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Original Article

ORIGINAL ARTICLE

BJØRNEREM ET AL.

MICROSTRUCTURAL DETERIORATION DURING MENOPAUSE

Menopause-Related Appendicular Bone Loss is Mainly Cortical and Results in Increased Cortical Porosity[1]

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ABSTRACT

After menopause, remodeling becomes unbalanced and rapid. Each of the many remodeling transactions deposits less bone than it resorbed, producing microstructural deterioration. Trabecular bone is said to be lost more rapidly than cortical bone. However, because 80% of the skeleton is cortical, we hypothesized that most menopause-related bone loss and changes in bone microstructure are cortical, not trabecular, in origin, and the result of intracortical remodeling. Distal tibial and distal radial microstructure were quantified during 3.1 years (range, 1.5 to 4.5 years) of follow-up using high-resolution peripheral quantitative computed tomography and StrAx1.0 software in 199 monozygotic and 125 dizygotic twin pairs aged 25 to 75 years in Melbourne, Australia. The annual increases in tibial cortical porosity accelerated, being 0.44%, 0.80%, and 1.40% in women remaining premenopausal, transitioning to perimenopause, and from perimenopausal to postmenopause, respectively. Porosity increased in the compact-appearing, outer, and inner transitional zones of the cortex (all $p < 0.001$). The annual decrease in trabecular bone volume/tissue volume (BV/TV) also accelerated, being 0.17%, 0.26%, and 0.31%, respectively. Little bone loss was observed before menopause. The reduction in BV/TV was due to a decrease in trabecular number ($p < 0.001$). The greatest bone loss, 7.7 mg hydroxyapatite (HA) annually, occurred in women transitioning from perimenopausal to postmenopause and of this, 6.1 mg HA (80%) was cortical. Results were similar for the distal radius. Despite microarchitectural changes, no significant bone loss was observed before menopause. Over 90% of appendicular bone loss occurs during and after menopause, over 80% is cortical, and this may explain why 80% of fractures are appendicular. © 2017 American Society for Bone and Mineral Research

KEYWORDS: BONE MICROARCHITECTURE; CORTICAL POROSITY; MENOPAUSE; PROSPECTIVE STUDY; TRABECULAR BONE

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Introduction

The microstructural design and material composition of bone are maintained by bone remodeling.[1,2] This cell-mediated renewal process is initiated at discrete points upon the surfaces of trabeculae, intracortical canals, and the endocortical surface lining the medullary canal.[3] Trabeculae are thin plate-like structures with a large surface area/matrix volume configuration that is an advantage for damage repair. When remodeling is initiated at points upon this surface, bone matrix is readily accessible to osteoclasts that remove it and osteoblasts that replace it with new bone.[1]

Cortical bone is assembled as a thick compact shell traversed by interconnected canals.[4] These canals are contained within a cortical bone volume that is fourfold larger than trabecular bone volume. Consequently, cortical bone has a lower surface area/matrix volume configuration that is less accessible to cells resorbing and replacing damaged bone. Thus, cortical bone is held to be remodeled more slowly than trabecular bone.[1]

During young adulthood remodeling is balanced; the volume of bone resorbed is replaced by an identical volume of new bone so no net structural deterioration occurs.[1,2] Around the time of menopause or shortly before, remodeling becomes unbalanced and rapid.[5] Now the large trabecular surface area becomes a liability.[6,7] Each of the many more remodeling events deposits less bone than was excavated making plate-like trabeculae more rod-like and producing trabecular perforation and complete loss of trabeculae.[8,9] Unbalanced remodeling upon intracortical canals and upon the endocortical surface lining the medullary canal produces cortical porosity and thinning.[4,6,10]

The rapidity of remodeling of trabecular bone, its reported loss prior menopause, and the appearance of cortical bone loss mainly after menopause, led to the view that the bone fragility predisposing to vertebral and distal radial fractures of postmenopausal osteoporosis is largely due to trabecular bone loss.[11–13] However, not all studies report bone loss before menopause, and some studies suggest bone loss is predominantly cortical in origin.[4,6]

Defining the relative contributions of cortical and trabecular bone to total bone

loss is important because over 80% of the skeleton is cortical.[4] Cortical bone is a major determinant of the strength of the appendicular skeleton,[14] the location of over 70% of all fractures in the community.[15] Moreover, making a compact structure such as the cortex porous reduces its strength more greatly that worsening the porosity of an already porous sponge-like structure like trabecular bone.[16]

We therefore hypothesized that (i) little bone loss occurs before menopause because remodeling remains balanced, (ii) most bone loss occurs during and after menopause, (iii) although trabecular bone is believed to be lost more rapidly than cortical bone, most bone loss will be cortical in origin because 80% of the skeleton is cortical.

Subjects and Methods

Subjects

We studied 324 healthy female twin pairs, 199 monozygotic (MZ) pairs, and 125 dizygotic (DZ) pairs, aged 27 to 75 years at baseline in Melbourne, Australia, during 2008–2011.[6,17] The twins were followed-up in 2011–2013. We excluded 39 women treated with hormone replacement therapy. After excluding bone scans with movement artifacts, we had valid measurements of the distal tibia and distal radius at both visits in 388 and 314 women, respectively. Of the 388 women, 180 (43.4%) remained premenopausal (a regular cycle in the last 3 months), 54 (13.0%) premenopausal women became perimenopausal (no cycles for 3 to 12 months), 34 (8.2%) perimenopausal women became postmenopausal (amenorrhea for >1 year), and 118 (28.4%) were postmenopausal at baseline. All women gave written informed consent. The Austin Health Ethics Committee approved the study.

Bone microstructure

High-resolution three-dimensional (3D) peripheral quantitative computed tomography (HR-pQCT) (XtremeCT; Scanco Medical AG, Brüttisellen, Switzerland; isotropic resolution of 82 μm) was used to obtain images at the nondominant distal tibia and distal radius.[18,19] Images were obtained with the X-ray source potential set to 60 kVp and a current of 900 μA. Scanning (integration) time was 2.8 min.

