Structural Adaptation to Changing Skeletal Load in the Progression Toward Hip Fragility: The Study of Osteoporotic Fractures*

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ABSTRACT

Longitudinal, dual-energy X-ray absorptiometry (DXA) hip data from 4187 mostly white, elderly women from the Study of Osteoporotic Fractures were studied with a structural analysis program. Cross-sectional geometry and bone mineral density (BMD) were measured in narrow regions across the femoral neck and proximal shaft. We hypothesized that altered skeletal load should stimulate adaptive increases or decreases in the section modulus (bending strength index) and that dimensional details would provide insight into hip fragility. Weight change in the \sim 3.5 years between scan time points was used as the primary indicator of altered skeletal load. "Static" weight was defined as within 5% of baseline weight, whereas "gain" and "loss" were those who gained or lost >5%, respectively. In addition, we used a frailty index to better identify those subjects undergoing changing in skeletal loading. Subjects were classified as frail if unable to rise from a chair five times without using arm support. Subjects who were both frail and lost weight (reduced loading) were compared with those who were not frail and either maintained weight (unchanged loading) or gained weight (increased loading). Sixty percent of subjects (n = 2559) with unchanged loads lost BMD at the neck but not at the shaft, while section moduli increased slightly at both regions. Subjects with increasing load (n = 580) lost neck BMD but gained shaft BMD; section moduli increased markedly at both locations. Those with declining skeletal loads (n = 105) showed the greatest loss of BMD at both neck and shaft; loss at the neck was caused by both increased loss of bone mass and greater subperiosteal expansion; loss in shaft BMD decline was only caused by greater loss of bone mass. This group also showed significant declines in section modulus at both sites. These results support the contention that mechanical homeostasis in the hip is evident in section moduli but not in bone mass or density. The adaptive response to declining skeletal loads, with greater rates of subperiosteal expansion and cortical thinning, may increase fragility beyond that expected from the reduction in section modulus or bone mass alone. (J Bone Miner Res 2001;16:1108-1119)

Key words: section modulus, dual-energy X-ray absorptiometry, adaptation to skeletal loading, subperiosteal expansion, skeletal homeostasis, Wolff's law, Frost's mechanostat, structural geometry

INTRODUCTION

COMMON OBSERVATIONS about persons with hip fracture care that they are physically inactive,^(1,2) have low body mass indices,⁽³⁾ and often have lost weight.^(2,4)

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that those forces in the elderly are diminished from levels earlier in life, particularly in those who have become physically frail.

Bone strength is influenced by the properties of the material (difficult to measure in vivo) as well as its structural distribution. For long bones, the structural distribution is described mathematically by the cross-sectional moment of inertia (CSMI). The CSMI quantifies the fact that the further away mass is distributed from its central bending axis, the greater its contribution to bending and torsional strength. Because the maximum stress in bending or torsion is on the outer (subperiosteal) surface, the structural component of strength is determined by the section modulus. The section modulus is CSMI/y, where y is the distance from the center of mass to the subperiosteal surface. In a recent study, we measured bone mineral density (BMD), section modulus, and other geometric properties at the femoral neck and proximal shaft of a large cross-sectional sample of the adult U.S. population (Third National Health and Nutrition Examination Survey [NHANES III]).⁽⁷⁾ In both genders, we saw a much smaller age-related decline in section modulus than in BMD; moreover, the age-related decline in section modulus diminished further when adjusted for body weight. These findings suggest that (1) the age-related decline in BMD may be mechanically compensated to minimize loss of bending strength and (2) this adaptation is modulated by body weight. The apparent mechanism for the discrepancy between trends in BMD and section modulus is a small but mechanically significant subperiosteal expansion of bone at both femoral neck and shaft. This expansion helps to maintain the section modulus at a level appropriate for current skeletal loads. These observations suggest that in long bones at least, this structural adaptation adjusts the bending strength to the loading conditions. Perhaps bone fragility in the frail elderly results at least in part from relative disuse as the skeleton adapts to diminished mechanical loads.⁽⁸⁾

The NHANES III data are from a cross-sectional sample and thus are not suitable for examination of the role of changing skeletal load on bone geometry. To explore this issue, we applied the same structural analysis to hip dualenergy X-ray absorptiometry (DXA) data from a large longitudinal sample of predominantly white, elderly women from the Study of Osteoporotic Fractures (SOF).⁽⁹⁾ In this study we used hip DXA data acquired at two time points, averaging 3.5 years apart. We expected that changes in skeletal loading would result in adaptation in proximal bending strength. To estimate changes in skeletal load we used weight change and a measure of frailty. Our specific hypotheses were the following:

- Those with unchanged skeletal loads would maintain bending strength, as estimated by static section moduli.
- Those with reduced skeletal loads would experience a reduced bending strength, as estimated by a decline in section moduli.
- Those with increased skeletal loads would require an increase in bending strength as estimated by an increase in section moduli.

