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Remodeling markers are associated with larger intracortical surface area but smaller trabecular surface area: A twin study

Åshild Bjørnerem [a,*], Ali Ghasem-Zadeh [b], Minh Bui [c], Xiaofang Wang [b], Christian Rantzau [d], Tuan V. Nguyen [e], John L. Hopper [c], Roger Zebaze [b], Ego Seeman [b]

[a] Department of Clinical Medicine, University of Tromsø, Norway
[b] Endocrine Centre, Austin Health, University of Melbourne, Melbourne, Australia
[c] Centre for MEGA Epidemiology, University of Melbourne, Australia
[d] The Bio21 Molecular Science and Biotechnology Institute, University of Melbourne, Australia
[e] Osteoporosis and Bone Biology Program, Garvan Institute of Medical Research, Sydney, Australia

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ABSTRACT

All postmenopausal women become estrogen deficient but not all remodel their skeleton rapidly or lose bone rapidly. As remodeling requires a surface to be initiated upon, we hypothesized that a volume of mineralized bone assembled with a larger internal surface area is more accessible to being remodeled, and so decayed, after menopause.

We measured intracortical, endocortical and trabecular bone surface area and microarchitecture of the distal tibia and distal radius in 185 healthy female twin pairs aged 40 to 61 years using high-resolution peripheral quantitative computed tomography (HR-pQCT). We used generalized estimation equations to analyze (i) the trait differences across menopause, (ii) the relationship between remodeling markers and bone surface areas, and (iii) robust regression to estimate associations between within-pair differences.

Relative to premenopausal women, postmenopausal women had higher remodeling markers, larger intracortical and endocortical bone surface area, higher intracortical porosity, smaller trabecular bone surface area and fewer trabeculae at both sites (all $p<0.01$). Postmenopausal women had greater deficits in cortical than trabecular bone mass at the distal tibia (-0.98 vs. -0.12 SD, $p<0.001$), but similar deficits at the distal radius (-0.45 vs. -0.39 SD, $p=0.79$). A 1 SD higher tibia intracortical bone surface area was associated with 0.22–0.29 SD higher remodeling markers, about half the 0.53–0.67 SD increment in remodeling markers across menopause (all $p<0.001$). A 1 SD higher porosity was associated with 0.20–0.30 SD higher remodeling markers. A 1 SD lower trabecular bone surface area was associated with 0.15–0.18 SD higher remodeling markers (all $p<0.01$). Within-pair differences in intracortical and endocortical bone surface areas at both sites and porosity at the distal tibia were associated with within-pair differences in some remodeling markers ($p=0.05$ to 0.09).

We infer intracortical remodeling may be self perpetuating by creating intracortical porosity and so more bone surface for remodeling to occur upon, while remodeling upon the trabecular bone surface is self limiting because it removes trabeculae with their surface.

Introduction

All genetic and environmental factors influencing bone's structural strength express their effects through the final common pathway of bone modeling and remodeling [1]. During growth, this cellular machinery adds bone onto, or removes bone from, its outer (periosteal) and inner (endosteal) envelopes to construct and reconstruct bone's external size, shape and internal architecture. At the completion of growth, periosteal bone formation slows profoundly while remodeling initiated upon the three components of its endosteal envelope (intracortical, endocortical and trabecular) continues, removing old or damaged bone and replacing it with new bone [2].

Around the fourth decade of life, remodeling becomes unbalanced; each time bone matrix is removed, less is deposited leaving a volume deficit [3,4]. Before menopause, this deficit is small, only about 1–2%, because 98–99% of the volume of bone removed is replaced by each basic multicellular unit (BMU), so remodeling and bone loss are slow and structural decay remains modest. After menopause, the bone volume deficit produced by each remodeling event and the intensity of remodeling increase [5,6].

The intensity of remodeling varies two to five-fold in pre- and postmenopausal women [7,8]. While remodeling increases during the

* Corresponding author at: Department of Obstetrics and Gynecology, Department of Clinical Medicine, University of Tromsø, 9037 Tromsø, Norway. Fax: +47 7762 6421.
E-mail address: ashild.bjornerem@uit.no (Å. Bjørnerem).

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menopausal transition, not all postmenopausal women remodel their skeleton rapidly, lose bone rapidly, suffer structural decay of their skeleton, or sustain fractures [9–13]. Thus, understanding the mechanisms contributing to the diversity in remodeling intensity is likely to assist in targeting women at risk for fractures so that treatment can be given to those who need it and avoided in those who do not.