The cortical and trabecular microstructure derived by image acquisition is based on photon attenuation by mineralized bone. The region of interest consisted of 110 CT slices obtained at 22.5 and 9.5 mm from a reference line at the endplate of the distal tibia

and distal radius, respectively. Scanning was done at a fixed distance from the endplate to maintain the same region of interest in this longitudinal study. The 49 most proximal slices were chosen because the relatively thicker cortex allows accurate assessment of porosity.

Porosity within the total cortex and its compartments (compact cortex, outer and inner transitional zones), matrix mineralization density, trabecular number, thickness, separation, and bone volume/tissue volume (BV/TV) were quantified using StrAx1.0, a non–threshold-based method that automatically segments bone from background, and then into its compartments in vivo (Straxcorp, Melbourne, Australia). The in vivo precision was 0.5% to 3.0%.[20] Daily quality control was carried out by scanning a phantom containing rods of hydroxyapatite (HA) (QRM Moehrendorf, Germany).

Porosity is the proportion of voxels within the cortical compartment that contain void. Once deposited, osteoid is mineralized reaching ≥80% of full mineralization (1200 mg HA/cm^3) within days. Matrix mineralization is quantified using StrAx1.0 by determining the mean density of voxels with attenuation between 80% and 100% of fully mineralized bone. These voxels are unlikely to contain a pore because a pore results in voxel attenuation <80% of the maximum. So, variation attenuation within 80% to 100% of full mineralization reflects heterogeneity in mineralization. Voxels attenuating photons <80% are used to calculate porosity.

Statistical analysis

Results are presented as means ± standard deviations (SDs). Absolute rates of change were calculated as the difference between the baseline and follow-up divided by years of follow-up. The percentage change was the absolute change divided by the baseline value. We tested whether the trait change differed from zero in women remaining premenopausal or transitioning from premenopausal to perimenopausal, perimenopausal to postmenopause, or moving further into the postmenopausal years. To account for the correlation within pairs we used the generalized estimating equation (GEE) method in regression analysis. All analyses were carried out using STATA software, version 13 (Stata Corporation, Inc., College Station, TX, USA; http://www.stata.com). Values of *p* were two-sided and significant if <0.05.

Results

Baseline and annual changes during 3.1 years (range, 1.5 to 4.5 years) in microstructure are shown in twins aged 25 to 75 years (Tables 1 and 2; Figs. 1–3). Details below refer to the distal tibia. Results for the distal radius were similar and are confined to the tables.

<Insert Table 1>

<Insert Table 2>

<Insert Figure 1>

<Insert Figure 2>

<Insert Figure 3>

Changes in morphology prior, during, and after menopause

The annual increase in cortical porosity accelerated during menopause, being 0.44% in women remaining premenopausal, doubling to 0.80% in women transitioning from premenopause to perimenopause, and tripling to 1.40% in women transitioning from perimenopause to postmenopause (all $p < 0.001$, Table 2, Fig. 1). In postmenopausal women remaining so, porosity increased by 0.83% annually (all $p < 0.001$). This pattern of increase in porosity was similar in the compact-appearing, outer and inner transitional zones of the cortex (all $p < 0.001$). The increase in porosity was associated with a decrease in matrix mineralization density ($p < 0.001$, Fig. 3).

Trabecular BV/TV decreased in premenopausal women remaining so, in women transitioning from premenopause to perimenopause, perimenopause to postmenopause, and in women remaining postmenopausal (Fig. 2). The reduction in trabecular BV/TV was associated with a decrease in trabecular number, an increase in residual trabecular thickness and separation (all $p < 0.001$, Table 2, Fig. 2).

Absolute amounts of cortical and trabecular bone lost

No significant annual bone loss was observed before menopause (Table 2, Fig. 4). The annual absolute amount of bone lost was 0.3 mg HA in women remaining premenopausal ($p = 0.586$) and 1.4 mg HA in women transitioning from premenopause to perimenopause ($p = 0.117$).

<Insert Figure 4>

The greatest amount of bone lost annually, 7.7 mg HA, occurred in women transitioning from perimenopause to postmenopause, and of this, 6.1 mg HA (80%) was cortical ($p < 0.001$, Table 2, Fig. 4). Of the 7.0 mg HA lost annually in postmenopausal

women remaining so, 6.0 mg HA (86%) was cortical ($p < 0.001$). The annual percentage amount of bone loss and change in bone microstructure are shown in Table 3.

<Insert Table 3>

Discussion

We report that cortical and trabecular microarchitecture deteriorate modestly with evidence of trabecular, but no net cortical, bone loss before menopause. Over 90% of bone loss occurs during and after menopause and over 80% of this bone loss is cortical in origin. Cortical bone is lost as a result of unbalanced intracortical remodeling, which increases cortical porosity. Trabecular bone is lost by perforation with complete loss of trabeculae leading to increased trabecular spacing.

The most rapid bone loss occurred in women transitioning from perimenopausal to postmenopause. The inverse association between porosity and matrix mineral density is likely to reflect rapid remodeling, which deteriorates microstructure but also reduces matrix mineral density as younger less mineralized bone replaces older more fully mineralized bone during each remodeling transaction.

Bone loss before menopause is modest

The necessary and sufficient morphological basis of bone loss and microstructural deterioration is remodeling imbalance; the deposition of a smaller volume of bone than was resorbed during a remodeling transaction.[1–3] The appearance of this negative bone balance is reported to occur around 40 to 45 years of age and worsens after menopause.[13] Sex hormone deficiency is accompanied by increases in the lifespan of osteoclasts, which excavate and perforate trabeculae rather than thinning them.[6,8,9] A reduction in the lifespan of osteoblasts also occurs worsening the remodeling imbalance.[7]

We observed both trabecular bone loss with a decrease in trabecular numbers and cortical bone loss with increased cortical porosity before menopause, but the amount of bone lost was modest and much less than observed in women transitioning into the perimenopause and postmenopause.