MATERIALS AND METHODS

Study population

The SOF is a large multicenter prospective study of nonblack postmenopausal women⁽⁹⁾ coordinated by the University of California at San Francisco with participants recruited from four areas in the United States: Baltimore, MD; Minneapolis MN; Portland OR, and the Monongahela Valley of Pennsylvania. Subjects were enrolled at the age of 65 years or older with the baseline exam between September 1986 and October 1988. At the second clinic visit to the centers, between January 1989 and December 1990, each subject received a scan of the left hip using a Hologic QDR 1000 (Hologic, Inc. Waltham, MA, USA) DXA scanner. Scans were repeated at the fourth clinic visit (August 1992–July 1994), an average of 3.5 years later (range, 1.8–5.2 years).

The osteogenic effect of skeletal loads is believed to be a function of frequencies and magnitudes of applied loads,^(10,11) that is, a function of muscle strength and activity level. Muscle strength was measured on SOF participants at both study time points but results were not useful for categorization (see Results and Discussion sections). Muscle mass generally is correlated with physical performance⁽¹²⁾ and should be useful in assessing skeletal loading effects. Unfortunately, body composition was measured only at the first time point. We therefore decided to use weight change as the primary descriptor of altered skeletal loading, based on knowledge that muscle mass generally scales with body mass. This decision is supported by earlier work showing that (1) the section modulus is related most strongly to body weight, $^{(13,14)}(2)$ weight loss is a risk factor for osteoporotic fracture, $^{(2,15-20)}$ and (3) weight gain might confer a protective effect.^(2,17) Therefore, we restricted analyses to participants with BMD and measured weight at both time points and measured height for at least one time point. A total of 4532 scan pairs met these criteria although a total of 345 pairs were excluded for technical reasons leaving 4187 data pairs for analysis.

Exclusion criteria for data pairs

In a longitudinal study, the DXA-based structural analysis is sensitive to inconsistent patient position (mainly because of hip rotation) and to inconsistent region location on the hip image. To minimize these effects, the analysis program was modified so that a template of the proximal femur from the baseline scan was saved with positions of all analysis regions. On subsequent scans the template was retrieved and superimposed on the current hip image by the user. If inconsistent hip positioning prevented template alignment, data for that scan pair was rejected; a total of 186 scan pairs were rejected in this manner. Further, we excluded data with unlikely extremes in differences in bone width between pairs because inconsistent region location or patient position between scans tends to have the greatest effect on width dimensions. Extreme differences were defined as >3 SD above and below the mean difference in bone width at either the femoral neck or the shaft, corresponding to ± 5 mm and ± 3 mm at the neck and shaft,



FIG. 1. Location of narrow "cross-sectional" analysis regions across narrowest point on femoral neck and across the femoral shaft 2 cm distal to the lesser trochanter. Typical mass profiles, shown on left, are used to derive subperiosteal widths, BMD, CSA, and section modulus. Estimates of cortical thickness employ assumptions of cross-sectional shape (see text).

respectively. These differences were considered biologically unlikely over a 4-year span based on results of a cross-sectional study of the U.S. population where mean difference in femoral neck width between the third and eighth decade (over a 50-year span) in white women was 3 mm.⁽⁷⁾ A total of 159 data pairs were excluded for this reason. The remaining data set included 4187 hip scan data pairs.

Analysis of structural parameters

The hip structure analysis (HSA) program has been described previously.^(7,21) In brief, the program measures BMD and geometry within narrow regions corresponding to thin cross-sectional slabs of bone viewed on edge. Regions were located across the femoral neck at its narrowest point and across the shaft, 2 cm distal to the midpoint of the lesser trochanter (Fig. 1). As in the previous study,⁽⁷⁾ we concentrated on these mixed cortical/trabecular and purely cortical sites, respectively. Since the NHANES analysis was conducted in 1995, the program was altered to lengthen the analysis regions from 3 to 5 mm along the bone axis to improve precision (signal-to-noise ratio). Between-scan measurement precision using the template methodology was assessed with five repeated hip scans on 3 adult individuals as part of a separate project.⁽²²⁾ Subjects were repositioned between scans taken with a Hologic QDR1000 DXA scanner. Averaged coefficients of variation for each measured parameter are listed in Table 1. Measured precision ranged from 1% to 2.4% and was somewhat better in the femoral shaft than in the neck region, probably because the shaft's nearly circular cross-section is less influenced by variation in femoral rotation.

