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Determinants of forearm strength in postmenopausal women

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Abstract

Summary—Bone strength at the ultradistal radius, quantified by micro-finite element modeling, can be predicted by variables obtained from high-resolution peripheral quantitative computed tomography scans. The specific formula for this bone strength surrogate ($-555.2 + 8.1 \times [\text{trabecular vBMD}] + 19.6 \times [\text{cortical area}] + 4.2 \times [\text{total cross-sectional area}]$) should be validated and tested in fracture risk assessment.

Introduction—The purpose of this study was to identify key determinants of ultradistal radius (UDR) strength and evaluate their relationships with age, sex steroid levels, and measures of habitual skeletal loading.

Methods—UDR failure load (~strength) was assessed by micro-finite element (μ FE) modeling in 105 postmenopausal controls from an earlier forearm fracture case-control study. Predictors of bone strength obtained by high-resolution peripheral quantitative computed tomography (HRpQCT) in this group were then evaluated in a population-based cohort of 214 postmenopausal women. Sex steroids were measured by mass spectrometry.

Results—A surrogate variable ($-555.2+8.1\times[\text{trabecular vBMD}]+19.6\times[\text{cortical area}]+4.2\times[\text{total cross-sectional area}]$) predicted UDR strength modeled by μ FE ($R^2=0.81$), and all parameters except total cross-sectional area declined with age. Evaluated cross-sectionally, the 21% fall in predicted bone strength between ages 40–49 years and 80+years more resembled the change in trabecular volumetric bone mineral density (vBMD) (–15%) than that in cortical area (–41%). In multivariable analyses, measures of body composition and physical activity were stronger predictors of UDR trabecular vBMD, cortical area, total cross-sectional area, and predicted bone strength than were sex steroid levels, but bio-available estradiol and testosterone were correlated with body mass.

Conclusions—Bone strength at the UDR, as quantified by μ FE, can be predicted from variables obtained by HRpQCT. Predicted bone strength declines with age with changes in UDR trabecular vBMD and cortical area, related in turn to reduced skeletal loading and sex steroid levels. The predicted bone strength formula should be validated and tested in fracture risk assessment.

Keywords

Bone density; Bone quality; Bone strength; Epidemiology; Finite element models

Introduction

In a preliminary study comparing postmenopausal women who had a distal forearm (Colles') fracture to similarly aged women with no osteoporotic fracture history, we found that the factor-of-risk (ϕ , the ratio of applied bone load to bone failure load) was 24% worse in the fracture cases [1]. Although each standard deviation (SD) increase in ϕ was associated with a threefold rise in fracture risk, the applied bone load (estimated impact force on the upper extremity during a fall forward on the outstretched arm) was the same in the two groups, and a history of recent falls was no more common among cases than controls. Instead, the difference in ϕ was accounted for by a 20% reduction in failure load (~strength) of the ultradistal radius (UDR) as determined by micro-finite element (μ FE) modeling of data from a high-resolution peripheral quantitative computed tomography (HRpQCT) scan on each subject. Boutroy and colleagues [2] subsequently showed that μ FE-estimated failure load, along with UDR bone density and geometry, accounted for over half of forearm fracture risk: Volumetric bone mineral density (vBMD) and cortical thickness (Ct.Th) were prominent contributors to this component of risk. We also found that UDR trabecular vBMD and Ct.Th were independent predictors of Colles' fracture risk [1, 3]. However, the extent to which such variables, obtainable from a variety of devices capable of 3-D skeletal assessments, can serve as a surrogate for bone strength estimated directly from complex biomechanical models of the UDR is uncertain, and we explore this issue in a larger sample of postmenopausal women from the community. In addition, few population-based data are available concerning the determinants of UDR trabecular and cortical bone. Specifically, it is unclear whether these two compartments respond differently to reductions in habitual skeletal loading or to decreasing sex steroid levels, as these reflect alternative mechanisms for age-related bone loss [4, 5]. Consequently, we also relate measures of body composition, strength, and physical activity, as well as sex steroid levels by sensitive liquid chromatography-tandem mass spectrometry, to highly precise assessments of UDR bone density and structure by HRpQCT.

