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ORIGINAL ARTICLE

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High-Impact Mechanical Loading Increases Bone Material Strength in Postmenopausal Women—A 3-Month Intervention Study

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ABSTRACT

Bone adapts to loading in several ways, including redistributing bone mass and altered geometry and microarchitecture. Because of previous methodological limitations, it is not known how the bone material strength is affected by mechanical loading in humans. The aim of this study was to investigate the effect of a 3-month unilateral high-impact exercise program on bone material properties and microarchitecture in healthy postmenopausal women. A total of 20 healthy and inactive postmenopausal women (aged 55.6 ± 2.3 years [mean ± SD]) were included and asked to perform an exercise program of daily one-legged jumps (with incremental number, from 3×10 to 4×20 jumps/d) during 3 months. All participants were asked to register their performed jumps in a structured daily diary. The participants chose one leg as the intervention leg and the other leg was used as control. The operators were blinded to the participant's choice of leg for intervention. The predefined primary outcome was change in bone material strength index (BMSi), measured at the mid tibia with a handheld reference probe indentation instrument (OsteoProbe). Bone microstructure, geometry, and density were measured with high-resolution peripheral quantitative computed tomography (XtremeCT) at the ultradistal and at 14% of the tibia bone length (distal). Differences were analyzed by related samples Wilcoxon signed rank test. The overall compliance to the jumping program was 93.6%. Relative to the control leg, BMSi of the intervention leg increased 7% or 0.89 SD ($p = 0.046$), but no differences were found for any of the XtremeCT-derived bone parameters. In conclusion, a unilateral high-impact loading program increased BMSi in postmenopausal women rapidly without affecting bone microstructure, geometry, or density, indicating that intense mechanical loading has the ability to rapidly improve bone material properties before changes in bone mass or structure. © 2018 The Authors. *Journal of Bone and Mineral Research* Published by Wiley Periodicals Inc.

KEY WORDS: HIGH-IMPACT MECHANICAL LOADING; BONE MATERIAL STRENGTH INDEX; POSTMENOPAUSAL WOMEN; OSTEOPOROSIS; BONE MICROINDENTATION

Introduction

Osteoporosis is a disease characterized by deteriorated bone microstructure, loss in bone mineral density (BMD), and reduced bone quality, leading to lower bone strength and increased risk of fracture.[1,2] Areal BMD (aBMD) assessed with dual-energy X-ray absorptiometry (DXA) is the gold standard for diagnosing osteoporosis and is a major determinant of the bone's ability to resist fracture.[2] Bone quality also contributes to fracture toughness[3] and is dependent on several factors such as macro- and microstructure, mineral content, matrix composition, and other intrinsic material properties.[3,4] Recently, the advent of a handheld device suitable for clinical use has enabled the assessment of bone material strength index (BMSi), a measure of cortical bone material strength, in humans. Previous studies have linked a low BMSi to decreased areal BMD,[5] increased cortical porosity,[6] and higher prevalence of fracture.[7]

Reduced mechanical loading accelerates the age-dependent bone loss,[8] whereas increased loading via weight-bearing physical activity is able to increase bone strength by redistributing the bone mass and changing its macro- and microarchitecture.[9,10] Several interventional studies have revealed that weight-loading exercise can increase the areal and cortical BMD,[11–15] as well as augment the cortical bone

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size, especially if the intervention is applied early in life. Thus, weight-bearing physical activity is an important factor for bone development, as well as for maintaining bone strength,[16,17] reducing falls,[18] and possibly reducing the risk of fracture.[19] However, it still remains unclear how bone material properties can adapt to increased loading.

Bone microstructure can now easily be assessed by noninvasive imaging using high-resolution peripheral quantitative computed tomography (HR-pQCT).[20] Exercise intervention trials in older women using HR-pQCT are lacking, but we recently reported that physical activity was associated with trabecular bone volume fraction, cortical cross-sectional area, and bone strength of the tibia in this group.[21]

Finding a suitable exercise program to maintain or even increase bone strength would be of great interest to possibly lower the risk for fracture. Jumping, similar to other high-impact loading exercises, has proven to be able to generate a substantial osteogenic response[11] and is an exercise easy to standardize for the participants.

The primary aim of the present study was to investigate how a 3-month unilateral high-impact exercise program affects BMSi in postmenopausal women. We hypothesized that physical activity regulates bone material properties and that increased loading could rapidly improve bone material strength before any density or microstructural effects would be apparent.

Subjects and Methods

Study design

In this intervention study, participants were asked to perform an exercise program consisting of daily one-legged jumps for 3 months. The participants chose one leg, without consideration of dominant side, as the intervention leg and consistently jumped on the same leg throughout the study. The non-interventional leg was used as a control. The study was registered at Clinicaltrials.gov before study start (https://clinicaltrials.gov/ct2/show/NCT02339051).[22] The primary and predefined outcome of this study was changes in BMSi, measured with the OsteoProbe device, in the limb subjected to loading in comparison to the control limb. Secondary outcomes included changes in total volumetric BMD (Tot.vBMD, mg/cm^3), cortical volumetric BMD (Ct.vBMD, mg/cm^3), cortical cross-sectional area (Ct.Ar, mm), and trabecular bone volume fraction (BV/TV, %), measured using HR-pQCT. The operators for both OsteoProbe and HR-pQCT measurements were blinded concerning each participant's choice of leg for intervention. Signed informed consent was provided by all study participants. The study was approved by the ethical review board in Gothenburg.

