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Differential Effects of Exercise on Tibial Shaft Marrow Density in Young Female Athletes

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Context: Increased mechanical loading can promote the preferential differentiation of bone marrow mesenchymal stem cells to osteoblastogenesis, but it is not known whether long-term bone strength-enhancing exercise in humans can reduce marrow adiposity.

Objective: Our objective was to examine whether bone marrow density (MaD), as an estimate of marrow adiposity 1) differs between young female athletes with contrasting loading histories and bone strengths and 2) is an independent predictor of bone strength at the weight-bearing tibia.

Design: Mid-tibial MaD, cortical area (CoA), total area, medullary area, strength strain index (SSI), and cortical volumetric bone mineral density (vBMD) (total, endocortical, midcortical, and pericortical) was assessed using peripheral quantitative computed tomography in 179 female athletes involved in both impact and nonimpact loading sports and 41 controls aged 17–40 years.

Results: As we have previously reported CoA, total area, and SSI were 16% to 24% greater in the impact group compared with the controls (all $P < .001$) and 12% to 18% greater than in the nonimpact group (all $P < .001$). The impact group also had 0.5% higher MaD than the nonimpact and control groups (both $P < .05$). Regression analysis further showed that midtibial MaD was significantly associated with SSI, CoA, endocortical vBMD, and pericortical vBMD ($P < .05$) in all women combined, after adjusting for age, bone length, loading groups, medullary area, muscle cross-sectional area, and percent fat.

Conclusion: In young female athletes, tibial bone MaD was associated with loading history and was an independent predictor of tibial bone strength. These findings suggest that an exercise-induced increase in bone strength may be mediated via reduced bone marrow adiposity and consequently increased osteoblastogenesis. **(*J Clin Endocrinol Metab* 98: 2037–2044, 2013)**

Because adipocytes and osteoblasts share a common bone marrow progenitor cell, the mesenchymal stem cell (MSC) (1), it has been suggested that age-related bone loss is related to a preferential differentiation toward the adipocyte rather than osteoblast lineage (2). This notion is supported by biopsy studies that have shown that marrow fat volume increases significantly with age and is related to reduced trabecular bone volume (3). Human studies using noninvasive imaging techniques have also reported that patients with osteoporosis and osteopenia have higher lev-

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Abbreviations: ANCOVA, analysis of covariance; CoA, cortical bone CSA; CSA, cross-sectional area; EndoD, endocortical vBMD; MaD, marrow density; MeA, medullary bone CSA; MidD, midcortical density; MSC, mesenchymal stem cell; MRI, magnetic resonance imaging; PeriD, pericortical vBMD; pQCT, peripheral quantitative computed tomography; CV_{RMS}, root mean squared coefficient of variation; SSI, strength strain index; ToA, total bone CSA; vBMD, volumetric bone mineral density.

els of marrow fat relative to age-matched controls with normal bone density (4). In healthy young women, it has also been shown that changes in marrow adiposity over 18–24 months were associated with changes in cortical bone area at the femoral midshaft (5). Given this close connection between bone and marrow adiposity, there has been considerable interest in identifying strategies that might reduce marrow adiposity and promote the preferential differentiation of MSCs into the osteoblast rather than adipocyte lineage to promote osteoblastogenesis and thereby improve bone strength (6).

There is a growing body of literature from in vivo and cell culture animal studies indicating that increased mechanical loading can stimulate MSC proliferation and differentiation (7, 8) and reduce adipogenesis and marrow fat volume, resulting in increased trabecular bone mass (7, 8). Conversely, the findings from short-term longitudinal studies have shown that immobilization or bed rest results in increased marrow adiposity (9, 10) and a decrease in osteogenesis with increasing adipogenesis (11). Indeed, in rodents, the removal of mechanical loading has been associated with decreased bone formation due to impaired osteoblast recruitment and differentiation and enhanced adipocyte differentiation of MSCs in the bone marrow (12). In humans, it has also been reported that 60 days of strict bed rest was associated with a marked increase in vertebral marrow adiposity in both healthy adult women (10) and men (13). Together, these findings provide evidence that mechanical signals play an important role in the differentiation of MSCs into either osteoblasts or adipocytes. However, in humans, it is not known whether long-term increased mechanical loading (exercise) can reduce marrow adiposity and, if so, whether exercise-induced changes in marrow fat are related to greater bone mass, more robust structure, and higher strength.

