Intracortical remodelling and porosity in the distal radius and post-mortem femurs of women: a cross-sectional study

Roger M D Zebaze, Ali Ghasem-Zadeh, Ann Bohte, Sandra Iuliano-Burns, Michiko Mirams, Roger Ian Price, Eleanor J Mackie, Ego Seeman

Summary

Background Osteoporosis research has focused on vertebral fractures and trabecular bone loss. However, non-vertebral fractures at predominantly cortical sites account for 80% of all fractures and most fracture-related morbidity and mortality in old age. We aimed to re-examine cortical bone as a source of bone loss in the appendicular skeleton.

Methods In this cross-sectional study, we used high-resolution peripheral CT to quantify and compare cortical and trabecular bone loss from the distal radius of adult women, and measured porosity using scanning electron microscopy. Exclusion criteria were diseases or prescribed drugs affecting bone metabolism. We also measured bone mineral density of post-mortem hip specimens from female cadavers using densitometry. Age-related differences in total, cortical, and trabecular bone mass, trabecular bone of cortical origin, and cortical and trabecular densities were calculated.

Findings We investigated 122 white women with a mean age of 62·8 (range 27–98) years. Between ages 50 and 80 years (n=89), 72·1 mg (95% CI 67·7–76·4) hydroxyapatite (68%) of 106·5 mg hydroxyapatite of bone lost at the distal radius was cortical and 34·3 mg (30·5–37·8) hydroxyapatite (32%) was trabecular; 17·1 mg (11·7–22·5) hydroxyapatite (16%) of total bone loss occurred between ages 50 and 64 years (n=34) and 89·4 mg (83·7–101·1) hydroxyapatite (84%) after age 65 years (n=55). Remodelling within cortex adjacent to the marrow accounted for 49·9 mg (45·4–53·7) hydroxyapatite (47%) of bone loss. Between ages 50–64 years (n=34) and 80 years and older (n=33), cortical density decreased by 127·8 mg (93·1–162·1) hydroxyapatite per cm^3 (15%, p<0·0001) before porosity trabecularising the cortex was included, but 374·3 mg (318·2–429·5) hydroxyapatite per cm^3 (43%, p<0·0001) after; trabecular density decreased by 18·2 mg (–1·4 to 38·2) hydroxyapatite per cm^3 (14%, p=0·06) before cortical remnants were excluded, but 68·7 mg (37·7–90·4) hydroxyapatite per cm^3 (52%, p<0·0001) after.

Interpretation Accurate assessment of bone structure, especially porosity producing cortical remnants, could improve identification of individuals at high and low risk of fracture and therefore assist targeting of treatment.

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Departments of Medicine and Endocrinology, Austin Health, University of Melbourne, Melbourne, VIC, Australia (R M D Zebaze MD, A Ghasem-Zadeh, A Bohte PhD, S Iuliano-Burns PhD, Prof E Seeman MD); **Department of Medical Technology and Physics, University of Western Australia, Perth, WA, Australia** (Prof R I Price PhD); **and Department of Veterinary Science, University of Melbourne, Melbourne, VIC, Australia** (M Mirams PhD, Prof E J Mackie Dr med vet)

Correspondence to:
Dr Roger M D Zebaze, Department of Endocrinology, Centaur Building, Repatriation Campus, Austin Health, Waterdale Road, Heidelberg, 3084, VIC, Australia
zebaze@unimelb.edu.au

Introduction

Bone modelling and remodelling are the final common pathways expressing all genetic and environmental factors affecting the attainment, maintenance, and decay of bone's material and structural strength.[1] During growth, this cellular machinery assembles the size, shape, and architecture of bone by depositing and removing material from the outer (periosteal) surface and the three (endocortical, intracortical, and trabecular) components of the inner (endosteal) surface (figure 1). At completion of growth, periosteal apposition slows and remodelling of the three inner surfaces maintains bone strength by removing and replacing old or damaged bone with an identical volume of new bone. Around midlife, remodelling becomes unbalanced so that every time bone matrix is remodelled, whether initiated for damage repair or adaptation to loading, more bone is removed than is replaced by cells of the basic multicellular unit, producing bone loss and structural decay.[2] Although this negative balance of a few percent can worsen as age advances, the driving force producing bone loss and structural decay is the remodelling intensity—the birth rate of the many new basic multicellular units arising on these surfaces after menopause in women and in both sexes late in life.[3]

The amount of bone loss and structural decay also relies on accessibility of the bone matrix to remodelling. This accessibility depends in part on how a volume of bone is designed in space. Remodelling is initiated on a bone surface. A volume of bone with a large exposed surface will be remodelled rapidly by the large number of basic multicellular units that can access and erode bone matrix beneath the surface.[3] A volume of trabecular or spongy bone has a larger surface than does an equal volume of cortical or compact bone and is thus exposed to more remodelling and is lost more rapidly than is cortical bone.[3] For this reason, trabecular bone loss and fractures of the vertebral body, which is a structure containing large amounts of trabecular bone, have dominated thinking and research into the structural basis of bone fragility for almost 70 years.[4,5]

This focus neglects the role of decay of cortical bone in pathogenesis of bone fragility, which is an omission that is difficult to reconcile with the epidemiology of fractures. About 80% of all fractures in old age are non-vertebral, arise at sites that are mainly cortical, and occur after age 60 years when the rate of trabecular bone loss decelerates.[6,7] Moreover, only 20% of bone is trabecular—80% is cortical. Even if completely eroded, trabecular bone loss cannot