Subjects

Healthy postmenopausal women aged 50 to 60 years were recruited by advertisements in local papers and at the Sahlgrenska University Hospital in Gothenburg. All volunteers were contacted by telephone and prescreened using a short set of questions enabling the exclusion of women who did not meet the inclusion criteria or fulfilled exclusion criteria. Exclusion criteria included a history of osteoporosis; regular weight-loading exercise (>1 time per week the last 3 months); current smoking; current or past (within 6 months) hormone-replacement therapy; fracture located at the ankle or lower leg; diseases or use of medication known to influence bone metabolism or fracture risk; and those who had initiated calcium or vitamin D supplementation in the preceding 6 months.[22]

A total of 67 women volunteered (Fig. 1). From these, 16 withdrew consent because of insufficient time to participate. In addition, 31 were excluded or did not meet the inclusion criteria: hormone-replacement therapy ($n = 7$); still menstruating ($n = 5$); exercised >1 time/week ($n = 5$); not within predefined age limits ($n = 4$); history of tibial fracture ($n = 3$); diseases likely to affect bone metabolism ($n = 3$); ongoing osteoporosis treatment ($n = 2$); and smoking ($n = 2$). Finally, 20 women were included at baseline.

Bone material strength index measured with microindentation

Reference point indentation (RPI) with the OsteoProbe device (Active Life Technologies, Santa Barbara, CA, USA) was used to measure BMSi. Measurements were performed on both legs at baseline and follow-up. The indentation site on each leg was determined by measuring the midpoint from the proximal end of the medial border of the tibial plateau to the distal edge of the medial malleolus. After administrating local anesthesia, the handheld OsteoProbe was inserted through the skin and periosteum until reaching the bone surface at the anterior face of the mid tibia. While keeping the device perpendicular to the bone surface, the probe was first established by a preload force of up to 10 N. With the probe well established, a trigger mechanism releases an impact force of 30 N (indentation measurement) for less than a millisecond. This force pushes the probe into the cortical bone, introducing a small micro-fracture, 375 μm across.[7,23] A distance is obtained (indentation distance increase [IDI]) from the position where the probe was established to the position right after the impact force has been actuated. The first measurement was routinely discarded because this measurement is highly influenced by passing through the soft tissue and the periosteum. In addition, 50 of 1058 (4.73%) measurements were discarded before any knowledge of the BMS value because of obvious errors in the measuring procedure, including malfunctioning of the probe

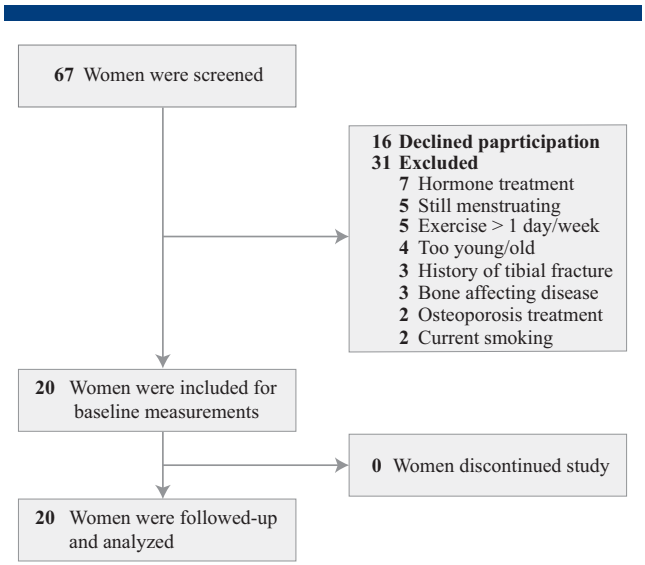

Fig. 1. Study population.

mechanism or the probe getting stuck into the bone. BMSi was therefore calculated as the average of at least 10 valid measurements at different tibial sites separated by >2 mm for each measurement. To calibrate the measurements, five additional measurements were made on a poly(methyl methacrylate) (PMMA) plastic calibration phantom. BMSi was then calculated by dividing the harmonic mean IDI obtained from the PMMA material by the IDI obtained from the impact into the bone, multiplied by 100.[24] The BMSi value is therefore inversely related to penetration depth, where a low BMSi value indicates that the probe created a larger cavity reflecting lower bone material strength. One operator performed all indentations except one follow-up measurement. The intraobserver coefficient of variance (CV) was 3.2% and calculated from duplicate measurements performed on 30 elderly women. The interobserver CV was 5.2% and obtained at the same leg, within 2 cm proximity, on 30 subjects by two different operators.

