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Construction of the Femoral Neck During Growth Determines Its Strength in Old Age

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ABSTRACT: Study of the design of the FN in vivo in 697 women and in vitro in 200 cross-sections of different sizes and shapes along each of 13 FN specimens revealed that strength in old age was largely achieved during growth by differences in the distribution rather than the amount of bone material in a given FN cross-section from individual to individual.

Introduction: We studied the design of the femoral neck (FN) to gain insight into the structural basis of FN strength in adulthood and FN fragility in old age.
Materials and Methods: Studies in vivo were performed using densitometry in 697 women and in vitro using high-resolution μCT and direct measurements in 13 pairs of postmortem specimens.
Results: The contradictory needs of strength for loading yet lightness for mobility were met by varying FN size, shape, spatial distribution, and proportions of its trabecular and cortical bone in a cross-section, not its mass. Wider and narrower FNs were constructed with similar amounts of bone material. Wider FNs were relatively lighter: a 1 SD higher FN volume had a 0.67 (95% CI, 0.61–0.72) SD lower volumetric BMD (vBMD). A 1 SD increment in height was achieved by increasing FN volume by 0.32 (95% CI, 0.25–0.39) SD with only 0.15 (95% CI, 0.08–0.22) SD more bone, so taller individuals had a relatively lighter FN (vBMD was 0.13 [95% CI, 0.05–0.20 SD] SD lower). Greater periosteal apposition constructing a wider FN was offset by even greater endocortical resorption so that the same net amount of bone was distributed as a thinner cortex further from the neutral axis, increasing resistance to bending and lowering vBMD. This was recapitulated at each point along the FN; varying absolute and relative degrees of periosteal apposition and endocortical resorption focally used the same amount of material to fashion an elliptical FN of mainly cortical bone near the femoral shaft to offset bending but a more circular FN of proportionally more trabecular and less cortical bone to accommodate compressive loads adjacent to the pelvis. This structural heterogeneity was largely achieved by adaptive modeling and remodeling during growth—most of the variance in FN volume, BMC, and vBMD was growth related.
Conclusions: Altering structural design while minimizing mass achieves FN strength and lightness. Bone fragility may be the result of failure to adapt bone's architecture to loading, not just low bone mass.
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Key words: femoral neck, architecture, external size, mineralized bone mass, volumetric density

INTRODUCTION

LONG BONES ARE levers. They must be strong and able to resist bending to accommodate loading, yet light enough to facilitate movement.[1] On average, taller individuals have longer and wider bones so it is intuitive that the construction of wider bones requires more material. However, more material increases bulk. Bulk takes time to grow, is costly to maintain and retards mobility. On average, shorter individuals have narrower bones, so it is intuitive that their construction requires less material. However, narrower bones, if constructed with less material, tolerate less loading.

Although greater stature requires more mass, greater width may not; a way of minimizing the amount of material needed in a cross-section without incurring the cost of more material, and smaller stature without paying the price of greater fragility, is to assemble wider and narrower bones using similar amounts of material distributed differently in space. For example, a sheet of paper of a given mass can be assembled into a wider or narrower cylinder depending on how tightly it is rolled. The same principle may apply to the construction of a tubular bone like the femoral neck (FN).

During growth, periosteal apposition increases the diameter of the FN, whereas concurrent endocortical resorption excavates a marrow cavity shifting the cortex further from the neutral axis.[2] This outward displacement of the cortex

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increases bending strength because resistance to bending is proportional to the fourth power of the distance from the neutral axis.[1,3] Thus, modifying the spatial distribution of similar amounts of material achieves strength by using the biomechanical advantage conferred by the spatial distribution of the material and achieves lightness by minimizing the amount of material needed to assemble the FN cross-section.[1]

The results presented here suggest that the contradictory needs of strength for load bearing and lightness for mobility are met by adaptive modeling and remodeling on bones' outer and inner envelopes throughout life, but mainly during growth. Differing absolute and relative degrees of periosteal apposition and endocortical resorption fashion the similar amount of bone achieving strength yet lightness by varying size, shape, proportions, and spatial distribution of cortical and trabecular bone, not total mass in a cross-section. FN fragility may be the result of failed structural adaptation to loading not just low bone mass.