One factor that may contribute to the differing extent of bone loss and structural decay from woman to woman is the accessibility of bone to being remodeled [3]. Bone remodeling is surface dependent [3]. Whatever triggers remodeling, for bone matrix remodeling to occur, there must be a surface for it to be initiated upon leading to the formation of a bone remodeling compartment (BRC) [14]. Within each BRC, precursor cells of the BMU are recruited and differentiate to form osteoclasts which remove damaged bone matrix beneath the surface after which osteoblasts refill the excavated canal within cortex or excavated trench upon trabecular and endocortical surfaces with newly synthesized bone [15].

No studies have examined whether the differences in the intensity of remodeling between women is accounted for, in part, by differences in the surface areas of intracortical, endocortical and trabecular components of the endosteal envelope that provides a surface for remodeling to be initiated upon. We hypothesized that remodeling intensity in women, as measured by bone remodeling markers, is associated with the intracortical, endocortical and trabecular bone surface areas. We tested this hypothesis in a cross sectional study of healthy individual twins, and by studying within-pair differences. The within-pair analyses assess associations between bone surface areas and remodeling markers controlling perfectly for age which influences both, and controls for unmeasured genetic and environmental factors shared by twin pairs.

Materials and methods

We studied 113 monozygotic (MZ) and 72 dizygotic (DZ) healthy female twin pairs aged 40–61 years living in Melbourne, Australia in 2008–2009. Using a questionnaire, we identified and excluded women with a hysterectomy before menopause, or with illnesses or drug therapy affecting bone, and a total of 370 women (185 pairs) participated. Of these 370 women, 113 were postmenopausal (amenorrhea for >1 year), 45 were perimenopausal (no cycles for 3–12 months), and 212 were premenopausal (a regular cycle in the last 3 months). We excluded 23 post-, 3 peri- and 3 premenopausal women using hormone replacement therapy (5 twin pairs and 19 individuals). This left 341 women for analyses using the generalized estimating equations (GEE) models (Tables 1–2) and the figures, and 161 complete twin pairs for within-pair analyses (Table 3). All gave written informed consent. The Austin Health Ethics Committee approved the study.

High-resolution 3-dimensional peripheral quantitative computed tomography (HR-3D-pQCT) (XtremeCT, Scanco Medical AG, Bassersdorf, Switzerland) was used to quantify cortical and trabecular morphology with an isotropic resolution of 82 μm [16]. Cross sectional area (CSA) and micro-architecture were measured at the non-dominant distal tibia and radius. The in vivo precision was 0.9 to 4.4% for the structure variables. Daily quality control was carried out by scanning a phantom containing rods of hydroxyapatite (QRM Moehrendorf, Germany). Radiation exposure was ~5 μSv per measurement.

Intracortical, endocortical and trabecular bone surface (BS) areas were estimated using marching cubes that create triangular models of the surfaces from 3D data [17]. Estimates were validated in vitro using 20-micron scans of excised trabecular cubes of the radius. Bone surface area/bone volume (BS/BV) by XtremeCT correlated with BS/BV by μCT-40 ($r^2 = 0.97$) but the absolute values were overestimated as the XtremeCT segmentation overestimates trabecular thickness (BS/BV = 17.4 vs. 11.3 1/mm by μCT-40), mean BS 2201 vs. 1920 mm^2 by μCT-40. Surfaces were expressed in absolute terms (mm^2), per unit total tissue volume (totTV; bone plus void), per unit cortical tissue volume (cortTV; cortical bone including its pores) and per unit trabecular tissue volume (trabTV; trabecular bone plus medullary voids). TotTV, cortTV and trabTV (mm^3) were estimated as the total, cortical and trabecular CSA (mm^2) times the scan length (104 slices × 0.082 mm thickness).

Table 1
Differences in traits between premenopausal and postmenopausal women.

