

## Femoral Neck Trabecular Bone: Loss With Aging and Role in Preventing Fracture

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**ABSTRACT:** Hip fracture risk rises 100- to 1000-fold over six decades of age, but only a minor part of this increase is explained by declining BMD. A potentially independent cause of fragility is cortical thinning predisposing to local crushing, in which bone tissue's material disintegrates at the microscopic level when compressed beyond its capacity to maintain integrity. Elastic instability or buckling of a much thinned cortex might alternatively occur under compression. In a buckle, the cortex moves approximately at right angles to the direction of load, thereby distorting its microstructure, eventually to the point of disintegration. By resisting buckling movement, trabecular buttressing would protect the femoral neck cortex against this type of failure but not against crushing. We quantified the effect of aging on trabecular BMD in the femoral neck and assessed its contribution to cortical elastic stability, which determines resistance to buckling. Using CT, we measured *ex vivo* the distribution of bone in the midfemoral necks of 35 female and 33 male proximal femurs from cases of sudden death in those 20–95 yr of age. We calculated the critical stress  $\sigma_{cr}$ , at which the cortex was predicted to buckle locally, from the geometric properties and density of the cortical zone most highly loaded in a sideways fall. Using long-established engineering principles, we estimated the amount by which stability or buckling resistance was increased by the trabecular bone supporting the most stressed cortical sector in each femoral neck. We repeated these measurements and calculations in an age- and sex-matched series of femoral necks donated by women who had suffered intracapsular hip fracture and controls, using histological measurements of cortical thickness to improve accuracy. With normal aging, trabecular BMD declined asymmetrically, fastest in the supero-lateral one-half (in antero-posterior projection) of the trabecular compartment. When viewed axially with respect to the femoral neck, the most rapid loss of trabecular bone occurred in the posterior part of this region (supero-posterior [S-P]), amounting to a 42% reduction in women (34% in men) over five decades of adult age. Because local cortical bone thickness declined comparably, age had no significant effect on the relative contributions of cortical and trabecular bone to elastic stability, and trabecular bone was calculated to contribute 40% (in men) and 43% (in women) to the S-P cortex of its overall elastic stability. Hip fracture cases had reduced elastic stability compared with age-matched controls, with a median reduction of 49% or 37%, depending on whether thickness was measured histologically or by CT (pQCT;  $p < 0.002$  for both). This effect was because of reduced cortical thickness and density. Trabecular BMD was similar in hip fracture cases and controls. The capacity of the femur to resist fracture in a sideways fall becomes compromised with normal aging because cortical thickness and trabecular BMD in the most compressed part of the femoral neck both decline substantially. This decline is relatively more rapid than that of femoral neck areal BMD. If elastic instability rather than cortical crushing initiates the fracture event, interventions that increase trabecular bone in the proximal femur have great potential to reduce fracture risk because the gradient defining the increase in elastic stability with increasing trabecular BMD is steep, and most hip fracture cases have sufficient trabecular bone for anabolic therapies to build on. **J Bone Miner Res 2009;24:1808–1818. Published online on May 4, 2009; doi: 10.1359/JBMR.090504**

**Key words:** osteoporosis, hip fracture, CT, cortical elastic stability, trabecular bone, BMD

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### INTRODUCTION

**T**HE STRENGTHENING ROLE of trabecular bone in the femoral neck has been of interest for two centuries,<sup>(1)</sup>

and destructive measurements of trabecular bone's effects have been ongoing for 50 yr.<sup>(2–4)</sup> Varying conclusions have been drawn, and contrasting estimates persist of the contribution of proximal femur trabeculae to fracture resistance in *ex vivo* mechanical testing.<sup>(5,6)</sup> The effect of age on hip strength needs to be better understood. BMD declines

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with age; however, age has a strong independent effect on fracture risk even after adjusting for BMD. Moreover, age-related loss of bending and compression resistance estimated from DXA-based hip structural analysis of the proximal femur or QCT is modest, amounting to only 15–25% in normal women over five decades.<sup>(7,8)</sup>

The sideways falls that typically lead to hip fracture<sup>(9)</sup> compress the posterior part of the thin, supero-lateral cortex of the femoral neck, labeled S-P in Fig. 1.<sup>(10)</sup> In young people, this region is supported by a network of trabeculae. Because of the action of the hip abductors, it is lightly loaded in walking,<sup>(11,12)</sup> the main physical activity of the middle-aged and elderly. In a sample of normal proximal femurs, spanning a wide age range, we found that, with aging, this part of the femoral neck cortex could develop a geometry that was predictably unstable in a fall, assuming trabecular support was absent.<sup>(13)</sup> Instability can take the form of local buckling, in which a portion of the cortex bursts inward or outward under the large compressive forces imposed by contact with the ground. Alternatively, the mineralized matrix might disintegrate at a molecular level (i.e., be crushed as rock can be crushed given sufficient pressure). It seemed possible that if the underlying trabecular bone is sufficiently well preserved, local buckling might be prevented during a sideways fall, despite cortical thinning. This would leave as the main candidate mechanism for fracture initiation the crushing of the superior cortex as proposed by Carpenter et al.<sup>(14)</sup>

These considerations have considerable implications for hip fracture prevention. Increased trabecular buttressing of the cortex is not suited to preventing cortical crushing, because the peri-trabecular bone marrow, being semiliquid, will tend to displace under pressure considerably more readily than the cortex can through crushing. On the other hand, adequate amounts of trabecular bone attached to the cortex might absorb energy generated by cortical instability, in the manner of a well-designed foundation or the damping and bracing structures used inside an aircraft wing.

Buckling, as a so-called “second-order” phenomenon, may be resisted quite efficiently in terms of the amount of bone needed to control it. When the buckle starts to form, it is governed by the elastic stiffness of the material, not its strength; only if the buckle becomes large does the strength of the material become a factor. In the buckling process, the material moves at right angles to the line of action of the compression force, and it only requires a small stiffness to resist this lateral movement, provided that force is present as soon as the movement begins. Thus, only a moderate density of well-located trabecular support may be required. The implications for anabolic therapies are obvious: hip fracture resistance in principle might be increased by treatments such as PTH(1-34) and PTH(1-84), which increase trabecular bone; however, if cortical crushing is the chief initiator of the fracture process, it might be necessary for anabolic treatments to thicken the cortex, if the hip is to be strengthened against fracture.