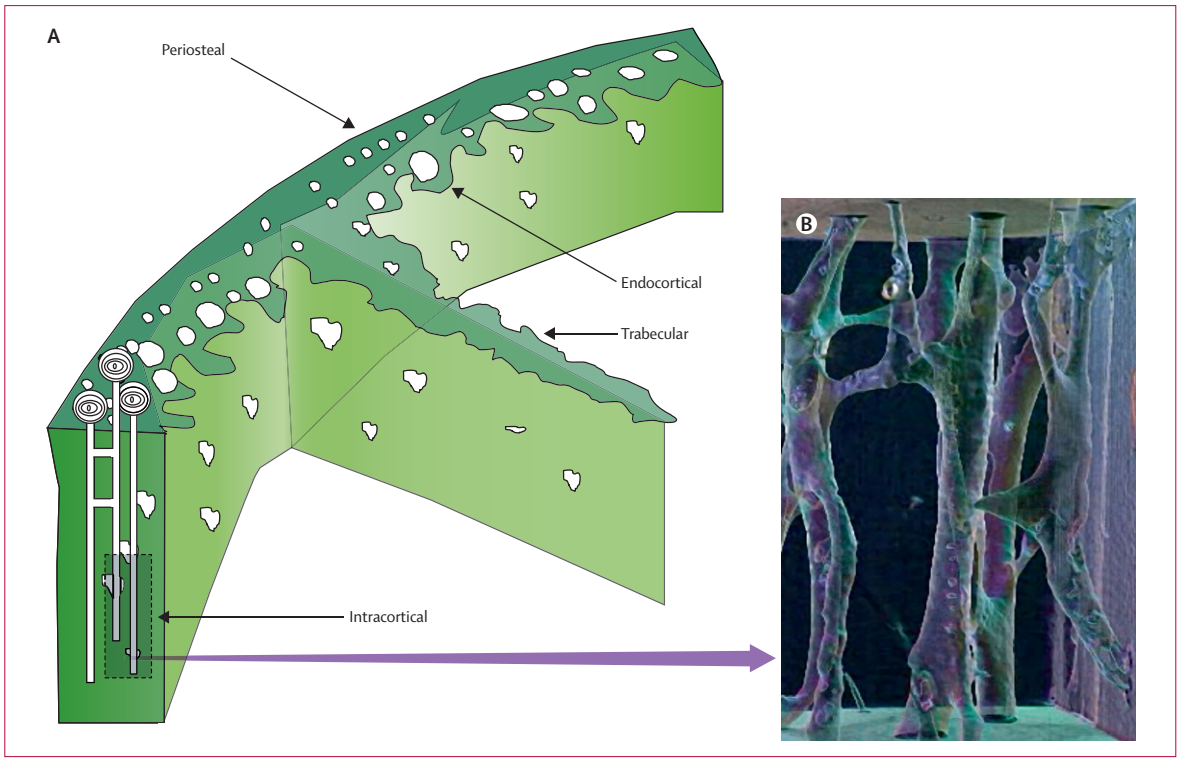

Figure 1: **Structure of bone**
(A) Cortical and trabecular bone, the periosteal (external) surface, and the three (endocortical, trabecular, intracortical) contiguous components of the endosteal (internal) surface on which matrix remodelling is initiated. (B) The intracortical surface formed by the lining of myriads of Haversian and Volkmann canals traversing the cortex. These canals are seen as pores in cross-section. Reconstructed with high-resolution quantitative CT, with permission from Dr M Knackstedt, Australian National University.

account for the halving of bone mass with age in women. Although the low surface-to-volume ratio of cortical bone in early adulthood makes this volume less accessible to being remodelled than is trabecular bone, cortical bone is not compact—the structure is traversed by many Haversian and Volkmann canals, the lining of which provide a surface area for remodelling that can be larger in absolute terms than the surface area enveloping the four-fold smaller trabecular bone volume (figure 1). We therefore aimed to re-examine cortical bone as a source of bone loss in the appendicular skeleton.

See Online for webappendix

Methods

Patients and procedures

Participants in our cross-sectional study were white female volunteers recruited in Melbourne, Australia, between 2006 and 2008, by advertisement for a study of age-related changes in bone structure. All volunteers were included in the study unless they had diseases or took prescribed drugs affecting bone metabolism. We measured bone structure at the distal radius using high-resolution peripheral quantitative CT (Xtreme CT, Scanco Medical AG, Brüttisellen, Switzerland), which had an isotropic voxel size of 82 μm. Attenuation data were converted to equivalent hydroxyapatite densities. The volume of interest was separated into a cortical and trabecular region with a threshold-based algorithm.[8] Cortical and trabecular volume and density were measured with a precision of 0·6–1·4%. We derived diminution in total, cortical, and trabecular bone mass across age using a series of calculations (webappendix p 1).

