Site-Specific Variance in Radius and Tibia Bone Strength as Determined by Muscle Size and Body Mass

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ABSTRACT

Purpose: To investigate the predictive ability of muscle cross-sectional area (MCSA) and body mass on bone mineral content, compressive bone strength index (BSI_c), and the polar stress-strain index (SSI_p) of the forearms and lower legs of middle-aged adults. **Methods:** A total of 53 healthy adults (37 male, 16 female; mean age 50.4; SD 2.1 y) were scanned with peripheral quantitative computed tomography (pQCT) to measure radius and tibia total and cortical bone mineral content, BSI_c, SSI_p, and forearm and lower-leg MCSA (BSI_c: 4% distal; SSI_p and MCSA at 65% and 66% radius and tibia shaft sites, respectively). Multiple regression models adjusted for sex and height were used to assess the relative variance in radius or tibia bone outcomes predicted by body mass and/or forearm or lower-leg MCSA. **Results:** Forearm MCSA independently predicted total bone-mineral content, BSI_c, and SSI_p in radius ($r_{\text{partial}} = 0.59, 0.56, 0.42$). Body mass was a negative predictor of radius BSI_c ($r_{\text{partial}} = -0.32$) and did not predict other radius outcomes when both body mass and MCSA were forced in the models. In the lower leg shaft, MCSA, and body mass predicted bone content and strength similarly when independently added to the models with sex and height. **Conclusions:** Forearm MCSA was a dominant predictor of radius bone content and estimated strength. In the tibia, both body mass and lower-leg MCSA contributed to predicting bone content and estimated strength.

Key Words: body weight; bone and bones; tomography scanners, X-ray computed; radius; muscle, skeletal; tibia.

RÉSUMÉ

Objectif : Étudier la capacité prédictive de la mesure de l'aire de la fibre perpendiculaire à son sens longitudinal d'un muscle (mesure dite de la « MCSA ») et du poids corporel sur le contenu minéral osseux, sur l'indice de force de compression de l'os (BSI_c) et sur l'indice tension-extension polaire (SSI_p) de l'avant-bras et de la portion inférieure de la jambe chez les adultes d'âge moyen. **Méthode :** Au total, 53 adultes en bonne santé (37 hommes, 16 femmes; âge moyen : 50,4 ans; écart-type de 2,1 ans) ont subi une tomographie périphérique quantitative par ordinateur (pQCT) en vue de mesurer le contenu total et cortical en minéraux du radius et du tibia, le BSI_c, le SSI_p et la capacité prédictive de la section transversale de l'avant-bras et de la portion inférieure de la jambe (BSI_c : 4 % distal; SSI_p et MCSA de 65 % et de 66 % pour le radius et le tibia, respectivement). De multiples modèles de régression adaptés en fonction du sexe et de la grandeur des participants ont été utilisés pour évaluer les variations relatives dans les résultats pour le radius ou le tibia projetés à l'aide de la mesure du poids corporel et de la capacité prédictive de la section transversale du muscle l'avant-bras ou de la portion inférieure de la jambe. **Résultats :** La MCSA de l'avant-bras a permis de prédire, à elle seule, le contenu minéral osseux total, le BSI_c et le SSI_p du radius ($r_{\text{partiel}} = 0,59, 0,56, 0,42$). Le poids corporel s'est avéré un prédicteur négatif du BSI_c du radius ($r_{\text{partiel}} = -0,32$) et n'a pas permis de prédire d'autres données lorsque le poids corporel et la MCSA étaient inclus aux modèles. Pour la partie inférieure de la jambe, la MCSA et le poids corporel ont permis de prédire le contenu osseux et la force de l'os de la même façon que lorsqu'ils étaient ajoutés individuellement aux modèles, avec le sexe et la grandeur. **Conclusions :** La section transversale du muscle (MCSA) de l'avant-bras est un prédicteur dominant du contenu osseux du radius et de sa force estimée. Pour le tibia, le poids corporel et la MCSA de la portion inférieure de la jambe ont aidé à prédire le contenu osseux et la force estimée.