	Premenopausal	Postmenopausal	Pre vs Post			Premenopausal	Postmenopausal	Pre vs Post		
	Mean (SD)	Mean (SD)	%Δ	ΔSD	P value*	Mean (SD)	Mean (SD)	%Δ	ΔSD	P value*
Age (years)	45.83 (3.47)	55.13 (3.40)								
Log Osteocalcin (ng/ml)	2.85 (0.31)	3.18 (0.33)	12.6	1.06	<0.001					
Log CTX (ng/ml)	−1.32 (0.46)	−0.82 (0.35)	37.8	1.09	<0.001					
Log P1NP (ng/ml)	3.60 (0.41)	4.01 (0.36)	11.4	1.00	<0.001					
	Distal Tibia					Distal Radius				
Total tissue volume (TV) (mm^3)	5614 (911)	5779 (886)	2.9	0.18	0.58	2121 (336)	2211 (329)	4.2	0.27	0.04
Bone surface (BS) (mm^2)	13759 (3348)	13738 (2959)	0.2	0.01	0.74	4886 (1114)	4720 (967)	−3.4	−0.15	0.71
BS/total TV (mm^2/mm^3)	2.43 (0.30)	2.36 (0.28)	−2.9	−0.23	0.58	2.29 (0.29)	2.12 (0.26)	−7.4	−0.59	0.004
Bone mass (mg HA)	1731 (264)	1572 (269)	−9.2	−0.60	<0.001	718 (109)	662 (123)	−7.8	−0.51	0.003
Cortical TV (mm^3)	1017 (159)	887 (162)	−12.8	−0.82	<0.001	464 (79.9)	433 (95.4)	−6.7	−0.39	0.02
Intracort BS (mm^2)	381 (165)	515 (195)	35.2	0.81	<0.001	45.3 (23.8)	70.1 (38.2)	54.7	1.04	<0.001
IntracortBS/total TV (mm^2/mm^3)	0.07 (0.03)	0.09 (0.04)	28.6	0.67	<0.001	0.02 (0.01)	0.03 (0.02)	50.0	1.00	<0.001
IntracortBS/cortical TV (mm^2/mm^3)	0.38 (0.15)	0.60 (0.25)	57.9	1.47	<0.001	0.10 (0.05)	0.17 (0.09)	70.0	1.40	<0.001
Endocort BS (mm^2)	811 (85.1)	848 (82.8)	4.6	0.43	0.02	556 (58.5)	579 (54.2)	4.1	0.39	0.009
EndocortBS/total TV (mm^2/mm^3)	0.147 (0.01)	0.148 (0.01)	0.1	0.08	0.17	0.265 (0.02)	0.263 (0.02)	0.1	0.09	0.22
EndocortBS/cortical TV (mm^2/mm^3)	0.82 (0.17)	1.00 (0.26)	22.0	1.06	<0.001	1.24 (0.28)	1.42 (0.40)	14.5	0.64	0.001
Porosity (%)	3.89 (1.45)	5.77 (2.07)	48.3	1.30	<0.001	1.24 (0.59)	1.84 (0.92)	48.4	1.02	<0.001
Bone mass (mg HA)	925 (162)	764 (171)	−17.4	−0.99	<0.001	425 (89.4)	384 (104)	−9.6	−0.46	0.005
Trabecular (medullary) TV (mm^3)	4567 (919)	4823 (906)	5.6	0.28	0.22	1623 (335)	1727 (347)	6.4	0.31	0.03
BS (mm^2)	12566 (3221)	12333 (2853)	−1.9	0.07	0.66	4271(1063)	4039 (926)	−5.4	−0.22	0.34
BS/ total TV (mm^2/mm^3)	2.22 (0.30)	2.12 (0.28)	−2.7	0.20	0.22	2.01 (0.29)	1.82 (0.26)	−9.5	−0.66	<0.001
BS/trabecular TV (mm^2/mm^3)	2.75 (0.33)	2.56 (0.34)	−6.9	−0.58	0.004	2.64 (0.35)	2.35 (0.37)	−11.0	−0.83	<0.001
Number (1/mm)	1.97 (0.31)	1.79 (0.30)	−9.1	−0.58	<0.001	1.90 (0.27)	1.69 (0.26)	−11.1	−0.78	<0.001
Thickness (mm)	0.073 (0.01)	0.074 (0.01)	1.4	0.08	0.12	0.072(0.01)	0.068 (0.01)	−5.6	−0.36	0.02
Bone mass (mg HA)	776 (208)	751 (206)	−3.2	−0.12	0.58	263 (72.4)	236 (66.4)	−9.1	−0.33	0.048

*P-values for difference between pre and postmenopausal women, using generalized estimating equation (GEE) models with robust standard error, adjusted for BMI, log estradiol and both whenever significant.
$\%\Delta_{post-pre} = 100 * (\overline{X}_{post} - \overline{X}_{pre}) / \overline{X}_{pre}$ and $\Delta SD_{post-pre} = (\overline{X}_{post} - \overline{X}_{pre}) / SD_{pre}$.
CTX, β-carboxyterminal cross-linking telopeptides of type I bone collagen (β-CTX), P1NP, procollagen type 1 amino-terminal propeptide.
TV, tissue volume, BS, bone surfae, HA hydroxyapatite.

