8 running (s)	19 (3)
Bone strength indices of the lower limb	
Femoral neck, Z (mm^3)	591 (105)
Tibial mid-shaft, $SSImax_{mid}$ (mm^3)	1169 (182)
Distal tibia, BSI_d (g^2/cm^4)	0.80 (0.19)

GRF= ground reaction force; Power = peak power production; Z= femoral neck section modulus; $SSImax_{mid}$= tibial mid-shaft density weighted maximal moment of inertia; BSI_d= distal tibia compressive bone strength index. [a]Calculated from counter movement jump.

Table 1. Descriptive and clinical characteristics of study participants (n=139).

Results

Table 1 shows the descriptive and clinical characteristics of the study participants. Mean age of the participants was 62 years (range 50 to 68) and BMI 27 kg/m^2 (range 19 to 35). Mean habitual phys-

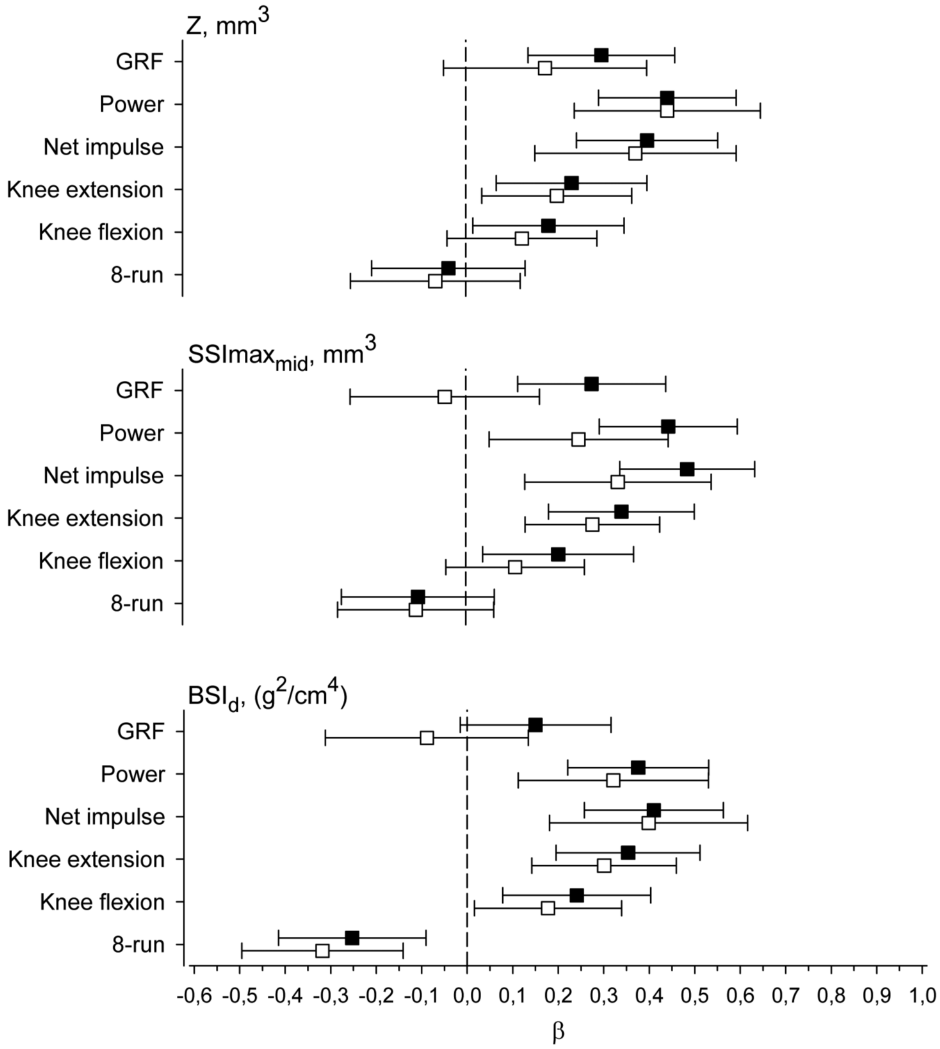

Figure 1. Univariate relationships between exercise related mechanisms and bone strength indices (β-values with 95% confidence intervals). ■= crude and □= height, weight and age adjusted bone strength indices. *Z=femoral neck section modulus; $SSImax_{mid}$=tibial mid-shaft density weighted maximal moment of inertia; BSI_d=distal tibia compressive bone strength index; GRF=ground reaction force; Power=peak power production; Net impulse=concentric net impulse; Knee extension=knee extension force; Knee flexion= knee flexion force; 8-run=figure-of-eight-running.*

ical activity of the study group was moderate (22 METh/week). Mean (SD) knee pain during last week was 17 mm (20).

Overall, univariate neuromuscular performance variables predicted significantly lower limb bone strength indices (Figure 1). After adjustment for height weight and age, counter movement jump peak power production remained the strongest independent predictor for femoral neck Z (β=0.44; p<0.001) and for distal tibial BSI_d (β=0.32; p=0.003). This was also true in concentric net impulse for femoral neck Z (β=0.37; p=0.001) and for distal tibia BSI_d (β=0.40; p<0.001). Additionally, knee extension force (β=0.30; p<0.001) and figure-of-eight-running test (β=-0.32; p<0.001) were among strongest independent predictors for distal tibia BSI_d after adjustments. In figure-of-eight-running test, faster time (thus negative value) predicts stronger bone. For tibial mid-shaft $SSImax_{mid}$, concentric net impulse (β=0.33; p=0.002) remained as the strongest independent predictor after adjustments.