Osteoporotic fractures are a common cause of long-standing pain, functional impairment, disability, and death in elderly populations.^{1,2} The most effective physical therapy for the prevention of falls and fractures in community dwelling older adults is a combination of balance and muscle strength training.³ Exercise can increase bone mass (specifically areal bone mineral density) at the lumbar spine and hip in postmenopausal

women⁴; however, the influence of exercise on bone mass and estimated strength at the upper extremity, especially at the fracture-prone wrist, is unknown.^{4,5} Thus, there is a pressing need to develop randomized controlled trials (RCTs) for primary and secondary prevention of bone loss and fragility in the forearm and wrist. The evidence obtained would also benefit the develop-

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ment of rehabilitation therapies for people with fractures of the wrist or forearm.⁶

Observational evidence of factors that determine bone mass and strength will facilitate the development of RCTs and tailored therapies for upper-extremity bones. Since bone mass and strength adapt to loading,^{7–10} and muscular forces produce the greatest natural loads on the skeleton,^{7,11–17} interventions aimed at enhancing muscle strength and size may also have the potential to enhance bone strength. Muscle mass and strength are positively associated with bone mass and strength, but the role of muscle in predicting bone strength independently from other measures of body size is less clear.^{7,11} For example, the relative importance of muscular¹⁴ and gravitational¹⁶ (interpreted as contribution of body weight) loads in providing mechanical and osteogenic stimuli to bone is debated.¹⁵ In this debate, the relationships of muscle, bone, body weight, and body size within the upper and lower limbs are often contrasted. In the “weight-bearing” lower extremity, muscle forces counterbalance the gravitational weight of adjacent body segments (e.g., head, arms, trunk) via moments (defined as muscle force times distance to the pertinent joint center). This balancing allows the body to remain upright during static and dynamic activities.¹⁸ Both body weight and muscle forces, therefore, are likely regulating lower-extremity bone mass and bone strength. In the “non-weight-bearing” upper extremity, muscle forces counter-balance external forces (e.g., dumbbell in hand), and body weight likely has little influence on bone mass and bone strength. Recent evidence to support these arguments is limited. Relationships between muscle and bone have been investigated in the whole body,¹⁹ arm,^{20,21} and leg.^{18,22–24} In addition, limb-specific associations between muscle force and bone mineral content in pubertal female individuals²⁵ and between lean mass and bone mineral content in adults²⁶ have been examined using dual-energy X-ray absorptiometry (DXA). However, to our knowledge no study has yet investigated the independent contributions of body weight and local muscle size (cross-sectional area, CSA) to the site-specific bone strength of the arm and leg within the same individuals. Such an investigation would provide a model for evaluating the relationships between these skeletal loads and bone while attenuating the influence of non-mechanical factors (genetic, endocrine, and nutritional) known to moderate muscle–bone relationships.¹³

There is some evidence in the literature that the muscle–bone relationships in the arms and legs differ between sexes. Bone size relative to muscle area at the forearm was reported to differ between post-pubertal male and female individuals.²⁷ Similarly, young adult women had a larger femoral cortex relative to thigh muscle.²⁸ This may be due to the wider pelvis in women, which results in higher bending moments and forces at the hip joint²⁹ and higher muscle forces required for

muscle balancing. In women, relatively larger cortices may also be directly related to the sex-specific genes or hormones affecting bone structure.²⁸ In premenopausal women, higher concentrations of estrogen may increase bone’s sensitivity to loading stimuli¹³ and pack “extra” bone into the female skeleton for reproductive purposes,³⁰ perhaps more in loaded than in less loaded sites. There are no direct comparisons of muscle cross-sectional area (MCSA) and estimates of bone strength between the arm and leg in the literature. A better understanding of the sex-specificity of the muscle–bone interplay in the arm and leg may help to explain the observed sex-specific pattern of upper extremity fractures.^{1,2}

Therefore, analysis of muscle–bone relationships in the arms and legs of the same individuals (representing both sexes) would allow for determination of the relative contributions of muscle force and body weight to bone mass and bone strength. This knowledge represents an important step toward designing primary and secondary bone strength interventions, and would advance the debate over muscular versus gravitational skeletal loading. The objective of our study, therefore, was to assess bone mineral content and estimated bone strength in relation to body mass and MCSA (a surrogate measure of muscle force^{20,31–34}) in the forearms and lower legs of healthy middle-aged adults. We adjusted our models for sex and height to test the following primary hypotheses: (1) Compared to body mass, MCSA will predict a greater portion of variance in bone mass and bone strength than body mass at the radius than at the tibia; (2) Both body mass and MCSA will explain variance in bone mass and strength at the distal tibia and tibia shaft. Secondly, we hypothesized that sex is an independent predictor of bone mass and strength at the lower leg only.