Regular participation in weight-bearing impact exercise has been shown to consistently enhance bone structure and strength at the loaded sites (14), especially during the first 2 decades of life (15). Based on data from the athletes included in this study, we previously reported that midtibia cortical bone area and the strength strain index (SSI), an estimate of bone strength, were 11% to 31% higher in those young female athletes involved in high-impact (volleyball, hurdling, triple jump, and high jump), odd-impact (soccer, tennis, squash, and badminton), and repetitive low-impact (endurance running) sports compared with athletes involved in high-magnitude (power lifting) and repetitive nonimpact sports (swimming) and physically active but not athletic controls (16–18). Therefore, the aim of this study was to use this same sample of young female athletes to examine the associations of different modes of exercise loading on tibial bone marrow density (MaD) (estimate of adiposity), and evaluate whether estimated marrow adiposity was an independent predictor of tibial bone density, structure, and strength. Finally, because there are reports that marrow stem cells primarily regulate osteogenesis at the endocortical surface (5, 19), we also evaluated the association between bone marrow adiposity and the apparent bone density across the tibial cortex.

Subjects and Methods

Participants

The participants in this study were 179 premenopausal women representing athletes with a long history in sports with different skeletal loading characteristics and 41 physically active, nonathletic controls (Table 1). Further details about the participants have been described previously (16–18). Briefly, the athletes were recruited through national sports associations and local athletics clubs. The age at which the athletes started their competitive career in sports and their training history were obtained from a questionnaire. Based on each athlete's sport, they were divided into 5 near-distinct types of loading groups as previously reported (20): 1) high-impact (triple and high jumpers and hurdlers), 2) odd-impact (soccer and squash players), 3) high-magnitude (power lifters), 4) repetitive low-impact (endurance runners), and 5) repetitive nonimpact (swimmers). The physically active reference subjects were mainly students from the Pirkanmaa University of Applied Sciences, Tampere, Finland. For this study, the athletes were divided into 2 contrasting loading groups because our previous studies have indicated a similar tibial midshaft phenotype for all athletes whose training involves impacts (16–18): 1) impact loading, which included those in the high-impact, odd-impact, and repetitive low-impact sports, and 2) nonimpact loading groups, which included those involved in high-magnitude and repetitive nonimpact sports. The study was conducted in agreement with the Helsinki declaration with the approval of the ethics committee of The Pirkanmaa Hospital District. Written informed consent was obtained from all participants.

Peripheral quantitative computed tomography assessment

Peripheral quantitative computed tomography (pQCT) was used to evaluate the cross-section of the tibial midshaft (50% from the distal endplate) (XCT 3000; Stratec Medizintechnik GmbH, Pforzheim, Germany) according to our standard procedures (21) (Figure 1). The pQCT scan (in-plane pixel size 0.5 × 0.5 mm, slice thickness 2.5 mm, tube voltage 60 kV operated at 0.3 mA) was taken from the dominant side. The pQCT images were first preprocessed using a modified version of a recent noise reduction algorithm introduced by Cervinka et al (22). This method was designed to permit more consistent detection of outer and inner cortical boundaries compared with commonly used median filtering in clinical research. Briefly, the original approach involves 2 steps; gray-level transformation and image filtering based on Bayes approach with use of Markov random fields with 3 × 3 linear neighborhood and redundant wavelet transform. However, in the present study, the gray-level trans-

Table 1. Descriptive Characteristics and the Mean (SD) Midtibial Bone MaD, Midshank Muscle Size, and Percent Fat and Bone Geometry, Density, and Strength of the 220 Premenopausal Athletes and Women Divided Into Impact and Nonimpact Loading Groups and the Control Group