MATERIALS AND METHODS

We studied 697 healthy Lebanese women between 20 and 87 yr of age without fractures, illnesses, or drug therapy that affect bone. They were recruited randomly from all parts of Lebanon by advertisements and from Red Cross and health organizations. The study was approved by the Lebanese Osteoporosis Prevention Society Ethics Committee. FN BMC and bone scan areas were measured using a GE Lunar Expert-XL densitometer (Madison, WI, USA). Precision error was 2%. Volumetric BMD (vBMD) at the FN was estimated as BMC divided by the external volume of the region, assuming that the FN is elliptical, which is a more accurate estimate of FN volume and vBMD than the circular model.[4]

Associations between bone size and BMC, and bone size and vBMD were adjusted for age, height, and weight. Relationships of height versus vBMD, bone size, and BMC were adjusted for age and weight. Relationships of weight versus vBMD, bone size, and BMC were adjusted for age and height. Associations between height, weight, and FN volume and BMC and vBMD were examined using regression analysis. The 95% CI of the slope of the fitted regression was calculated for each curve.

In vitro studies were carried out using 26 postmortem specimens (right and left proximal femurs) from 13 white women (mean age, 69 yr; range, 29–85 yr) who died of illnesses unrelated to bone disease. All specimens were stored at –20°C. FN external volume was measured by submersion. The volume of the femoral head and then the femoral head and FN to the intertrochanteric line was determined by water displacement. FN volume was calculated by subtraction. Four measurements were made per sample (CV = 9%).[4] BMC was measured using the Lunar Prodigy densitometer with the specimens submerged in 10 cm 0.9% saline and internally rotated by 15° (CV = 2–4%). Submersion in water simulates the clinical situation used to derive bone mass.[5] FN vBMD was calculated as the FN BMC divided by volume. vBMD is an apparent volumetric density, a measure of the amount of mineralized bone in the whole FN volume including the marrow.[6]

Table 1. Age, Height, Weight, FN Width, FN Volume, FN BMC, and FN vBMD of the Study Population

	Mean ± SD	*Range*	*CV**
Age (yr)	59.0 ± 10.4	20–87	17.4%
Height (cm)	154.4 ± 6.6	135–177	4.2%
Weight (kg)	67.1 ± 11.9	37–110	15.6%
FN volume (ml)	12.4 ± 1.84	7.5–18.5	15%
FN width (cm)	3.23 ± 0.24	2.52–3.96	7.4%
FN BMC (g)	3.74 ± 0.6	2.0–6.2	16%
FN vBMD (g/cm^3)	0.31 ± 0.06	0.15–0.59	19.3%

* The CV, range divided by the mean, reflects the dispersion of the data around the mean.

The spatial distribution of cortical and trabecular bone was quantified in 13 left FN specimens using high-resolution μQCT. The 3D tomographic images at a scale of 1024^3 with a 63-μm voxel size were generated and image processing separated cortical and trabecular bone using an erosion/dilation algorithm.[7] Two hundred slices along the FN from the neck-shaft junction to the FN head were obtained for each specimen. For each slice, the total cross-sectional area (CSA) was the area defined by the periosteal envelope. The shape of the cross-section was quantified as the percentage of the area of the smallest circle that contains the total FN CSA (percent circularity).[4] This approach accounts for all diameters around the cross-section. Differences in these structural elements along the FN were presented graphically using only 20 of the 200 slices for clarity (every 5% distance along the FN). Statistical significance was set at the 5% level (two-tailed).

RESULTS

Age, height, weight, FN volume, BMC, and vBMD varied greatly in the 697 pre- and postmenopausal women (Table 1). The wide scatter of values around their age-specific means was already present in young adulthood (Fig. 1, left, arrows). In a model including age, height, and weight, age accounted for only 2%, 23%, and 15% of the variances in FN volume, BMC, and vBMD, respectively (Fig. 1, right), so the position (percentile) of an individual's trait in the population largely originated during growth.