METHODS

Participants

A total of 60 adults (37 male, 23 female), were recruited from the Saskatchewan Growth and Development Study to participate in this investigation.³⁵ Participants were required to be free of musculoskeletal conditions affecting functional capacity, muscle strength, and bone health. Approval was given by the University of Saskatchewan Biomedical Research Ethics Board, and participants provided written informed consent before undergoing testing.

Anthropometry and health

We measured participants’ standing height to the nearest 0.1 cm using a wall-mounted stadiometer (Holtain Ltd., Croswell, UK). Body weight was measured with a digital scale (Mettler Toledo, Mississauga, ON) to the nearest 0.5 kg with participants lightly clothed and without footwear. Radius length was measured from the proximal lateral border of the head of the radius to the

Table 1 Descriptive Statistics for Background Characteristics and Musculoskeletal Outcomes

	Patient group; mean and (SD)		
	Male; <i>n</i> = 37	Female; <i>n</i> = 16	Total; <i>n</i> = 53
Age, y	51.6 (0.6)	47.6 (1.5)	50.4 (2.1)
Height, cm	178.7 (7.3)	163.4 (2.9)	174.1 (9.5)
Body mass, kg	89.0 (19.2)	64.7 (11.0)	81.6 (20.4)
Forearm MCSA, mm ²	4990.0 (661.6)	2948.5 (429.8)	4323.4 (1133.6)
Lower leg MCSA, mm ²	8580.7 (1003.7)	7178.6 (1015.6)	8103.4 (1201.8)
Radius ToC, mg/mm	154.7 (21.2)	108.1 (16.8)	140.3 (29.4)
Radius BSI _c , mg ² /mm ⁴	53.2 (11.6)	35.7 (8.4)	47.8 (13.4)
Radius CoC, mg/mm	133.9 (21.2)	96.9 (14.5)	121.8 (25.9)
Radius SSI _p , mm ³	502.2 (122.3)	279.3 (59.7)	429.4 (149.2)
Tibia ToC, mg/mm	399.8 (66.2)	304.5 (33.1)	371.0 (72.8)
Tibia BSI _c , mg ² /mm ⁴	124.6 (28.2)	89.0 (16.1)	113.9 (30.0)
Tibia CoC, mg/mm	439.4 (58.4)	349.5 (38.2)	408.8 (67.5)
Tibia SSI _p , mm ³	3251.6 (556.4)	2259.2 (417.5)	2913.8 (696.2)

MCSA = muscle cross-sectional area; ToC = total content; BSI_c = compressive bone strength index; CoC = cortical content; SSI_p = polar stress-strain index.

most distal point of the radius styloid process, using an anthropometric tape measure.⁵¹ Tibia length was measured from the base of the medial malleolus to the superior margin of the medial epicondyle.⁵¹ All anthropometric landmarks were palpated; measures were repeated three times, and the median value was recorded. Current medical conditions, medications, bone and joint health, and menstrual history over the past 12 months (for women only, to confirm premenopausal status) were identified using a standard questionnaire.⁵² Premenopausal status was defined as having menstruated within the previous 12 months as well as in the past 3 months.⁵³ Women who did not fit this definition were defined as peri- or post-menopausal and were excluded from the analysis.

Peripheral Quantitative Computed Tomography

We measured bone and muscle properties of the non-dominant forearm and lower leg with peripheral quantitative computed tomography (Stratec Medizintechnik GmbH, Pforzheim, Germany). We performed a scout scan over the joint line and positioned the reference line at the medial tip of the distal endplate of both the radius and the tibia. Cross-sectional slices (2.4 mm thick) with a pixel size of 0.4 mm were obtained at a scan speed of 20 mm/s at 4% and 65% (of radius length) and at 4% and 66% (of tibia length) proximal from the reference line.