Table 2
Association between remodeling markers (Log osteocalcin, Log β-carboxyterminal) cross-linking telopeptides of type I bone collagen (β-CTX) and Log procollagen type 1 amino-terminal propeptide (P1NP) and tibia and radius intracortical and endocortical bone surface (BS) areas per unit of cortical tissue volume (TV), trabecular BS per unit of trabecular TV (mm^2/mm^3), and intracortical porosity (%).

	Log Osteocalcin (ng/ml)		Log CTX (ng/ml)		Log P1NP (ng/ml)		First principle component	
	Univariate	Adjusted [a]	Univariate	Adjusted [a]	Univariate	Adjusted [a]	Univariate	Adjusted [a]
Distal tibia								
IntracorticalBS/corticalTV	0.39***	0.29***	0.34***	0.24***	0.32***	0.22***	0.40***	0.28***
EndocorticalBS/corticalTV	0.30***	0.07	0.21***	−0.04	0.20***	−0.01	0.26***	−0.02
TrabecularBS/trabecularTV	−0.17**	−0.09	−0.25***	−0.18**	−0.22***	−0.15**	−0.25***	−0.17**
Intracortical porosity	0.39***	0.30***,[b]	0.34***	0.20***,[b]	0.32***	0.20***,[b]	0.40***	0.25***,[b]
Distal radius								
IntracorticalBS/corticalTV	0.25***	0.14*	0.26***	0.15**	0.21***	0.11	0.26***	0.12*
EndocorticalBS/corticalTV	0.27***	0.15*	0.18**	0.04	0.16***	0.05	0.22***	0.06
TrabecularBS/trabecularTV	−0.22***	−0.09	−0.22***	−0.10	−0.20***	−0.08	−0.27***	−0.13*
Intracortical porosity	0.18**	0.10*,[b]	0.20**	0.09[b]	0.16**	0.07[b]	0.18**	0.04[b]

Numbers are standardized coefficients in generalized estimating equation (GEE) models with remodeling markers as the dependent variables.
[a] The multivariable models with BS are adjusted for BMI, all other surfaces and menopausal stage.
[b] The multivariable models with intracortical porosity are adjusted for BMI and menopausal stage, but are not adjusted for the surfaces.
* $p<0.05$.
** $p<0.01$.
*** $p<0.001$.

Fasting blood collected between 8 and 10 am was assayed for serum osteocalcin, β-carboxyterminal cross-linking telopeptides of type I collagen (CTX) and procollagen type 1 amino-terminal propeptide (PINP) by electrochemiluminescence immunoassay (Elecsys 1010 Analytics, Roche Diagnostics, Germany, intra- and inter-assay CV 3–8%). Serum estradiol (E2) was assayed using a DiaSorin RIA (sensitivity 2 pg/ml, intra- and inter-assay CV 4–6%).

Linear regression and unpaired t-tests assume data from different individuals are independent. In twin pairs, the measurements correlate so the use of such methods is inappropriate [18]. The Generalized Estimating Equations (GEE) [19] extend generalized linear models by taking the within pair correlations into account when estimating regression coefficients and their standard errors. The GEE method with Huber–White sandwich robust standard error was used to estimate the differences in means of remodeling markers and bone traits between pre- and postmenopausal women adjusting for BMI and log estradiol. This method was also used to compare the difference between cortical and trabecular mass deficits (in SD) at the distal tibia and radius in post- relative to premenopausal women. The F-test was used to test whether the SDs of cortical and trabecular mass were equal in pre- and postmenopausal women at each site. The deficits were calculated by taking the difference between the individual postmenopausal mass and the mean premenopausal mass divided by the pooled SD, where the pooled SD was obtained by combining the SD from both groups weighted by the sample size.