	Impact (n = 122)	Nonimpact (n = 57)	Referents (n = 41)	*P* Value
Age, y	23.1 (4.8)	22.2 (5.1)	24.1 (3.6)	.15
Height, cm	170 (7)[d,f]	167 (7)	165 (5)	<.001
Tibial length, mm	417 (18)[d,e]	410 (17)	404 (13)	<.001
Weight, kg	62.7 (9.0)	63.3 (9.0)	60.4 (7.8)	.23
BMI, kg/m^2	21.5 (2.4)[e]	22.7 (3.3)	22.1 (2.4)	<.05
Years training	10.4 (4.2)	9.6 (4.2)		.24
OCP use, %	47	56	56	.42
Marrow fat and soft tissue				
Marrow fat density, mg/cm^3	0.964 (0.015)[b,e]	0.959 (0.014)	0.959 (0.013)	<.05
Shank muscle CSA, cm^2	55.6 (7.6)[d,f]	53.5 (9.6)	50.5 (8.3)	<.001
Shank percent fat, %	22.2 (5.7)[d,f]	25.3 (5.2)[c]	30.2 (5.3)	<.001
Bone geometry and strength				
CoA, mm^2	374 (44)[d,g]	312 (38)	299 (39)	<.001
ToA, mm^2	497 (57)[d,g]	437 (52)	411 (48)	<.001
MeA, mm^2	123 (29)	125 (26)	113 (20)	.23
SSI, mm^3	2180 (360)[d,g]	1790 (330)	1650 (300)	<.001
vBMD, mg/cm^3				
Cortical	1124 (18)[c,e]	1128 (19)	1135 (16)	<.01
Endocortical	1144 (22)[b,e]	1150 (22)	1156 (19)	<.05
Midcortical	1207 (18)[d,g]	1216 (20)	1226 (16)	<.001
Pericortical	1196 (20)[d,g]	1211 (22)	1220 (20)	<.001

Abbreviations: BMI, body mass index; OCP = oral contraceptive use.

[a] All values are unadjusted means ± SD. *P* values for MaD, soft tissue, and all bone measures are based on ANCOVA adjusted for age, tibial length, and weight. Descriptive characteristics, bone geometry and strength, and vBMD results have been reported previously from this dataset (16–18).

[b–d] Versus controls: [b] $P < .05$; [c] $P < .01$; [c] $P < .001$.

[e–g] Versus nonimpact loading group: [e] $P < .05$; [f] $P < .01$; [g] $P < .001$.

formation was not used, but only the second step was employed to reduce noise level of pQCT images. The preprocessed images were used in all further analyses. Root mean squared coefficient of variation (CV_{RMS}) was calculated for all muscle, bone, and marrow indices from two successive measurements, with participant repositioning between scans, from 8 nonathletic women aged 19 to 35 years.

Marrow analysis

Marrow adiposity was estimated by analyzing bone MaD (milligrams per cubic centimeter) at the midtibia. The analysis was conducted using custom-made Java software by separating the marrow fat from the bone using a threshold of 80 mg/cm^3, which corresponds to 1.05 times the physical density of red marrow (23) (Figure 1). Using previously published equations from Schneider and colleagues (23), MaD is reported as a physical density based on the pQCT-measured linear attenuation coefficients, which were converted to machine-independent Hounsfield units (H) as follows: $H = [(\mu_{marrow}/\mu_{water}) - 1] \times 1000$, where μ_{marrow} is the measured linear attenuation coefficient of bone marrow and μ_{water} is the linear attenuation coefficient for water, which is calibrated to 0.261 1/cm for the measurement device used in the present study (21). Thereafter, the physical density was calculated as $MaD = 1.018 + (0.893 \times H/1000)$ mg/cm^3.

Marrow contains both hematopoietic and yellow fatty tissue. Marrow mass density has been calculated to vary from 0.928 g/cm^3 (91.9% fat) to 1.08 g/cm^3 (3.3% fat) based on the chemical composition derived from human tissue samples (24). Thus, the higher the MaD, the lower the fraction of marrow fat and adiposity (25). The short-term CV_{RMS} for MaD in our laboratory is 0.5%.

Soft-tissue analysis

Midshank sc fat cross-sectional area (CSA) (in square millimeters) and muscle CSA (in square millimeters) were analyzed using custom-made Java software. The preprocessed data were further filtered (7 × 7 median filter) to produce continuous muscle and fat areas. Fat CSA was segmented from the data using −40 mg/cm^3 lower and 40 mg/cm^3 upper thresholds. Similarly, muscle CSA was segmented using 40 and 200 mg/cm^3 as the thresholds (Figure 1). To determine percent fat, density-weighted limb area was calculated from the data by weighing each of the pixels with its pQCT measured density. Similarly, density-weighted fat area was calculated by weighing the fat pixels with their density. Percent fat was subsequently derived by dividing the density-weighted fat area with the density-weighted limb area and multiplying by 100. The short-term CV_{RMS} of repeated measures for muscle CSA, fat CSA, and percent fat vary from 1.1% to 2.3% in our laboratory.