This paper describes the effects of aging on the trabecular bone of the femoral neck in men and women and presents calculations of trabecular bone’s effects on

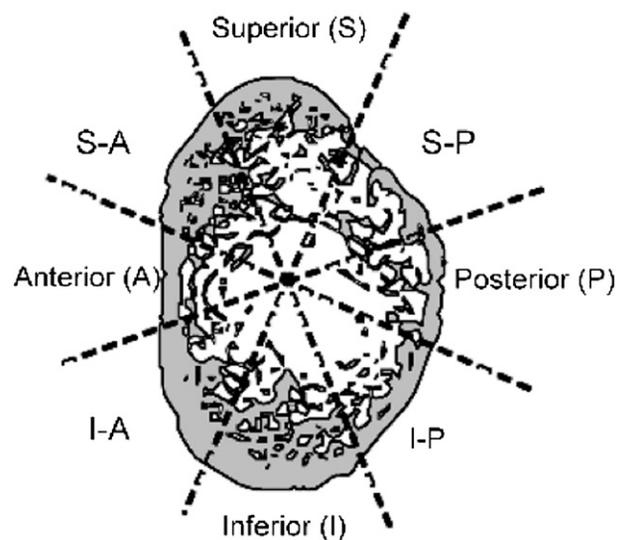


FIG. 1. Sketch of the cross-section of the femoral neck at mid-cortex level. For the purposes of our sectoral analysis, the cortices were divided into eight octants: A, anterior; I, inferior; P, posterior; S, superior; I-A, infero-anterior; S-A, supero-anterior; I-P, infero-posterior; S-P, supero-posterior. Reproduced from Bell et al.<sup>(27)</sup>

cortical stability (i.e., resistance to local buckling at the midfemoral neck in a sideways fall). Data from women with intracapsular hip fractures who donated femoral neck cross-sectional biopsies and age-matched controls are also included. The theory used in these calculations is well established for the analysis of beams supported by foundations comprised of networks (such as trabecular bone) that cannot be resolved into individual elements and is sometimes referred to as the “beam on elastic foundation” technique.<sup>(15)</sup>

## MATERIALS AND METHODS

### *Femur samples and scans*

Samples from the Melbourne Femur Collection (MFC) were reviewed from 71 subjects >20 yr of age who died suddenly and in previously normal health. Ethical approval for this study was given by the Victorian Institute of Forensic Medicine’s in-house ethics committee, promulgated under Australian National Health and Medical Research Council guidelines, and informed consent was obtained from the next-of-kin (compliance 60%). CT scans of the 68 (35 female) proximal femurs<sup>(16)</sup> showing no visible evidence of hip arthritis in a special purpose CT scanner (Densiscan 1000; Scanco Medical, Zurich, Switzerland)<sup>(17)</sup> with a quoted resolution of 0.275 mm; 140 serial slices 1 mm thick, spaced 1 mm apart, were generated. These were imported into Pixotec’s Slicer Dicer software v4 to create a 3D reconstruction, from which the midfemoral neck cross-sectional image was obtained. We validated the measurements by comparing Pixotec Slicer Dicer reconstructions with the pQCT-derived cross-sections obtained directly from 20 correctly oriented specimens.<sup>(13)</sup> For cross-section

moment of inertia,  $Z$  (section modulus), and the proportion of marrow space occupied by trabecular bone,  $r^2$  exceeded 0.97 ( $p < 0.0001$ ), and Slicer Dicer was found to have degraded resolution only slightly when reconstructing in the original plane after rotation in silico.<sup>(13)</sup> The process of reprojection of out-of plane scans leads to loss of resolution depending on the shape and size of the voxels, which were 1 mm thick in the axis of the femoral neck. Most specimens needed correction of their orientation with Slicer Dicer of the order of 5–10° of arc. We selected the reconstructed slice from each subject that had an eccentricity (ratio of major to minor diameters) closest to 1.40 for further analysis.<sup>(18)</sup> Each image was segmented into eight segments radiating from the center of the cross-section's area, with the radial edges of each segment subtending an angle of 45° (Fig. 1).

To explore structural changes associated with hip fracture, we scanned 40 additional femoral neck specimens at the higher quoted resolution of 0.180 mm, 18 from cases of intracapsular hip fracture and 22 age-matched controls. These were a slightly enlarged series of scans as previously described.<sup>(17,19)</sup> In addition, histological sections at the midneck region of these specimens, located as close as possible to the image plane, were examined microscopically, and the mean thickness of the cortex in the supero-posterior octant was calculated from individual measurements made at intervals of 3° of radial arc as described by Bell et al.<sup>(20)</sup>

#### *Extraction and analysis of data on trabecular (cancellous) bone*

To segment the cortical and trabecular bone, the data array for the chosen slice was imported into MATLAB and the function “Laplacian of Gaussian method” in MATLAB's image processing toolbox was used to define the apparent inner and outer boundaries of the cortex. This process is the equivalent of the “full width half maximum” method of Hangartner and Gilsanz.<sup>(21)</sup> The tissue internal to the defined inner margin of the cortex was considered a mixture of trabecular bone and bone marrow.

The trabecular BMD of each trabecular bone sector (TBD) was calculated according to the formula of Hangartner and Overton,<sup>(22)</sup> a relationship derived from a first-generation <sup>125</sup>I-based pQCT machine that the manufacturers preserved with the machine we used:  $TBD = \{[\text{Mean Gray Level (Cancellous Bone)} \times 0.00784314 - 0.241] / (1.421 - 0.241)\} \times 2.2 \text{ g/cm}^3$ .

#### *Correction of cortical thickness data for the partial volume effect*

We showed previously<sup>(13)</sup> that measurements of cortical thickness generated from the same scans by this equipment, which are known to be influenced by the partial volume effect, could be used to estimate the same thicknesses measured microscopically on adjacent histological sections using a linear regression equation.<sup>(19)</sup> (SD < 0.5 mm). This formula was used to generate estimates of mean cortical thicknesses from the pQCT apparent thicknesses for each sector or octant.

#### *Estimating the contribution of subcortical trabeculae to raising the level of the critical stress*

Structures are susceptible to two modes of failure: material or yield failure (in tension or compression) and buckling (compression only). For local buckling to be a candidate mechanism for the initiation of a femoral fracture, the calculated critical stress ( $\sigma_{cr}$ ) at the point most susceptible to local buckling should not greatly exceed the yield stress of cortical bone (~185 MPa<sup>(23)</sup>) and should be lower than the stress likely to lead to ultimate failure in compression.