Bone loss accelerates during menopause and is mainly cortical, not trabecular

Trabecular bone is only 20% of the total bone matrix volume and so accounted for only ~20% of all the bone lost annually during and after menopause. The complete loss of

trabeculae resulted in lessening of trabecular bone loss because these structures are completely and irreversibly resorbed leaving disconnected widely spaced trabeculae. Mean trabecular thickness increased because of preferential loss of thinner trabeculae.[6]

Cortical bone constitutes 80% of skeletal mineralized bone volume.[4] This fourfold larger volume is held to be enveloped by *relatively* smaller bone surface area comprising the intracortical surface formed by the canals traversing the cortex and the endocortical surface lining the medullary canal. Consequently, the larger cortical bone volume is believed to be remodeled and lost more slowly than the trabecular bone volume, which is held to have a larger trabecular bone surface area per unit bone volume. We confirm that cortical bone accounted for 70% of all the bone lost during and after menopause but we did not detect more rapid loss of trabecular than cortical bone in this prospective study.[4,6]

Unlike the self-limiting nature of trabecular bone loss, cortical bone loss was self-perpetuating.[6] Intracortical remodeling initiated upon canal surfaces enlarge them focally, they coalesce and so the internal surface area formed by the enlarged canals facilitates more remodeling of an ever-decreasing cortical matrix volume. Trabecular surfaces decrease as trabeculae are lost but cortical surfaces increase as intracortical porosity increases. The latter provides a greater surface area for remodeling to be initiated upon and so cortical bone loss continues. Indeed, Han and colleagues[21,22] report that remodeling upon intracortical and endocortical envelopes contributes about 50% of the total surface participating in remodeling while the remaining 50% proceeds upon the trabecular envelope. Hence the notion of the greater surface area to bone matrix volume ratio of trabecular than cortical bone may need reassessment.

The inability to detect the rise in cortical porosity before menopause is likely to be the result of errors in image analysis.[20] At a voxel size of 82 μm and spatial resolution of 100 to 120 μm, voxels containing a pore also contain matrix, which excludes that voxel and its porosity from analysis, underestimating the rise in cortical porosity before and during menopause.

The most rapid bone loss occurred in women transitioning from perimenopause to postmenopause. As women become postmenopausal, the number of remodeling sites upon the trabecular, intracortical, and endocortical surfaces increases the surface extent

of resorption, which exceeds the surface extent of formation because fewer remodeling sites initiated in early in menopause are only now entering their refilling phase.[7] (Refilling is not instantaneous, there is a delay and then refilling occurs over several months, so refilling of cavities dug in early menopause occurs some months later.)

This perturbation of the surface extent of resorption and formation is responsible for the accelerated net loss of trabeculae and accelerated rise in cortical porosity. Slowing of loss occurs later, not because remodeling slows, but rather because the surface extents of resorption and formation increase, but again resemble each other and proceed as the high rate of remodeling continues in the postmenopause. The many cavities being excavated are now matched by incomplete refilling of the similarly high numbers of resorption sites initiated in perimenopause.[23] Bone loss and structural deterioration continue, but more slowly than during the accelerated phase of bone loss.[24]

Cortical and trabecular bone loss and bone fragility

The notion that rapid trabecular bone loss, vertebral fractures, and forearm fractures are hallmarks of postmenopausal osteoporosis needs reappraisal.[4,25–27] About 80% of all fractures in the community are nonvertebral and occur at locations composed primarily of cortical bone. Cortical bone loss accounts for ~70% of all appendicular bone loss; only ~30% is trabecular.[4] Of the cortical bone lost, most is lost by intracortical remodeling producing intracortical porosity. An increase in porosity in "compact" cortical bone reduces its resistance to bending out of proportion to the amount of bone lost.[16]

This study has several limitations. The sample size and number of twin pairs are modest and follow-up is relatively short. Measurements of microarchitecture are vulnerable to movement artifact, particular at the distal radius. Only microstructure of peripheral sites can be quantified using HR imaging technology, so menopausal changes in microstructure at the spine and proximal femur could not be assessed. Changes at these latter sites during menopause may differ from the observations made at these peripheral sites. We could not determine whether the increase in porosity was due to an increase in the size of existing canal cross-sections, creation of new canals, or both. In the derivation of matrix mineral density, a contribution of pores under 25 μm in diameter cannot be excluded.

In summary, little bone is lost before menopause. Bone loss becomes detectable

when remodeling imbalance appears and remodeling rate accelerates at the time of menopause. Trabecular bone loss is self-limiting because perforation removes them. Cortical bone loss is self-perpetuating because intracortical remodeling increases the surface available for initiation of remodeling so that more of the larger cortical bone matrix volume is remodeled and lost accounting for most bone loss. Cortical bone loss has a more deleterious effect on cortical strength than does trabecular bone loss on trabecular strength and is likely to contribute to the occurrence of nonvertebral fractures, which constitute 80% of all fractures.

Disclosures

AGZ is remunerated by StraxCorp as senior image analyst. RZ has received grant and/or research support from Amgen, Merck Sharp & Dohme, Servier, Warner-Chilcott, AKP, Genzyme, Sanofi, GSK, and Pfizer; he is a shareholder and a director of the board of StraxCorp. ES has received research support and lecture fees from Amgen, Allergan, Asahi, Genzyme, and Merck Sharp & Dohme; he is a director of the board and shareholder in StraxCorp. The remaining authors state that they have no conflicts of interest.

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Authors' roles: Study design and conduct: ÅB, XW, MB, AGZ, RZ, JLH, and ES. Data collection: ÅB, AGZ, and XW. Responsibility for StrAx analysis: RZ. Statistical analyses: MB. Drafting manuscript: ÅB, XW, MB, AGZ, RZ, JLH, and ES. Data interpretation and approving final version of manuscript: ÅB, XW, MB, AGZ, RZ, JLH, and ES.

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References

1. Parfitt AM. Skeletal heterogeneity and the purposes of bone remodelling: implications for the understanding of osteoporosis. In: Marcus R, Feldman D, Nelson DA, Rosen CJ, editors. Osteoporosis. San Diego, CA: Academic Press; 2008. p. 71–89.