Bone analysis

A threshold value of 550 mg/cm^3 was used to analyze tibial SSI (cubic millimeters), total bone CSA (ToA) (square millimeters), cortical bone cross-sectional area (CoA) (square millime-

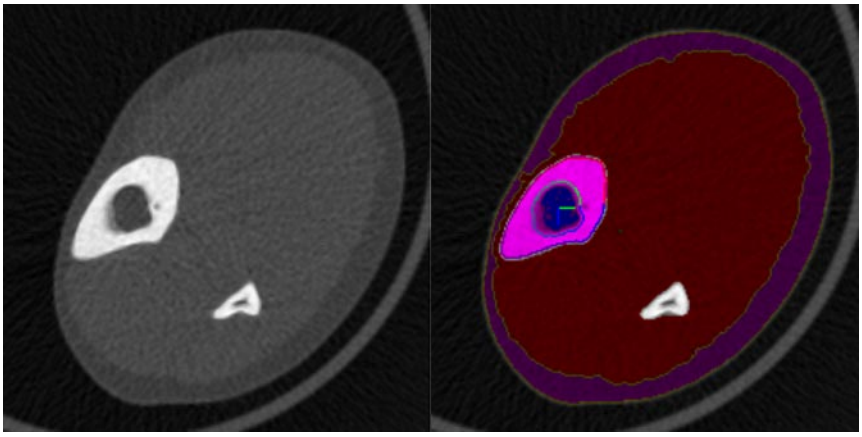

Figure 1. Illustration of segmenting bone, marrow, and soft tissues from the midtibial pQCT image (before segmentation on the left, segmented on the right). The endosteal border used for the density distribution analysis is highlighted in blue/green and the periosteal border with blue/red. Muscle area is tinted with red and sc fat with purple. Bone area from which the marrow was segmented is tinted with purple, and the area for which marrow density was calculated is tinted with blue.

ters), and medullary CSA (MeA) (square millimeters). A threshold value of 690 mg/cm^3 was used in analyzing total tibial cortical vBMD (milligrams per cubic centimeter) (26). Briefly, all pixels below the threshold of 690 mg/cm^3 within the tibial region of interest were removed from the image. Furthermore, to eliminate the partial volume effect, 1 layer of pixels was peeled from the endosteal and periosteal borders. Then the radial distribution of cortical vBMD within the midtibial cortex was assessed by dividing the remaining cortical area into 3 concentric rings with the same thickness (the thickness of the rings varied around the cortex according to anatomy). The innermost ring represented the mean endocortical vBMD (EndoD), the middle ring the midcortical density (MidD), and the outermost ring the pericortical vBMD (PeriD). All bone analyses were executed with custom-made analysis software that has been described in detail previously (26) (Figure 1). The short-term CV_{RMS} for the reported bone traits in our laboratory is 0.4% to 0.8%.

Statistical analysis

Unless otherwise noted, all results are reported as means and SDs. Analysis of covariance (ANCOVA) was used to evaluate group differences for all bone traits (SSI, CoA, ToA, MeA, CoD, EndoD, midcortical density, and PeriD), MaD, and soft tissue (muscle CSA and percent fat), after adjusting for age, tibial length, and body mass. Where applicable, percentage group differences were calculated from estimated marginal means based on the ANCOVA with the control group or the nonimpact group value as the denominator. Pearson correlation coefficients were used to assess the association between MaD with age, body mass index, and all bone and soft tissue variables. Multiple regression analysis was performed using bone traits as the dependent variable and age, tibial length, muscle CSA, percent fat, MeA, loading group (impact vs nonimpact and controls), and MaD as predictors. All regression analyses were run on Z-transformed data to produce β-coefficients comparable between variables and models. ANCOVA was used to investigate whether there were differences in the slope between the regression curves for contrasting loading groups (impact vs nonimpact and controls combined). Statistical analyses were conducted with SPSS version 18.0.1 (SPSS Inc, Chicago, Illinois) software, and the significance level was set at $P \leq .05$.

Results

As we have previously reported (17, 18), the athletes and controls were aged 17 to 40 years, and there were no amenorrheic women in any group (Table 1). The proportion of women using hormonal contraceptives did not differ between the groups ($P = .42$), varying from 47% to 56% in the different exercise loading and control groups (17, 18). In line with the bone trait results reported previously from this dataset (16–18), CoA, ToA, and SSI were 16% to 24% greater in the impact group compared with the controls (all $P < .001$) and 12% to 18% greater than in the nonimpact loading group (all $P < .001$). There were no significant differences between the nonimpact group and the controls for any of the bone traits. For midtibial vBMD, the impact group had 0.6% to 2.0% lower total vBMD, EndoD, MIdD, and PeriD than the nonimpact and control groups (P ranging from $<.05$ to $<.001$).