The data in vivo and in vitro for the 26 whole FN specimens showed that an individual's FN volume and BMC were not in the same percentile in their respective trait distribution—a larger or smaller FN volume was not associated with a correspondingly larger or smaller BMC; these two traits were independent (Fig. 2, top), so that a larger FN volume was constructed with relatively less bone—a 1 SD larger FN volume had a 0.67 (95% CI, 0.61–0.72) SD lower vBMD (Fig. 2, bottom). A 1 SD increment in height was associated with a 0.32 (95% CI, 0.25–0.39) SD increment in FN volume but only a 0.15 (95% CI, 0.08–0.22) SD increment in BMC; a 1 SD taller person had a 0.13 SD (95% CI, 0.05–0.20) lower FN vBMD: a wider FN in a taller individual was constructed with relatively less bone,

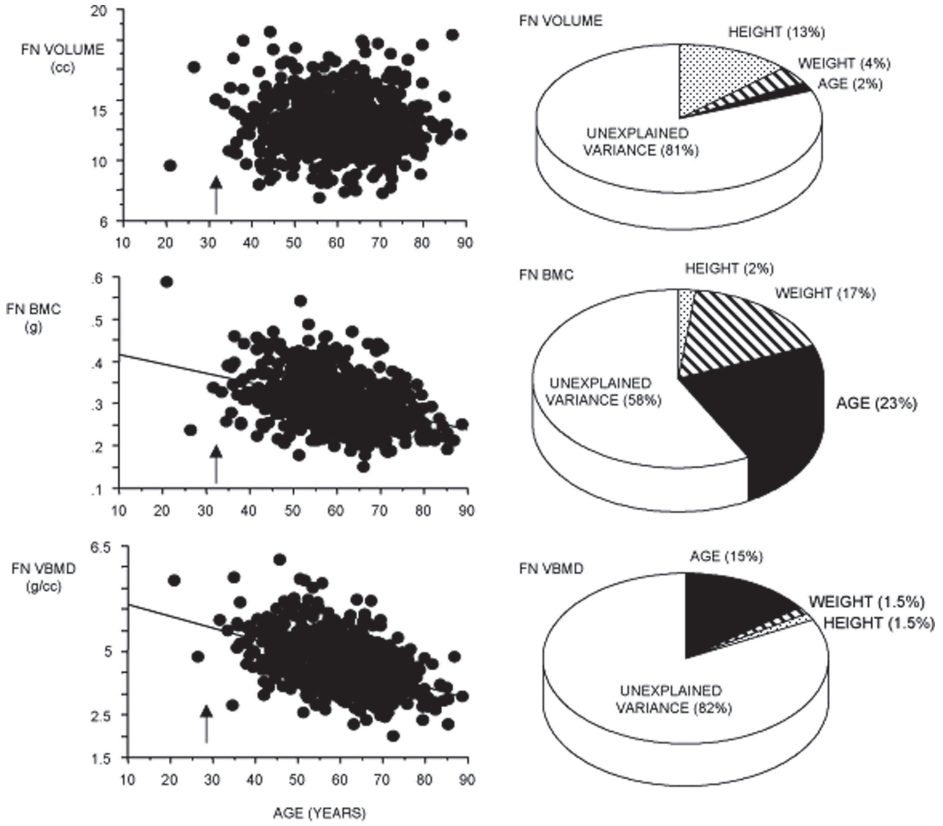

FIG. 1. (Left) Variance (scatter) in FN volume, BMC, and vBMD was established in young adulthood (arrows). (Right) Age, height, and weight explained little of the variance in each trait.

whereas a narrow FN was constructed with relatively more bone (Fig. 2, right).

In contrast, a 1 SD increment in weight was associated with a 0.20 (95% CI, 0.12–0.27) SD increment in FN volume but a 0.36 (95% CI, 0.29–0.43) SD increment in BMC, so that a 1 SD heavier person had a 0.15 (95% CI, 0.07–0.22) SD higher FN vBMD. Heavier individuals had a wider FN built with relatively more bone. Because height and weight had opposite effects of similar magnitude, BMI and vBMD were independent ($r = 0.06$, not significant). A 1 SD increment in BMI was associated with a 0.11 (95% CI, 0.04–0.19) SD increment FN volume and a 0.18 (95% CI, 0.11–0.25) SD increment in BMC, so that an individual with a higher BMI did not have a higher or a lower vBMD.

On average, women with higher bone mass and a wider FN were younger, taller, and heavier (Table 2). As shown in Fig. 3, having FN volume in the highest tertile did not increase the likelihood of having a high BMC; over one half of those in the upper tertile for FN volume had BMC in the lower or middle tertile. Likewise, not all subjects having FN volume in the lowest tertile had BMC in the lowest tertile; >50% had BMC in the middle or highest tertile. Thus, variance in FN vBMD was the result of varying combinations of both FN volume and BMC. FN volume accounted for 43% and BMC accounted for only 33% of variance in vBMD. Of this 33% variance in vBMD accounted for by BMC, 83% was growth related, whereas 17% was age related (Fig. 3, right). Twenty-four percent of variance in vBMD was unexplained. Of the 76% explained variance in vBMD, 90% was attributable to growth-related events: differences in FN volume and BMC attained during growth. Only 10% was the result of differences in the net diminution in BMC during aging.