Post-mortem specimens

Specimens of the right femur were removed from white women who died from illnesses unrelated to bone disease, and stored at –20°C. Samples were obtained 1 cm below the lesser trochanter, midshaft, and mid-femoral neck and were dehydrated and embedded in methyl methacrylate. Cross-sections were cut with a low-speed saw (Isomet, Lake Bluff, IL, USA) then ground and polished. The surfaces were carbon-coated and examined with a scanning electron microscope (FEI Quanta FEG [field emission gun] 200, Hillsboro, OR, USA) fitted with an annular solid-state back-scattered electron detector. We obtained consecutive and overlapping micrographs of every section at ×150 magnification to reconstruct the entire cross-section using Adobe Photoshop Elements 3. Pores (Haversian canals, Volkmann canals, and remodelling cavities) were placed into a separate image to calculate their areas and perimeters (Image Pro-Plus, version 4.1).

Osteons help to distinguish growth plate-derived trabeculae from cortical remnants, but the distinction is difficult. Trabecular surfaces of specimens from women older than 65 years were estimated on the assumption that 20% of bone in the section was trabecular and trabecular thickness was 100 μm. This assumption was conservative because trabecular fraction in old age is lower than 20% and most trabeculae have disappeared, so trabecular surfaces could be overestimated because they might be surfaces of cortical remnants. Specimens were submerged in 10 cm of 0·9% weight/volume saline and internally rotated 15° for measurement of bone mineral density (Lunar Prodigy DXA, Madison, WI, USA). The coefficient of variation was 2%.

The study was approved by the ethics committee of Austin Health, Melbourne, Australia. All women signed a consent form.

Statistical analysis

Analyses were done with SPSS (version 15.0). Differences between age groups in total, cortical, and trabecular bone mass, trabecular bone of cortical origin, and cortical and trabecular densities were expressed in absolute terms or as percentage differences (with 95% CI or SD) after height and weight adjustment. We used linear regression to examine age-related changes in cortical bone volume before and after adjustment for cortical density and to assess the relation between intracortical porosity and bone mineral density T scores. Unpaired *t* tests were used to compare diminution in cortical bone before and after inclusion of cortical remnants in the compact-appearing cortex and to assess diminution in trabecular bone before and after removal of cortical remnants from the marrow cavity. Significance levels (0·05) were two-tailed.

Role of the funding source

The sponsors of the study had no role in study design, data collection, analysis, or interpretation, or in the writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

We investigated 122 white women with a mean age of 62·8 (SD 19·4; range 27–98) years. Bone mass at the distal radius diminished between ages 50 and 80 years (n=89). Of the 106·5 mg hydroxyapatite lost with age, 68% (95% CI 63·5–71·7) was cortical and 32% (28·6–35·5) was trabecular, and only 16% (11·0–21·2) was lost between ages 50 and 64 years (n=34), whereas 84% (78·6–94·9) was lost subsequently (n=55; table). Between ages 50 and 64 years, trabecular bone mass decreased by 22·4% (12·1–32·6) and cortical bone mass by 4% (0·2–7·0) relative to their values at age 50 years (p<0·0001). Thus, trabecular bone diminished more rapidly than did cortical bone after menopause, but absolute amounts lost during these postmenopausal years were similar (table, figure 2). Bone loss did not lessen in old age; four-fold more bone was lost between age 65 and 80 years (n=22) than was lost between 50 and 64 years (n=34), and most bone lost in the 65–79 year age group was cortical, not trabecular (table). After age 80 years (n=33), about 90% of diminution in bone mass was cortical (table, figure 2).

Post-mortem femur specimens were obtained from 24 women with a mean age of 69 (range 29–99) years. In specimens from women younger than 50 years (n=2), the surface available for remodelling did not differ between cortical and trabecular compartments (p=0·67; figure 2) and cortical pores were uniformly distributed and of similar size (figure 3). In specimens from women aged 65–79 years (n=15) and 80 years and older (n=7), the intracortical surface produced by coalescent pores was larger than the trabecular surface (both p<0·0001) and larger than in specimens from young individuals, forming an average perimeter for remodelling of 2·5 m, reaching roughly 4 m per cross-section after age 65 years (figures 2–4). By age 80 years, surfaces were mainly intracortical (figures 2 and 3). Thus, bone loss in old age is mainly cortical because intracortical surfaces exceed trabecular surfaces.

With age, pores within the cortex adjacent to the marrow cavity coalesced, leaving cortical remnants that looked similar to trabeculae (figure 4). Only the remaining thinned cortex beneath the periosteum retained a compact

	n	Cortical loss			Trabecular loss (mg hydroxyapatite)	p value	Total bone loss (mg hydroxyapatite)
		Total cortical (mg hydroxyapatite)	By porosity in compact-appearing cortex (mg hydroxyapatite)	By porosity producing trabecularisation (mg hydroxyapatite)			
27–49 years	33	..	..	..	..	..	..
50–64 years	34	7·3 (2·8 to 11·7)	2·7 (-1·7 to 7·1)	4·6 (0·6 to 8·6)	9·7 (2·9 to 16·4)	0·55	17·1 (11·7 to 22·5)
65–79 years	22	50·2 (37·7 to 62·7)	12·4 (3·2 to 21·5)	37·8 (28·6 to 46·9)	22·9 (14·5 to 31·3)	0·001	73·1 (62·6 to 83·5)
≥80 years	33	14·6 (7·8 to 21·4)	7·1 (1·6 to 12·6)	7·5 (1·1 to 13·3)	1·7 (-2·8 to 6·0)	0·003	16·3 (10·5 to 22·1)
Total	122	72·1 (67·7 to 76·4)	22·2 (18·6 to 22·7)	49·9 (45·4 to 53·7)	34·3 (30·5 to 37·8)	<0·0001	106·5 (102·5 to 110·4)

Data are mean (95% CI). p values are for comparison of total cortical loss and trabecular loss.