Bone geometry and microarchitecture

An HR-pQCT device (XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland) was used to scan the tibia of both legs in all subjects. Each tibia was measured at the standard measuring site recommended by the manufacturer (ultradistal) and at 14% of tibia bone length (distal). An anatomically formed carbon fiber shell, especially designed for the tibia (Scanco Medical AG) was used to immobilize the subject's leg during the scan. Measured volume of interest at the tibia was carried out according to a standardized protocol previously described.[20] Briefly, a reference line is manually placed at the center of the endplate of the distal tibia. The first CT slice is obtained at either 22.5 mm or at 14% of the tibia length from this line. With a nominal isotropic resolution of 82 μm, 110 parallel CT slices were obtained at each skeletal site, delivering a three-dimensional representation of an approximately 9-mm section of the tibia in the proximal direction. All scans were analyzed with the manufacturer's standard in vivo analysis protocol and processed according to Laib and colleagues.[25] In short, a semi-automated algorithm placed a contour at the periosteal surface of the bone to delineate it from soft tissue. All contours were inspected and manually adjusted if they were visually deviated from the periosteal boundary; for example, if soft tissue was included within the region of interest (ROI). With these contours, an automated threshold-based algorithm separates cortical from trabecular bone resulting in parameters for both bone compartments. The trabecular BV/TV was derived from the BMD measured of the trabecular compartment by assuming fully mineralized bone (1200 mg/cm^3). Trabecular microstructure was assessed by a thickness independent 3D algorithm identifying the trabeculae ridges (trabeculae centers). The trabecular number (Tb.N; mm^{-1}) was hence directly available by characterizing it as the inverse of the average spacing of the ridges.[26] In concurrence with defined histomorphometrical assumptions,[27] BV/TV and Tb.N could then be used to derive trabecular thickness (Tb.Th; μm) (Equation 1).

$$Tb.Th = \frac{BV/TV}{Tb.N} \qquad \text{(Equation 1)}$$

The same device, software, and operator were used throughout the whole study. The coefficients of variation (CV) for the bone measurements obtained at the ultradistal site were total volumetric bone density (0.2%), trabecular bone volume fraction (0.8%), trabecular number (1.9%), and trabecular thickness (2.6%), and at the distal site was total volumetric bone density (0.3%). All measurements were inspected and graded by one operator. Motion artifact grading was performed according to a scale provided by the manufacturer where each section was given a number between one and five. Images graded one to three were of acceptable quality and used in the analysis. All obtained images were graded as three or better and the common regions of interest for all follow-up measurements were above 97%.

Cortical evaluation

Extended analysis of the cortical bone compartment was performed with an incorporated customized version of the manufacturer's Image Processing Language (IPL v5.08b Scanco Medical AG) where cortical parameters were assessed according to a previously described method.[28] An automatically placed endosteal contour, carefully inspected and manually corrected if needed, was used to separate the cortical bone compartment from the trabecular bone compartment. Cortical porosity was identified in the encompassed area, which, in short, meant distinguishing Haversian canals from erosions, transcortical foramen, and artifacts—mainly void induced by surface coarseness. As the final step, the cortical overlay and the porosity image were combined, forming a detailed cortical compartment from which the parameters of cortical bone volume (Ct.BV; mm^3) and cortical pore volume (Ct.Po.V; mm^3) could be obtained. The cortical porosity (Ct.Po; %) was then calculated as the fraction of Ct.Po.V in the total cortical compartment (Equation 2). In addition, variables such as cortical volumetric BMD (Ct.vBMD; mg/cm^3), cortical thickness (Ct.Th; mm), and cortical area (Ct.Ar; mm^2) were obtained. The CV for cortical evaluation parameters at the ultradistal site were cortical vBMD (0.4%), cortical porosity (0.9%), and cortical area (0.6%), and at the distal site cortical vBMD (0.3%), cortical porosity (4.1%), and cortical area (0.7%).

$$Ct.Po. = \frac{Ct.Po.V}{(Ct.Po.V + Ct.BV)} \qquad \text{(Equation 2)}$$

Regional analysis

Cortical evaluation at the distal tibia was also performed on anatomic subregions of the bone. The evaluation of regional variation of cortical microstructure has the capacity to improve sensitivity to longitudinal microstructural changes.[29,30]

Regional analysis was performed with respect to anatomic quadrants (anterior, posterior, medial, lateral) defined based on the imaging coordinate system. Consistent positioning within the imaging coordinate system was made possible by the rigid boot cast used during image acquisition. Regional masks were automatically created using MATLAB (MathWorks, Natick, MA, USA) and subsequently applied to the derivative images of the cortical analyses described above. Mean Ct.vBMD, Ct.Th, and Ct.Po were calculated within each regional mask, yielding individual values for each anatomic subregion.

Areal BMD and body composition

Areal bone mineral density (g/cm^2) of the lumbar spine (L_1 to L_4), total hip, and femoral neck, as well as total body lean and fat mass was assessed at baseline using a DXA device (Hologic Discovery A, Waltham, MA, USA). The CV for the aBMD

measurements were femoral neck (1.3%), total hip (0.8%), lumbar spine (0.7%), total lean (0.6%), and total fat (1.1%).

Lifestyle, physical activity, and medical history

All participants completed a questionnaire regarding medical history, such as diseases, medications, previous fractures, and family history of fractures or osteoporosis, as well as exercise habits. The questionnaire also collected information regarding menstruation, including ages for onset of menarche and menopause, as well as information regarding use of oral contraceptive and hormone-replacement therapy. The international physical activity questionnaire (IPAQ) was used to assess current participation in physical activities at baseline and follow-up.[31] With IPAQ, participants reported their weekly frequency and duration of participation in physical activity in a range from low, moderate, and vigorous during the last 7 days. In addition, participants were asked to report their jumping as well as other daily physical activity in a structured daily diary.