The independence of FN volume and BMC was recapitulated in each of 200 slices along each of 13 FN specimens. Total FN CSA and medullary area varied along a FN, but total bone area in each slice was similar (Fig. 4). The area that was bone material was independent of the total FN CSA (bone plus medullary void): a larger total CSA was constructed with a similar amount of bone but more medullary void; thus, the percentage of the total FN CSA occupied by bone was less in a wider than narrower FN cross-section. The way the similar amount of bone was distributed differed in each slice along the FN. Near the shaft, the bone was largely cortical, and the thickness varied most at each point around the FN perimeter, being greatest inferiorly (Fig. 4A). Moving proximally toward the femoral head, the FN became increasingly circular, proportionally less cortical and more trabecular (Fig. 4B). At the FN-femoral head junction, bone was largely trabecular, and the cortical thicknesses around the perimeter varied least (Fig. 4C). Thus, the FN did not have a single periosteal or medullary diameter or cortical thickness.

DISCUSSION

Wider bones were not necessarily made with more bone, and narrower bones were not made with less. Similar

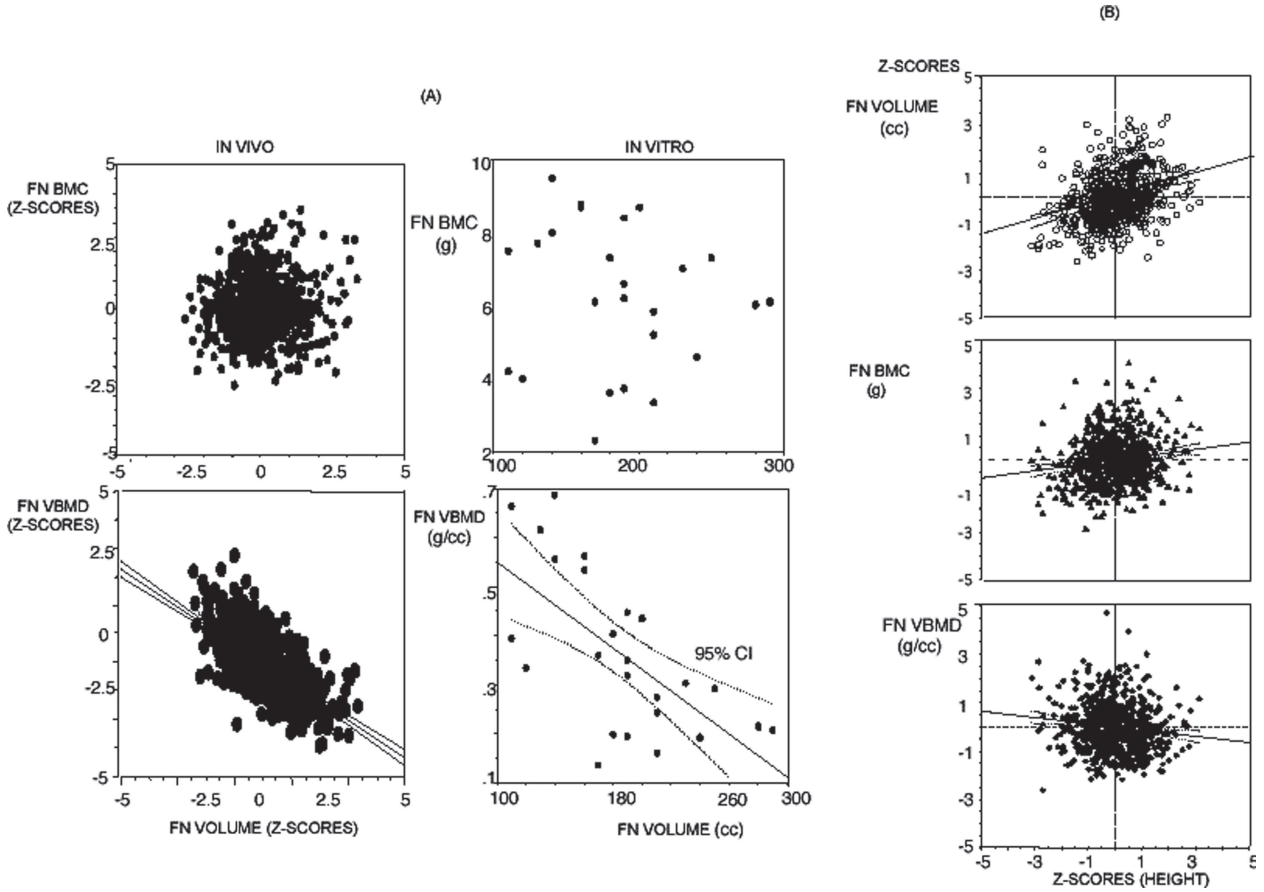

FIG. 2. (A) In vivo and in vitro, FN volume and BMC were independent, so the larger the FN, the lower the vBMD. (B) Increasing height was associated with higher FN volume and BMC and lower vBMD.

TABLE 2. AGE, HEIGHT, AND WEIGHT (MEANS ± SE) OF WOMEN ACCORDING TO TERTILES OF FN VOLUME AND FN BMC

	Tertiles of FN volume and BMC		
	Lower	*Middle*	*Upper*
Age	65.5 ± 0.60	59.3 ± 0.57	54.4 ± 0.65
Height	147.3 ± 0.23	154.4 ± 0.10	161.5 ± 0.65
Weight	63.9 ± 0.75	67.4 ± 0.75	69.9 ± 0.78

amounts of bone were used to construct the FN wider and narrower cross-sections. Wider bones contained relatively less bone so they had a lower vBMD. Narrower bones contained relatively more bone so they had a higher vBMD. Taller individuals achieved greater FN size by sacrificing vBMD; shorter individuals achieved strength by assembling their narrower FN with a higher vBMD.