The GEE model was also used to estimate the relationship between remodeling markers and first principal component (weight combination of the remodeling markers) and bone surface area in univariate and multivariate analyses adjusting for BMI and menopausal stage. We also assessed these relationships by regressing within-pair differences against one another using robust regression analyses [20,21]. As the relationship between each remodeling marker and each bone surface area and cortical porosity (assessed using GEE and locally weighted smooth regression) showed no evidence of a non-linear relationship in the whole sample, pre- and postmenopausal women, we considered linear relationships only. The plots of the linear fitted line for each remodeling marker and each bone surface area and cortical porosity showed no deviation from parallelism, the tests for interaction in GEE models showed no significant differences (all $p>0.05$). However, the intercepts differed significantly so analyses were adjusted for menopausal stage. All analyses were performed using published available *R* [22] and GEE packages [23].

Results

The mean duration of the postmenopausal period in the postmenopausal women was 6.0 years (range 1–22). Relative to premenopausal women, postmenopausal women had higher remodeling markers, larger intracortical and endocortical BS/cortTV, higher intracortical porosity, smaller trabecular BS/trabTV and fewer trabeculae at the

Table 3
Within-pair differences in remodeling markers (Log osteocalcin, Log β-carboxyterminal) cross-linking telopeptides of type I collagen (β-CTX) and Log procollagen type 1 amino-terminal propeptide (P1NP) by within-pair differences in tibia and radius, intracortical and endocortical bone surface (BS) areas per unit of cortical tissue volume (TV), trabecular BS per unit of trabecular TV and intracortical porosity.

	Log osteocalcin (ng/ml)			Log CTX (ng/ml)			Log P1NP (ng/ml)			First principal component		
	Estimate	SE	p	Estimate	SE	p	Estimate	SE	p	Estimate	SE	p
Distal tibia												
Intracort BS/cortTV (mm^2/mm^3)	0.22	0.13	0.09	0.40	0.21	0.06	0.26	0.18	0.16	1.25	0.66	0.06
Endocort BS/cortTV (mm^2/mm^3)	0.22	0.13	0.09	0.15	0.22	0.50	0.06	0.18	0.75	0.66	0.68	0.33
TrabBS/trabTV (mm^2/mm^3)	−0.08	0.08	0.37	−0.11	0.14	0.43	−0.16	0.12	0.17	−0.47	0.44	0.29
Intracortical porosity (%)	0.02	0.01	0.08	0.04	0.02	0.06	0.03	0.02	0.09	0.14	0.07	0.05
Distal radius												
IntracortBS/cortTV (mm^2/mm^3)	0.36	0.44	0.42	1.17	0.69	0.09	0.15	0.61	0.81	2.13	2.22	0.34
EndocortBS/cortTV (mm^2/mm^3)	0.16	0.08	0.05	0.22	0.13	0.09	0.09	0.12	0.46	0.76	0.42	0.07
TrabBS/trabTV (mm^2/mm^3)	−0.08	0.08	0.31	−0.04	0.13	0.75	−0.06	0.11	0.58	−0.26	0.41	0.79
Intracortical porosity (%)	0.03	0.03	0.35	0.10	0.06	0.08	0.04	0.05	0.40	0.23	0.18	0.20

Analyzed using robust regression method with remodeling markers as the dependent variables, without adjustment for covariates.

distal tibia and radius (all $p<0.01$, Table 1, Fig. 1). Postmenopausal women had greater deficits in cortical than trabecular bone mass at the distal tibia (−0.98 vs. −0.12 SD, $p<0.001$), but similar deficits at the distal radius (−0.45 vs. −0.39 SD, $p=0.79$).

At the distal tibia, intracortical and endocortical BS/cortTV correlated directly with bone markers (Fig. 2, Table 2). A 1 SD higher intracortical BS/cortTV was associated with 0.22–0.29 SD higher remodeling markers adjusted for menopause, BMI and the other surfaces. Likewise, a 1 SD higher porosity was associated with 0.20–0.30 SD higher remodeling markers; each increment was about half the 0.53–0.67 SD higher remodeling markers observed in post- relative to pre-menopausal women. By contrast, endocortical BS/cortTV was not associated with remodeling markers after adjustment for the other surfaces. Moreover, a 1 SD lower trabecular BS/trabTV was associated with a 0.15–0.18 SD higher remodeling markers after similar adjustments. Likewise, within-pair differences in tibia intra- and endocortical BS/cortTV and porosity were associated with within-pair differences in some remodeling markers (p ranging from 0.05 to 0.09, Table 3). Similar but weaker associations were found for the distal radius.