Methods

Study subjects

Following approval by Mayo Clinic's Institutional Review Board, subjects were recruited from an age-stratified random sample of Rochester, MN residents and included 375 women and 325 men [6]. This analysis was based on 214 of the original 248 postmenopausal women (98% white by self-report) who had a HRpQCT scan of the wrist (mean $\pm$ SD age, 68.1 $\pm$ 11.4 years; range, 41 to 99 years) about 2 years following the baseline examination [7].

The derivation of our predicted bone strength surrogate variable was based on 105 postmenopausal women with no history of an osteoporotic fracture who served as controls in a recently published forearm fracture case-control study [3]. Fifty-seven of them were also members of the community cohort evaluated here.

Written informed consent was obtained from all subjects before participation in the study.

Bone strength estimates

As also described in detail previously [3], bone failure load (~strength) under compression at the UDR was obtained from the μ FE models that had been developed for each of the 105 control women. Failure loads calculated from such μ FE models correlated highly ($r=0.85$) with compressive loads producing Colles' fractures in 100 cadaveric forearms [8].

Bone structure assessments

As also described elsewhere using HRpQCT [9], bone volume/total volume (BV/TV, %) of the UDR was derived from trabecular vBMD (mg/cm³), and a trabecular thickness-independent structure extraction was employed to identify three-dimensional ridges; trabecular number (Tb. N, per millimeter) was taken as the inverse of the mean spacing of the ridges [10]. Trabecular thickness (micrometers) was calculated as BV/TV $\div$ Tb.N and trabecular spacing (Tb.Sp, micrometers) as (1-BV/TV) $\div$ Tb.N. Tb. Sp.SD, the standard deviation of Tb.Sp, is a measure of trabecular variation [11]. Validation studies show excellent correlation ($r\geq 0.96$) for these parameters from HRpQCT (resolution, 82 μ m) compared to gold-standard ex vivo μ CT (resolution, ≤ 20 μ m) [12]. Connectivity density (1/mm³) is another measure of trabecular architectural organization, while the structure model index (SMI) assesses whether trabeculae are more plate-like (lower values) or more rod-like (higher values). The cortex was segmented from the gray scale image with a Gaussian filter and subsequent thresholding at ~ 560 mg/cm³ [10]. Cortical vBMD and area (square millimeters) were measured directly, and the periosteal circumference was calculated from the contour; cortical thickness (Ct.Th, millimeters) was then calculated as area $\div$ circumference. Excellent correlation ($r=0.98$) has also been shown with Ct.Th measurements by ex vivo μ CT [13]. Total cross-sectional area (CSA, square millimeters) of the UDR was taken as the mean of the innermost 104 of 110 CT slices.

Body composition and physical activity

Habitual loads on the radius were estimated from lean body mass of the "arms" region from a whole body scan using dual-energy X-ray absorptiometry (DXA) with the Lunar Prodigy instrument (GE Medical Systems, Madison, WI) and software version 6.10.029, which also determined total body lean (grams) and fat mass (grams). The same device was used to measure areal BMD (aBMD) of the UDR. In addition, we assessed grip strength with a hand dynamometer (NK DIGIT-grip model DGR 001, NK Biotechnical Corporation, Minneapolis, MN). We also estimated physical activity levels over the preceding 12 months, assessing the frequency, duration and intensity of various daily activities [14]. Caloric

expenditure estimates (kilocalories) were based on body weight, the intensity and duration of activity and published metabolic equivalent task (MET) values [15]. Body mass index (BMI) was defined as weight (kilograms)÷height (meters squared).

Sex steroid measurements

Fasting serum samples were obtained at the baseline visit. Sex steroids were measured by liquid chromatography-tandem mass spectrometry (API 5000, Applied Biosystems-MDS Sciex, Foster City, CA) as described elsewhere [16]. Values as low as 1 ng/dl for testosterone (T) and 1.25 pg/ml for estradiol (E₂) were detectable by this method. The non-sex hormone binding globulin, biologically active (Bio) fraction was measured as previously described [17]; inter-assay CVs for Bio-T and Bio-E₂ were each <12%.