Anthropometry

Height was measured using a standardized wall-mounted stadiometer to the nearest 0.1 cm. Two measurements were performed, and if they differed more than or equal to 5 mm, a third measurement was performed. An average was calculated and in case of three measurements, the two most similar values were used. Body weight was measured using digital scales to the nearest 0.1 kg.

Exercise intervention

The one-legged jumps were performed without shoes according to a protocol with a gradually increased frequency (week 1: 3×10 jumps/d; week 2: 3×15 jumps/d; weeks 3 to 6: 3×20 jumps/d; and weeks 7 to 12: 4×20 jumps/d). Participants were instructed to jump and land on the back of the foot without mitigating the shock in order to increase the impact and loading on the leg. Using the reported number of jumps completed, a total number of jumping days could be calculated. With this information, total compliance to the intervention of each participant was calculated by summing the reported number of days with performed jumps divided by the total number of days for the intervention (90 days). All participants were contacted weekly by telephone during the study to ensure correct recollection of performed jumps and to increase compliance to the protocol.

Statistical analysis

The total differences were calculated by subtracting the difference in the exercise limb to the control limb at follow-up from the difference in the exercise limb to the control limb at baseline ($\Delta\text{Total} = \Delta\text{Follow-up} - \Delta\text{Baseline}$). Paired sample *t* test was then used to evaluate if the changes in BMSi and bone structure parameters were significantly different at follow-up compared with baseline. Results were presented as mean difference with 95% confidence intervals (CIs). The percentage change in bone variables were given by the total change compared with baseline measurements for the intervention limb. Target enrollment for the study was 28 women, aiming to detect an assumed increase of 2% with 80% statistical power and a type I error level of 0.05 (two-sided). Because the participants acted as their own control, the standard deviation (SD) in BMSi was expected to be low. For the 20 participants included, the observed difference of 7% in BMSi (ΔTotal over BMSi for the intervention leg at baseline) generated a post hoc statistical power of 80%. The software SPSS version 23 (IBM Corp., Armonk, NY, USA) was used for all analyses and $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics and compliance to intervention protocol

A total of 20 women were included in the study, and baseline characteristics are presented in Table 1. All participants completed the intervention and were included in the final analysis (Fig. 1). The mean age of the cohort was 55.5 years (range 51.4 to 59.1) and the median time since menopause was 4.9 years (interquartile range [IQR] 2.3 to 7.4). None of the participants reported any weight-bearing physical activity the last 7 days before inclusion. Overall compliance to the exercise program was 97.8% (IQR 90.8% to 100%). The median number of days between final measurement and end date of the exercise program was 8.5 (range 0 to 18 days). The included women had a BMD *T*-score of −1.15 ± 0.66 (mean ± SD) of the femoral neck, −0.67 ± 0.76 at the total hip, and −0.98 ± 0.80 of the lumbar spine (Table 1).

Effects of jumping intervention on bone material properties in the tibia

The predefined[22] primary outcome was total difference between follow-up and baseline in the jumping limb in comparison to the control limb. BMSi measured in the intervention leg increased (mean difference 5.17; 95% confidence interval [CI] 0.70–9.64; $p = 0.03$) when normalized for the control leg (Table 2). The increase corresponded to a 7%, or 0.89 SD, increase in comparison to the mean baseline BMSi of the

Table 1. Baseline Characteristics of All Participants Included in the Final Analysis

No. of participants	20
Age (years)	55.5 ± 2.3
Weight (kg)	64.5 ± 7.5
Height (cm)	166.7 ± 5.7
Body mass index (kg/m^2)	23.3 ± 3.3
Body fat (%)	35.0 ± 4.6
Age at menarche (years)	13.0 ± 1.3
Age at menopause (years)	49.5 ± 3.6
Weight bearing physical activity (h/week)	0 ± 0
Time since menopause (years)	4.9 (2.3–7.4)
Follow-up time (days)	98.5 (92.8–104)
End of intervention to measurement (days)	8.5 (2.8–13.5)
Bone mineral density	
Total hip (g/cm^2)	0.86 ± 0.09
Femoral neck (g/cm^2)	0.72 ± 0.08
Lumbar spine (g/cm^2)	0.94 ± 0.09
Total hip *T*-score	−0.67 ± 0.76
Femoral neck *T*-score	−1.15 ± 0.66
Lumbar spine *T*-score	−0.98 ± 0.80

Results are presented as mean ± SD for normally distributed variables. For non-normally distributed variables, median and interquartile range was used.