We assessed previously the more posterior part<sup>(10)</sup> of the supero-lateral cortex as seen in antero-posterior projection (labeled S-P in Fig. 1), thought to transmit the greatest compressive loads in a sideways fall. This force was resolved into compressive and bending vectors and the load transmitted through the superior cortex calculated using beam theory whereas local elastic stability was estimated without regard to trabecular support.<sup>(13)</sup> We now reassess whether this region might be susceptible to local buckling or instability in the presence of support from subcortical trabeculae. We recalculated the most likely critical stress experienced by the S-P cortex in a sideways fall given the amount of trabecular support received by the cortex. The calculations are detailed in the appendix.

The question arose as to how much, if any, decline in trabecular BMD with age would reduce the ability of trabecular bone to buttress the cortex and prevent it failing through local elastic instability. The effect of trabecular bone was defined as the difference between  $\sigma_{cr}$  values calculated with and without the term relating to trabecular bone in Equations 3 and 4 of the Appendix; this difference (i.e., the component depending on the trabecular bone contribution to critical stress) was:

$$\begin{aligned} & 0.58E_c \sqrt{\frac{t}{D \cdot E_{ratio}}} \\ & = 0.58 \sqrt{\frac{t \cdot E_c \cdot E_t}{D}} \end{aligned}$$

where  $E_c$  is the cortical elastic modulus,  $E_t$  is the trabecular modulus,  $t$  is the local thickness of the cortex, and  $D$  is the effective distance over which the trabecular bone can compress, approximated by the depth of trabeculae from the endosteal surface to the center of trabecular area.  $E_c$  is reduced below its potential maximum through the effect of cortical porosity.<sup>(24)</sup>

#### *Statistical analysis*

The effect of age on trabecular BMD (individual octants or all trabecular bone) was assessed using simple regression analysis for men and women separately. To test for case-control differences between groups, distributions were first tested for normality, and generally a Wilcoxon test was used. To assess the significance of observed differences in age effects across octants in the MFC data, repeated-measures multivariate ANOVA (MANOVA) was used to determine the differences and their statistical significance between octants in the size of the age effect across all eight

TABLE 1. Characteristics of Subjects Studied [Medians Shown With (25th and 75th Centiles)]

Parameter	MFC women	MFC men	PM controls (women)	Hip fracture (women)
Number of subjects	35	33	22	18
Minimum age (yr)	20	20	62	63
Maximum age (yr)	95	84	100	89
Median age (yr)	68.5 (41.0, 75.0)	69.0 (41.0, 75.0)	83 (77.8, 87.3)	79 (76.3, 85.3)
Minimum height (cm)	145	153		
Maximum height (cm)	184	190		
Median height (cm)	163 (154, 167)	173 (167, 180)		
Minimum BMI (kg/m <sup>2</sup> )	16.9	15.0		
Maximum BMI (kg/m <sup>2</sup> )	34.4	35.9		
Median BMI (kg/m <sup>2</sup> )	25.3 (20.0, 28.9)	24.5 (22.3, 27.2)		
Minimum E (MPa × 10 <sup>3</sup> )*	6.19	6.60	9.34	4.76
Maximum E (MPa × 10 <sup>3</sup> )*	10.74	10.26	13.05	12.59
Median E (MPa × 10 <sup>3</sup> )*	9.35 (8.18, 10.03)	8.57(8.02, 9.22)	11.22 (9.98, 12.27)	8.87 (7.31, 11.60)

Medians shown with (25th,75th) centiles.

\* NB for cortical bone, calculated as described by Mayhew et al.<sup>(17)</sup> MFC samples scanned at lower resolution than biopsies from hip fracture cases and controls. This affects apparent E values because the partial volume effect causes more distortion at lower resolutions.

BMI, body mass index (kg/m<sup>2</sup>).

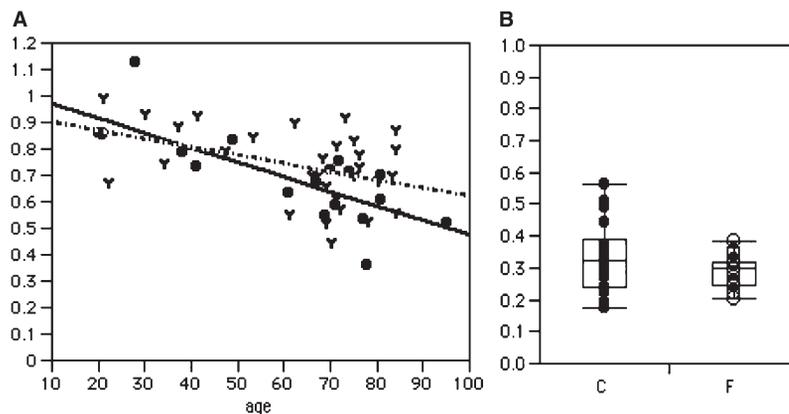


FIG. 2. (Left) Areal femoral neck BMD (in g/cm<sup>2</sup>) in the MFC samples ▼, men; ●, women. For details of measurements and calculations, see text. (Right) Whole cross-section trabecular BMDs calculated from pQCT scan data (g/cm<sup>3</sup>) in femoral neck biopsies from 18 hip fracture (F) cases and 22 age-matched controls (C).

octants, in addition to the mean age effect. The covariates height and weight and their significant interactions with sex and octant were included in the MANOVA. To test for hip fracture case-control differences, repeated-measures MANOVA was used with and without age adjustment. All statistical tests were implemented in JMP (SAS Institute, Cary, NC, USA).

## RESULTS

Table 1 gives the characteristics of the Australian and UK subjects studied. Because of their condition, no reliable height estimates were available for the UK cases and controls, and many weights were missing from the patient's notes, so adjusting for weight and height in the case-control comparisons was not possible.