These observations in vivo were verified in vitro in 26 whole FN specimens using densitometry: wider and narrower FNs were constructed with similar amounts of material. Therefore, wider bones had lower vBMD, and narrower bones had higher vBMD. This was recapitulated along the length of each of 13 FN specimens using μCT: larger and smaller total FN cross-sections were constructed with similar amounts of material distributed in different proportions of cortical and trabecular bone. When the total FN cross-section was larger, the material was distributed as a relatively thinner cortex using more empty (medullary) space. Near the femoral shaft, the bone was largely cortical, and near the femoral head, it was largely trabecular and proportionally less cortical.

These data suggested that modification of the spatial distribution of a similar amount of bone to construct wider and narrower bones in taller and shorter individuals serves the contradictory survival needs of strength for loading and lightness for mobility. The need for more material to build wider bones was averted by the greater resistance to bending produced by displacement of the relatively thinner cortex from the neutral axis.[1,3,8] In narrower bones, the greater liability to bend is averted using a relatively thicker cortex.

The amount of material needed to build wider and narrower bones is minimized by varying the absolute and relative amounts of periosteal apposition and endocortical resorption. For a wider bone to have the same cortical area as a narrower bone, it must have a thinner cortex distributed around its larger perimeter. This is the result of greater endocortical resorption relative to its periosteal apposition, so the larger bone is more "empty," and it has a lower vBMD. Likewise, a narrower bone results from less peri-