Correlation between bone strength indices and body composition is shown in Table 2. In those who had body composition measured (n=87), lean mass correlated with all bone strength indices, whereas fat mass did not. After Sidak adjustment, correlation between lean mass and femoral neck Z and tibial mid-shaft $SSImax_{mid}$ remained significant.

Discussion

This study provided new information that neuromuscular performance predicted bone strength along lower limb at femoral

Bone strength indices of the lower limb	Lean mass	Fat mass
Femoral neck, Z (mm^3)	0.32 (0.11 to 0.51)*	0.08 (-0.14 to 0.29)
Tibial mid-shaft, $SSImax_{mid}$ (mm^3)	0.53 (0.37 to 0.66)***	0.17 (-0.06 to 0.39)
Distal tibia, BSI_d (g^2/cm^4)	0.22 (0.03 to 0.38)	0.08 (-0.13 to 0.29)

*Z= Femoral neck section modulus; $SSImax_{mid}$= tibial mid-shaft density weighted maximal moment of inertia; BSI_d= distal tibia compressive bone strength index. Sidak adjusted probabilities: *p<0.05, **p<0.001, ***p<0.001.*

Table 2. Correlation coefficients (95% CI) between bone strength indices and body composition.

neck, tibial mid-shaft and distal tibia. Concentric net impulse and peak power production during counter movement jump were the strongest predictors of the lower limb bone strength indices. In addition, knee extension force and figure-of-eight-running were among strongest predictors of bone strength in lower limb. However, figure-of-eight-running (acceleration, deceleration and fast turning during test) time predicted only distal tibia BSI_d. This is in line with the previous findings, which indicate that the highest measurable strain during running occurs at the distal tibia and calcaneus with the greatest strain being generated at the cortex under compression[26].