Table: **Age-related bone loss in the intracortical and trabecular compartments**

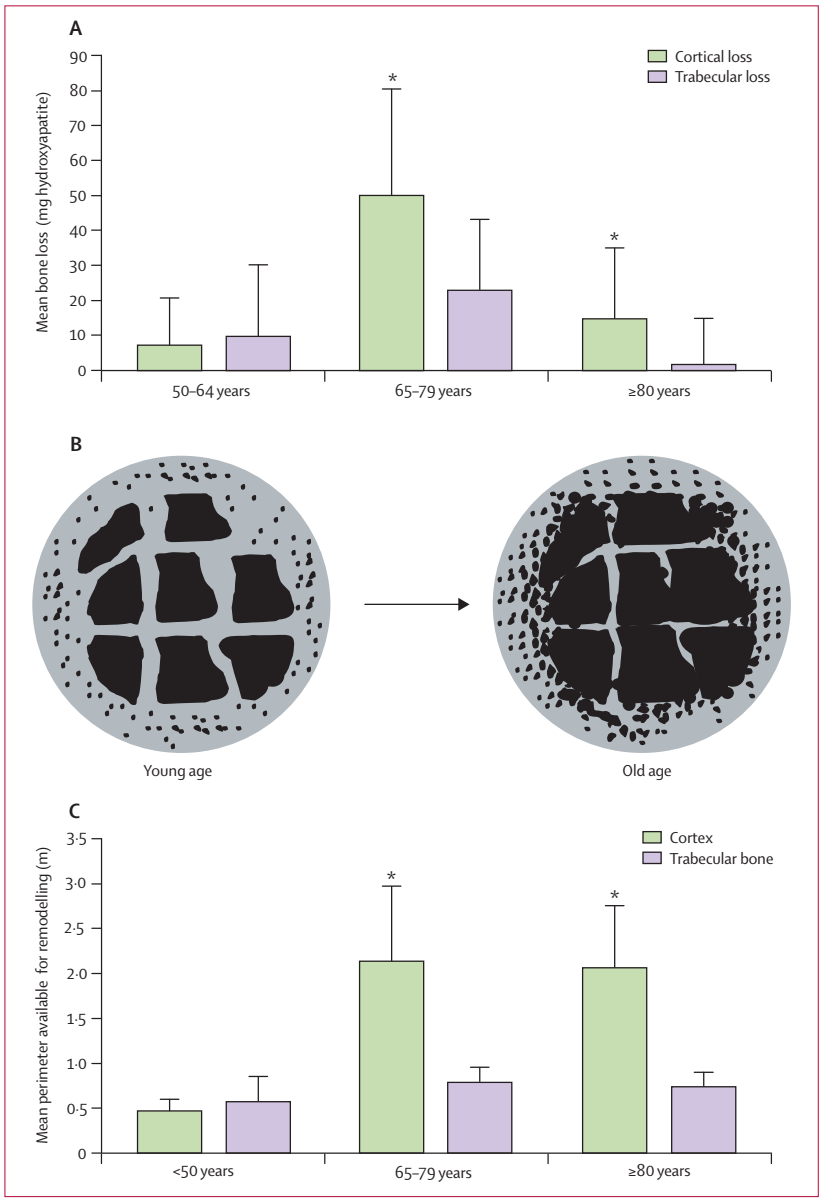

Figure 2: **Age-related bone loss and remodelling**
(A) Cortical and trabecular bone loss in the distal radius in different age groups. (B) Remodelling of cortical and trabecular bone. (C) Surface available for remodelling in cortical and trabecular compartments of post-mortem specimens from women in different age groups. Data were obtained at the subtrochanteric region. Error bars show SDs. *p<0·0001.

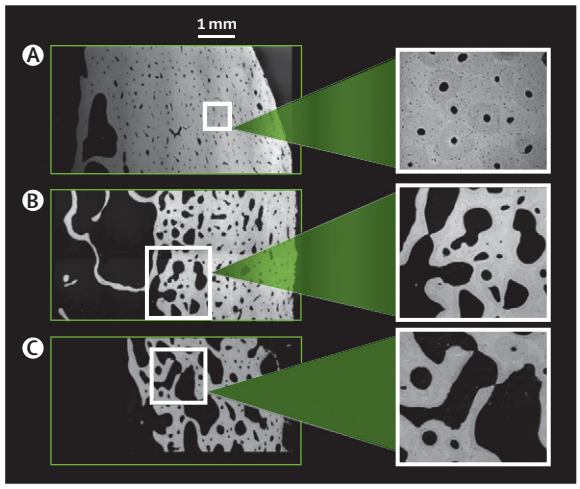

Figure 3: **Porosity in post-mortem specimens from three women of different ages**
(A) Micrograph of a specimen from a 29-year-old woman. Pores are regular in shape and evenly distributed in the cortex. (B) Micrograph of a specimen from a 67-year-old woman. Pores are large, irregularly shaped, and have coalesced in cortex adjacent to the marrow producing cortical remnants. (C) Micrograph of a specimen from a 90-year-old woman. Most of the cortex is trabecularised by large and coalesced pores. Micrographs are of anterior subtrochanteric specimens.