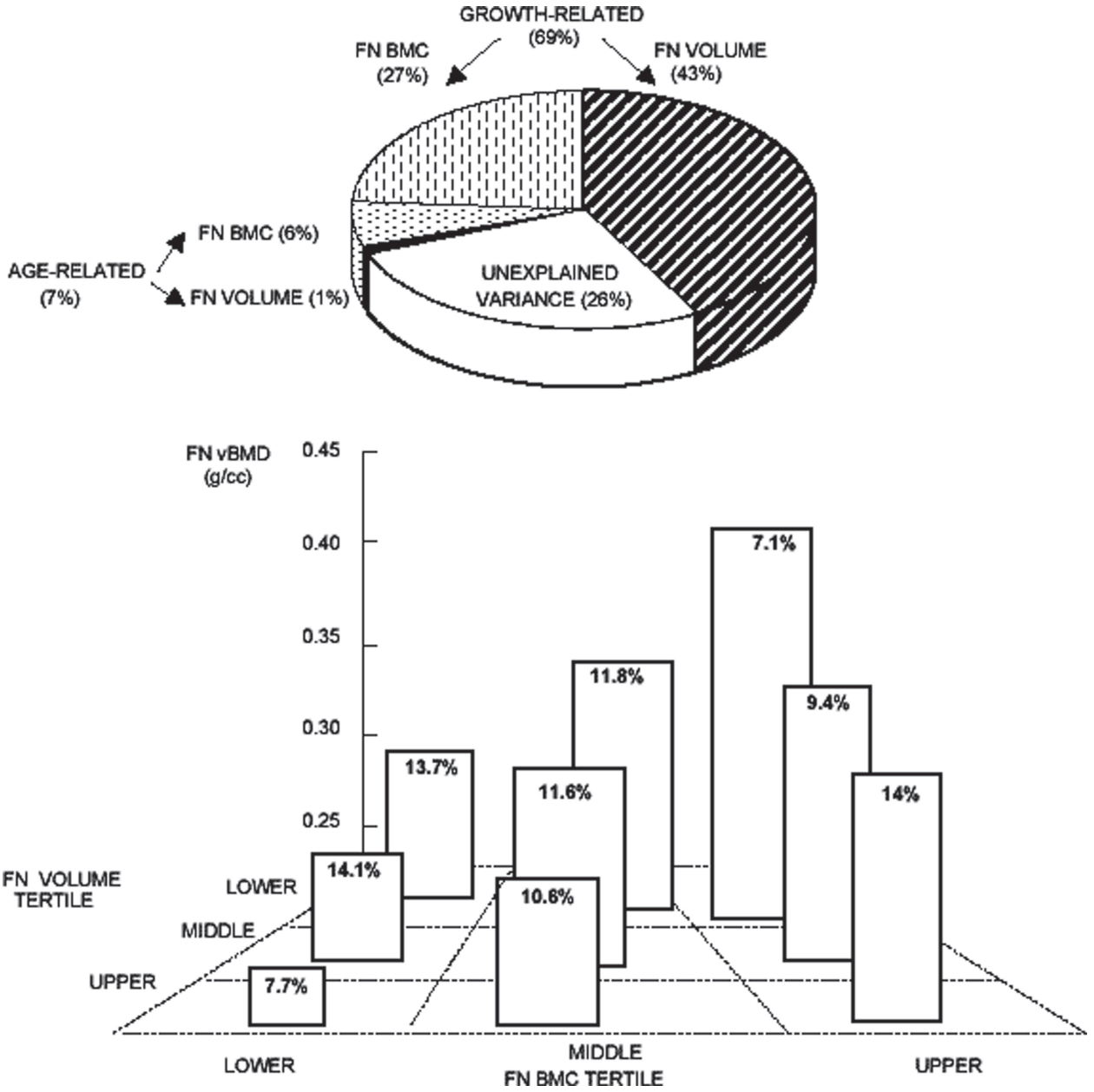

FIG. 3. (Top) Total variance in FN vBMD explained by growth-related and age-related differences in FN volume and BMC. Variances in these traits during growth contribute 69% (27% BMC, 42% FN volume), whereas variances in these traits during aging contribute only 7% (6% BMC, 1% FN volume). The remaining 26% of vBMD variance was unexplained. (Bottom) vBMD in the population is constituted by different proportions of FN volume and mass. Most individuals with low vBMD do not have low BMC; on the contrary, >50% have either normal or high BMC.

osteal apposition, but even less endocortical resorption, to build the thicker cortex and higher vBMD.

The same principle applies along an FN as well as from FN to FN—strength is optimized, and bulk is minimized by adaptive periosteal and endocortical modeling and remodeling at each point around the FN and along it. Varying the absolute and relative extent of focal modeling and remodeling on these surfaces alters the external size, shape, cortical thicknesses, and trabecular architecture without net gain or loss of bone material. Tubular bones are not drinking straws with the same dimensions throughout. There is no single periosteal or medullary diameter or cortical thickness; mean values obscure the biological variance seen in these dimensions that reflects the diversity of shapes produced by the adaptive modeling and remodeling responsible for the strength of a single bone.