Statistical analysis

Pearson correlation coefficients were used to evaluate the relation between previously determined μ FE-modeled bone strength estimates [3] and key bone density and structure variables obtained directly from the Xtreme CT scans among the 105 control women. Correlations were compared using the method of Meng et al. [18]. Assuming a linear relationship, we calculated the standard error of the estimate (SEE) to assess the percentage error involved in predicting directly modeled UDR strength using the HRpQCT variables. To standardize results, the SEE was expressed as a percentage relative to the mean of the dependent variable.

The HRpQCT bone density and structure variables that best accounted for overall μ FE-estimated bone strength in the 105 control women were then evaluated in the population-based cohort of 214 postmenopausal women. Relations of bone density, structure, and strength with age were studied using Pearson correlation and linear regression, as were associations of these variables with body composition, physical activity, grip strength, and sex steroid levels. Model assumptions were assessed and a log transformation used where appropriate; age-adjustment was accomplished by including age in the models. To get a better sense of the relative importance of variables measured in different units, we standardized them to a mean of 0 and a variance of 1 in some analyses. Results were analyzed with and without the inclusion of 74 women on estrogen therapy, six on a selective estrogen receptor modulator, and three on bisphosphonate therapy for osteopenia. Because there was no significant difference in the results with their exclusion, we retained them in the final analysis.

Results

Prediction of bone strength by HRpQCT in the control women

Among the 105 postmenopausal women with no history of an osteoporotic fracture, many HRpQCT parameters were significantly correlated with μ FE-estimated compressive strength at the UDR. Of particular interest was trabecular vBMD (age-adjusted $r=0.78$; $P<0.001$). After adjusting for trabecular vBMD and age, cortical vBMD ($r=0.28$; $P=0.004$), cortical thickness ($r=0.40$; $P<0.001$), cortical area ($r=0.57$; $P<0.001$) and total CSA ($r=0.32$; $P=0.001$) were still associated with μ FE-estimated bone strength, but the trabecular structural variables were no longer significant (Table 1). In a multivariable analysis, also delineated in Table 1, trabecular vBMD was the strongest predictor of modeled UDR bone strength ($R^2=0.59$). The addition of cortical area ($R^2=0.74$) and total CSA ($R^2=0.81$) improved the model still further. SMI was also significant in the multivariable analysis, but the addition of SMI contributed little to predictive power ($R^2=0.83$). Since SMI is not available on all pQCT devices, we predicted bone strength using the following formula:

$$-555.2 + 8.1 \times (\text{trabecular vBMD}) + 19.6 \times (\text{cortical area}) + 4.2 \times (\text{total CSA})$$

with an adjusted R^2 of 0.81 ($P < 0.001$) and a SEE of 9.5%, as illustrated in Fig. 1. UDR aBMD was not as good a surrogate of μ FE-modeled bone strength ($R^2 = 0.54$; $P < 0.001$), with a SEE of 14.8%.

Cross-sectional changes in bone structure and strength in the community cohort

In the entire population-based cohort of 214 postmenopausal women, cortical area declined with age ($r = -0.51$; $P < 0.001$) more dramatically than did trabecular vBMD ($r = -0.14$; $P = 0.036$), while total CSA increased slightly ($r = 0.09$; $P = 0.182$), as illustrated in Fig. 2. Presuming that the bone strength prediction formula we developed from the analysis of the control women applies to postmenopausal women generally, we predicted UDR strength for each subject and found that the decline in predicted bone strength ($r = -0.33$; $P < 0.001$) was greater than the change in trabecular vBMD but less than that in cortical area (Fig. 2). Between ages 40–49 years and 80+ years, predicted strength fell by 21%, which more resembled the 15% decline in trabecular vBMD than the 41% reduction in cortical area. Nonetheless, when both were standardized to a mean of 0 and a variance of 1 (to account for the fact that trabecular vBMD and cortical area are measured in different units), the coefficients of the two variables were of similar magnitude.

Risk factors for bone structure and strength in the community cohort

In univariate analyses, serum sex steroid levels were positively associated with trabecular vBMD, cortical area, total CSA, and predicted UDR strength for the most part, as were body composition, strength, and physical activity (Table 2). Multivariable models, adjusting for age, revealed that body mass (BMI, total body lean mass, lean mass of the arms region), grip strength, and physical activity were also positively associated with most of the key bone density, structure, and strength parameters (Table 3). Among the 131 women not on hormone therapy, Bio-T was also predictive of cortical area and overall predicted bone strength. Because sex steroid levels were not measured on the women undergoing hormone treatment, sex steroids were not considered in the overall analysis of all 214 women shown also in Table 3. Note, however, that none of the models accounted for more than about 40% of the variance in each skeletal parameter.