Table 2. Changes in Bone Parameters

	Measurements				Differences				
	Control leg		Intervention leg						
	Baseline	Follow-up	Baseline	Follow-up	ΔControl	ΔIntervention	ΔTotal	p	p^*
BMSi	76.6 ± 5.5	74.8 ± 6.2	73.4 ± 5.8	76.8 ± 9.0	−1.76 (−5.31, 1.80)	3.42 (−0.55, 7.38)	5.17 (0.70, 9.64)	**0.03**	**0.046**
HR-pQCT (ultradistal)									
Tot.vBMD (mg/cm^3)	260 ± 50	260 ± 50	264 ± 50	264 ± 50	−0.78 (−1.63, 0.07)	0.29 (−0.64, 1.21)	1.07 (−0.12, 2.25)	0.08	0.08
BV/TV (%)	11.5 ± 2.5	11.4 ± 2.6	11.7 ± 2.8	11.8 ± 2.8	−0.06 (−0.12, 0.00)	0.01 (−0.04, 0.06)	0.07 (−0.00, 0.14)	0.06	0.08
Tb.N (mm^{-1})	1.71 ± 0.25	1.70 ± 0.23	1.73 ± 0.25	1.70 ± 0.25	−0.01 (−0.06, 0.05)	−0.03 (−0.07, 0.00)	−0.03 (−0.09, 0.03)	0.34	0.44
Tb.Th (μm)	67.1 ± 11.5	66.8 ± 12.3	67.6 ± 11.3	68.9 ± 11.1	−0.25 (−2.29, 1.79)	1.25 (−0.11, 2.61)	1.50 (−0.82, 3.82)	0.19	0.20
Ct.vBMD (mg/cm^3)	900 ± 64	897 ± 60	891 ± 66	889 ± 66	−2.83 (−7.41, 1.76)	−1.54 (−4.95, 1.87)	1.29 (−4.60, 7.17)	0.65	0.50
Ct.Ar (mm^2)	111 ± 13	111 ± 13	115 ± 14	115 ± 15	0.11 (−1.03, 1.26)	−0.06 (−1.12, 1.00)	−0.17 (−1.41, 1.06)	0.77	0.58
Ct.Po (%)	6.45 ± 2.09	6.51 ± 1.91	7.12 ± 2.48	7.15 ± 2.57	0.07 (−0.23, 0.36)	0.03 (−0.19, 0.24)	−0.04 (−0.38, 0.30)	0.81	0.14
HR-pQCT (distal)									
Tot.vBMD (mg/cm^3)	453 ± 69	452 ± 69	455 ± 72	454 ± 72	−1.41 (−2.46, −0.36)	−1.24 (−2.28, −0.20)	0.17 (−1.03, 1.37)	0.77	0.94
Ct.vBMD (mg/cm^3)	1030 ± 41	1026 ± 42	1029 ± 41	1026 ± 41	−3.28 (−5.07, −1.50)	−2.98 (−4.87, −1.10)	0.30 (−1.98, 2.58)	0.79	0.77
Ct.Ar (mm^2)	155 ± 14	155 ± 14	158 ± 14	158 ± 14	−0.04 (−0.66, 0.58)	−0.14 (−0.77, 0.49)	−0.10 (−0.79, 0.59)	0.77	0.88
Ct.Po (%)	2.22 ± 1.10	2.28 ± 1.10	2.27 ± 1.11	2.29 ± 1.13	0.06 (−0.03, 0.15)	0.02 (−0.07, 0.10)	−0.04 (−0.14, 0.06)	0.41	0.37

BMSi = bone material strength index; HR-pQCT = high-resolution peripheral quantitative computed tomography; vBMD = volumetric bone mineral density; ultradistal = standard section for HR-pQCT measurements; distal = measurements at 14% of tibia length; Tot.vBMD = total volumetric bone mineral density; BV/TV = trabecular bone volume fraction; Tb.N = trabecular number; Tb.Th = trabecular thickness; Ct.vBMD = cortical volumetric bone mineral density; Ct.Ar = cortical area; Ct.Po = cortical porosity.

Differences for control and intervention leg were calculated between baseline and follow-up. ΔControl = difference between follow-up measurement and baseline measurement for the control leg. ΔIntervention = difference between follow-up measurement and baseline measurement for the intervention leg. ΔTotal = difference between the intervention leg and control leg at follow-up and baseline. Differences were analyzed with a two-related paired sample t test (p) and related samples Wilcoxon signed rank test (p^*) for ΔTotal, where $p < 0.05$ was considered significant and is presented in bold.

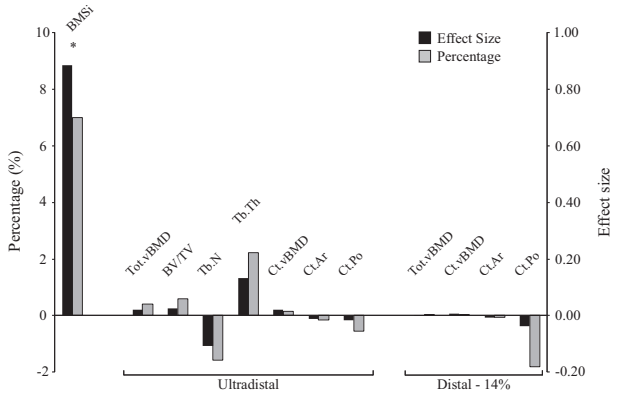

Fig. 2. Changes in bone parameters stated by effect size (black bars) and percentage (gray bars) compared with jumping leg value at baseline. Comparisons were made with two-related paired sample *t* test. Ultradistal corresponds to the manufacturer's standard section and distal corresponds to 14% of tibia bone length. BMSi = bone material strength index; Tot.vBMD = total volumetric bone mineral density; BV/TV = trabecular bone volume fraction; Tb.N = trabecular number; Tb.Th = trabecular thickness; Ct.vBMD = cortical volumetric bone mineral density; Ct.Ar = cortical area; Ct.Po = cortical porosity. *Significant results with $p < 0.05$.

jumping leg (Fig. 2). Each participant's response to the intervention is shown in Fig. 3. The change in BMSi in the intervention leg, not normalizing for the control leg, did not reach statistical significance ($p = 0.07$; Table 2).