Comparison of the between-group differences for MaD revealed that the impact loading group had 0.5% higher MaD compared with both the nonimpact and control groups (both $P < .05$) (Table 1). Soft-tissue analysis revealed that the impact group had 18% to 20% larger shank muscle CSA than the nonimpact ($P < .01$) and control groups ($P < .001$). Both athletic groups had 20% to 27% lower shank fat percentage ($P < .01$ to < 0.001) than the controls, with the impact group having 9% lower values than the nonimpact group ($P < .01$).

MaD was positively associated with SSI ($r = 0.16$; $P < .05$) and CoA ($r = 0.31$; $P < .001$) in all women combined (Figure 2) and inversely associated with MeA ($r = -0.31$; $P < .001$) and percent fat ($r = -0.21$; $P < .01$). There was no significant association between MaD and ToA ($r = 0.13$; $P = .06$) or cortical vBMD ($r = 0.12$; $P = .09$). With regard to the relationships between MaD and CoA separately in the impact group and the combined nonimpact and control groups, the slopes of the regression lines were similar, even after adjusting for age, tibial length, MeA, muscle CSA, and percent fat (Figure 2). In all women, multivariate regression analysis showed that MaD was an independent predictor of SSI, CoA, EndoD, and PeriD

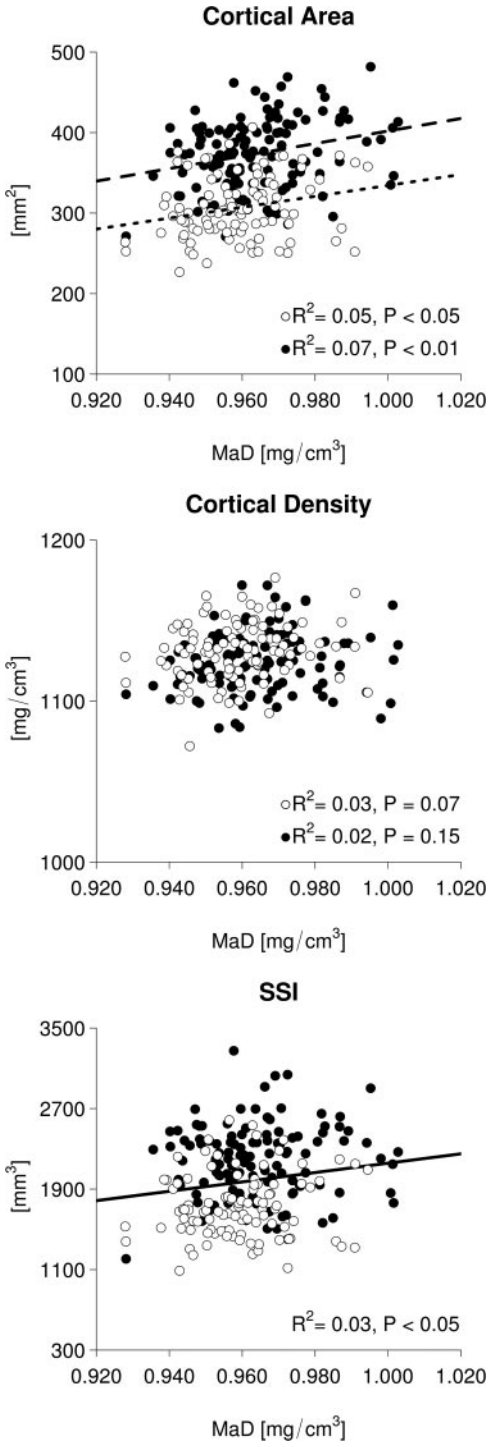

Figure 2. Associations between midtibial MaD and tibial midshaft SSI, CoA, and total cortical vBMD in all 220 premenopausal athletes and the referent controls. The data were regrouped for a comparison of the impact group (solid circles, dashed line) with the pooled nonimpact loading and control groups (open circles, dotted line). The solid line is fit for pooled data of all 3 groups.

after adjusting for age, tibial length, loading group, MeA, muscle CSA, and percent fat (Table 2). Overall, MaD explained an additional 1.2% to 4.8% of the variance in SSI, CoA, EndoD, and PeriD after accounting for the above covariates.