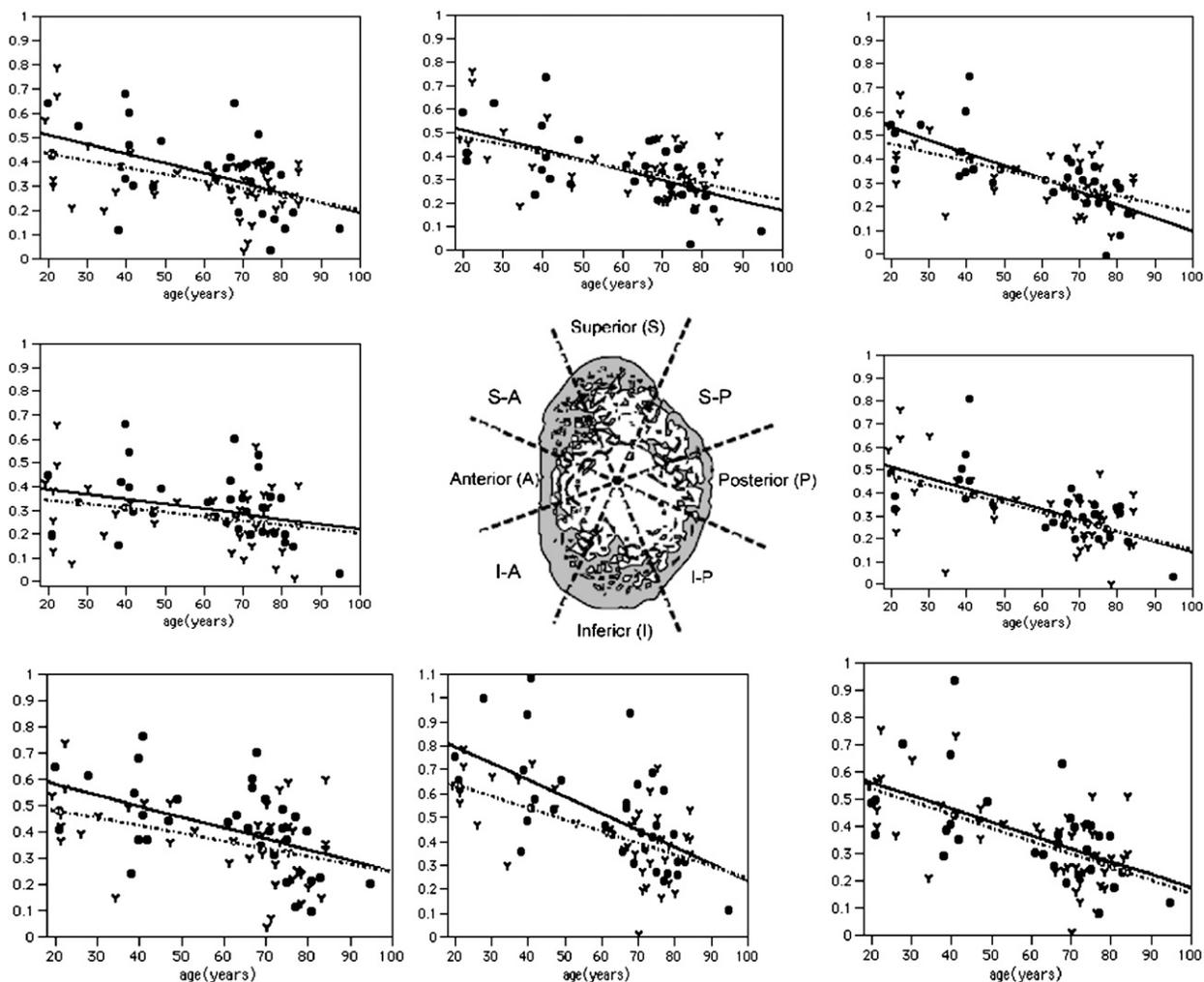
### Comparison of pQCT with histological measurements of cortical thickness: cases and controls

The histologically measured cortical thickness in the S-P octant correlated moderately well with the pQCT

measurement in the biopsy samples, and there was no significant effect of case-ness ( $n = 39$ ,  $r^2_{\text{adj}} = 0.24$ ). The root mean square error of an estimate of histological thickness was 0.18 mm, similar to the resolution of the scanner. The regression constant was not significantly different from zero, and when the regression line was forced through the origin, the regression coefficient was reduced from 0.93 to 0.86 mm/mm, suggesting scope for future improvement in accurate measurement of thin cortices with pQCT.

### Effects of age: MFC

The decline with age in calculated areal BMD (g/cm<sup>2</sup>) is shown in Fig. 2. The declines with age in overall trabecular BMD (TBD, g/cm<sup>3</sup>) were similar in men and women using independent tests, amounting to 0.042 g/cm<sup>3</sup> per decade (Fig. 2). When examined independently by octant, the age effect was nonsignificant in only one location: the anterior octant in both men and women. In the other seven octants, trabecular BMD declined significantly ( $p < 0.002$ ) in both men and women (Fig. 3). In a combined MANOVA model including both sexes, age had the dominant effect ( $p < 0.0001$  across all octants), and this effect differed substantially between octants ( $p < 0.0001$ ). Height had a weak



**FIG. 3.** Trabecular BMD ( $\text{g}/\text{cm}^3$ ) in men (▼) and women (●) as a function of age in eight octants described in the text. Regression lines, shown separately for men (pecked lines) and women (solid lines), are not significantly different in gradient between the sexes in any octant ( $p > 0.05$ ). As shown by the miniaturized version of Fig 1 at center, graphs begin at top center (superior octant S) and rotate counterclockwise in the following order: S-A, A, I-A, I, I-P, P, S-P.

effect across octants to increase TBD ( $p = 0.043$ ). Also, female sex had a weak effect to increase TBD across octants ( $p = 0.029$ ), but the effect varied between octants ( $p = 0.045$ ) and was modified by body weight, so that heavier women showed somewhat faster loss of TBD with age than their lighter peers, whereas the reverse was true for men ( $p = 0.012$ ). No other significant effect was found.

Removing the weaker effects to leave sex and age as the only independent determinants, the interaction between them was nonsignificant ( $p > 0.1$ ). The most rapid loss of TBD occurred in the supero-posterior (S-P) octant, equivalent to a 42% reduction in women (34% in men  $p < 0.0001$  for both sexes) over five decades of age. However, the differences between the different octants in the magnitude of the aging effect were less significant in men ( $p = 0.07$ ) than in women ( $p < 0.0001$ ). MANOVA also showed that the effect of female sex to increase BMD was confined to the inferior and infero-anterior octants. Specifically in the S-P octant, age had no significant effect on the ratio of cortical to trabecular bone because they declined at similar relative rates.

Surface curvature of the S-P octant, used in the calculation of critical stress, decreased slightly with age ( $p = 0.07$ , men and women), consistent with gradual expansion of femoral midneck cross-sectional area.