We analyzed the scans using Stratec XCT software, version 6.0. Distal scans (4% site) were analyzed for total cross-sectional bone area (ToA, mm²), bone mineral density (ToD, mg/cm³), and content (ToC, mg/mm). This was done by using Contour Mode 1 with a threshold of

280 mg/cm³ to separate bone from soft tissue. Distal bone strength was estimated as the bone strength index in compression (BSI_c, mg²/mm⁴), calculated as ToD² × ToA.³⁶ The shaft scans (65% and 66% sites) were analyzed for the cortical bone mineral content (CoC, mg/mm), and the polar stress-strain index (SSI_p, mm³).^{37,38} was used to estimate bone strength in torsion. Separation Mode 4 with inner and outer thresholds of 480 mg/cm³ was used to define cortical bone. MCSA (mm²), as a surrogate for muscle strength,²⁰ was also determined at the 65% radius and 66% tibia shaft using Contour Mode 1 with a threshold of 40 mg/cm³ and Muscle Filter CO₂. Precision (CV%_{RMS}) ranged between 4% and 12% for bone content and strength outcomes and was approximately 2% for MCSA measurements in our lab.²⁰

Statistical analysis

We report mean and standard deviations for background characteristics (age, height, body mass) and musculoskeletal outcomes for all participants. For descriptive purposes, we also provide this information for female and male participants.

We used forced-entry multiple regression analyses to explain variance in ToC, BSI_c, CoC, and SSI_p at both radius and tibia. Age did not contribute to the primary models and was therefore omitted for the final analysis (data not shown). Body mass and MCSA were then independently added to the first two models. The final model included sex, height, body mass, and MCSA. An additive model was assumed. We assessed multicollinearity between the independent variables in each model by the variance inflation factor (VIF), with the maximum tolerable value defined as 10. We report adjusted coefficients

Figure 1 Scatter plot and the coefficient of determination (R^2) of the linear relationship between the estimated compressive bone strength (BSI_c) and A) MCSA and B) body mass in the distal radius (solid circle) and tibia (open triangle).

of determination (R^2 Adj.), change in R^2 , standardized beta (β), partial correlation (r_{partial}), and p -values. We considered $p < 0.05$ significant. Statistical analysis was performed using SPSS v.18.

RESULTS

Of the 60 adults recruited, seven women were not considered premenopausal and were therefore excluded from the analysis. A total of 53 adults (37 male, 16 female) were included in the final analysis. Their background characteristics, bone and muscle outcomes are shown in Table 1. The bivariate relationships between MCSA or body mass and BSI_c, SSI_p, and ToC in the forearm and lower leg are illustrated in Figures 1–3. The VIF was below the maximum tolerable value for each variable entered into the regression models, indicating that none of the predictors were redundant (data not shown).

Radius

When body mass was added into the model including sex and height, only the prediction of variance (R^2) in

Figure 2 Scatter plot and the coefficient of determination (R^2) of the linear relationship between the total content (ToC) and A) MCSA and B) body mass in the distal radius (solid circle) and tibia (open triangle).

radius ToC (60% to 63%, $p = 0.034$) and SSI_p (58% to 61%, $p = 0.045$) improved. The addition of forearm MCSA into the model with sex and height improved the prediction of variance (R^2) in radius ToC (60% to 75%, $p = 0.001$), BSI_c (38% to 50%, $p = 0.001$), CoC (48% to 52%, $p = 0.025$) and SSI_p (58% to 68%, $p = 0.001$) (Table 2). When both body mass and forearm MCSA were forced into the model including sex and height, the prediction of variance (R^2) in radius ToC (60% to 75%, $p = 0.001$), and SSI_p (58% to 67%, $p = 0.002$) improved to the same level as that of the model with sex, height, and MCSA only (see Table 2); prediction of variance (R^2) in radius CoC remained the same (56% to 58%, $p = 0.058$). Prediction of variance (R^2) in BSI_c improved with both body mass and MCSA (38% to 54%, $p = 0.001$). With sex, height, MCSA, and body mass in the model, body mass was a negative predictor of radius BSI_c ($\beta = -0.41$, $p = 0.031$), and body mass did not predict variance in ToC ($\beta = -0.13$, $p = 0.36$), CoC ($\beta = 0.05$, $p = 0.80$), or SSI_p ($\beta = -0.02$, $p = 0.92$) (see Table 2).

The contribution of sex to the prediction of variance in radius ToC, BSI_c, CoC, and SSI_p varied across the

Figure 3 Scatter plot and the coefficient of determination (R^2) of the linear relationship between the estimated torsional bone strength (SSI_p) and A) MCSA and B) body mass in the radius (solid circle) and tibia (open triangle).

models. Sex was a significant predictor of ToC, BSI_c, CoC, and SSI_p ($r_{\text{partial}} = -0.43$ to -0.35 , $p \leq 0.02$) in the model including sex and height as well as in the model including sex, height, and body mass ($r_{\text{partial}} = -0.45$ to -0.37 , $p \leq 0.02$) (see Table 2). When forearm MCSA was introduced, however, sex was no longer a significant predictor of the variance in ToC, BSI_c, CoC, and SSI_p ($r_{\text{partial}} = -0.12$ to 0.03 , $p > 0.05$) in either the model including sex and height or the model including sex, height, and body mass ($r_{\text{partial}} = -0.12$ to 0.15 , $p > 0.05$) (see Table 2).