appearance and contained enlarged though not confluent pores. In old age, excavation of the remaining compact cortex left further cortical remnants. Examination showed intact endocortical surface in several regions, with extensively eroded cortex beneath, suggesting that cortical thinning can occur by coalescence of intracortical pores. If thinning occurred exclusively by endocortical resorption into cortex or by coalescence of endocortical and intracortical resorptive cavities, pores trabecularising cortex would communicate with the marrow cavity through the endocortical surface. Reconstruction of pores adjacent to the marrow into 3D images with high-resolution (12 µm) CT ex vivo confirmed that large coalescent pores (canals in longitudinal section) remained intracortical without communicating with the marrow cavity (specimens from a 78-year-old woman are shown in webvideo 1 and webvideo 2). Moreover, in the 122 women studied, the diminution in cortical volume with age (r –0·6, slope –3·1, intercept 1025·9, p<0·0001) was abolished after adjustment for cortical density, which is a surrogate of cortical porosity.

On the basis of ex-vivo specimen analysis, cortical remnants and trabeculae overlapped in size; diameters ranged from 50 µm to 500 µm for cortical remnants and from 50 µm to 300 µm for trabeculae (figure 5). As established with high-resolution peripheral quantitative CT in vivo, cortical remnants accounted for 2·1 mg (0·9–3·2) hydroxyapatite of the 33·8 mg hydroxyapatite (6%, 2·9–9·4) of trabecular-appearing bone present in the marrow cavity in women aged 50–64 years, 5·8 (4·4–7·1) of 25·6 mg hydroxyapatite (22·5%, 17·1–27·8) in women aged 65–79 years, and 17·6 (14·9–19·8) of 26·7 mg hydroxyapatite (66%, 56·0–74·1) in women aged 80 years and older. We concluded that trabecularisation of the cortex obscures true age-related trabecular bone loss. Between ages 50–64 years and 80 years and older, trabecular density at the distal radius decreased 18·2 mg (–1·4 to 38·2) hydroxyapatite per cm³ (13·7%, –1·1 to 28·7; p=0·06) before, but 68·7 mg (37·7–90·4) hydroxyapatite per cm³ (51·7%, 28·4–68·0; p<0·0001) after, exclusion of cortical remnants—ie, inclusion of cortical remnants in measurement of trabecular density led to a four-fold underestimation of age-related decrease. By age 80 years, trabecular density was overestimated by 45·7 mg