2. Parfitt AM. Targeted and non-targeted bone remodeling: relationship to basic

multicellular unit origination and progression. Bone. 2002;30(1):5–7.
3. Parfitt AM, Mathews CH, Villanueva AR, Kleerekoper M, Frame B, Rao DS. Relationships between surface, volume, and thickness of iliac trabecular bone in aging and in osteoporosis. Implications for the microanatomic and cellular mechanisms of bone loss. J Clin Invest. 1983;72(4):1396–409.
4. Zebaze RM, Ghasem-Zadeh A, Bohte A, et al. Intracortical remodelling and porosity in the distal radius and post-mortem femurs of women: a cross-sectional study. Lancet. 2010;375(9727):1729–36.
5. Seeman E, Delmas PD. Bone quality—the material and structural basis of bone strength and fragility. N Engl J Med. 2006;354(21):2250–61.
6. Bjørnerem Å, Ghasem-Zadeh A, Bui M, et al. Remodeling markers are associated with larger intracortical surface area but smaller trabecular surface area: a twin study. Bone. 2011;49(6):1125–30.
7. Seeman E. Age- and menopause-related bone loss compromise cortical and trabecular microstructure. J Gerontol A Biol Sci Med Sci. 2013;68(10):1218–25.
8. Eriksen EF, Langdahl B, Vesterby A, Rungby J, Kassem M. Hormone replacement therapy prevents osteoclastic hyperactivity: a histomorphometric study in early postmenopausal women. J Bone Miner Res. 1999;14(7):1217–21.
9. Manolagas SC. Choreography from the tomb: an emerging role of dying osteocytes in the purposeful, and perhaps not so purposeful, targeting of bone remodeling. Bonekey Osteovision. 2006;3:5–14.
10. Shigdel R, Osima M, Ahmed LA, et al. Bone turnover markers are associated with higher cortical porosity, thinner cortices, and larger size of the proximal femur and non-vertebral fractures. Bone. 2015;81:1–6.
11. Riggs BL, Wahner HW, Melton LJ III, Richelson LS, Judd HL, Offord KP. Rates of bone loss in the appendicular and axial skeletons of women. Evidence of substantial vertebral bone loss before menopause. J Clin Invest. 1986;77(5):1487–91.
12. Riggs BL, Melton IL III, Robb RA, et al. Population-based study of age and sex differences in bone volumetric density, size, geometry, and structure at different skeletal sites. J Bone Miner Res. 2004;19(12):1945–54.
13. Riggs BL, Melton LJ, Robb RA, et al. A population-based assessment of rates of

bone loss at multiple skeletal sites: evidence for substantial trabecular bone loss in young adult women and men. J Bone Miner Res. 2008;23(2):205–14.
14. Holzer G, von Skrbensky G, Holzer LA, Pichl W. Hip fractures and the contribution of cortical versus trabecular bone to femoral neck strength. J Bone Miner Res. 2009;24(3):468–74.
15. Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson A. The burden of osteoporotic fractures: a method for setting intervention thresholds. Osteoporos Int. 2001;12(5):417–27.
16. Schaffler MB, Burr DB. Stiffness of compact bone: effects of porosity and density. J Biomech. 1988;21(1):13–6.
17. Bjørnerem Å, Bui QM, Ghasem-Zadeh A, Hopper JL, Zebaze R, Seeman E. Fracture risk and height: an association partly accounted for by cortical porosity of relatively thinner cortices. J Bone Miner Res. 2013;28(9):2017–26.
18. Laib A, Hauselmann HJ, Ruegsegger P. In vivo high resolution 3D-QCT of the human forearm. Technol Health Care 1998;6(5–6):329–37.
19. Boutroy S, Bouxsein ML, Munoz F, Delmas PD. In vivo assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. J Clin Endocrinol Metab. 2005;90(12):6508–15.
20. Zebaze R, Ghasem-Zadeh A, Mbala A, Seeman E. A new method of segmentation of compact-appearing, transitional and trabecular compartments and quantification of cortical porosity from high resolution peripheral quantitative computed tomographic images. Bone. 2013;54(1):8–20.
21. Han ZH, Palnitkar S, Rao DS, Nelson D, Parfitt AM. Effect of ethnicity and age or menopause on the structure and geometry of iliac bone. J Bone Miner Res. 1996;11(12):1967–75.
22. Han ZH, Palnitkar S, Rao DS, Nelson D, Parfitt AM. Effects of ethnicity and age or menopause on the remodeling and turnover of iliac bone: implications for mechanisms of bone loss. J Bone Miner Res. 1997;12(4):498–508.
23. Seeman E. Pathogenesis of bone fragility in women and men. Lancet. 2002;359(9320):1841–50.
24. Burt LA, Bhatla JL, Hanley DA, Boyd SK. Cortical porosity exhibits accelerated rate

of change in peri- compared with post-menopausal women. Osteoporos Int. 2017;28(4):1423–31.
25. Zebaze R, Seeman E. Cortical bone: a challenging geography. J Bone Miner Res. 2015;30(1):24–9.
26. Bala Y, Zebaze R, Ghasem-Zadeh A, et al. Cortical porosity identifies women with osteopenia at increased risk for forearm fractures. J Bone Miner Res. 2014;29(6):1356–62.
27. Ahmed LA, Shigdel R, Joakimsen RM, et al. Measurement of cortical porosity of the proximal femur improves identification of women with nonvertebral fragility fractures. Osteoporos Int. 2015;26(8):2137–46.

Figure Captions

Fig. **1.** Annual changes of the distal tibia porosity of the total cortex, CC, OTZ, and ITZ, by baseline age in women remaining premenopausal (yellow dots), becoming perimenopausal (green dots), becoming postmenopausal (orange dots), and remaining postmenopausal (white dots). CC = compact-appearing cortex; OTZ = outer transitional zone; ITZ = inner transitional zone.

Fig. **2.** Annual changes of the distal tibia trabecular BV/TV, trabecular number, trabecular thickness, and trabecular separation by baseline age in women remaining premenopausal (yellow dots), becoming perimenopausal (green dots), becoming postmenopausal (orange dots), and remaining postmenopausal (white dots). BV/TV = bone volume/tissue volume.

Fig. **3.** Annual changes of the distal tibia matrix mineralization density by baseline age in in women remaining premenopausal (yellow dots), becoming perimenopausal (green dots), becoming postmenopausal (orange dots) and remaining postmenopausal (white dots). The inverse association between baseline porosity of the total cortex and matrix mineral density, and the inverse association between annual change in porosity and matrix mineralization density (both $p < 0.001$).