For the two analysis regions, profiles of bone mass (Fig. 1) were derived from one bone margin to the other and then averaged along the 5-mm length of the region. Subperiosteal width was computed as the blur-corrected distance between profile margins. Cross-sectional area (CSA) was computed

as the profile integral divided by the effective density of bone mineral ($\rho_m = 1.05$).⁽²³⁾ After deriving the center of mass of the profile, the CSMI was derived from the integral of mass times the square of the distance from the center of mass, divided by (ρ_m) . Conventional BMD was measured in the standard manner. Note that CSA represents the total area of bone in the cross-section with soft tissue voids removed and is linearly related to the bone mineral content (BMC; total mineral mass) in the cross-section. Section modulus was computed as the ratio of CSMI to half the subperiosteal width. Estimates of mean cortical thickness were derived using simple models of neck and shaft cross-sections as hollow annuli. The neck region model further assumed that a fixed 60% of the neck mass was in the cortex, with the space within filled with the mass remainder as trabecular bone.⁽⁷⁾ We include an estimate of the relative thickness of the femoral neck cortex, expressed here as the buckling ratio,⁽²⁴⁾ and defined as the ratio of the subperiosteal radius (width/2) to the mean cortical thickness.⁽²⁴⁾ The femoral neck region (Fig. 1) across its narrowest point is narrower (5 mm vs. 15 mm) and located more proximally than the standard Hologic neck region; while BMD trends are comparable,⁽⁷⁾ absolute values differ somewhat because of differences in region position and algorithmic details.

Categorization of change in skeletal loading

Weight change was calculated as the difference in weight between exams 2 and 4 and expressed as percent change relative to weight at exam 2. Subjects were grouped into three categories by percent change in body weight. "Static" weight was defined as within 5% of visit 2 weight; "gain" and "loss" categories were those with weight changes greater or less than 5%, respectively. Even in an elderly population, weight change may not necessarily represent change in musculoskeletal load; hence, we used an available measure of functional ability for further discrimination. The ability of the subject to rise from a chair five times in

TABLE	1. SHORT-TERM PRECISION IN BMD AND SECTION
	PROPERTIES FROM FIVE SCAN REPETITIONS
	ON 3 ADULT SUBJECTS

	Region	
Parameter	Narrow neck	Shaft
BMD	1.9%	1.2%
CSA	1.6%	1.1%
Subperiosteal width	1.0%	1.1%
Section modulus	2.4%	1.6%
Estimated mean cortical thickness	2.4%	2.0%

Values are percent CVs averaged over the 3 subjects for analyses employing the image template.

succession without using arm support has been shown previously to be an independent predictor of osteoporotic fracture.⁽²⁾ This functional parameter was used here to separate those with declining physical abilities from those with static or increasing weight, that is, to reduce ambiguity in classifications of unchanged and increased skeletal loading. By including only frail individuals in the weight losers group, we sought to identify a test group of those with clearly diminished musculoskeletal loading. For the indicator of frailty we used whether or not the subject was able or willing to rise from a chair five times in succession without supporting themselves with their arms.⁽²⁾ This variable was measured at visit 4 and was used here to exclude those with reductions in neuromuscular function from the static and increasing weight groups to ensure that these groups represented individuals with unchanged and increasing musculoskeletal loading, respectively. The frailty indicator was then used to isolate those individuals with reduced weight who had become frail and thus could be reasonably characterized as having undergone reduced musculoskeletal loading. To further characterize the physical condition of these loading categories, we also used other measures of physical strength and performance recorded at visits 2 and 4. Details of these measurements have been described previously⁽²⁾ and include abductor, quadriceps and grip strengths, normal and fast walking speeds, and whether or not subjects walked for exercise. Because strength measures and walking speeds are body size and age dependent, subgroup means were adjusted for age and body size (knee height and weight).

Statistical analysis

Results were imported into Statview version 5.0 (SAS Institute, Inc., Carey, NC, USA) for statistical analysis. The significance of differences in BMD and structural variables between visits 2 and 4 was assessed with a paired *t*-test. Changes in these variables were then expressed as percent change per year relative to the baseline (visit 2) value and adjusted for age. Differences in BMD, geometry, and other variables between weight change and frailty categories were analyzed by two-way analysis of variance (ANOVA) to test the independent effects of frailty and weight change. Unpaired *t*-tests were used to delineate differences between categories.

RESULTS

Relationships between bone properties and strength measurements, fat-free mass, and body weight

The choice of body weight as the primary descriptor of skeletal loading effects was made after examination of univariate regressions of BMD and structural properties on body weight, fat-free mass (FFM), and the measurements of muscle strength recorded at visit 2. FFM was measured using bioelectric impedence at visit 2.⁽²⁾ Coefficients of determination (R^2) from these regressions are listed in Table 2 for bone measurements at the neck and shaft regions. The strongest relationships were between FFM and section modulus, explaining 30% and 46% of variability in the neck and shaft, respectively. Relationships between FFM and CSA were nearly as strong at both sites whereas those with BMD and estimated cortical thickness were weaker. Correlations between FFM and subperiosteal width were significant (p <0.0001) but relatively poor. The strong relationship between FFM and bone geometry suggests its use in the investigation of skeletal loading effects, but FFM was not measured at visit 4. Although relationships between bone measurements and muscle strength measurements were significant (Table 2), they were much weaker than with FFM or body weight. Because correlations between bone geometry and weight were nearly as strong as with FFM, weight was chosen as the primary skeletal loading descriptor.

Physical condition and general characteristics

Table 3 lists means and SDs for general characteristics of the study sample as well as characteristics of the different skeletal loading comparison groups at visits 2 and 4. All strength measurements and walk speeds in the subgroups were adjusted for knee height, weight, and age.