Effects of exercise intervention on bone microarchitecture

The intervention did not affect change in any of the HR-pQCT-assessed secondary outcomes, measured either at the ultradistal or distal tibia site (Table 2). The HR-pQCT images at the distal tibia site (14%) were divided into four regions (anterior, posterior, medial, and lateral) to determine if the jumping intervention affected bone geometry and microstructure differently in different subregions of the bone. No significant differences were observed for any of the microstructural parameters in any of the four regions (Table 3).

The association between baseline characteristics as well as bone variables and the total difference for BMSi (ΔTotal for BMSi) was analyzed (Table 4). Participants with higher aBMD, especially at the lumbar spine, had smaller increases in BMSi in response to the exercise program. Bone parameters measured with HR-pQCT at baseline or the change in these variables during the study were not significantly correlated to the jumping exercise program response in BMSi.

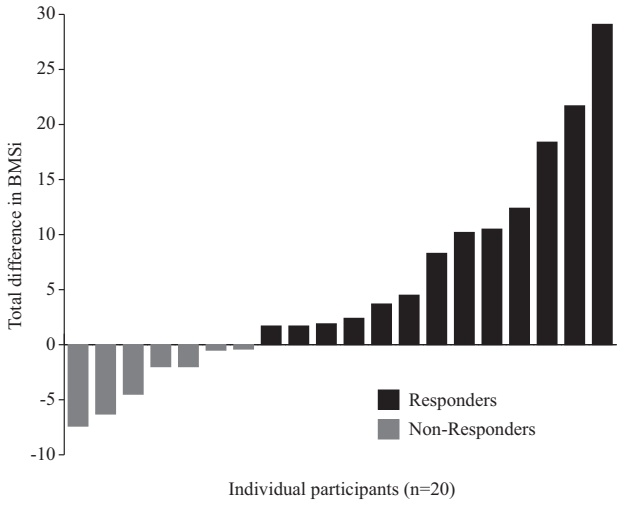

Fig. 3. The individual total differences in BMSi between follow-up and baseline in the jumping limb in comparison to the control limb are shown for all included study subjects ($n = 20$). Study subjects with positive results are shown as responders (black) and those with negative results as non-responders (gray). BMSi = bone material strength index.

Discussion

In this intervention study, we investigated if BMSi can be increased by mechanical loading and hypothesized that bone can adapt rapidly to suddenly increased loading with a mechanism preceding the loading-induced density increase and adaptations in bone macro- and microstructure. After 3 months of the jumping exercise program, there was a substantial increase in BMSi in the intervention leg compared with the control leg, whereas no changes were observed for volumetric BMD or bone microarchitecture. This study is the first to demonstrate that the bone has the ability to adapt quickly in terms of BMSi in response to high-impact loading.

Daily one-legged jumping exercise increased BMSi in participants by 7% in 3 months, without affecting any of the other bone parameters. An exercise intervention has previously been shown to affect anterior and posterior parts of the cortical geometry, which has increased the anterior-posterior bending strength.[9] To reassure that the global analysis of the entire bone did not fail to detect potential local changes, regional analysis of the bone was also performed, which did not reveal an effect of the intervention on any bone parameter, irrespective of analyzed subregion. These findings confirm our hypothesis that exercise loading regulates bone material properties as reflected by the increase in BMSi, without simultaneously causing changes in BMD or bone microstructure.

The lack of effect of the jumping intervention on other bone parameters is in line with previous studies indicating more prolonged interventions, 6 months or longer, in order to see effects of high-intensity training on BMD.[32] Such results are mainly found for young individuals, before or at the time of puberty,[11–14] whereas few studies have shown significant improvements of bone mass or geometry within this time span in postmenopausal women, who are thought to adapt less than younger individuals.[33,34] Because all parameters for bone mass and its distribution were unaffected by the intervention, the change in BMSi most probably lie within other factors of bone quality, perhaps involving the bone matrix. However, any subresolution structural changes not possible to measure with the used HR-pQCT technique could have occurred. The bone matrix consists mainly of type I collagen surrounded by crystals of hydroxyapatite.[35] The balance for this crystal is vital because a too high amount makes the bone stiff and brittle, whereas a too low concentration makes it tough but susceptible to deformation. Therefore, a well-balanced bone matrix gives the bone its optimal ductility and strength. As an example, patients