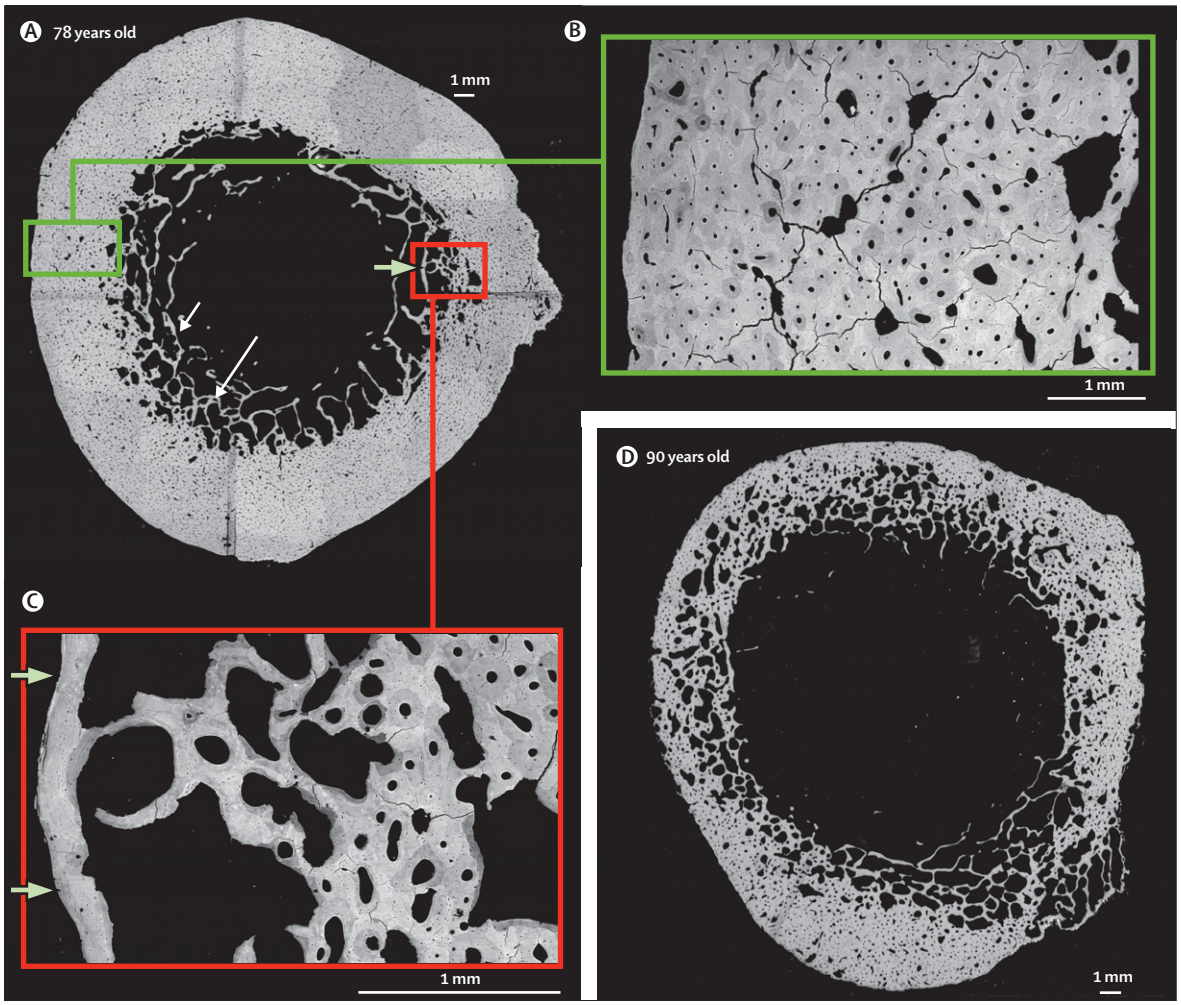

Figure 4: **Cortical porosity in post-mortem specimens from women aged 78 and 90 years**
(A) Micrograph of a specimen from a 78-year-old woman. Intracortical porosity is extensive and associated with cortical thinning due to transformation of the inner cortex into a trabecularised structure of cortical remnants. White arrows show areas containing cortical remnants. Cortex adjacent to periosteum (B) appears compact with enlarged pores, but without trabecularisation. The sum of perimeters of Haversian canals and remodelling cavities in the entire cross-section is 4·07 m. (C) The preserved endocortical envelope (shown by arrows) suggests that cortical thinning occurred from within the bone. (D) Micrograph of a specimen from a 90-year-old woman. Cortex is largely porous and looks similar to a sponge. Micrographs are from anterior subtrochanteric specimens. Cracks are preparation artifacts.

(16·0–108·1) hydroxyapatite per cm³ (66·5%, 23·3–157·1) when cortical remnants were erroneously included in the calculation (figure 5).

Comparison of micrographs at the subtrochanteric region and at the femoral midshaft in specimens from young and old women revealed the predominance of porosity trabecularising cortex adjacent to the marrow (figure 3; webappendix pp 2–4). Of the total diminution in bone mass at the distal radius between ages 50 and 80 years, 47% (40·0–52·1) was the result of porosity trabecularising the cortex and 21% (15·7–25·8) was the result of porosity in the cortex that remained compact (together producing 68% of the bone loss; table). By comparison, trabecular bone loss was 32%. Thus, intracortical remodelling and porosity trabecularising the cortex was the main source of bone loss and produced 1·5 times more bone loss than was recorded in the trabecular compartment. Between ages 50–64 years and 80 years and older, cortical density at the distal radius decreased by 127·8 mg (93·1–162·1) hydroxyapatite per cm³ (14·8%, 10·8–18·8; p<0·0001) before accounting for porosity that converted cortex adjacent to the marrow into cortical remnants, but 374·3 mg (318·2–429·5) hydroxyapatite per cm³ (43·4%, 36·9–49·8; p<0·0001) after—ie, omission of porosity producing cortical remnants led to a three-fold underestimate of the age-related increase in porosity. The magnitude of this underestimate increased with age (figure 5).

Cortical bone loss due to intracortical porosity was poorly captured by densitometry. In the subtrochanteric regions of post-mortem specimens, bone mineral density T scores correlated poorly with porosity (r –0·28, slope –0·05, intercept 0·28, p=0·19). Of 13 specimens with T scores higher than –1·0 SD, seven had high