#### *Effects associated with hip fracture*

Comparing the cases of hip fracture to controls, there was no statistically significant association of fracture status with trabecular BMD with or without (Figs. 2 and 4) age adjustment. The median thickness of the cortex in the supero-posterior octant was lower in the cases of hip fracture when measured histologically (median thickness, 0.55 versus 0.76 mm;  $p = 0.039$ , Wilcoxon test). However, when measured by pQCT, the difference was less impressive (median thickness, 0.75 versus 0.79;  $p = 0.46$ ). The median areal femoral neck BMD ( $\text{g}/\text{cm}^2$ ), calculated as described by Mayhew et al.,<sup>(17)</sup> was 0.55  $\text{g}/\text{cm}^2$  in the cases and 0.59  $\text{g}/\text{cm}^2$  in the controls ( $p = 0.14$ ), whereas the median S-P surface radius of curvature (see Appendix) was

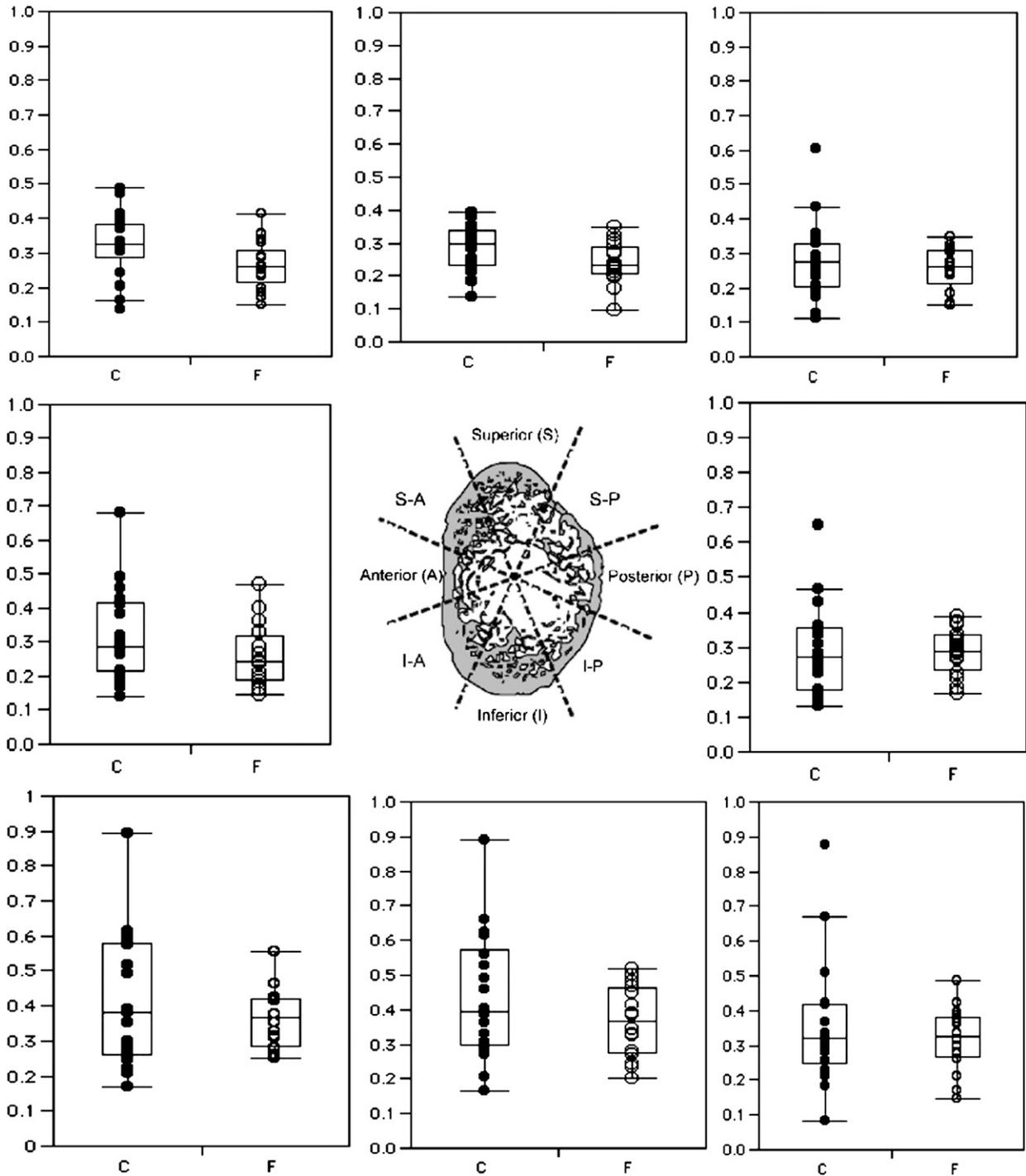


FIG. 4. Femoral neck biopsies from 18 hip fracture (F) cases and 22 age-matched controls (C). Trabecular BMDs calculated from pQCT scan data ( $\text{g}/\text{cm}^3$ ) shown in octants. The identities of the eight octants are shown as in Fig 3.

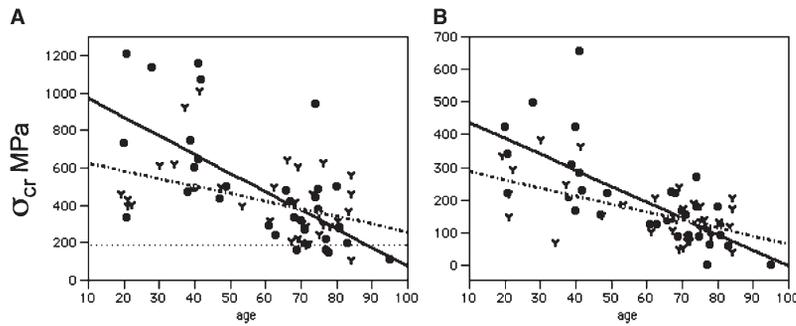
higher to a borderline extent in the fracture cases (37 versus 25 mm;  $p = 0.08$ ).