Of the total variance in remodeling markers, tibia intracortical BS/cortTV accounted for 4–11%, and trabecular BS/trabTV for less than 3%, with no independent contribution from endocortical BS/cortTV after adjusting for BMI, all surfaces and menopausal stage. Menopause accounted for 20–24% of the variance leaving 65–73% unexplained.

Discussion

We report that remodeling markers were positively associated with intracortical surface area and intracortical porosity, and negatively associated with trabecular surface area. Relative to premenopausal women, postmenopausal women had higher remodeling markers, greater intracortical porosity providing a larger intracortical surface area, but a smaller trabecular surface area, for remodeling to occur upon, and greater deficits in cortical than trabecular bone at the distal tibia and equal deficits at the distal radius.

The associations between bone surface areas measured in vivo and circulating bone remodeling markers are consistent with remodeling increasing intracortical porosity and so intracortical surface area as pores in cross section (or canals in longitudinal section) form the intracortical surface area of haversian canals upon which remodeling occurs [24]. As this is a cross sectional study, we cannot determine whether surface causes remodeling, remodeling causes surfaces or both but irrespective of whether any causal relationship is unidirectional or bidirectional, the intracortical surface area achieved at the completion of growth is likely to be more important than any increment in intracortical surface area produced by remodeling because the negative balance produced by each remodeling event is small. Any increment in surface area produced by a residual greater surface concavity is small compared to the pre-remodeled surface area.

In cortical bone, with time, protracted remodeling is likely to enlarge the surface area. Remodeling excavates more surface for remodeling to occur upon and so remodeling may be self perpetuating. Surface does not cause remodeling, it is facilitatory; when a signal from damage or osteocyte apoptosis arises within mineralized bone matrix, this signal can more easily find a surface for remodeling to be initiated upon because there is now more surface area per unit cortical bone matrix volume. By contrast, trabecular surface area correlated weakly but inversely with remodeling markers. This is consistent with remodeling on trabecular surfaces being self-limiting; remodeling on trabecular surfaces removes trabeculae with their surfaces.

As proposed by Parfitt, whatever the origin and stimulus initiating bone matrix remodeling, one structural feature determining whether the bone matrix volume will be remodeled and decayed is the surface/volume configuration of bone itself; bone's structural design partly determines its own decay [3]. Trabecular bone has a larger surface/volume ratio than cortical bone so that any point within the bone matrix of a