Fig. **4.** Amount of tibial cortical and trabecular bone loss as a percentage of annual loss of

total (BMC) (mg HA) in women Pre to Pre, Pre to Peri, and Post to Post. Values of *p* within each group tested whether the total annual losses were different from zero. BMC = bone mineral content; HA = hydroxyapatite; Pre to Pre = premenopausal remaining premenopausal; Pre to Peri = premenopausal becoming perimenopausal; Post to Post = postmenopausal remaining postmenopausal.

Table 1. Baseline Microarchitecture of the Distal Tibia and Distal Radius by the Menopausal Stage of the Participants

	Premenopausal remaining premenopausal	Premenopausal to perimenopausal	Perimenopausal to postmenopausal	Postmenopa
Age (years), mean (range)	40.7 (27–50)	47.5 (40–54)	51.8 (46–55)	60.5 (48–
Distal tibia, sample size, *n*	180	56	34	118
Total cortical porosity (%)	57.9 ± 4.57	56.7 ± 4.13	58.4 ± 5.54	64.7 ± 6.
Compact cortical porosity (%)	39.2 ± 4.55	38.0 ± 4.38	40.7 ± 6.62	48.0 ± 7.
Outer TZ porosity (%)	40.2 ± 3.39	39.5 ± 2.93	41.7 ± 4.76	48.5 ± 7.
Inner TZ porosity (%)	84.1 ± 2.88	83.6 ± 2.35	83.9 ± 2.70	86.5 ± 3.
Cortical BMC (mg HA)	571 ± 74.6	563 ± 69.9	559 ± 73.7	495 ± 82
Matrix mineralization density (%) (%)(%)	65.7 ± 1.25	66.4 ± 1.09	65.9 ± 1.29	63.8 ± 1.
Trabecular number (1/mm)	2.81 ± 0.57	2.94 ± 0.52	2.99 ± 0.57	2.41 ± 0.
Trabecular thickness (mm)	0.19 ± 0.01	0.19 ± 0.01	0.19 ± 0.01	0.19 ± 0.
Trabecular separation (mm)	1.30 ± 0.25	1.26 ± 0.22	1.25 ± 0.25	1.47 ± 0.
Trabecular BMC (mg HA)	228 ± 76.1	219 ± 77.6	230 ± 74.3	207 ± 89
Total BMC (mg HA)	799 ± 121	781 ± 110	789 ± 114	702 ± 13
Distal radius, sample size, *n*	157	43	24	90
Total cortical porosity (%)	53.2 ± 5.73	50.8 ± 4.17	51.2 ± 5.52	57.8 ± 7.
Compact cortical porosity (%)	35.3 ± 4.13	33.5 ± 3.37	34.1 ± 4.30	41.4 ± 7.
Outer TZ porosity (%)	38.6 ± 3.19	37.1 ± 2.41	37.7 ± 2.92	45.0 ± 6.
Inner TZ porosity (%)	84.7 ± 3.08	83.8 ± 2.67	84.4 ± 2.60	86.1 ± 3.
Cortical BMC (mg HA)	267 ± 42.7	271 ± 32.6	278 ± 40.0	238 ± 43
Matrix mineralization density (%)	66.4 ± 1.53	67.2 ± 1.13	67.3 ± 1.22	65.0 ± 1.
Trabecular number (1/mm)	2.30 ± 0.55	2.48 ± 0.39	2.44 ± 0.52	2.07 ± 0.
Trabecular thickness (mm)	0.19 ± 0.01	0.19 ± 0.01	0.19 ± 0.01	0.20 ± 0.
Trabecular separation (mm)	1.40 ± 0.34	1.30 ± 0.24	1.35 ± 0.25	1.52 ± 0.
Trabecular BMC (mg HA)	64.8 ± 26.3	61.4 ± 20.7	62.2 ± 24.9	58.8 ± 28
Total BMC (mg HA)	332 ± 55.6	332 ± 42.5	341 ± 47.5	296 ± 56

Values are mean ± SD, mean (range), or *n*, as indicated.

TZ = transitional zone; BMC = bone mineral content; HA = hydroxyapatite; SD = standard deviation.

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Table 2. Annual Absolute Change in Microarchitecture of the Distal Tibia and Distal Radius by the Menopausal Stage of the Participants

	Premenopausal remaining premenopausal	Premenopausal to perimenopausal	Perimen postme
Distal tibia			
Total cortical porosity (%)	0.44 ± 0.03 (<0.001)	0.80 ± 0.06 (<0.001)[a]	1.40 ± 0.0
Compact cortical porosity (%)	0.32 ± 0.03 (<0.001)	0.67 ± 0.07 (<0.001)[a]	1.41 ± 0.1
Outer TZ porosity (%)	0.33 ± 0.03 (<0.001)	0.61 ± 0.06 (<0.001)[a]	1.33 ± 0.1
Inner TZ porosity (%)	0.23 ± 0.02 (<0.001)	0.37 ± 0.02 (<0.001)[a]	0.53 ± 0.0
Cortical BMC (mg HA)	0.45 ± 0.35 (0.242)	–0.91 ± 0.59 (0.256)	–6.12 ± 0.
Matrix mineralization density (%)	–0.25 ± 0.02 (<0.001)	–0.41 ± 0.03 (<0.001)[a]	–0.60 ± 0.
Trabecular number (1/mm)	–0.12 ± 0.01 (<0.001)	–0.15 ± 0.01 (<0.001)[a]	–0.19 ± 0.
Trabecular thickness (mm)	0.30 ± 0.02 (<0.001)	0.42 ± 0.03 (<0.001)[a]	0.49 ± 0.
Trabecular separation (mm)	3.79 ± 0.28 (<0.001)	4.95 ± 0.43 (<0.001)	6.29 ± 0.
Trabecular BMC (mg HA)	–0.71 ± 0.29 (0.015)	–0.51 ± 0.37 (0.200)	–1.55 ±
Total BMC (mg HA)	–0.26 ± 0.51 (0.586)	–1.42 ± 0.72 (0.117)	–7.67 ± 1.
Distal radius			
Total cortical porosity (%)	0.29 ± 0.04 (<0.001)	0.61 ± 0.08 (<0.001)[a]	1.17 ± 0.1
Compact cortical porosity (%)	0.23 ± 0.04 (<0.001)	0.61 ± 0.09 (<0.001)[a]	1.26 ± 0.1
Outer TZ porosity (%)	0.19 ± 0.04 (<0.001)	0.54 ± 0.07 (<0.001)[a]	1.19 ± 0.1
Inner TZ porosity (%)	0.06 ± 0.02 (<0.001)	0.18 ± 0.03 (<0.001)[a]	0.34 ± 0.0
Cortical BMC (mg HA)	0.11 ± 0.23 (0.467)	–0.76 ± 0.37 (0.047)[a]	–3.19 ± 0.
Matrix mineralization density (%)	–0.18 ± 0.02 (<0.001)	–0.33 ± 0.04 (<0.001)[a]	–0.57 ± 0.
Trabecular number (1/mm)	–0.08 ± 0.01 (<0.001)	–0.10 ± 0.01 (<0.001)	–0.14 ± 0.
Trabecular thickness (mm)	0.31 ± 0.02 (<0.001)	0.44 ± 0.03 (<0.001)[a]	0.45 ± 0.
Trabecular separation (mm)	2.63 ± 0.28 (<0.001)	3.88 ± 0.35 (<0.001)[a]	4.73 ± 0.
Trabecular BMC (mg HA)	0.24 ± 0.11 (0.085)	0.44 ± 0.15 (0.003)	–0.47 ± 0
Total BMC (mg HA)	0.35 ± 0.23 (0.145)	–0.32 ± 0.37 (0.408)	–3.67 ± 0.