Discussion

The main finding from this study was that young female adult athletes involved in weight-bearing impact sports had higher tibial bone MaD, reflecting lower marrow adiposity, compared with athletes involved in nonimpact loading sports and nonathletic controls. Furthermore, in all young women, the MaD was an independent predictor of tibial midshaft cortical area and bone strength, independent of loading history, body size, or body composition. Taken together, these findings provide additional indirect evidence that bone marrow adiposity plays an important role in modulating bone metabolism through its influence on promoting the preferential differentiation of MSCs into either osteoblasts or adipocytes (1, 27).

The finding that the female athletes engaged in impact loading sports had higher MaD and stronger bones than those involved in nonimpact loading activities or the controls is consistent with the results from in vitro and in vivo studies that have established that MSC differentiation is biased toward osteoblastogenesis with increased mechanical loading (7, 8, 28–30). Furthermore, in both growing and young adult rats, high-impact jump training and running have been shown to decrease marrow fat volume and enhance bone formation or trabecular bone volume (8). From a mechanistic perspective, there is evidence that increased loading can increase the expression of the runt-related transcription factor 2 (Runx2), which plays a critical role in promoting differentiation of osteoblasts, and decrease the expression of peroxisome proliferator-activated receptor-γ2 (PPARγ2), a transcription factor that promotes adipogenesis (7, 8). In humans, there are several reports that magnetic resonance imaging (MRI)-measured bone marrow adiposity responds to changes in skeletal loading in a fashion consistent with the modulation of MSC differentiation (10, 13). For example, in healthy young men who underwent 60 days of bed rest with or without exercise, Trudel et al (13) reported that there was a significant increase in vertebral marrow fat in inactive participants after bed rest, which was prevented in those undertaking resistance exercise alone or with whole-body vibration training. Taken together, the above findings support our results and the hypothesis that increased loading may enhance the osteogenic potential of bone marrow cells to increase bone mass and strength by promoting osteoblastogenesis at the expense of adipogenesis.

There is considerable evidence from human clinical studies using MRI or spectroscopy demonstrating that patients with osteopenia, osteoporosis, and vertebral fractures have higher levels of marrow fat than age-matched controls and/or those with normal BMD (4, 31). Although it has been suggested that this may simply represent pas-

Table 2. Regression Models of the Association Between Tibial Midshaft Bone Traits and Age, Tibial Length, Muscle CSA, MeA, Percent Fat, MaD in all 220 Premenopausal Athletes and Controls

					Cortical vBMD, mg/cm^3							
	SSI, mm^3		CoA, mm^2		Total		Endocortical		Midcortical		Pericortical	
	β	*P* Value	*β*	*P* Value	*β*	*P* Value	*β*	*P* Value	*β*	*P* Value	*β*	*P* Value
Loading group	0.71	<.001	0.85	<.001	−0.49	<.001	−0.40	<.01	−0.62	<.001	−0.86	<.001
Age, y	0.08	.05	0.06	.15	0.38	<.001	0.27	<.001	0.42	<.001	0.43	<.001
Tibial length, mm	0.33	<.001	0.37	<.001	0.18	<.01	0.05	.50	−0.05	.46	0.04	.49
MeA, mm^2	0.39	<.001	0.09	<.05	−0.33	<.001	−0.33	<.001	−0.08	.21	0.01	.91
% fat	0.01	.77	−0.01	.91	−0.12	.09	−0.24	<.01	−0.11	.09	−0.03	.69
Muscle CSA, cm^2	0.24	<.001	0.29	<.001	−0.11	.09	−0.16	<.05	−0.31	<.001	−0.21	<.001
MaD, mg/cm^3	0.18	<.001	0.21	<.001	0.02	.80	−0.24	<.001	−0.08	.21	0.12	<.05
Model R^2	0.68	<.001	0.66	<.001	0.29	<.001	0.27	<.001	0.39	<.001	0.39	<.001

β-Coefficients (*β*) represent the Z-transformed unstandardized coefficients. Loading group represents either impact, nonimpact loading, or control. R^2 represents coefficient of determination of the multivariate linear regression model.