Tibia

In the lower leg, adding body mass into the model with sex and height improved the prediction of variance (R^2) in tibia ToC, CoC, and SSI_p by up to 9% ($p < 0.05$), while the prediction of variance in tibia BSI_c did not change. When lower-leg MCSA was added into the model, the prediction of variance (R^2) in tibia CoC and SSI_p improved by up to 8% ($p < 0.02$) (see Table 3), while the prediction of variance in ToC and BSI_c re-

mained the same. The prediction of variance (R^2) in tibia ToC and BSI_c did not significantly improve when both body mass and lower-leg MCSA were entered into the model including sex and height, but tibia CoC and SSI_p improved significantly, by up to 10% ($p < 0.02$) (see Table 3).

Sex predicted variance in BSI_c, CoC, and SSI_p when lower leg MCSA was not included in the models. However, sex did not remain a significant predictor of variance when lower leg MCSA was added into the model with sex, height, and body mass.

DISCUSSION

Our main objective was to investigate the explanatory value of body mass and muscle size for tibia and radius bone mass, and estimated strength in healthy middle-aged adults. In addition, we were interested in the role of sex in determining radius and tibia bone mass and strength (after adjusting for stature, body mass, and/or MCSA).

Our findings suggest that the relationship between bone, body mass, and muscle size differs between arm and leg. Muscle size was consistently the dominant predictor of bone content and strength in the radius, whereas results in the tibia were less consistent, with muscle size and body mass varying in relative predictive value. Our results agree with previous evidence of the close relationship between MCSA and bone strength estimates in the arm^{20,21} and leg,^{18,22–24} and with DXA-derived data suggesting that this relationship differs between the upper and lower limbs.^{25,26} Our study adds to this literature by illustrating the site-specificity of the relationship between pQCT-derived bone measures of strength and local muscle area within the forearms and lower legs of the same individuals. Although the cross-sectional evidence obtained does not provide information on causality, our observations suggest that in the lower leg, bone mass varies with body weight (mass $\times$ gravity), torsional strength varies with muscle size/forces, and gender determines compressive bone strength. In the forearm, bone properties appear to be primarily a function of muscle size/force, with no independent role for gender. BSI_c demonstrated the only independent predictive value for body mass in the forearm, with a significant negative correlation. In the forearm, muscle size likely reflects muscle forces generated to bear external loads. Although muscle forces counterbalance the weight of the upper extremities themselves, the frequency, magnitude, and relative influence of these counterbalancing forces is likely less than total-body weight-bearing forces at the lower leg. A recent twin study supports this notion, reporting similar genetic regulation of bone strength in the distal tibia and radius but a greater influence of environmental factors (e.g., regular weight-bearing loads) on distal tibia strength.³⁹ Similarly, studies comparing gymnasts and non-gymnasts have reported greater differ-

Table 2 Details of the Regression Models Predicting Total Content (ToC) and Cortical Content (CoC) and Compressive (BSI_c) and Torsional (SSI_p) Bone Strength of the Radius