*Calculated critical stress*

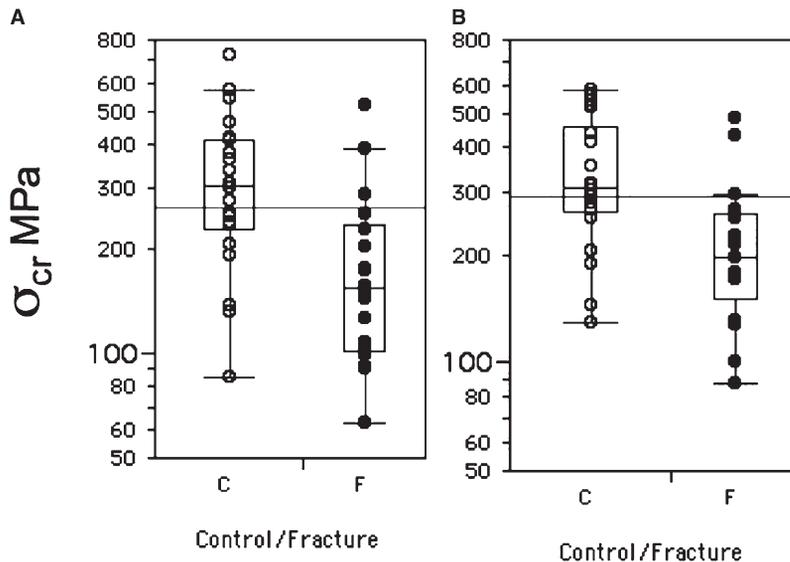
Figure 5 shows the calculated critical stress ( $\sigma_{cr}$ ) in the S-P octant of the femoral neck midcortex as a function of age in the MFC men and women; the calculations were

performed as described in the Appendix. The size of the effect of cancellous bone on  $\sigma_{cr}$  in these subjects is also shown as a function of age.

The cases of hip fracture had reduced calculated critical stress values compared with their controls of a similar age. When estimates of S-P thickness from pQCT were used to calculate  $\sigma_{cr}$  instead of histological measurements,  $\sigma_{cr}$  was a median of 25 (IQR, 2, 55) MPa higher. Using the



**FIG. 5.** Relationship between calculated critical stress ( $\sigma_{cr}$ ) in the supero-posterior cortex with trabecular support and age in years in the MFC samples (left). The dashed line is located at the reported yield stress for cortical bone from Burstein et al.<sup>(23)</sup> The component of  $\sigma_{cr}$  attributable to the subcortical trabeculae is also shown (right). Units of measurement for  $\sigma$ : megapascals. Linear regressions shown separately for men and women. Note the regressions of sigma on age decline more rapidly in women than in men.



**FIG. 6.** Calculated critical stress in the S-P cortex in cases of hip fracture and controls. (Left) The calculations used histological measurements of cortical thickness. (Right) Densitometric thickness measurements were used. The box and whisker plots show medians, 25,75% ranges, and 10,90% ranges. Ordinate scale is in MPa and is shown logarithmically because distributions deviate markedly from normal.

histological measurements, only 6 of 18 hip fracture cases had  $\sigma$  values exceeding the yield strain of cortical bone reported by Burstein et al. (185 MPa),<sup>(23)</sup> whereas only 3 of 22 controls had  $\sigma_{cr}$  values <185 MPa. Whether the histological or the densitometric estimates of cortical thickness was used in the calculation of  $\sigma_{cr}$ , the difference between cases and controls was highly significant ( $p < 0.002$  Wilcoxon, for each measure), the differences in medians between cases and controls being 149 and 112 MPa, respectively (Fig. 6).

Overall, the proportion of critical stress attributed to trabecular bone in the MFC subjects was age invariant and amounted to (median, interquartile range) 43% (29%, 54%) in women and 40% (31%, 50%) in men. However, the hip fracture cases had a higher median proportion of critical stress attributable to trabecular bone at 57% (41%, 72%). Their British age-matched controls were similar to the Australian MFC women, with the median proportion being 41% (28%, 56%);  $p$  for case-control difference was 0.015 (Wilcoxon).

## DISCUSSION

In this study based on a sample of femurs that was reasonably representative of a large U.S. population,<sup>(13)</sup> we

described the effects of age and osteoporosis, as indicated by a prior hip fracture, on the trabecular (cancellous) bone of the midfemoral neck. A stabilizing effect of trabecular bone on the femoral neck cortex would enhance protection against local buckling in a sideways fall, and we estimated the size of this effect, using classical methods, at ~40% of the overall critical stress ( $\sigma_{cr}$ ) for local buckling. Loss of trabecular bone with normal adult female aging seems substantial, being proportionately larger than in the cortical plus trabecular bone of the femoral neck as a whole. Loss of trabecular bone of the supero-lateral one half of the femoral neck (A-P projection) parallels the higher rates of bone loss seen in the supero-lateral one half of the cortex (represented here by the S, S-A, and S-P sectors) when contrasted to the infero-medial one half.<sup>(25,26)</sup> Hip fracture cases had no excess of trabecular bone loss beyond that expected to occur through normal aging, confirming our previous results.<sup>(27)</sup> In consequence, candidates for hip fracture depend on their trabecular bone for more than one half of their  $\sigma_{cr}$ , because they suffer a preferential loss of cortical bone that becomes severe with advanced age.

The tension cortex in a sideways fall is the thick infero-medial cortex and its thickness is rather age-invariant,<sup>(13)</sup> so failure primarily in tension (as may occur in long bone diaphyses) in the femoral neck is probably uncommon. Our results suggest that in a fall the partial preservation of

trabeculae in the femoral neck helps protect it against the adverse effects on fracture risk of gradual age-related widening<sup>(28,29)</sup> and cortical thinning occurring elsewhere. Nevertheless, with aging, hip fracture risk still increases 10-fold every 20 yr.<sup>(30)</sup> This raises questions as to the potential for intervening to better preserve trabecular bone, particularly in the supero-lateral part of the femoral neck.

Subcortical trabeculae and their associated marrow would only give a compressed cortex in an osteoporotic femur protection against local crushing if rigidly prevented from flowing away from zones of high pressure. The cortex of the femoral neck is perforated by vascular channels, so bone marrow pressure-load relationships in a fall are likely to be complex, transient, and unhelpful in preventing cortical crushing. Structures are susceptible to two modes of failure; the one most investigated currently being material or yield failure in tension or compression. For assessing this, in vivo QCT-based structural analysis and finite element (FEA) modeling in its more advanced nonlinear realization is being increasingly used. As recently reviewed by Keaveny and Bouxsein,<sup>(31)</sup> high-resolution clinical whole body CT scanning of the hip combined with FEA suggests that many candidates for hip fracture might initiate their fracture through localized compressive overload in the cortex as suggested by Carpenter et al.<sup>(14)</sup> and others.<sup>(32–34)</sup> When the load on trabeculae in the fall configuration was studied ex vivo with greatly improved resolution using microfinite element analysis by Verhulp et al.,<sup>(35)</sup> the osteoporotic femur also seemed to bear most of its compressive load in the superior cortex. By providing a plausible explanation for an alternative form of local structural failure, caused by elastic instability of this highly loaded cortex, our study highlights the potentially great mechanical importance of femoral neck trabecular bone.