On average, these elderly women lost 0.3 kg of weight and 1 cm of height between the two examinations. At visit 4 about 50% of subjects overall walked for exercise and 9% were classified as frail (i.e., unable to rise from a chair five times without using their arms). Two-thirds of these women maintained their body weight within 5% of the visit 2 baseline, while weight declined in 18% and increased in 15%. The proportion of women in the frail category was largest among weight losers (13.7%), intermediate among gainers (9.8%), and least among those with static weight (7.9%). Those in the frail category were 2.7 years older and based on knee and standing heights, were slightly taller on average. The frail subgroup overall had weaker abductor strength at visit 2 and weaker grip and quadriceps strengths at both visits; both normal and fast walking speeds were significantly slower than in the nonfrail subjects at visit 4 (p < 0.0001). Less than one-half as many frail subjects indicated that they walked for exercise (23%) compared with nonfrail subjects (53%).

With regard to physical performance differences among weight change categories, independent of frailty category, weight losers had lower grip and quadriceps strengths at both time points and slower walk speeds than other weight change groups (p < 0.0001). At visit 4 but not visit 2,

			Subperiosteal	Section	Mean cortical
Parameter	BMD	CSA	width	modulus	thickness
Narrow neck region					
FFM	0.162	0.289	0.057	0.297	0.152
Body weight	0.173	0.276	0.034	0.261	0.163
Grip strength	0.024	0.042	0.008	0.045	0.022
Quad strength	0.031	0.045	0.003*	0.046	0.029
Abductor strength	0.036	0.038	NS	0.022	0.035
Shaft region					
FFM	0.182	0.383	0.103	0.464	0.155
Body weight	0.213	0.397	0.070	0.434	0.185
Grip strength	0.021	0.046	0.014	0.058	0.018
Quad strength	0.024	0.049	0.013	0.061	0.020
Abductor strength	0.050	0.065	0.001*	0.043	0.046

TABLE 2. R^2 VALUES FROM UNIVARIATE REGRESSIONS OF BMD AND GEOMETRIC PARAMETERS AT THE NECK AND SHAFT
Region on FFM. Body Weight, and Measured Strengths from the SOF

All measurements were acquired at visit 2. Except as noted, all regressions were significant at the p < 0.0001 level. *p < 0.05.

weight gainers had lower grip strengths (p = 0.05) than those with static weight but their lower quadriceps strength did not reach statistical significance (p = 0.06). Neither walk speeds were significantly slower in weight gainers compared with those with static weight.

BMD and cross-sectional geometry

The average percent changes per year in BMD and crosssectional geometry are displayed in Table 4 for the total population and the weight change subgroups. The differences between time points in the total population were significant by paired *t*-test and on average, changes were relatively greater at the femoral neck than at the shaft. BMD declined in both regions but more rapidly at the neck. In addition, CSA declined and subperiosteal width increased. Despite the decline in CSA at both sites, section modulus increased by approximately 0.2%/year at both neck and shaft. The estimated mean cortical thicknesses declined at both sites and buckling ratio of the femoral neck increased by 1.2%/year.

After changes in BMD and geometry were age-adjusted and divided into weight change and frailty subgroups, differences between groups are evident. Significance levels for the independent effects of weight change and frailty categories from the two-way ANOVA are listed in the last two columns of Table 4. Weight change has a highly significant effect on all parameters except shaft subperiosteal width. The independent effects of the frailty category are significant in the femoral neck for all parameters except CSA and section modulus and in the shaft for all parameters except subperiosteal width.

At both neck and shaft regions, section moduli show significant declines among weight losers, improvements among weight gainers, and small positive changes among those with static weight. Overall, frailty had a negative influence on weight change effects on section moduli, reducing or eliminating positive changes and exacerbating negative changes, although the influence of frailty did not reach significance in the femoral neck (p = 0.09). Among frail weight losers, the section modulus declined more rapidly in the purely cortical shaft than in the neck. Underlying these adaptive changes in section modulus are mass and dimensional changes that differ in pattern between the mixed cortical/trabecular neck and the purely cortical shaft. CSA declined at the neck and shaft in those who lost weight whereas women with static weight had decreased CSA only at the neck. Those who gained weight maintained CSA at the neck and increased CSA at the shaft. Some subperiosteal expansion appears to be nearly universal in this elderly cohort, but the degree of expansion is both greater in magnitude and more variable between groups in the femoral neck than in the shaft. Shaft subperiosteal width increased overall in the population, but rates of change were not detectably influenced by weight change or frailty category. In contrast, femoral neck subperiosteal expansion was influenced by both weight change and frailty. Both weight losers and gainers showed increased rates of femoral neck expansion compared with the static weight group, and this effect was enhanced considerably by the presence of frailty. Among weight losers, the decline in femoral neck BMD was associated with decreased CSA and subperiosteal expansion whereas the decline in shaft BMD was associated with decreased CSA only. When subperiosteal expansion is accompanied by increased CSA, as in the shafts of weight gainers, the change in CSA exceeds that of BMD, indicating that BMD underestimated the gain in bone. The changes among frail weight losers, who show increased rates of both femoral neck bone loss and subperiosteal expansion, lead to a wider, thinner-walled neck. These combined effects produce a 3%/year change in the neck cortical buckling ratio (Fig. 2).