Discussion

The aims of this study were twofold: To evaluate a surrogate variable (predicted bone strength) that might assess bone strength at the UDR better than bone density per se and to compare the relative influence of sex steroid levels and skeletal loading variables on predicted bone strength and its key determinants. Although bone strength can be quantified accurately in vivo by μ FE modeling [19], this may not be practical for large epidemiologic studies. Instead, most such studies have depended on aBMD by DXA as a surrogate. UDR aBMD is correlated with failure load at the distal radius in biomechanical testing ex vivo [20, 21] and, indeed, with μ FE-estimated bone strength [3]. However, the latter correlation ($r = 0.75$) was less than the correlation seen here between predicted and modeled μ FE bone strength ($r = 0.90$) in the control women, and the ability of aBMD to estimate directly calculated bone strength was not nearly as good ($R^2 = 0.54$; $SEE = 14.8\%$) as the model creating our predicted strength variable ($R^2 = 0.81$; $SEE = 9.5\%$). Indeed, the latter was about as good as was a combination of UDR total vBMD with cortical area ($R^2 = 0.86$) in predicting radius failure load ex vivo [20]. More generally, those authors found that combining bone

geometry with bone density improved the prediction of failure load and that such predictions by UDR aBMD alone were less accurate ($R^2=0.60$).

Although many aspects of bone density and structure contribute to bone strength [22], trabecular vBMD had the strongest correlation with modeled UDR strength in this analysis. After accounting for trabecular vBMD, none of the trabecular structural variables available by HRpQCT was significantly associated with bone strength. SMI was a predictor of bone strength in the multivariable analysis but contributed little to the variance. By contrast, cortical vBMD, thickness and area, as well as total CSA of the distal radius, were still independent predictors of μ FE-modeled UDR strength. Cortical area appeared to be the best of these in our analysis, but others have found similar high correlations with cortical thickness [2]. In these cross-sectional data, the age-related fall in cortical area was more dramatic ($r=-0.51$) than the decline in trabecular vBMD ($r=-0.14$). This is consistent with other work [23–26], as well as with baseline data from the entire population sample, where the correlation with age between 20 and 90 years was somewhat stronger for UDR cortical area ($r=-0.31$) than trabecular vBMD ($r=-0.23$) assessed using an older pQCT device [6]. Both the more rapid decrease in cortical bone and apparent relative sparing of trabecular bone may result in part from age-related trabecularization of the UDR cortex [23, 27]. The decline in overall predicted bone strength in the present study ($r=-0.33$) was intermediate between the cross-sectional changes in cortical area and trabecular vBMD, and may have been influenced somewhat by the slight age-related increase in total CSA since bone size is generally considered a determinant of bone strength. An age-related decline in μ FE-modeled UDR strength was likewise described among 74 women age 20 to 79 years from a primary care practice, although the actual rate of change across that age-range was not reported [26].

Two competing, though not mutually exclusive, conceptualizations view age-related bone loss as the expected physiologic response to reductions in habitual skeletal loads [4] or the result of declining sex steroid levels [5]. We previously reported that physical activity fell by 0.60%/year among women between ages 20 and 90 years, leading to a -0.23% /year change in total lean body mass and a -0.31% /year change in lean mass in the “arms” region of the total body scan [28]; such changes were accompanied by substantial reductions in UDR aBMD [29]. In this context, our measures of body size, muscle mass, grip strength, and physical activity almost all correlated with UDR trabecular vBMD, cortical area, and total CSA, as well as with predicted bone strength. BMI was the strongest determinant of bone density, structure, and strength in most multivariable models, as found also by others [24]. While generally considered a measure of adiposity, BMI also reflects lean mass [30]. Indeed, BMI was highly correlated with lean mass even in the “arms” region of the total body scan ($r=0.55$; $P<0.001$). In the univariate analyses, total body fat mass, and total lean mass correlated comparably with most parameters. Physical activity was also positively associated with the various density, structure, and strength parameters but was an independent predictor only of cortical area. Grip strength did not independently predict any parameter. Note, however, that these variables explained only a modest portion of the variance in bone density, structure and strength, and we previously showed that reduced skeletal loading was unable to account for age-related bone loss [28].