	4% Distal Site								65% Shaft Site							
	ToC (mg/mm)				BSI _c (mg ² /mm ⁴)				CoC (mg/mm)				SSI _p (mm ³)			
	<i>R</i> ² Adj.	β	<i>p</i> - value	<i>r</i> _{partial}	<i>R</i> ² Adj.	β	<i>p</i> - value	<i>r</i> _{partial}	<i>R</i> ² Adj.	β	<i>p</i> - value	<i>r</i> _{partial}	<i>R</i> ² Adj.	β	<i>p</i> - value	<i>r</i> _{partial}
Radius																
Model 1	0.60				0.38				0.48				0.58			
Sex*		−0.45	0.002	−0.43		−0.48	0.007	−0.38		−0.45	0.007	−0.39		−0.36	0.014	−0.35
Height		0.39	0.005	0.38		0.17	0.312	0.14		0.31	0.058	0.28		0.47	0.002	0.44
Model 2	0.63				0.39				0.49				0.61			
Δ	0.04		0.034		0.004		0.57		0.03		0.12		0.04		0.045	
Sex		−0.45	0.001	−0.45		−0.48	0.007	−0.38		−0.45	0.006	−0.40		−0.36	0.012	−0.37
Height		0.19	0.250	0.17		0.10	0.626	0.07		0.13	0.504	0.10		0.26	0.126	0.23
Body Mass		0.28	0.034	0.30		0.09	0.574	0.08		0.24	0.120	0.23		0.28	0.045	0.29
Model 3	0.75				0.50				0.52				0.68			
Δ	0.15		0.001		0.15		0.001		0.05		0.025		0.10		0.001	
Sex		0.04	0.788	0.02		0.01	0.993	0.01		−0.16	0.424	−0.12		0.03	0.837	0.03
Height		0.07	0.586	0.04		−0.14	0.420	−0.12		0.12	0.503	0.10		0.21	0.149	0.21
MCSA		0.85	0.001	0.39		0.84	0.001	0.49		0.51	0.025	0.33		0.69	0.001	0.50
Model 4	0.75				0.54				0.51				0.67			
Δ	0.16		0.001		0.19		0.001		0.05		0.080		0.10		0.002	
Sex		0.10	0.514	0.10		0.21	0.330	0.15		−0.18	0.412	−0.12		0.04	0.821	0.03
Height		0.12	0.387	0.13		0.02	0.919	0.02		0.10	0.611	0.08		0.21	0.177	0.20
Body Mass		−0.13	0.356	−0.14		−0.41	0.031	−0.32		0.05	0.799	0.04		−0.02	0.921	−0.02
MCSA		0.97	0.001	0.59		1.21	0.001	0.56		0.46	0.105	0.24		0.42	0.004	0.42

*Males = 1; Females = 2.

Δ = change in *R*² from Model 1.Adjusted coefficient of determination (*R*² Adj., bolded) provides the amount of variation explained by the regression model, standardized beta coefficient (β) indicates the predictive power and partial correlation coefficient (*r*_{partial}) the independent contribution of the predictor variable in the model.

ences in bone mass and bone strength at the distal radius than at the tibia,^{40,41} which are likely due to a relatively greater difference in the loading of the upper and lower extremity between gymnasts and controls.

Between and within the arm and leg, the association between MCSA and bone seemed to vary for the outcomes measured at the distal and mid-shaft sites. The highest explanatory value exhibited by MCSA was for total bone-mineral content (ToC) at the distal radius, whereas at the distal tibia ToC was best explained by height. At the mid-shaft of the radius, the distribution (SSI_p) and the total amount of cortical bone mineral content (CoC) were best explained by MCSA; at the mid-shaft of the tibia, body mass best explained SSI_p and CoC. These findings share similarities with results from gymnast studies, which found that loading adaptation to gymnastic training was best captured by total bone-mineral content (ToC) in the distal radius and by distribution of cortical content (i.e., geometry) at the shaft sites, as reflected by the greater strength estimate (SSI_p).^{40,41} Thus, ToC and SSI_p warrant consideration when defining primary outcomes for future exercise in-

terventions. Although BSI_c is commonly used to estimate distal bone strength in pQCT studies, it has been validated only in cadaveric tibia.⁴² Furthermore, the ability of BSI_c (85%) and that of ToC (75%) to predict failure load were not vastly dissimilar in this cadaver study.⁴²

In this study, muscle size did not fully explain variance in bone outcomes. These results agree with studies of racquet sport athletes that controlled for genetic, hormonal, and nutritional variability while assessing the unilateral effects of physical activity.^{43,44} Larger muscle and bone size were observed at both forearm⁴⁵ and humerus⁴³ in these athletes. However, the difference in variance between forearm and upper-arm bones was not explicitly explained by a difference in forearm⁴⁵ and upper-arm muscle.⁴³ Comparisons of forearm bone and muscle differences between gymnasts and their matched non-gymnast controls provided similar evidence. Structural adaptation in the distal forearm bone associated with gymnastic loading was not fully accounted for by differences in forearm muscle size indices.²¹ The disagreement between bone and muscle adaptation in these studies may be explained by the limitations of imaging-

Table 3 Details of the Regression Models Predicting Total Content (ToC) and Cortical Content (Coc) and Compressive (BSI_c) and Torsional (SSI_p) Bone Strength of the Tibia