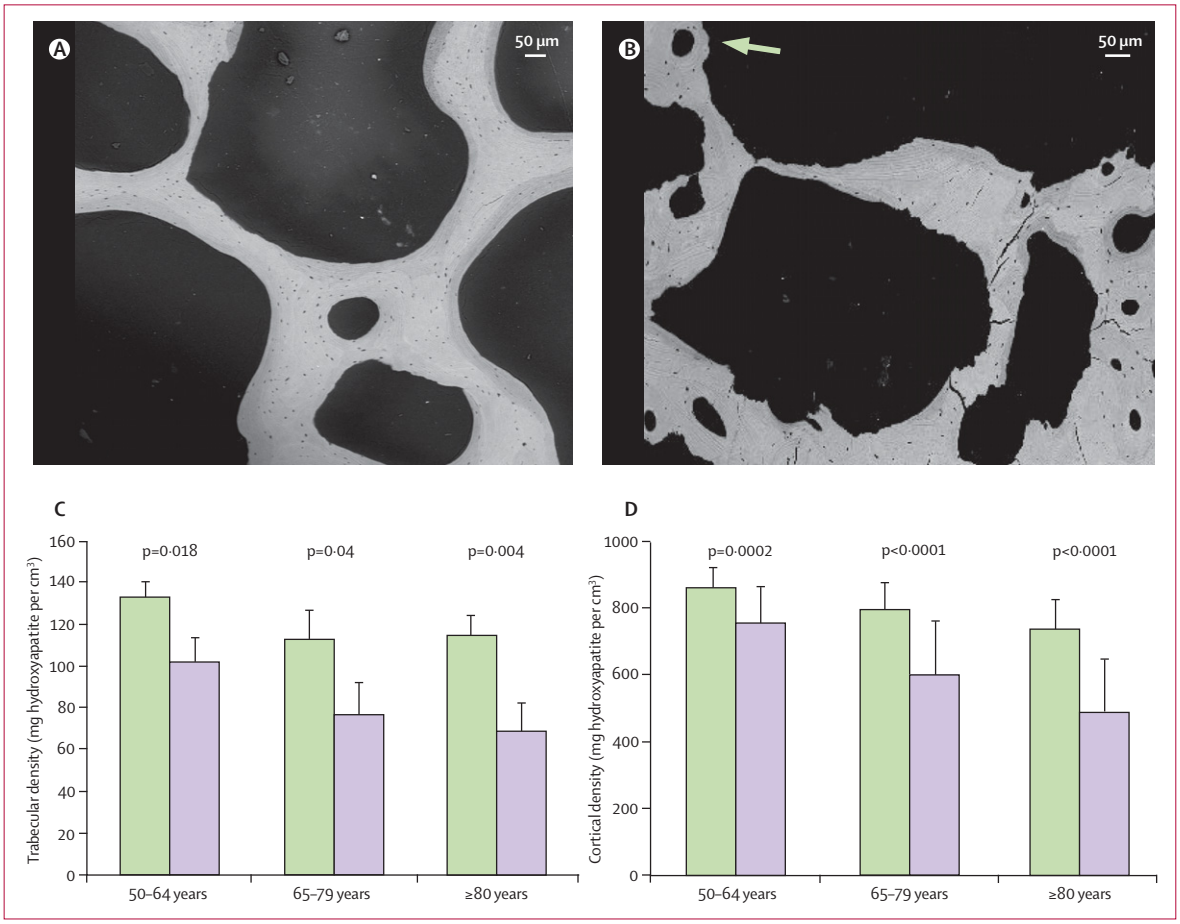

Figure 5: **Cortical and trabecular densities**

(A) Micrograph showing trabeculae of growth plate origin. Trabeculae are organised and have smooth surfaces. (B) Micrograph showing cortical remnants, which are chaotically connected and have crenated surfaces. Arrow shows an osteon present in a remnant, which is consistent with this sample being cortical in origin. Micrographs were obtained from femoral neck specimens. Cracks are preparation artifacts. Graphs show mean trabecular (C) and cortical (D) densities for the age groups. In (C), green bars show density when cortical remnants were included in the calculation; purple bars show density excluding cortical remnants. In (D), green bars show density when porosity that trabecularised the cortex was omitted from the calculation; purple bars show density when this porosity was included. p values are for comparison of high and low density estimates for each age group. Error bars show SDs.

porosity. Of 11 specimens with T scores lower than –1·0 SD (ie, osteopenia or osteoporosis), five had low porosity (<20%) (webappendix p 5).

Discussion

We report that, contrary to prevailing views, bone loss at peripheral sites in the first 15 years after menopause makes only a small contribution to total bone loss across life. These findings reconcile the epidemiology and pathogenesis of non-vertebral fractures; most fractures in old age are non-vertebral and occur at predominantly cortical sites after age 65 years, most bone loss occurs after this age, and most bone loss is cortical, not trabecular, at peripheral sites.[7] About 50% of cortical bone loss at peripheral sites was the result of remodelling within the cortex adjacent to the marrow. This intracortical remodelling thinned the cortex from within by cavitation, leaving cortical remnants that looked similar to trabeculae. Inclusion of these cortical remnants as trabeculae led to overestimation of trabecular density in old age, which in turn resulted in a four-fold underestimate of age-related trabecular bone loss. Additionally, calculation of porosity in the residual compact cortex without inclusion of porosity that trabecularised the cortex resulted in a three-fold underestimate of the age-related porosity increase. This porosity was not captured with bone densitometry or quantitative CT.

The dominance of cortical over trabecular bone loss in peripheral sites is probably attributable to the increasing exposure of intracortical surfaces that is produced by rising intracortical porosity, as incompletely refilled excavated sites increase in number and coalesce. By contrast, excavation of trabecular surfaces perforates and removes trabeculae with their surfaces, so a decreasing amount of remodelling occurs in the trabecular compartment. The enlarging intracortical surface area makes the large volume of cortical bone accessible to remodelling from the inside as well as from the

endocortical surface.[9] Han and colleagues[10] reported that the intensity of remodelling on the intracortical surface was twice that recorded on trabecular surfaces.

Recognition of the role of intracortical remodelling in pathogenesis of bone loss has important implications for understanding of bone fragility. Increased porosity reduces bone strength. A 4% rise in porosity increases crack propagation through bone by 84%.[11] An increase in porosity from 4% to 10% more than halves the peak stress that can be tolerated by bone before fracture.[12] The ability of bone to deform without cracking decreases three-fold as porosity increases from 4% to 20%.[13] The results of these ex-vivo experiments probably underestimate the effect of porosity on loss of bone strength in vivo, because the magnitude of porosity that we documented in elderly participants is up to 46% and makes cortical bone appear similar to a sponge (figure 4). The age-related increase in porosity from 4% in young adulthood to 12% around age 60 years is an underestimate.[14] Porosity is increased in patients with hip fractures.[15]

Cortical remnants have a chaotic trabecular architecture and are unlikely to confer equivalent strength to healthy trabecular bone (figure 5; webvideos 1 and 2). Evidence for compromised bone strength resulting from cortical remnants is indirect. In primary hyperparathyroidism, risk of vertebral fracture is increased, but trabecular density is normal or high.[16] We propose that bone strength is reduced because normal or high trabecular density is the result of cortical remnants, not a compensatory trabecular thickening in response to cortical bone loss or an anabolic effect of parathyroid hormone.[17]

Most people with fractures do not have osteoporosis (T score <–2·5 SD) and most with osteoporosis do not sustain fractures.[18] Bone mineral density was poorly associated with intracortical porosity; some individuals with normal density have high porosity showing bone loss and bone fragility, whereas individuals with osteoporosis can have low peak bone mass and low porosity with little bone loss. Hence, accounting for porosity could improve identification of individuals at high and low risk of fracture and therefore assist targeting of treatment.