Serum Bio-E₂, and to a lesser extent Bio-T, were also correlated with predicted UDR strength and its determinants in the univariate analyses. In the multivariable analyses, however, only Bio-T was an independent risk factor for cortical area and predicted UDR strength. Bio-T was not associated with trabecular vBMD after adjustment for BMI, but BMI and Bio-T were correlated ($r=0.32$; $P<0.001$) when one outlier Bio-T value >30 ng/dl was excluded. As reported previously [25], however, serum Bio-E₂ was more strongly associated with UDR trabecular vBMD than was Bio-T. Considered in isolation, Bio-E₂ was a stronger predictor than Bio-T of UDR bone density, structure, and strength, but Bio-E₂

was not selected in any of the multivariable models. This may be explained partly by the correlation of estrogen levels with body mass [31], which was stronger here ($r=0.48$; $P<0.001$) than that seen for Bio-T. In addition, a more detailed study showed that Bio-E₂ was significantly correlated with UDR trabecular and cortical vBMD in older postmenopausal women, who have low Bio-E₂ levels, but the age-adjusted correlation with cortical bone was not significant among middle-aged women with intermediate Bio-E₂ levels; no correlation with cortical or trabecular vBMD was seen in estrogen-replete premenopausal women [32]

Our study had a number of strengths and limitations. The population-based cohort was recruited from an age- and sex-stratified random sample of the community, but most of the women were white; men were excluded from this analysis. Moreover, the data used in the analysis were cross-sectional. On the other hand, this study employed state-of-the-art in vivo assessments of UDR density and structure by HRpQCT (“noninvasive bone biopsy”), and bone strength assessments had been made at a distal region, which appears to provide the best estimate of bone failure load at the radius [33]. Likewise, we had access to highly sensitive sex steroid assays [16]. However, the skeletal loading variables were less refined, as DXA measurements may overestimate muscle mass [34] and “arms” region muscle mass may not be a good surrogate for muscles that actually load the forearm [35]. Finally, questionnaire-based assessment of physical activity is problematic in sedentary women.

Despite these limitations, it appears that our surrogate measure, predicted bone strength, may provide a better estimate of bone strength as modeled by μ FE than does UDR aBMD. However, the specific formula used to predict bone strength was derived from this dataset and has yet to be validated in other populations. Moreover, it remains to be seen whether predicted strength is any better than UDR aBMD in assessing future fracture risk. We did find that the age-related decline in predicted bone strength ($r=-0.33$) was not nearly as strong as the decline previously observed cross-sectionally for UDR aBMD ($r=-0.58$) or total wrist aBMD ($r=-0.67$) in postmenopausal women [36], indicating that the fall in aBMD may overestimate the actual loss of UDR strength with aging [7, 37]. This contrasts with recent results at the proximal femur, where the age-related reduction in femoral strength as assessed by finite element analysis was much greater (-55%) than was apparent from the -26% decline in femoral neck aBMD among women between ages 30 and 85 years [38]. The decline in predicted bone strength at the UDR, and its key determinants, accompanies reductions in habitual bone loading as assessed by BMI, lean body mass, and physical activity. Bone density, structure, and strength were also positively associated with sex steroid levels in the univariate analyses, but we were unable to partition the relative contributions of sex steroids from body composition because they were correlated. Nonetheless, these results call attention to the potential importance of evaluating risk factors for bone loss within specific compartments of bone as expressions of different osteoporosis phenotypes.