DISCUSSION

The methods used in this longitudinal study permit us to investigate simultaneously conventional BMD as well as

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		Weight	losers	Static	weight	Weight	gainers
		Excluded					
		nonfrail	Frail	Nonfrail	Excluded frail	Nonfrail	Excluded frail
	Total population	(n = 66I)	(n = 105)	(n = 2559)	(n = 219)	(n = 58I)	(n = 63)
Age (years; visit 4)	72.8 ± 4.5	77.4 ± 4.8	79.3 ± 4.9	76.0 ± 4.2	79.1 ± 5.5	74.8 ± 3.9	77.1 ± 5.0
Knee height (cm; visit 1)	49.4 ± 2.4	49.3 ± 2.4	50.3 ± 2.5	49.3 ± 2.3	50.8 ± 2.9	49.3 ± 2.3	50.1 ± 2.6
Height (cm; visit 2)	159.4 ± 5.9	158.7 ± 6.0	159.6 ± 6.7	159.4 ± 5.7	161.4 ± 6.3	159.3 ± 5.9	160.7 ± 6.3
Height (cm; visit 4)	158.3 ± 6.0	157.3 ± 6.2	157.7 ± 7.2	158.4 ± 5.8	160.0 ± 6.5	158.5 ± 6.0	159.6 ± 6.4
Weight (kg; visit 2)	66.8 ± 12.0	67.6 ± 12.6	71.4 ± 13.7	66.1 ± 11.3	71.1 ± 15.8	66.1 ± 11.7	70.7 ± 13.8
Weight (kg; visit 4)	66.5 ± 12.4	61.1 ± 11.2	64.2 ± 12.7	66.1 ± 11.4	70.9 ± 16.0	71.9 ± 12.8	78.2 ± 15.3
BMI (kg/m; visit 2)	26.3 ± 4.4	26.8 ± 4.7	28.0 ± 5.1	26.0 ± 4.2	27.2 ± 5.4	26.0 ± 4.3	27.3 ± 4.9
BMI (kg/m ² ; visit 4)	26.2 ± 4.6	24.2 ± 4.2	25.2 ± 4.7	26.0 ± 4.3	27.1 ± 5.4	28.3 ± 4.7	30.2 ± 5.5
% FFM (visit 2)	60.6 ± 5.8	60.2 ± 5.7	58.3 ± 5.8	60.2 ± 5.7	58.9 ± 6.2	61.1 ± 5.7	58.7 ± 6.3
Abductor strength (visit 2)	11.3 ± 3.2	11.1 ± 3.0	9.9 ± 2.8	11.4 ± 3.0	10.3 ± 3.0	11.5 ± 3.2	10.5 ± 2.9
Quadriceps strength (visit 2)	60.0 ± 25.8	58.8 ± 24.5	50.9 ± 25.6	61.3 ± 24.5	51.0 ± 24.3	61.3 ± 25.0	51.0 ± 21.8
Quadriceps strength (visit 4)	58.9 ± 24.2	57.9 ± 21.7	45.2 ± 21.2	60.1 ± 22.5	50.9 ± 22.8	60.1 ± 23.5	37.8 ± 15.8
Grip strength (visit 2)	19.0 ± 4.6	18.7 ± 4.4	17.7 ± 4.6	19.4 ± 4.3	18.0 ± 4.5	19.5 ± 4.4	17.7 ± 4.5
Grip strength (visit 4)	18.2 ± 4.0	17.8 ± 3.5	15.8 ± 4.1	18.5 ± 3.7	17.1 ± 3.8	18.3 ± 3.7	16.8 ± 3.4
Normal gait speed, (m/s; visit 4)	0.95 ± 0.21	0.94 ± 0.18	0.75 ± 0.23	0.99 ± 0.18	0.80 ± 0.20	0.97 ± 0.18	0.807 ± 0.203
Fast walking speed (m/s; visit 4)	1.25 ± 0.30	1.24 ± 0.26	1.02 ± 0.39	1.29 ± 0.238	1.04 ± 0.31	1.29 ± 0.23	1.02 ± 0.236
% Who walk for exercise (visit 4)	50.4%	45.4%	26.7%	54.9%	26.9%	51.7%	36.5%

Main comparison subgroups were (1) reduced skeletal loading—frail weight losers, (2) unchanged skeletal loading—nonfrail static weight subgroup, and (3) increased skeletal loading—nonfrail weight gainers. Data for subgroups in main comparison are in bold text. Measurements of physical condition and functional ability also are included. Gait speeds and strength measures in subgroups were adjusted for age, knee height, and weight. BMI, body mass index.