Table 3. Regional Changes in HR-pQCT Variables Measured at the Distal Tibia

	Measurements				Differences				
	Control leg		Intervention leg						
	Baseline	Follow-up	Baseline	Follow-up	ΔControl	ΔIntervention	ΔTotal	p	p^*
Cortical porosity (%)									
Global	2.22 ± 1.10	2.28 ± 1.10	2.27 ± 1.10	2.29 ± 1.13	0.06 (–0.03, 0.15)	0.02 (–0.07, 0.10)	–0.04 (–0.14, 0.06)	0.41	0.37
Anterior	2.24 ± 1.27	2.16 ± 1.17	2.13 ± 0.98	2.08 ± 0.97	–0.08 (–0.21, 0.06)	–0.05 (–0.18, 0.08)	0.03 (–0.18, 0.24)	0.79	0.72
Posterior	1.80 ± 1.05	1.93 ± 1.16	1.89 ± 1.24	1.91 ± 1.28	0.13 (–0.02, 0.28)	0.02 (–0.11, 0.15)	–0.11 (–0.24, 0.01)	0.08	0.09
Medial	2.00 ± 1.30	2.04 ± 1.27	1.93 ± 1.05	2.03 ± 1.09	0.03 (–0.07, 0.13)	0.10 (–0.06, 0.26)	0.07 (–0.13, 0.26)	0.50	0.81
Lateral	2.81 ± 1.50	2.94 ± 1.50	3.05 ± 1.47	3.07 ± 1.52	0.14 (–0.06, 0.33)	0.01 (–0.09, 0.12)	–0.12 (–0.34, 0.09)	0.25	0.10
Cortical vBMD (mg/cm^3)									
Global	1030 ± 41	1026 ± 42	1029 ± 41	1026 ± 41	–3.28 (–5.07, –1.50)	–2.98 (–4.87, –1.10)	0.30 (–1.98, 2.58)	0.79	0.77
Anterior	1021 ± 47	1019 ± 49	1022 ± 48	1020 ± 47	–1.75 (–4.61, 1.10)	–2.82 (–5.19, –0.45)	–1.07 (–5.57, 3.44)	0.63	0.88
Posterior	1049 ± 43	1047 ± 45	1048 ± 45	1047 ± 47	–2.51 (–5.72, 0.71)	–0.97 (–3.68, 1.74)	1.54 (–1.39, 4.47)	0.28	0.22
Medial	1047 ± 48	1043 ± 49	1049 ± 44	1045 ± 44	–4.19 (–7.10, –1.28)	–4.16 (–7.13, –1.20)	0.03 (–3.78, 3.83)	0.99	0.85
Lateral	1004 ± 45	999 ± 47	999 ± 44	995 ± 43	–4.29 (–7.90, –0.68)	–4.20 (–7.75, –0.65)	0.09 (–4.73, 4.90)	0.97	1.00
Cortical thickness (mm)									
Global	2.29 ± 0.24	2.28 ± 0.25	2.31 ± 0.24	2.31 ± 0.24	–0.01 (–0.02, 0.01)	–0.01 (–0.02, 0.01)	0.00 (–0.02, 0.01)	0.72	0.71
Anterior	2.33 ± 0.25	2.31 ± 0.26	2.32 ± 0.29	2.30 ± 0.28	–0.02 (–0.03, –0.01)	–0.02 (–0.04, 0.00)	0.01 (–0.02, 0.03)	0.66	0.60
Posterior	2.20 ± 0.26	2.19 ± 0.26	2.22 ± 0.25	2.21 ± 0.26	–0.01 (–0.03, 0.00)	–0.01 (–0.02, 0.01)	0.01 (–0.01, 0.03)	0.46	0.41
Medial	2.28 ± 0.29	2.29 ± 0.30	2.35 ± 0.33	2.35 ± 0.32	0.01 (–0.01, 0.03)	0.00 (–0.01, 0.02)	–0.01 (–0.04, 0.01)	0.35	0.27
Lateral	2.32 ± 0.30	2.31 ± 0.31	2.34 ± 0.26	2.33 ± 0.26	0.00 (–0.02, 0.02)	–0.01 (–0.03, 0.01)	–0.01 (–0.03, 0.01)	0.36	0.33

vBMD = volumetric bone mineral density.

Differences between defined regions of the distal tibia (14% of bone length) measured with high-resolution peripheral quantitative computed tomography were calculated for control and intervention leg between baseline and follow-up. ΔControl = difference between follow-up measurement and baseline measurement for the control leg. ΔIntervention = difference between follow-up measurement and baseline measurement for the intervention leg. ΔTotal = difference between the intervention leg and control leg at follow-up and baseline. Differences were analyzed with a two-related paired sample t test (p) and related samples Wilcoxon signed rank test (p^*) for ΔTotal where $p < 0.05$ was considered significant and is presented in bold.