sive accumulation of fat within the increasing marrow space due to age-related bone loss, several studies in healthy young adults have reported an inverse association between axial and appendicular bone marrow fat and CT-measured CoA (5, 25, 32). In agreement with these findings, we found similar significant associations between tibial MaD and the CoA and whole bone strength in healthy young active adult women aged 17 to 40 years, independent of age, tibial length, muscle CSA, percent fat, and MeA. Although the MaD accounted for only an additional 2.8% to 3.7% of the variance in CoA and SSI in our study, this is consistent with the results from a previous study in 255 teenagers and young adults that reported that midfemur marrow fat accounted for 0.8% to 3.5% of the variance in femoral CoA in females and males, respectively (25). Together, these results add to the growing body of literature indicating that a reduction in bone strength and its determinants (mass and structure) may be driven by the preferential differentiation of MSCs into adipocytes rather than osteoblasts. Additional indirect evidence to support this notion is provided by data from a longitudinal study in healthy young women that found that changes in marrow adiposity over 18 to 24 months were associated with changes in CoA at the femoral midshaft (5).

The finding that marrow density was not significantly associated with ToA is also in line with the results from previous studies that reported no relationship between appendicular marrow fat and bone CSA in the femoral shaft of young healthy females (5, 25). This supports the notion that MSCs may predominantly regulate osteogenesis at the endosteal surface. In agreement, we found that midtibial MaD was inversely associated with the adjacent EndoD. That is, lower marrow fat was associated with lower EndoD. Although reduced density may not be considered a positive adaptation at first, it is an often reported phenomenon associated with positive bone geometric changes (33–35). Indeed, it has recently been reported that young adults with larger bones have lower cortical volumetric BMD (vBMD) at tibial diaphysis than people with smaller bones (35). Also, athletes with bigger bones have been reported to have lower cortical vBMD than nonathletes with smaller bones at the tibia (33, 34). Wilks et al (34) speculated that the decreased cortical vBMD at the athletes' tibia, which is subjected to greater loading compared with controls, may be related to loading-induced microdamage leading to increased bone turnover (intracortical remodeling) that is associated with a decrease in the mean degree of bone mineralization, increased intracortical porosity, and/or incomplete secondary mineralization, resulting in reduced vBMD. Certainly, decreased bone turnover is associated with higher bone vBMD and vice versa as indicated by the studies in postmenopausal osteoporosis, where antiresorptive treatment shifts the BMD distribution histogram to higher values and, conversely, anabolic intermittent PTH treatment to lower values (36). Consequently, we postulate that reduced marrow adiposity reflects higher rates of bone turnover, which is seen as reduced EndoD caused by increased intracortical porosity and/or incomplete secondary mineralization of endosteal cortical region.

There are several limitations in this study. First, the cross-sectional design does not reveal causality, nor is it free from selection bias. Second, we used pQCT to quantify bone marrow adiposity. MRI is the main modality used for the noninvasive assessment of bone marrow adiposity because of its superior ability to distinguish between red and yellow marrow (37). However, a recent validation study reported that there is a high level of agreement between bone and marrow fat quantification by micro-CT with histology analysis in both young and old rats (38). Nevertheless, MaD as determined by pQCT should be considered an estimate of marrow adiposity. Finally, this study assessed marrow adiposity only at a single cross-section of the midtibia, which comprises almost exclusively yellow marrow (39). This fact might have attenuated the associations between bone and fat. However, as

reported above, several previous studies have shown that appendicular bone marrow fat is inversely related to CoA at the femur (5, 25) and that this relationship is consistent along the length of the femoral diaphysis (32). Also, MRI-derived measures of marrow fat at the pelvis, hip, and lumbar spine have been shown to be interrelated (40). Although additional studies are still needed to evaluate the effects of increased loading on marrow adiposity at different skeletal sites, based on the available evidence it would appear that there may be systematic changes in marrow adiposity in response to aging or disease.

In summary, we have demonstrated that tibial bone marrow adiposity, as estimated by pQCT-measured MaD, is modulated by loading history and is an independent predictor of tibial bone strength in young adult women. Importantly, the finding that regular weight-bearing impact exercise during the first 3 decades of life was associated with lower marrow adiposity and increased bone strength provides further evidence to support the notion that marrow fat plays a key role in osteoblastogenesis and bone strength. Although human intervention trials are needed to confirm the possible role of exercise as a strategy to alter mesenchymal differentiation potential, these findings have important clinical implications given that increased marrow adiposity has been associated with osteoporosis and an increased fracture risk (4, 6, 31).

Acknowledgments

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