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Fig. 1. Correlation of overall bone strength in the ultradistal radius calculated directly from μ FE models with strength predicted by a combination of trabecular vBMD, cortical area, and total cross-sectional area among 105 community women with no history of an osteoporotic fracture

Fig. 2. Correlations with age of trabecular volumetric bone mineral density (vBMD) (a), cortical area (b), total cross-sectional area (CSA) (c) and predicted strength (d) of the ultradistal radius among 214 postmenopausal Rochester, MN women

Table 1

Distribution of HRpQCT variables, Pearson correlations, and predictors of overall μ FE-modeled bone strength among 105 community women with no history of an osteoporotic fracture

HRpQCT variables	$\bar{x}$ (SD)	r^a	Adjusted for trabecular vBMD r^b	Multivariable standardized estimate ^c
Total vBMD (mg/cm ³)	333 (78)	0.61 ***	0.23 *	—
Trabecular vBMD (mg/cm ³)	138 (41)	0.78 ***	—	0.41 ***
Trabecular number (1/mm)	1.64 (0.37)	0.65 ***	−0.08	—
Trabecular thickness (μ m)	70 (11)	0.52 ***	0.02	—
Trabecular separation (Tb.Sp., μ m)	595 (280)	−0.51 ***	0.17	—
Tb.Sp. standard deviation (μ m)	294 (216)	−0.48 ***	0.16	—
Structure model index	2.33 (0.38)	−0.72 ***	−0.15	−0.22 **
Connectivity density (1/mm ³)	3.04 (1.08)	0.74 ***	0.11	—
Cortical vBMD (mg/cm ³)	881 (80)	0.31 **	0.28 **	—
Cortical thickness (mm)	0.84 (0.23)	0.53 ***	0.40 ***	—
Cortical area (mm ²)	53 (13)	0.65 ***	0.57 ***	0.48 ***
Total cross-sectional area (mm ²)	225 (36)	0.19 *	0.32 **	0.28 ***

* $P < 0.05$;

** $P < 0.01$;

*** $P < 0.001$

^a Partial correlation adjusted for age

^b Correlation adjusted for age and trabecular vBMD

^c Variables standardized to a mean of 0 and a variance of 1 to account for the different units of measurement

Table 2

Age-adjusted Pearson correlations of serum sex steroid levels and habitual skeletal loading measures with ultradistal radius bone structural parameters and predicted strength among 214 postmenopausal Rochester, MN women

Risk factors	Trabecular vBMD	Cortical area	Total CSA	Predicted strength
Log [Bio E ₂ (pg/ml)] ^a	0.27**	0.24**	0.11	0.34***
Bio T (ng/dl) ^a	0.16	0.21*	-0.15	0.15
Body mass index (kg/m ²)	0.25***	0.26***	0.10	0.33***
Total body fat mass (g)	0.26***	0.23**	0.15*	0.34***
Total body lean mass (g)	0.23***	0.15*	0.41***	0.38***
Body arms lean mass (g)	0.24***	0.22**	0.45***	0.44***
Grip strength (kg)	0.13	0.15*	0.29***	0.27***
Physical activity (kcal)	0.23***	0.25***	0.22**	0.35***

*
P<0.05;

**
P<0.01;

P<0.001

^aDone only on women not on hormone therapy

Table 3

Age-adjusted multivariable models predicting ultradistal radius bone structure and strength among 214 postmenopausal Rochester, MN women

Variable	Trabecular vBMD standardized estimate ^a	Cortical area standardized estimate ^a	Total CSA standardized estimate ^a	Predicted strength standardized estimate ^a
Subset of 131 postmenopausal women not on hormone therapy (includes sex steroid measurements)				
Age (year)	0.03	−0.45 ***	0.21 *	−0.04
Body mass index (kg/m ²)	0.34 ***			
Arms lean mass (g)			0.44 ***	0.34 ***
Physical activity (kcal)		0.27 ***		0.35 ***
Bio-T (ng/dl)		0.19 **		0.15 *
Body lean mass (g)	0.20 *			
Body fat mass (g)				
Adjusted R ²	0.21	0.37	0.14	0.41
Entire cohort of 214 postmenopausal women (excludes sex steroid measurements)				
Age (year)	−0.09	−0.47 ***	0.33 ***	−0.10
Body mass index (kg/m ²)	0.25 ***	0.23 ***	−0.57 ***	
Arms lean mass (g)			0.61 ***	0.32 ***
Physical activity (kcal)				0.26 ***
Body lean mass (g)				
Body fat mass (g)			0.41 **	
Adjusted R ²	0.07	0.31	0.25	0.31

* $P < 0.05$;

** $P < 0.01$;

*** $P < 0.001$

^a Variables standardized to a mean of 0 and a variance of 1 to account for the different units of measurement