Management refers to diagnosis, investigation, and treatment. We suggest that diagnosis (risk assessment) should include accurate assessment of bone structure, especially porosity producing trabecularisation (cortical remnants), because this process is the major source of bone loss. Present ex-vivo and in-vivo methods neglect intracortical porosity producing cortical remnants and so underestimate the age-related increase in porosity, age-related decrease in trabecular density (because cortical remnants are seen as trabeculae), and amount of bone lost, and so underestimate the age-related increase in fragility. New methods are needed to accurately quantify the true loss of cortical bone resulting from porosity in both compact and trabecularised cortex and the true loss of trabecular bone. From these data, improved sensitivity and specificity of identification and targeting of treatment to individuals at risk of fracture should be possible.

Despite evidence of heterogeneity in pathogenesis of bone fragility, approaches to treatment are not driven by specific pathogenetic mechanisms and morphology causing bone fragility in individual patients.[19] We suggest that management should be targeted at the prevailing structural abnormalities causing fragility. Both cortical and trabecular bone are likely to be lost early, and drugs affecting both types will be appropriate. Late in life, when little trabecular bone remains, drugs targeting cortical bone will be needed. Individuals with high intracortical remodelling and evolving porosity might need early intervention, perhaps before age 65 years, because treatment initiated late (as is commonly done) is unlikely to reverse severe porosity. Targeting of these individuals is feasible because methods now exist to assess cortical porosity in vivo.[20,21]

Present treatments reduce non-vertebral fractures by only 20–30%. Studies are needed to better define mechanisms causing fragility of cortical bone, and when this research is complete, new targets might emerge—for example, intracortical remodelling and porosity. Only one group of investigators using an antiresorptive drug reported a reduction in porosity, and this finding was confined to reduction of pores of small dimensions.[22] Non-vertebral fracture risk reduction is about half the anti-vertebral fracture effectiveness reported with the same drugs.[23] Few treatments reduce hip fractures in people older than 75 years when porosity is coalescent and cortical thinning is severe.[24,25] Although this finding might be the result of the contribution of trauma and changes in material composition of bone, cortical porosity is likely to be an important contributor to fragility. Treatment is either initiated too late or might have little effect on intracortical remodelling.

Our findings do not diminish the contribution of trabecular bone to pathogenesis of bone fragility. Accelerated trabecular bone loss is important in pathogenesis of vertebral fractures, but cortical bone loss is also likely to contribute. The roles of cortical bone, intracortical remodelling, and porosity in vertebral fragility need further study. Investigators have reported a proportion of cortical bone in vertebral bodies ranging from 30% to 60%, with the cortex contributing 38–75% of the vertebral body's strength.[26–29]

The cross-sectional design of our study was a limitation, because we inferred losses in bone mass from comparison across ages. Secular trends in porosity might have produced errors in estimation of age-related increases in porosity. Similarly, that we noted thinner cortices in old individuals than in their younger counterparts might have been partly attributable to some individuals having thin cortices at the completion of growth, rather than cortical bone loss. However, any error introduced was likely to have been small because young people nowadays are taller and have thinner and probably more porous cortices than did their

predecessors.[30] Large bones have low cortical density, which is a surrogate measure of porosity (Zebaze and co-workers, unpublished results). Another potential limitation was the use of a threshold-based image segmentation algorithm, which might have affected the relative amounts of cortical and trabecular bone according to the threshold used. However, our findings were substantiated by direct measurement from scanning electron microscope images.

Our results have implications for the epidemiology, pathogenesis, investigation, and therapeutic treatment of bone fragility. Most fractures in old age are not vertebral and most occur after rather than before age 65 years. Most bone loss is cortical, not trabecular, and occurs after age 65 years by intracortical rather than endocortical or trabecular remodelling. Bone loss and resulting structural decay are poorly captured by methods used in clinical and research settings. Failure to recognise the magnitude of intracortical remodelling, the effect of intracortical porosity in producing most of the bone loss with age, and the resultant structural decay and fragility disregards valuable information. Identification of the mechanisms causing intracortical remodelling is likely to improve our understanding of the pathogenesis of bone fragility and increase the sensitivity and specificity of fracture-risk prediction. Recognition of the role of intracortical porosity in bone fragility also provides a reasoned approach to deciding when and whom to treat and provides a new target for the prevention and reversal of bone fragility.

Contributors

RMDZ, RIP, EJM, and ES designed the study, interpreted the data, and wrote the report. RMDZ, AG-Z, and AB analysed the data. RMDZ, AG-Z, AB, SI-B, and MM obtained and handled participants' data. Specifically, AB and MM were responsible for in-vitro experiments, whereas AG-Z and SI-B were responsible for in-vivo experiments. RMDZ contributed to both in-vitro and in-vivo experiments.

Conflicts of interest

We declare that we have no conflicts of interest.

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