	4% Distal Site								65% Shaft Site							
	ToC (mg/mm)				BSI _c (mg ² /mm ⁴)				CoC (mg/mm)				SSI _p (mm ³)			
	<i>R</i> ²	β	<i>p</i> -value	<i>r</i> _{partial}	<i>R</i> ²	β	<i>p</i> -value	<i>r</i> _{partial}	<i>R</i> ²	β	<i>p</i> -value	<i>r</i> _{partial}	<i>R</i> ²	β	<i>p</i> -value	<i>r</i> _{partial}
	Adj.				Adj.				Adj.				Adj.			
Tibia																
Model 1	0.43				0.30				0.45				0.57			
Sex*		-0.28	0.082	-0.24		-0.37	0.040	-0.29		-0.35	0.039	-0.31		-0.29	0.055	-0.28
Height		0.44	0.008	0.36		0.24	0.170	0.19		0.38	0.026	0.33		0.53	0.001	0.48
Model 2	0.48				0.31				0.53				0.62			
Δ	0.06		0.024		0.02		0.184		0.09		0.006		0.06		0.012	
Sex		-0.28	0.070	-0.26		-0.37	0.039	-0.29		-0.35	0.026	-0.33		-0.29	0.042	-0.31
Height		0.18	0.337	0.14		0.08	0.729	0.05		0.06	0.748	0.05		0.27	0.119	0.24
Body Mass		0.35	0.024	0.32		0.23	0.184	0.19		0.43	0.006	0.40		0.35	0.012	0.37
Model 3	0.44				0.33				0.52				0.64			
Δ	0.03		0.140		0.04		0.105		0.08		0.010		0.07		0.004	
Sex		-0.21	0.237	-0.18		-0.28	0.149	-0.22		-0.23	0.158	-0.21		-0.17	0.232	-0.18
Height		0.38	0.031	0.32		0.18	0.353	0.14		0.29	0.077	0.27		0.44	0.003	0.44
MCSA		0.21	0.140	0.22		0.25	0.105	0.25		0.34	0.010	0.38		0.33	0.004	0.42
Model 4	0.46				0.31				0.53				0.64			
Δ	0.06		0.109		0.04		0.266		0.10		0.014		0.08		0.011	
Sex		-0.27	0.127	-0.23		-0.29	0.150	-0.22		-0.29	0.085	-0.26		-0.20	0.174	-0.21
Height		0.19	0.375	0.14		0.14	0.550	0.09		0.12	0.554	0.09		0.35	0.050	0.30
Body Mass		0.33	0.133	0.23		0.06	0.816	0.04		0.29	0.153	0.22		0.15	0.382	0.13
MCSA		0.02	0.904	0.02		0.22	0.292	0.16		0.19	0.295	0.16		0.25	0.097	0.25

*Males = 1; Females = 2.

 Δ = change in *R*² from Model 1.Adjusted coefficient of determination (*R*² Adj., bolded) provides the amount of variation explained by the regression model, standardized beta coefficient (β) indicates the predictive power and partial correlation coefficient (*r*_{partial}) the independent contribution of the predictor variable in the model.

based surrogates of muscle force (such as MCSA). Although muscle force and size are highly correlated,^{20,31–34} single-site MCSA may not best characterize the total muscle-induced load applied to a given bone during locomotion and physical activity. For example, unilateral differences in the size of the humerus (loaded and stabilized by muscles that do not span its length at both elbow and shoulder joints) were not fully explained by the unilateral differences in biceps and triceps muscle size at the mid-shaft.⁴³ On the other hand, these results may indicate that other factors, such as direct impacts from gymnastics moves or vibrations from playing tennis, may contribute directly (independent of muscle) to the adaptation of bone tissue.⁴³

A secondary objective of our study was to assess sex-specificity in muscle–bone interactions for the arm and leg. We hypothesized that sex would be a significant independent predictor in the lower leg only. Our results indicate that sex is in fact a significant predictor of bone mass and estimated bone strength in both forearm and lower leg, but only in models that do not include MCSA. We have previously reported similar observations in the

forearms of men and women in their sixties.²⁰ For body mass models, with the exception of distal tibia ToC, sex was a significant independent predictor in every model that did not include MCSA. The inclusion of MCSA in any model, however, removed sex as a significant independent predictor. It is likely that MCSA specifically accounts for sex-based differences in bone size and strength, while measures of height and body mass (which are indiscriminate with respect to male and female body composition ratios) may be limited.²⁸ However, these results need to be confirmed by comparing site-specificity in the muscle–bone relationship between a larger sample of women and men.