For example, it is likely that, adjacent to the femoral shaft, greater bending or compressive stresses from the trunk increase FN periosteal apposition, inferiorly producing an elliptical FN and a thicker cortex to buttress stress at this point. These contours of bone are not found in individuals immobilized because of neurological disease in

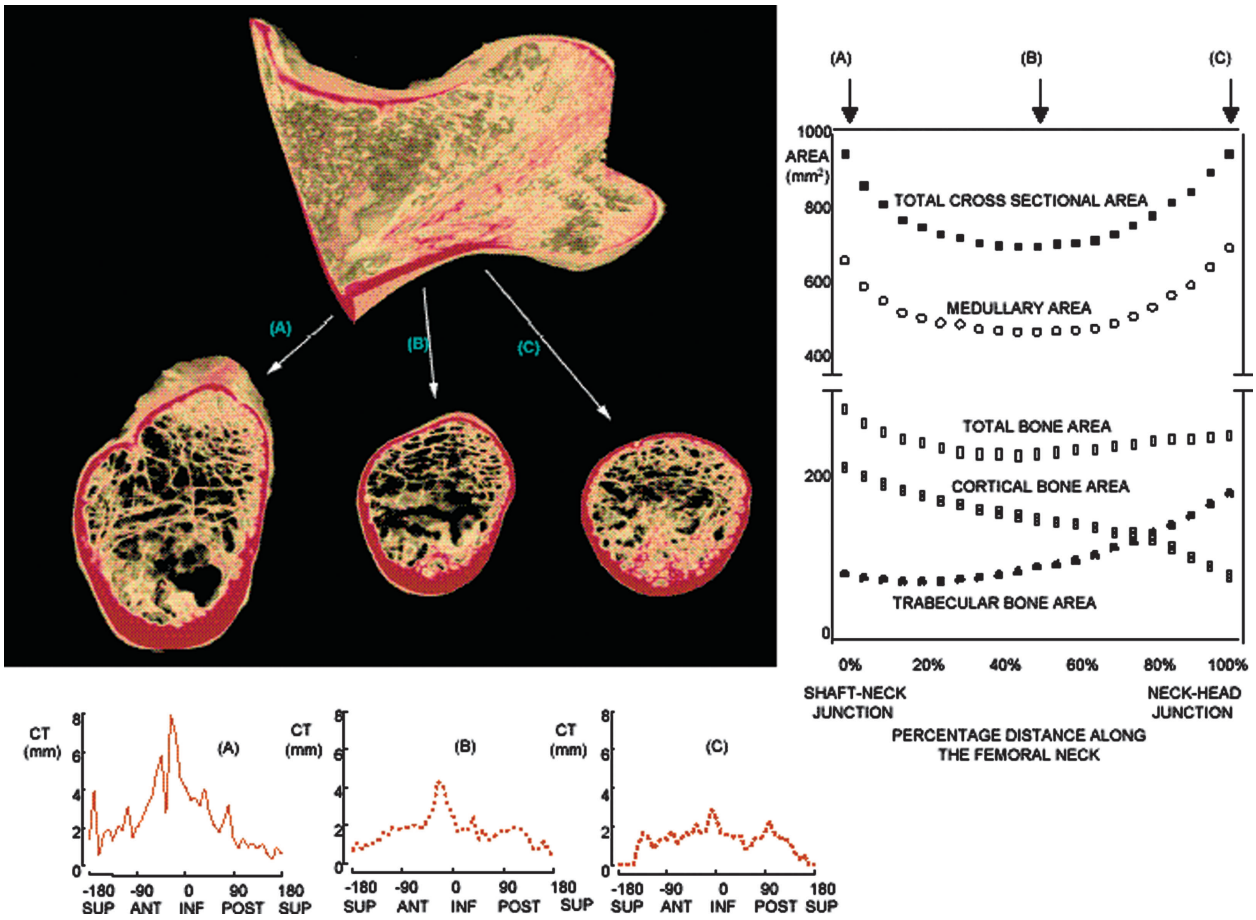

FIG. 4. A left FN section measured using μCT scanning is shown with three cross-sections along the FN (A) neck-shaft junction, (B) midfemoral neck, and (C) neck-head junction. Variability in the cross sectional shape is apparent with ellipticity and a thicker cortex inferiorly in A, with increasing circularity and a greater proportion of trabecular than cortical bone near the femoral head. The right panel shows the changes in total cross-sectional area, medullary and total cortical and trabecular bone areas from the neck-shaft junction to the neck-head junction. Total bone area remained similar along the FN, although size, shape, cortical, and trabecular bone areas differ. CT, cortical thickness; sup, ant, inf, post, superior, anterior, inferior, and posterior, respectively.