It is worth considering the postulated chain of events in nonmathematical terms. A sideways fall tends to increase varus of the femoral cantilever momentarily. The femoral neck marrow will then move infero-medially to accommodate the change in shape of the femur. With the marrow cavity fractionally altered in volume, a likely trigger to cortical oscillation is created, and in an elastically unstable cortex, local buckling might result. Trabecular bone's apparent role is to dampen these oscillatory effects as well as to resist outward or inward movement of a thinned cortex under compression. Whereas this beneficial effect declined with age in approximate proportion to the age-related thinning of the cortex itself, its magnitude varied considerably between individuals. It was also proportionately higher in hip fracture cases.

The role of the material properties of the bone tissue and their possible deterioration with aging is also relevant. In a fall onto the greater trochanter, a load exceeding the so-called yield stress will cause microscopic damage; however, depending on whether the bone tissue is tough or brittle, the energy absorbed by yield may allow the femur to avoid catastrophic failure with a microscopic degree of impaction at worst. Toughness is this capacity to absorb energy after yield is initiated. However, toughness is only of use in preserving the integrity of a femoral cortex that remains elastically stable. If the structure becomes elastically

unstable at or around the yield stress, displacement of tissue will be too great to allow toughness to maintain integrity, and the energy of the fall is likely to deliver a complete fracture.<sup>(13)</sup> It remains a valid proposition that bone tissue toughness in many older individuals could cease to contribute substantially to preventing hip fracture in a fall.

Femoral neck bending resistance as quantified by DXA-derived<sup>(7,36)</sup> or QCT-derived<sup>(8)</sup> section modulus ( $Z$ ) declines rather little with age; 15–25% over five decades. Our data therefore remain compatible with a model of the aging femur in which femoral neck  $Z$  remains equilibrated with changing loading patterns. Expansion of diameter<sup>(28,29)</sup> allows less bone tissue to maintain a constant  $Z$ .<sup>(37)</sup> The changing character of the load on the femoral neck seems to play an unfortunate role in increasing fragility. The relative preservation of the inferior part of the femoral neck, associated with walking,<sup>(38)</sup> means that  $Z$  should increase unless balanced by loss of bone tissue in the upper neck. This, when it occurs, reduces structural stability.<sup>(36)</sup> Crabtree et al.<sup>(25)</sup> found evidence that aging was associated with a larger relative loss of bone mineral in the upper (supero-lateral) one half of the femoral neck than in its lower, or infero-medial one half. In the largest prospective study of hip fracture explicitly studying the upper and lower halves of the femoral neck DXA region, Duboef et al.<sup>(39)</sup> showed that only the upper or supero-lateral BMD in the femoral neck region predicted intracapsular hip fracture and not the lower or infero-medial BMD.

The effects of osteoporosis, as indicated by a hip fracture, and of aging on the femoral neck were different in our study. Aging has its principle effects increasing width of the femoral neck combined with cortical thinning and trabecular bone loss, accompanied by increased remodeling indices.<sup>(40,41)</sup> In hip fracture, bending resistance is further reduced,<sup>(42)</sup> and additional loss of elastic stability develops because of additional thinning and porosity of the femoral neck cortex<sup>(17,43)</sup> without a disease-specific effect on trabecular bone. No mismatch is evident between habitual loading and bone tissue in normal aging. Perhaps in hip fracture cases these differential effects on cortical and trabecular bone occur because increased resorption leads to the conversion of more cortical to trabecular bone by a process of accelerated "trabecularization."<sup>(44–46)</sup> It remains to be seen whether the improved cortical thickness achieved by young female athletes loading their hips in many directions additional to stance and walking, as shown by Nikander et al.,<sup>(47)</sup> can be maintained long-term by lifetime physical activity.

Currently, the details of trabecular connections, anisotropy, and thicknesses required by potentially more precise techniques for estimating cortical instability or materials failure (e.g., finite element analysis) are not available or require approximation, because of the limited resolution of most pQCT methodology including ours, especially if translated into the clinic. Our study incorporates simplifications, and the accompanying mechanical analysis should be regarded as exploratory. No allowance is made for the differences in material properties between young and old bone in its propensity to crack,<sup>(48,49)</sup> nor in the effects of these properties or of microarchitectural changes<sup>(50)</sup> on

crack propagation in the femoral neck cortex. It is assumed that trabecular bone effectively behaves like an isotropic network so that its modulus is independent of orientation. The algebraic simplifications involved in the part of Hetenyi's method of analysis used by us are mentioned, but these are unlikely to exceed in magnitude those arising from the simplifications involved in modeling the femoral neck as a nonuniform annulus formed of cortical sectors connected to a trabecular foundation. In osteoporosis, many trabeculae are disconnected or missing, and whole regions without bone can appear in the femoral marrow space,<sup>(12)</sup> so elongating considerably the femoral neck cortex's effectively unsupported length. The quantitative estimation of instability is imprecise because of lack of knowledge of precise geometry and material properties. Engineering design relies on experiment or the provision of generous safety margins for avoidance of structural failure, particularly where the limit of elastic stability is close to the yield stress where failures in engineering structures have unexpectedly occurred because of local imperfections. Our purpose could not be to provide a fully quantitative analysis of hip fracture mechanics, which must await better-resolution CT studies as are now becoming possible, although even these would be specific only to the particular specimen studied. We were able to show the likely magnitude of the relative effect of the trabeculae on cortical stability. A further consideration is that in using noninvasive methods for studying cortical thickness and its effects on elastic stability, we have not been able to completely eliminate the effects of bias introduced by the partial volume effect. Although we used the data of Crabtree et al.<sup>(19)</sup> to estimate true cortical thickness by reference to a histological "gold standard" method, some local overestimation of cortical thickness persisted, leading to possible overestimates of  $\sigma_{cr}$  in the S-P cortex when measured with our pQCT equipment. Thus, in future work based on CT, consideration should be given to the better estimation of cortical thickness when true thickness values are <1 mm.

There are also the well-known limitations of case-control studies and cross-sectional studies that are vulnerable to confounding by unrecognized determinants and cohort effects, respectively. We used a location in the femoral neck for our analysis (an eccentricity ratio of 1.4:1) that is based on the work of Kuiper et al.<sup>(18)</sup> This would benefit from further validation for its age invariance, and both cortical bone thickness and trabecular bone volume change markedly along the neck axis so we cannot guarantee that our results are as relevant to basal or subcapital as to midneck fractures.