These results may have some clinical implications. Age-related muscle and bone loss occurs a decade sooner in the upper limbs than in the lower limbs,⁴⁶ and lower-limb bone strength is likely preserved by regular loading during weight-bearing activities.²¹ This suggests that regular loading of the forearms may be an effective preventive or rehabilitative modality for enhancing or maintaining radius bone strength. This hypothesis is further supported by findings from studies of zero-gravity space

flight and prolonged bed rest. During space flight, a significant loss of bone is reported in the tibia, while the radius remains relatively unaffected.⁴⁷ The observed resilience of radius bone during space flight is likely due to the ambulatory responsibilities the arms inherit for weightless orientation, stabilization, and movement of the body around the space craft.⁴⁷ These arm-loading activities do not regularly occur in bed-rest studies, in which participants are lying with head tilted down for weeks to months at a time.⁴⁸ Prolonged bed rest has been shown to result in reduced MCSA and loss of bone mass in both the forearm and the lower leg, but the losses are considerably greater in the lower leg.⁴⁸ Interestingly, the greatest loss of bone-mineral content in the lower leg occurred at the distal tibia; however, an exercise intervention group demonstrated a trend toward the preservation of bone-mineral content.⁴⁸ This evidence highlights the importance of regular muscle loading as a stimulus for maintenance of bone strength. At the lower extremity, upright postural loading and dynamic locomotive loading are required for bone strength adaptation and maintenance. Similarly, a lack of loading exposure and related adaptation may predispose the upper limb bones to fracture in the event of a fall. A lack of exposure may help explain why the distal radius is the most common osteoporotic fracture site, accounting for 1.7 million fractures per year worldwide.²

Results from our comparison may prove useful to those designing interventions with specific exercises to strengthen bones at the wrist and forearm. Physical activity has the potential to prevent age-related decline in muscle and bone strength and is an attractive strategy to reduce fracture risk.⁴⁹ However, there are no RCTs assessing the influence of exercise on bone structure and strength in the forearm.⁵ Exercise interventions assessing bone's structural adaptation have concentrated on the lower extremity, and studies assessing the upper extremity have focused on distal radius measurements, without concomitant assessment of forearm muscle adaptation.⁵⁰ The observed site-specificity of the muscle–bone relationship may indicate that interventions aimed at strengthening the distal radius will require a specific loading regime that may differ from those designed for the lower extremity. We hypothesize that the ability of specific muscles to influence site-specific bone strength will vary with the nature of the loading activity. Thus, imposing exercises that enable a variety of forearm and upper-arm muscles to function (e.g., wall-standing push-ups) may provide a loading stimulus to which the upper extremity is less accustomed, and thus may lead to enhanced bone adaptation. On the other hand, the dominance of forearm muscle size in explaining radius bone strength may indicate that optimal bone adaptation is produced by further forearm muscle hypertrophy. In either case, RCTs are needed to test the effectiveness and feasibility of specific training regimens in enhanc-

ing bone strength at the clinically relevant wrist and forearm.

LIMITATIONS

Our study was limited by its cross-sectional, observational nature and small sample size. Because of the small sample size, we pooled both sexes in our analysis. Small sample size also reduced our ability to address any possible interactions, and we therefore assumed an additive model for each of our regression analyses. We did not collect information on physical activity levels for all participants. We also relied on self-reported menopausal status for female participants. A larger, population-based cohort of participants across the human lifespan (ideally with prospective measures) is needed to confirm our finding of site-specificity in the bone–muscle relationship and address the possible sex-specificity of these relationships.

KEY MESSAGES

What is already known on this topic

Muscular forces provide osteogenic stimulus for bone. Space- and age-related muscle and bone loss occur earlier in the lower extremities than in the upper extremities, reflecting the importance of regular postural and locomotive forces in maintaining bone strength in weight-bearing versus non-weight-bearing skeletal sites.

What this study adds

Our results indicate that the muscle–bone relationship differs between the forearm and the lower leg. Forearm muscle size is a dominant predictor of radius bone strength, whereas bone strength in the tibia is influenced by both body mass and lower-leg muscle size.

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