Table 4. Correlation Coefficients (*r*) for Baseline Characteristics, aBMD, Cortical Bone Microstructure, and Total Change in BMSi

	ΔTotal BMSi	*p* Value	ΔTotal BMSi	*p* Value
Age (years)	0.08	0.74		
Weight (kg)	−0.05	0.85		
Height (cm)	0.41	0.07		
Body mass index (kg/m^2)	−0.23	0.34		
Body fat (%)	0.09	0.72		
Age at menarche (years)	−0.07	0.77		
Age at menopause (years)	0.20	0.40		
Time since menopause (years)	−0.11	0.63		
End of intervention to measurement (days)	−0.07	0.76		
Compliance (%)	0.004	0.99		
BMSi for the intervention leg at baseline	−0.20	0.41		
DXA				
Total hip (g/cm^2)	−0.34	0.14		
Femoral neck (g/cm^2)	−0.38	0.10		
Lumbar spine (g/cm^2)	−0.55	**0.01**		
HR-pQCT (ultradistal)	Baseline		Over time	
Total volumetric bone mineral density (mg/cm^3)	−0.31	0.19	−0.28	0.24
Trabecular bone volume fraction (%)	−0.09	0.70	0.04	0.87
Trabecular number (mm^{-1})	−0.08	0.73	−0.29	0.22
Trabecular thickness (mm)	−0.02	0.95	0.26	0.27
Cortical volumetric bone mineral density (mg/cm^3)	−0.29	0.21	−0.36	0.12
Cortical area (mm^2)	−0.39	0.09	−0.18	0.46
Cortical porosity (%)	0.31	0.18	0.27	0.26
HR-pQCT (distal)				
Total volumetric bone mineral density (mg/cm^3)	−0.22	0.35	0.29	0.22
Cortical volumetric bone mineral density (mg/cm^3)	−0.09	0.71	−0.10	0.66
Cortical area (mm^2)	−0.18	0.45	0.24	0.30
Cortical porosity (%)	0.18	0.46	−0.08	0.75

aBMD = areal bone mineral density; BMSi = bone material strength index; DXA = dual-energy X-ray absorptiometry; HR-pQCT = high-resolution peripheral computed tomography; ultradistal = standard section for HR-pQCT measurements; distal = measurements at 14% of tibia length for HR-pQCT measurements.

Correlation coefficients presented for baseline characteristics, average values between intervention leg and control leg at baseline for HR-pQCT variables, and total change in BMSi (ΔTotal). Also presented are the correlations for ΔTotal for the HR-pQCT variables and ΔTotal for BMSi. Significance was defined as $p < 0.05$.

with an altered type I collagen structure (osteogenesis imperfecta) generates a more fragile bone.[36]

The microindentation technique used in this study is designed to measure the bones resistance to microfracture by separating mineralized collagen microfibers and thereby introducing microcracks.[37] The response from our short intervention trial might therefore have a more instantaneous effect on collagen cross-links than the slower-working process of bone mineralization. Collagen cross-links have been shown to be of great importance for bone strength in mouse models where mice treated with ß-aminopropionitrile (BAPN), an inhibitor of enzymatic cross-linking formation, showed a decrease in bone strength.[38] These cross-links are affected by physical activity.[39] Mice treated with BAPN concomitantly with exercise showed a reduced effect of BAPN, which indicates that physical activity increases collagen cross-linking and thereby bone strength.[38,39] In addition, non-collagenous proteins (eg, osteopontin) could also be affected by the increased loading where their function as "glue" between mineralized collagen fibrils, which enables the helical structure to lengthen and reduces the stress imposed upon mineral platelets, could be affected. Rapid changes in BMSi have also been reported with other interventions. BMSi was found to rapidly increase after only 7 weeks of per oral glucocorticoid treatment with simultaneous denosumab or teriparatide treatment, whereas a combination of calcium and vitamin D together with glucocorticoids decreased BMSi over 10% during this time period.[40]

The observed response in BMSi seems in part to be associated with lower aBMD. Participants with higher aBMD in the spine had significantly less response in BMSi (−0.55; $p = 0.01$), and similar trends, however nonsignificant, were observed for total hip and femoral neck. We hypothesize that participants with higher aBMD have less to gain in fast improvement of bone material properties when the bone is exposed to suddenly increased high-intensity loading than participants with lower aBMD.

The variation in the response to the jumping intervention in BMSi could be attributable to a number of reasons. First, there is always a risk that compliance in reality was not as good as reported by the participating women. Second, we cannot with complete certainty know that participating women performed the jumping exercises as instructed because the program was home based. Third, participants may vary in body size to bone size and shape ratio, which could influence the applied strain on the tissue level and therefore the adaptation response.

This study had some limitations. With only 20 participants included, the post hoc generated statistical power was not as high as intended (80%), which should be taken into consideration when analyzing these results. With a self-reported activity, there might be a skewed image reported for how well participants have performed the exercise program. It could have been better if all participants did monitored jumps at the clinic or were asked to wear an accelerometer to assess all physical activity and also capture all jumps. In addition, the indentations were not performed at the exact same location as the HR-pQCT structural measurements, meaning that extremely local effects may have been missed. The study also has strengths. Even if the adherence to the exercise program was self-reported, compliance must be considered as high. To minimize the problems with recollection of jumping or loss of motivation, one and the same study personnel called every participant each week for the complete study period.

In conclusion, we found that a 3-month high-impact jumping exercise program was able to substantially increase BMSi in postmenopausal women, while no changes were observed for bone geometry and microarchitecture traits, indicating a novel mechanism to rapidly strengthen the bone subjected to increased loading.

Disclosures

ML has received lecture or consulting fees from Amgen, Lilly, Meda, UCB Pharma, Renapharma, Radius Health, and Consilient Health. All other authors state that they have no conflicts of interest.

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