		Weight	losers*	Static N	veight*	Weight a	gainers*	Significan	ce of effect
Parameter	Total population	Excluded nonfrail	Frail	Nonfrail	Excluded frail	Nonfrail	Excluded frail	Weight change	Frailty
Narrow neck region									
BMD	-0.69%	-1.18%	-1.84%	-0.56%	-0.93%	-0.37%	-0.82%	< 0.0001	< 0.0001
CSA	-0.44%	-0.96%	-1.14%	-0.36%	-0.59%	(-0.05%)	(-0.19%)	< 0.0001	(0.11)
Subperiosteal width	0.28%	0.25%	0.77%	0.23%	0.37%	0.36%	0.72%	0.0033	< 0.0001
Section modulus	0.19%	-0.40%	-0.69%	0.32%	(0.05%)	0.56%	(0.39%)	< 0.0001	(60.0)
Est. mean cortical thickness	-0.74%	-1.25%	-1.96%	-0.60%	-1.00%	-0.40%	-0.87%	< 0.0001	< 0.0001
Mean cortical buckling ratio	1.20%	1.76%	3.21%	1.01%	1.70%	0.98%	2.07%	< 0.0001	< 0.0001
Shaft region									
BMD	-0.19%	-1.05%	-1.56%	(0.00)	-0.26%	0.57%	(0.50%)	< 0.0001	0.024
CSA	-0.11%	-1.02%	-1.55%	(-0.02%)	(-0.16%)	0.76%	0.61%	< 0.0001	0.012
Subperiosteal width	0.09%	(0.05%)	(0.02%)	0.09%	0.12%	0.20%	(0.13%)	(0.16)	(0.66)
Section modulus	0.16%	-0.63%	-1.17%	0.25%	(0.01%)	0.96%	(0.58%)	< 0.0001	0.0021
Est. mean cortical thickness	-0.18%	-1.15%	-1.75%	(-0.08%)	-0.27%	0.68%	(0.65%)	< 0.0001	0.04

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FIG. 2. Pictorial representation (not to scale) of geometric and mass changes observed in the main skeletal loading comparison groups at the neck and shaft regions. Unchanged and increased loading groups are those with unchanged or increasing weight between study visits, after excluding those categorized as frail. The loading decrease group includes only frail weight losers (see text). Corresponding rates of change per year in these parameters are summarized below the representation.

engineering properties dependent on the shape and size of the bone cross-section. In this article we are concerned primarily with how hip bone mass and structural geometry adapt to changes in skeletal loading over time and whether that adaptation provides insight into the onset of hip fragility. Although weight change effects alone were highly significant, the clearest picture is seen by looking at the three subgroups in which loading changes are least ambiguous, that is, those with static or increasing weight who did not become frail, and those who lost weight and were classified as frail. These groups best represented subjects with unchanged, increasing, and decreasing skeletal loads, respectively. The observed changes for these subgroups are shown pictorially in Fig. 2, for the neck and shaft regions, with the corresponding annual changes in BMD and geometry listed below the representation. The results are consistent with our hypotheses; changes in hip loading are associated with mechanically appropriate alteration in the section modulus, an index of bending and torsional strength. However, the details of how that adaptation is achieved differ in important ways between the purely cortical shaft and the mixed cortical/trabecular neck. These differences help to explain why BMD changes as it does with age and why reduced loading might be more likely to cause fragility in the femoral neck than in the shaft.

Why section modulus and not BMD?

It is not surprising that adaptation to changing load should be evident in the section modulus. Normal physical activities load long bones mainly in bending and torsion,^(6,25) modes that produce mechanical stresses that peak on the subperiosteal surface. At any given bending or torsional load, peak stress magnitudes are related inversely to the section modulus. To maintain long bone strength over time, adaptation should ensure that maximum stresses do not exceed certain levels, thus should be evident in the section modulus. Indeed, despite declines in BMD, those with constant skeletal loads (Fig. 2) not only maintained section moduli at the neck and shaft but also showed slight increases. Among those with increasing skeletal loads, we observed greater increases in section moduli, consistent with their increased skeletal loads. Most importantly, for implications in hip fragility, those with decreasing skeletal load showed significant reductions in section moduli. A generalized implication of these results is that section moduli represent an endpoint in mechanical homeostasis in long bones. That is, as aging progresses, bone modeling and remodeling processes adjust the geometry to increase or decrease the section modulus as demands of skeletal loading change. However, because in aging long bones the bending strength represented by a given amount of mass or density changes as the bone expands, one should not expect homeostasis in BMD or BMC. That mass or density should not necessarily be conserved differs from the concept of mechanical homeostasis described by Kimmel,⁽²⁶⁾ but the end result is theoretically consistent.⁽²⁶⁾