growth. Adjacent to the femoral head, adaptation to compressive stresses may produce a more circular FN with largely trabecular bone with a thin cortex varying little around the perimeter. The reciprocal relationship between cortical and trabecular bone along the FN is likely to be a way of distributing stresses—more trabecular bone when stresses are predominantly compressive or shear and more cortical bone when stresses are largely bending. However, in addition to these reciprocal changes in the proportion of cortical and trabecular bone along the FN, other parameters such as the spatial arrangement of trabeculae and the distribution of the cortical thicknesses around the perimeter also play important roles in determining the mode and magnitude of stresses withstood by a given cross-section of the FN.

This diversity—the spread of values around their age-specific mean—was present in young adulthood. Thus, the position of an individual's FN volume and BMC in the 5th, 50th, or 95th percentile of the population distribution is established at some time during growth. Moreover, the data in vivo and in vitro showed that an individual's FN volume and BMC did not occupy the same percentile in their respective trait distribution; otherwise, a larger FN volume would be associated with a higher BMC. This was not observed. On the contrary, because FN volume and BMC were independent, a wider FN was constructed with relatively less bone and a narrower bone was constructed with relatively more.

Thus, FN vBMD is not just a function of the net amounts of bone accrued during growth or lost during aging; the spatial distribution of the bone mass is critical because bones are hollow cylinders. Differences in vBMD were more likely to be determined by differences in FN volume (produced by differences in periosteal apposition during growth) than differences in BMC, and differences in BMC were more likely to originate during growth than aging. For example, a low vBMD was more likely to be caused by attainment of a wider FN volume by greater periosteal apposition and relatively greater endocortical resorption during growth (distributing a similar amount of bone as a thinner cortex) than greater net bone loss during aging. Correspondingly, a high vBMD was more likely to be

caused by attainment of a smaller FN volume by less periosteal apposition and relatively less endocortical resorption during growth (distributing a similar amount of material as a thicker cortex) than less net bone loss during aging.

The role of periosteal apposition in establishing FN strength is recognized.[8–11] However, attention has focused on the contribution of poverty of age-related periosteal apposition to the emergence of bone fragility by failing to compensate for endocortical bone loss. This work emphasizes that periosteal apposition during growth is the main determinant of bone size throughout life and an important determinant of bone mass and vBMD in old age.

These observations do not diminish the role of age-related bone loss in the pathogenesis of bone fragility.[12] The effects of bone loss depend on structural characteristics achieved during growth. In a wider FN, with a thinner cortex, endocortical resorption is likely to be more deleterious than in an individual with a thicker cortex.[12–14] As a group, women with hip fractures and their healthy premenopausal daughters have wider FNs with lower vBMD.[13] Blacks have thicker cortices and trabeculae. At completion of growth, they seem to lose bone at a similar rate and are less susceptible to fractures.[15]

The inferences made from these observations are constrained by several limitations. First, the work is cross-sectional. Secular changes in bone size and rates of loss cannot be excluded; therefore, the relative contributions of growth- and age-related diminution in bone mass or increment in bone size may reflect secular trends. Second, we studied the FN, a common site of fracture. The architectural organization of other tubular bones or the femur at other sites may differ. Third, FN volume in vivo is an estimate based on the assumption that it approximates an ellipse. Deviations from this may introduce errors.[4] Fourth, we assume that periosteal apposition is the only determinant of cross-sectional size; however, growth plate characteristics and behavior may also contribute to cross-sectional size and shape.[16]

In conclusion, bone modeling and remodeling on the periosteal and endocortical surfaces throughout life determine the absolute and relative positions of these two surfaces and result in FN size, shape, and architecture. The variance and relative positions of FN volume and mass in their respective trait distributions in the population are largely established during growth. Whether this occurs during intrauterine growth or postnatal growth is not known. Similar net amounts of material in a cross-section are used but are distributed differently in space so that from one individual to another, and from cross-section to cross-section along a FN, wider FNs avoid bulk by using relatively less bone. Narrower FNs avoid fragility by using relatively more. The prevention of bone fragility, and its reversal, are likely to be better achieved by methods that conserve or restore bone architecture, not only bone mass.

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