Values are mean ± SE (*p* value). Values of *p* represent whether changes differed from 0 within groups.

TZ = transitional zone; BMC = bone mineral content; HA = hydroxyapatite; SE = standard error of the mean.

[a]$p < 0.05$ for differences in changes between premenopausal to perimenopausal versus premenopausal remaining premenopausal using generalized estimating equation.

[b]$p < 0.05$ for differences in changes between perimenopausal to postmenopausal versus premenopausal remaining premenopausal using generalized estimating equation.

[c]$p < 0.05$ for differences in changes between perimenopausal to postmenopausal versus premenopausal to perimenopausal using generalized estimating equation.

[d]$p < 0.05$ for differences in changes between postmenopausal versus premenopausal remaining premenopausal using generalized estimating equation.

[e]$p < 0.05$ for differences in changes between postmenopausal versus premenopausal to perimenopausal using generalized estimating equation.

[f]$p < 0.05$ for differences in changes between postmenopausal versus perimenopausal to postmenopausal using generalized estimating equation.

Table 3. Annual Percentage Change in Microarchitecture of Distal Tibia and Distal Radius by Menopausal Stage

	Premenopausal remaining premenopausal	Premenopausal to perimenopausal	Perimen postme
Distal tibia			
Total cortical porosity (%)	0.79 ± 0.06 (<0.001)	1.43 ± 0.11 (<0.001)[a]	2.43 ± 0.1
Compact cortical porosity (%)	0.84 ± 0.09 (<0.001)	1.81 ± 0.19 (<0.001)[a]	3.64 ± 0.3
Outer TZ porosity (%)	0.86 ± 0.08 (<0.001)	1.56 ± 0.16 (<0.001)[a]	3.19 ± 0.2
Inner TZ porosity (%)	0.27 ± 0.02 (<0.001)	0.44 ± 0.03 (<0.001)[a]	0.63 ± 0.0
Cortical BMC (mg HA)	0.09 ± 0.06 (0.184)	–0.14 ± 0.10 (0.305)	–1.08 ± 0.
Matrix mineralization density (%)	–0.39 ± 0.03 (<0.001)	–0.62 ± 0.04 (<0.001)[a]	–0.91 ± 0.0
Trabecular number (1/mm)	–4.04 ± 0.27 (<0.001)	–5.02 ± 0.36 (<0.001)	–6.41 ± 0.
Trabecular thickness (mm)	1.60 ± 0.11 (<0.001)	2.26 ± 0.16 (<0.001)[a]	2.66 ± 0.
Trabecular separation (mm)	3.11 ± 0.22 (<0.001)	3.99 ± 0.34 (<0.001)	4.87 ± 0.4
Trabecular BMC (mg HA)	–0.25 ± 0.14 (0.069)	–0.13 ± 0.18 (0.521)	–0.64 ± 0
Total BMC (mg HA)	–0.16 ± 0.17 (0.345)	–0.28 ± 0.22 (0.320)	–1.73 ± 0.
Distal radius			
Total cortical porosity (%)	0.54 ± 0.09 (<0.001)	1.22 ± 0.16 (<0.001)[a]	2.31 ± 0.2
Compact cortical porosity (%)	0.69 ± 0.13 (<0.001)	1.84 ± 0.25 (<0.001)[a]	3.78 ± 0.4
Outer TZ porosity (%)	0.53 ± 0.10 (<0.001)	1.45 ± 0.19 (<0.001)[a]	3.23 ± 0.4
Inner TZ porosity (%)	0.08 ± 0.02 (<0.001)	0.221± 0.03 (<0.001)[a]	0.40 ± 0.0
Cortical BMC (mg HA)	0.04 ± 0.08 (0.479)	–0.27 ± 0.14 (0.055)[a]	–1.12 ± 0.
Matrix mineralization density (%)	–0.26 ± 0.04 (<0.001)	–0.49 ± 0.06 (<0.001)[a]	–0.85 ± 0.0
Trabecular number (/mm)	–3.00 ± 0.31 (<0.001)	–4.30 ± 0.41 (<0.001)[a]	–5.87 ± 0.4
Trabecular thickness (mm)	1.64 ± 0.13 (<0.001)	2.36 ± 0.18 (<0.001)[a]	2.43 ± 0.
Trabecular separation (mm)	2.00 ± 0.20 (<0.001)	3.02 ± 0.27 (<0.001)[a]	3.61 ± 0.4
Trabecular BMC (mg HA)	0.44 ± 0.22 (0.079)	0.70 ± 0.24 (0.003)	–0.59 ± 0
Total BMC (mg HA)	0.48 ± 0.22 (0.048)	0.43 ± 0.25 (0.072)	–1.71 ± 0

Values are mean ± SE (*p* value). Values of *p* represent whether changes differed from 0 within groups.