Theoretical support

The underlying mechanism for skeletal adaptation was articulated in Frost's mechanostat theory.⁽⁸⁾ Although the precise details of the process are incompletely understood,

bone tissue is believed to respond to daily variations in the microscopic distortions (strains) caused by loading forces. The mechanostat operates to maintain skeletal strains between certain optimal limits. When average skeletal strains fall consistently below the lower limit, bone remodeling rates increase so that net loss continues until average strains increase back into the optimal range. Strains exceeding the upper limit cause bone formation (modeling); bone is added until strains are reduced to the optimal range. In a long bone under bending and torsional load, strains are lowest on internal surfaces near the center of mass and increase radially outward through the cross-section peaking on the subperiosteal surface. Remodeling occurs mainly on the endosteal and trabecular surfaces⁽²⁷⁾ where bending and torsional strains are smallest; modeling occurs mainly on the subperiosteal surface where those strains are highest. Increased loading should therefore stimulate modeling in the form of subperiosteal expansion and/or down-regulate turnover on endocortical and trabecular surfaces. Diminished loading should reduce strains on internal endosteal and trabecular surfaces, up-regulating remodeling rates. Superimposed on this adaptation to changing loading conditions are the effects of normal remodeling on endocortical and trabecular surfaces.

Van der Meulen and colleagues^(28,29) provided a theoretical model of a long bone that illustrates response to remodeling turnover during normal aging as well as to altered skeletal loading. Predictions of this theoretical model generally are consistent with the overall patterns of geometric change we observed in this study. The loss phase of normal bone turnover causes a temporary reduction of (endocortical) bone mass; continued mechanical loading causes skeletal strains to increase, not at the site of loss, but on the subperiosteal surface. With constant loading levels through adulthood, the model predicted gradual increases in endocortical diameter as bone is lost and a competing increase in subperiosteal diameter as bone is added.⁽³⁰⁾ This pattern caused a slight upward trend in the section modulus with age consistent with our observations in those with unchanged skeletal loading (Fig. 2). Although not discussed by these authors, $^{(28-30)}$ the aforementioned changes produce a downward trend in BMD that we observed in this study. Because the bending strength contribution of bone mass varies as the square of its distance from the center of mass of the cross-section, less subperiosteal gain is needed to compensate for a given endosteal loss. Strength is maintained or increased in the presence of net loss of bone mass (and density) because the bone gets bigger in diameter.

Differences in adaptation between neck and shaft

There were differences in the details of section modulus adaptation between the neck and shaft (Fig. 2). Unchanged loading produced comparable increases in neck and shaft section moduli. But in the purely cortical shaft, this was accomplished by a slight increase in subperiosteal width; changes in the amount of bone (CSA), cortical thickness, or in BMD were nonsignificant. In the femoral neck, the section modulus was adjusted by expanding subperiosteal width at twice the rate of that in the shaft. This was accompanied by net bone loss and cortical thinning. Reduction in femoral neck BMD in this case was caused by both bone loss and subperiosteal expansion.

When skeletal loads were altered, differences in adaptation response between the neck and shaft were even more remarkable. With increased loads, the amount of bone remained the same at the femoral neck and increased at the shaft. However, because of subperiosteal expansion, BMD changed at both sites, decreasing at the neck and increasing in the shaft. The effects of decreasing loads may be particularly important in helping to explain the relatively greater femoral neck fragility in the frail elderly. In the shaft, reduced loading mainly increased endosteal bone loss with no accompanying subperiosteal expansion. This contrasts with the femoral neck, where declining skeletal loads apparently accelerate both endosteal bone loss and subperiosteal bone formation. This latter observation implies that in the elderly femoral neck, stimulatory subperiosteal strains are actually increased under reduced skeletal loads. This apparent paradox may be ultimately consistent with the mechanostat and is important in explaining why bone loss is more likely to cause fragility at the neck than at the shaft. In the femoral neck, reduced loading should stimulate accelerated resorption on both endocortical and trabecular surfaces. An important function of femoral neck trabeculae is to brace the thin cortical shell from within, but as trabeculae thin and lose connectivity, it is likely that this internal cortical support is compromised. Loss of trabecular support may in turn cause increased subperiosteal strains and subperiosteal bone apposition, even under diminished loads. There are alternative explanations to these observed changes in the femoral neck; much work remains to be done to model these processes to determine if they are theoretically viable.

Toward femoral neck fragility

As skeletal loading demands diminish in the elderly, the mechanostat calls for a reduction in the section modulus. Theoretically, this adaptation in a tubular bone could occur by either contraction of the outer diameter or expansion of the inner diameter. However, as far as we know, the former process requiring subperiosteal resorption does not accompany normal aging.⁽³¹⁾ The unidirectional expansion of long bones through adult life leaves the elderly with larger diameter, but thinner-walled bones. A small loss of bone mass may lead to a greater increment in bone fragility than in a younger, narrower, and thicker-walled bone. We further suspect that the way that the femoral neck adapts to reduced loading, for example, by causing a wider, thinner-walled bone, may generate a dimensionally unstable condition and may be responsible for its relatively greater fragility in the elderly. When thick-walled tubes are bent to failure, they crack from the outer curvature of bending (e.g., break a pencil in your hands). However, when tubes with thin walls relative to their diameters are subjected to bending, they tend to fail by local buckling (crumpling inward on the inner curvature like a bent soda straw). The importance of this distinction is that failure of the thick-walled tube is predicted by the section modulus. However, in the thin-walled tube, the section modulus would overestimate the load required to cause failure by local buckling. Whether local buckling is at all likely in a femoral neck internally supported by trabecular bone is the subject of a separate theoretical investigation. However, it is worth noting that the buckling ratio changed at a greater rate than any other parameter in the SOF population overall and increased fastest among those with decreased loads.