In our study, lower limb concentric net impulse and peak power production, e.g. fast bone loading, predicted lower limb bone strength indices. These findings may mirror the fact that bones adapt their strength through increased strain and stress which are caused by increased loads through forceful muscle contractions[7]. It has been shown, that an 18-month progressive high impact exercise program strengthened the section modulus Z (mean difference 47 mm^3, 95% CI: 1 to 92) compared to controls in sedentary premenopausal women[5]. It is known that bone's response to loading is site-specific, and depended on the strain magnitude, rate distribution, strain rate and cycles in the target bone[26]. Strain rate is shown to be most effective for maximal adaptive bone response in animal experiments[27]. This is supporting our results, which show that fast and forceful movements are important determinants of lower limb bone strength. When this is translated to human exercise, high impact (e.g. jumping) or odd impact (e.g. squash) exercise loadings with high strain rates and strain magnitudes are reported to be the best way to improve bone strength in femoral neck, distal tibia and tibial mid-shaft[5,28].

Furthermore, regular exercise is a promising non-pharmacological method that can prevent the risk of osteoporotic fractures by improving bone quality and preventing falls[29,30] and it is also recommended treatment for mild knee OA[31]. Despite the fact that high impact loading on regular basis is proposed to be best way to strengthen bones[28], typical osteogenic exercises with high-impact loading may not be applicable in postmenopausal women with mild knee OA[17]. On the other hand, our recent study indicated that progressively implemented high-impact jumping exercise did not have unfavourable effects on the biochemical properties of the knee cartilage. Further, among postmenopausal women with mild knee OA, impact jumping exercise did not cause knee pain and it had favourable effects on physical function (e.g. lowered fall risk factors for osteoporotic fractures)[12]. Taking into account the results of the present and previous studies[12,17,28], lower limb power training, in addition to strength training, could be emphasized in OA and OP training and rehabilitation programs. Nevertheless, cross-sectional study design is not able to demonstrate causal relations; therefore the findings remain purely hypothesis generating.

It has been shown that variation in body mass might not be one of the strongest determinants of skeletal rigidity in lower limbs[15,32-34] as had been previously proposed[35,36]. Results of the present study support these findings, showing that neuromuscular performance predicted bone strength indices both in femur and in tibia. Also, in our analysis lean mass correlated significantly with femoral neck Z and tibial mid-shaft $SSImax_{mid}$, whereas fat mass did not have correlation with bone strength indices. Our observations are in line with a recent study, in which positive correlations was found among lean mass, bone density and bone microstructure in obese adults with metabolic syndrome[37]. Thus the results highlight the role of exercise and dynamic loading instead of passive loading by body mass in lower limb skeletal rigidity. Variations in fat mass between individuals can potentially double the load the skeleton is required to bear[38]. In addition to all other unfavorable effects of weight gain, e.g. increased mortality[39], it can also aggravate osteoarthritis of the knee in postmenopausal women. Therefore other options instead of weight gain are needed to improve the skeletal properties. Better neuromuscular performance is found to be associated with better skeletal rigidity[11] and regular exercise has other beneficial benefits on human body than just weight reduction, such as improved muscle strength, joint range of motion, balance, proprioception and cardiovascular fitness. Thus exercise increases daily physical activity and decreases risk of falling in OA patients[40]. Therefore regular exercise can be recommended as a means to improve skeletal health.

The main strengths of this study were the relatively large subject group and bone strength indices being measured from several locations in the lower limb: femoral neck, tibial mid-shaft and distal tibia. However, knee and distal femur regions were not measured which can be considered as a minor limitation. This study included only 50-68-year-old Caucasian females with mild knee OA recruited as part of the study groups of two larger randomized controlled trials with distinct inclusion/exclusion criteria, and thus results of the present study cannot be generalized to other groups. As aforementioned, cross-sectional design is not able to demonstrate causal relations and as well-known, that limits interpretation of the results.

In conclusion, this study shows that in 50-68 year old postmenopausal women with mild knee OA, neuromuscular performance traits predicted lower limb bone strength in every measured skeletal site. These results provide new and more relevant information when interpreting the effects of neuromuscular performance on bone. This data will help when planning meaningful contents and instructions for bone health related interventions as well as studies among postmenopausal women with mild knee OA.

Acknowledgements

This study was funded by the Academy of Finland, The Social Insurance Institution of Finland (KELA) and Finnish Cultural Foundation.

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