Our finding of a substantial stabilizing effect of trabecular bone in the femoral neck might help explain the paradox that patients with hip osteoarthritis almost never suffer a femoral neck fracture, whereas they are as vulnerable as controls to trochanteric fractures.<sup>(51-53)</sup> These patients have an ~50% increase in trabecular bone, but not cortical bone, in the femoral neck compared with age-matched controls and patients with hip fracture.<sup>(54,55)</sup>

In conclusion, our data raise the exciting possibility that 3D imaging (e.g., with clinical CT) could in the future be used routinely to improve the prediction of hip fracture and to decide when to intervene therapeutically. We

envisage that combining an approach to modeling the femoral neck's risk of fracture through local cortical instability with assessing risk through alternative fracture mechanisms such as excessive compression (crushing), bending, and torsion, as reviewed by Keaveny and Bouxsein,<sup>(31)</sup> is highly promising and should be evaluated for a possible future role as a surrogate endpoint in therapeutic trials. There are also practical implications for understanding and controlling the hip fracture epidemic. For example, an over-stereotyped gait-related stimulus might maintain bending resistance while permitting elastic instability to develop. Also, regular loading targeted to the S-P cortex may need to be life-long as occurs naturally when the femur is straightened (extended) at the hip from a flexed position. Even the rather low amount of trabecular bone seen in the elderly hip contributes appreciably toward increasing femoral neck cortical elastic stability. This effect of subcortical trabecular bone could be considerably enhanced by increasing its density therapeutically (e.g., with currently available or expected anabolic agents). Future pharmacologic stimulators of subperiosteal or endosteal bone formation or implanted matrices able to encourage either new trabecular or cortical bone formation might therefore have important roles in hip fracture prevention.

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## APPENDIX

This analysis requires that surface curvature be measured as the local radius of the external cortical surface.<sup>(13)</sup> Each cross-section analyzed was converted into a shape bounding the periosteal surface by delineating the pixels at the periosteal surface by their  $x, y$  coordinates. The octant of interest was isolated, and the boundary pixels were examined in sequential groups of three using groups of three consecutive non-co-linear points drawn from these boundary pixels. The mean of these estimates of radius ( $R$ ) was calculated and used in the calculations of critical stress. To avoid the artefactual lowering by the so-called partial volume effect of cortical density in thin cortices, we assumed the true tissue density of cortical bone to have the density of the densest sector, which avoids systematic error.<sup>(21)</sup> We adjusted our calculated cortical thickness data so that they matched measurements made histologically as reported by Crabtree et al.<sup>(19)</sup> This allowed us to calculate the critical stress  $\sigma$  at which the curved cortical sector of interest would become critically unstable in the absence of trabeculae as:

$$\sigma_{CR} = 0.61 \frac{t}{R} \times E_c \quad (1)$$

where  $t$  is the local thickness of the cortex (adjusted as described above) and  $E_c$  the elastic modulus of cortical bone tissue estimated from the BMD in the densest, usually inferior sector, given by Carter and Hayes<sup>(24)</sup> as  $\text{density}^3 \times 2875/\sqrt{2.73 \text{ MPa}}$ . The factor 0.61 in equation 1 arises from bone tissue's Poisson's ratio, assumed to be 0.3.

In the absence of curvature, or where it gives a higher estimate of critical stress, the Euler buckling formula can apply:

$$\sigma_{EU} = \frac{t^2 \pi^2}{12L^2} \times E_c = \frac{0.82t^2}{L^2} \times E_c \quad (2)$$

where  $L$  is the length of the cortex along the femoral neck's axis under consideration and  $\pi$  is 3.142.  $\sigma_{EU}$  provides a lower bound below which  $\sigma_{CR}$  does not fall as  $R$  is increased. However, this equation applies to a beam with pinned ends as applied previously, whereas the two ends of the cortical sector may more legitimately be considered fixed, through their attachment to the head of the femur and the greater trochanter, respectively. For an uncurved sector with fixed rather than pinned ends that extends in an axial direction throughout the whole length of the femoral neck,  $\sigma_{EU}$  should be increased by a factor of 4 compared to equation 2.<sup>(15)</sup>  $L$  was a mean of 3.15 cm (95% CI, 2.93, 3.38) measured from pencil beam Hologic QDR 1000 DXA images after appropriate scaling and assuming that the centers of fixation were 0.2 cm deep to the surfaces of the greater trochanter and femoral head at the points these landmarks merged with the femoral neck.

Hetenyi<sup>(15)</sup> derived an empirically validated set of equations to describe the limit of elastic stability in the case of a beam with fixed ends receiving support from an elastic foundation. With a relatively modest approximation, the effect of the foundation could be written as a linear addition to the critical load of a beam that was without foundation support. Turning his expression into a stress for a sector that is flat in the plane normal to the axis of the femoral neck:

$$\sigma_{EU} = \left[ 3.29 \frac{t^2}{L^2} + 0.58 \sqrt{\frac{t}{D \cdot E_{ratio}}} \right] \cdot E_c \quad (3)$$

By analogy, the effect of a stiff foundation on a curved beam's elastic stability can also be taken into account by an additional stress term, giving:

$$\sigma_{CR} = \left[ 0.61 \frac{t}{R} + 0.58 \sqrt{\frac{t}{D \cdot E_{ratio}}} \right] \cdot E_c \quad (4)$$

where  $D$  is the distance from the endosteal margin to the center of area of the trabeculae and  $E_{ratio}$  is the ratio of the elastic moduli of cortical:trabecular bone (note that the elastic moduli of cortical and trabecular bone independently increase elastic stability above zero trabecular BMD in proportion to their individual square roots).

$D$  was determined from the position of the centroid from the whole cross-sectional images of the femoral neck cross-sections.<sup>(17)</sup>

Hernandez et al.<sup>(56)</sup> showed that the elastic modulus of trabecular bone depends on both the fraction of bone plus marrow occupied by mineralized trabeculae (CnBAR) and also the true density (in  $\text{g/cm}^3$ ) of the trabeculae. These values were calculated as follows. The results of Loveridge et al.<sup>(57)</sup> relating the density of trabecular bone to gray level from scanning electron microscopy were assumed to be linear. This allowed us to calculate the mean densities of trabecular bone tissue in cases and controls (MFC subjects were assumed to be controls). Having reported volumetric trabecular density (TBD) as grams per cubic millimeter bone plus marrow, net of a soft tissue contribution, the CnBAR values were calculated as simple ratios of TBD to Loveridge et al.'s mean densities for the trabecular bone tissue, depending on whether the subject was a control or a case.