Subperiosteal expansion

For many years it has been believed that because the femoral neck lacks a true periosteum, it should not be subject to expansion in adulthood.⁽³²⁾ There has been ample evidence, mostly cross-sectional, that femoral shaft diameters increase with age.^(7,33-39) Some evidence shows expansion of the femoral neck,^(7,36,40,41) though this is mostly based on low-resolution imaging methods. A noteworthy exception is the article by Heaney and colleagues who used serial radiographs on 170 middle-aged white women to show average subperiosteal expansions of 0.14%/year and 0.23%/year at the femoral neck and shaft, respectively.⁽⁴²⁾ In this article subperiosteal expansion averaged 0.28%/year at the neck and 0.09%/year in the shaft in a much larger but considerably older postmenopausal cohort. This is double the rate of expansion observed by Heaney in the neck and one-half the rate he observed in the shaft. Perhaps rates of femoral neck subperiosteal expansion increase in the elderly. Our data do show a weak but significant increase in the rates of subperiosteal expansion at the neck with age (R = 0.05; p = 0.002), not apparent in the shaft. Results from the cross-sectional NHANES study⁽⁷⁾ suggest that this might be true in women but this should be verified in longitudinal data including younger individuals.

Body weight and skeletal load

Although it is believed that muscle force dominates skeletal adaptation,^(6,43) the observable changes in skeletal dynamics occur over long timescales presumably from the cumulative influence of daily strains generated from normal activities. In this article we have looked at weight change as the primary index of changing skeletal load but weight per se cannot represent a mechanical stimulus because bone is not known to respond to static loads.^(44,45) Certainly the effect of weight change is in the magnitudes of the dynamic muscle loads on the skeleton required to move the body in normal activities. The stimulatory influence of the resulting dynamic strains is also a function of strain frequency, for example, the activity level of the individual-not captured by weight change. Because changes in activity level appear more quickly in muscle, an examination of the effects of changes in muscle mass by DXA or bioelectric impedence may provide a more accurate assessment of the effects of changing skeletal load on bone. The relatively strong correlation between FFM and section modulus (Table 2) suggests that this might be the case.

Limitations of this work

There are reports that show that change in body composition may cause systematic error in DXA-measured parameters with Hologic scanners.⁽⁴⁶⁻⁴⁸⁾ Our algorithms differ somewhat from those of Hologic, particularly in bone margin definition. We have yet to analyze systematically these error sources with our methods, but the error observed by Tothill⁽⁴⁷⁾ of an increase in bone area with increasing BMC should cause an equivalent increase in subperiosteal width with CSA in our methods. A univariate regression of subperiosteal width on CSA yielded a positive correlation with a slope of 0.11 although the regression explained only 2.4% (R^2) of the variability in bone width. After correcting these parameters for age and body size the slope was reduced to 0.048 and R^2 was reduced to 0.3%, suggesting little effect other than that caused by body (bone) size. The multiple linear regression of femoral neck section modulus on FFM and fat mass was significant (p < 0.0001) for both parameters with positive β -coefficients of 0.025 for FFM and 0.002 for fat mass. The addition of fat mass to the model only improved the R^2 from 0.297 to 0.300, suggesting that the additive influence of body composition on femoral neck section modulus is small.

There also are methodological limitations to use of twodimensional DXA data to measure bone geometry; no commercial DXA scanner was designed with this purpose in mind. Clearly, there are problems in the measurement of subtle dimensional changes on three-dimensional bones from relatively poor quality DXA images. The assumption used to estimate cortical thickness in the femoral neck, that 60% of the mass is in the cortex, is obviously an approximation. There is evidence of disproportionate loss of neck cortical bone in hip fracture cases; hence, our neck cortical dimensions may be overestimated.^(49,50) It is critical that these dimensional observations be corroborated by others using higher-resolution imaging methods in longitudinal study.

In this longitudinal study on the effects of changing skeletal load on hip BMD and geometry in elderly women, the hip appears to adapt by adjusting the section modulus, an engineering index of bending strength, to the new loading conditions. This suggests that mechanical homeostasis is achieved with respect to bending strength. A feature of the adaptation is subperiosteal expansion at both the neck and the shaft. One consequence of subperiosteal expansion is that it will reduce BMD; any observed change in BMD in a long bone may or may not reflect bone loss. The adaptation to reduced loading conditions results in reduction in the section modulus. But in the femoral neck, adaptation accelerated both rates of cortical thinning and subperiosteal expansion, resulting in a broader but thinner-walled (lowdensity) femoral neck. This condition may be dimensionally unstable, causing a greater increase in fragility than apparent in the reduced section modulus.

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