TZ = transitional zone; BMC = bone mineral content; HA = hydroxyapatite; SE = standard error of the mean.

[a]$p < 0.05$ for differences in changes between premenopausal to perimenopausal versus premenopausal remaining premenopausal using generalized estimating equation.

[b]$p < 0.05$ for differences in changes between perimenopausal to postmenopausal versus premenopausal remaining premenopausal using generalized estimating equation.

[c]$p < 0.05$ for differences in changes between perimenopausal to postmenopausal versus premenopausal to perimenopausal using generalized estimating equation.

[d]$p < 0.05$ for differences in changes between postmenopausal versus premenopausal remaining premenopausal using generalized estimating equation.

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[e]$p < 0.05$ for differences in changes between postmenopausal versus premenopausal to perimenopausal using generalized estimating equation.
[f]$p < 0.05$ for differences in changes between postmenopausal versus perimenopausal to postmenopausal using generalized estimating equation.

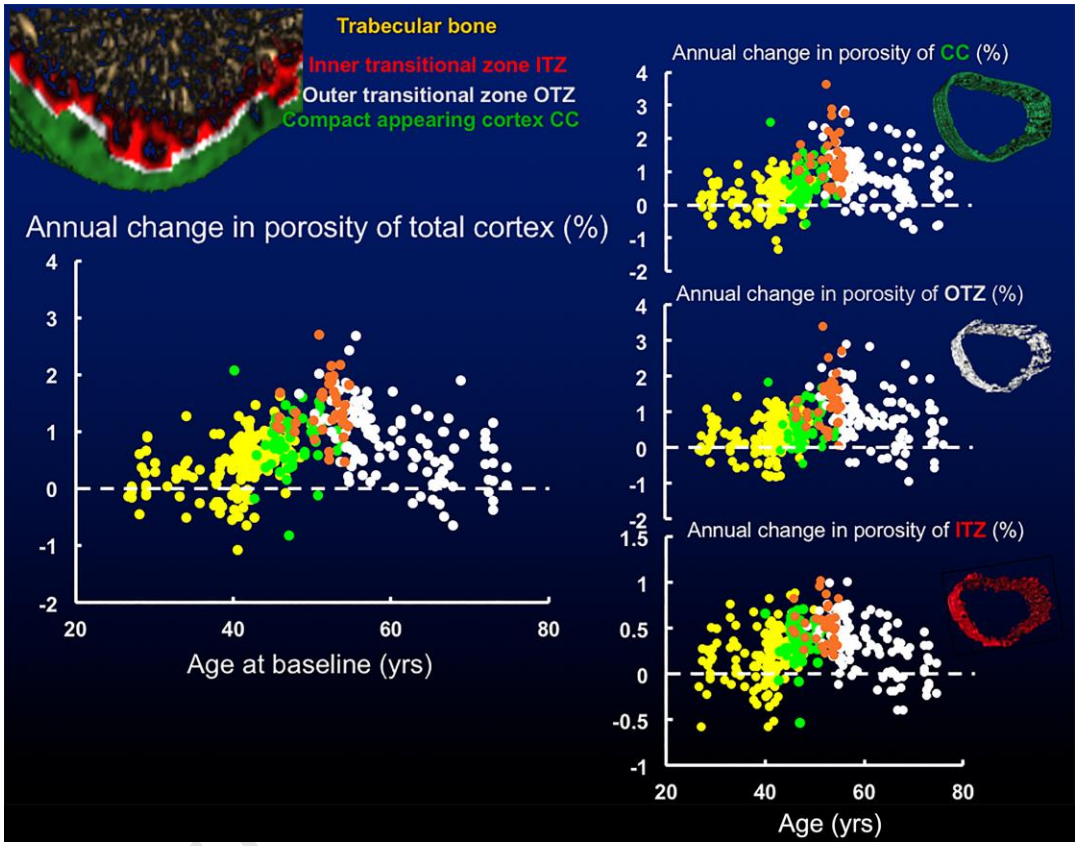

Figure 1

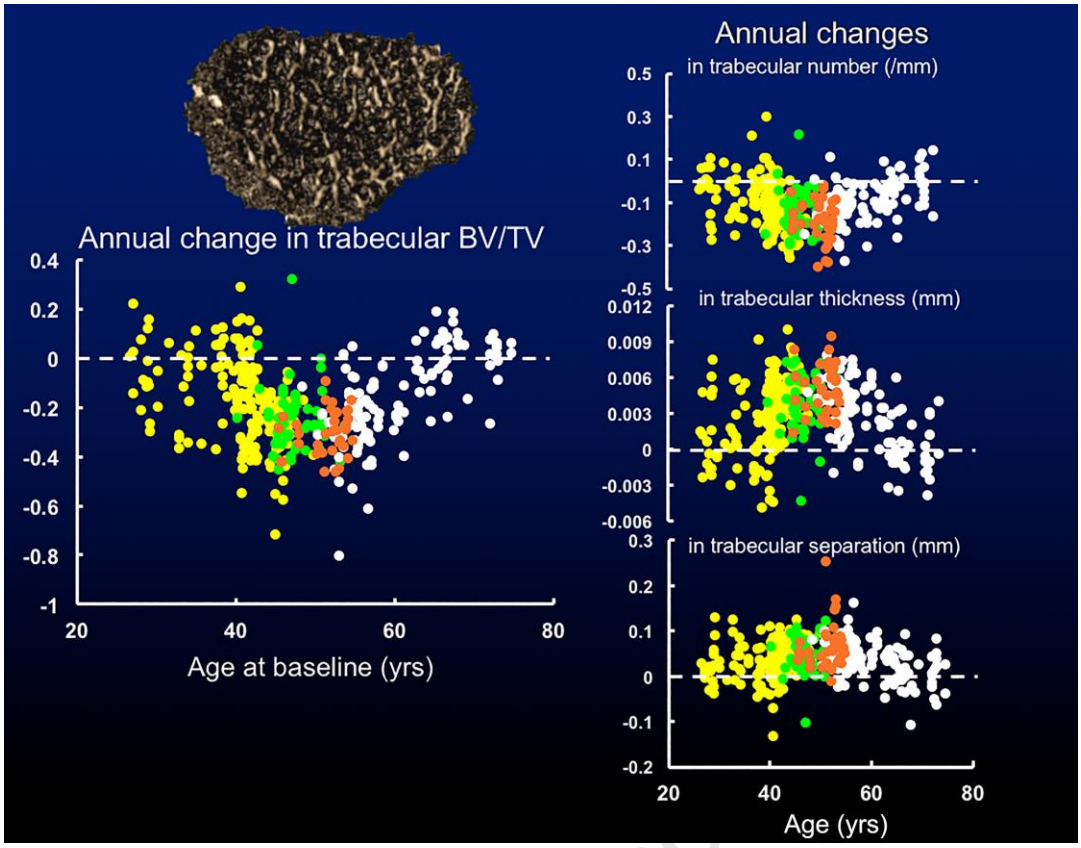

Figure 2

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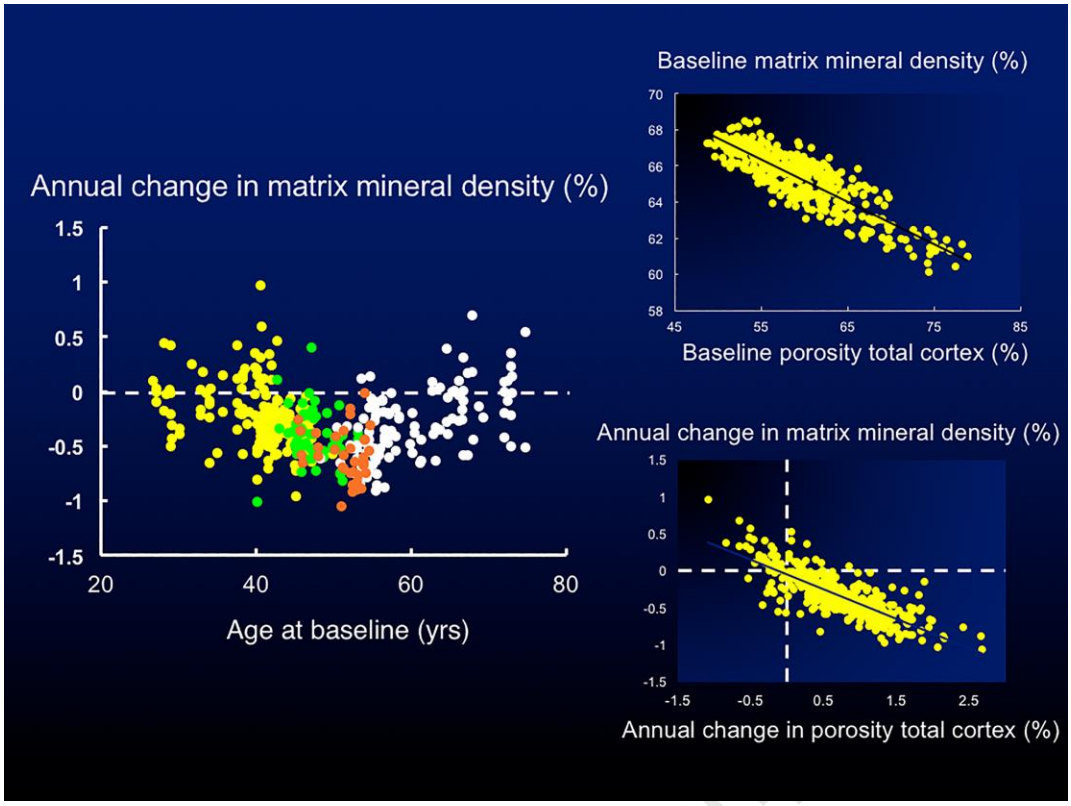

Figure 3

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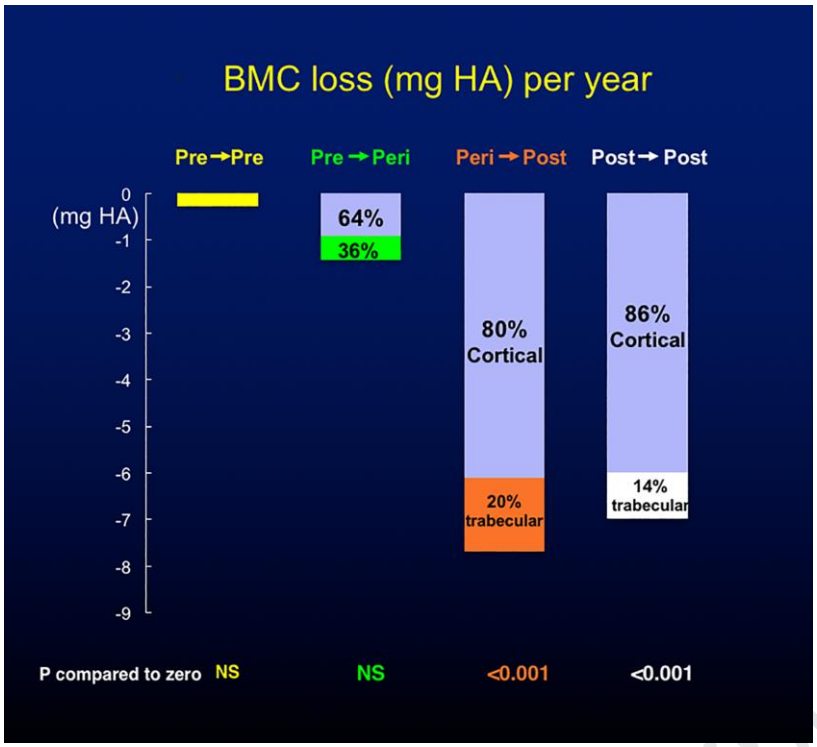

Figure 4

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