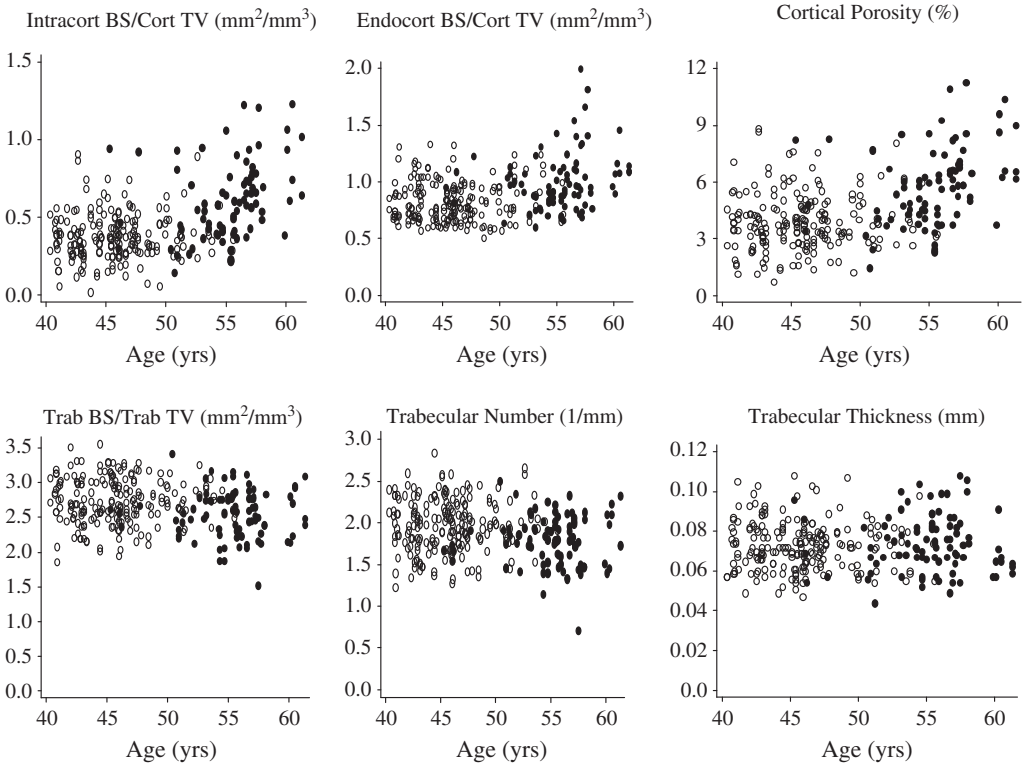

Fig. 1. At the distal tibia, relative to premenopausal women (open dots), postmenopausal women (filled dots) had larger intracortical and endocortical bone surface area per unit of cortical tissue volume (IntracortBS/cortTV), greater intracortical porosity, smaller trabecular bone surface area per unit of trabecular tissue volume (TrabBS/trabTV) and lower trabecular number, but not thinner trabeculae.

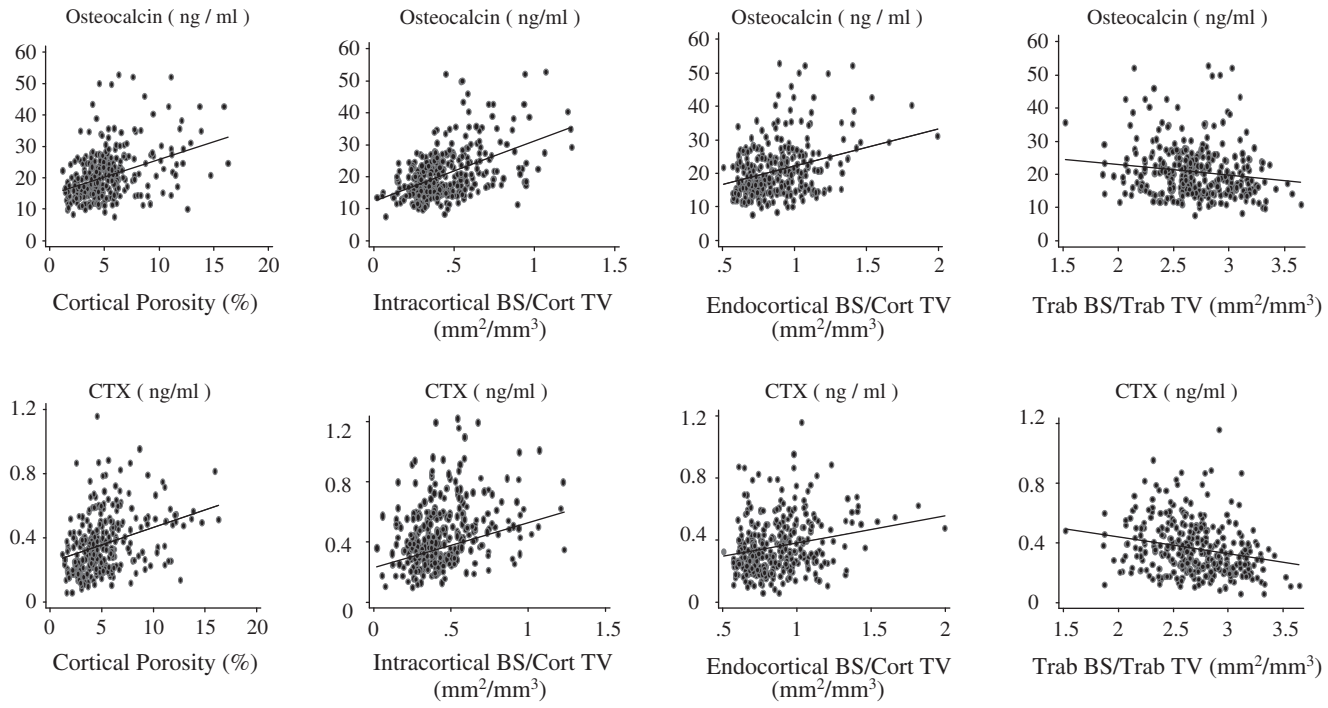

Fig. 2. Bone remodeling markers osteocalcin and β- carboxyterminal cross-linking telopeptides of type I bone collagen (β-CTX) correlated directly with tibia intracortical and endocortical surface area/cortical tissue volume (TV) but inversely with trabecular surface area/trabecular TV.

trabecular plate is near a surface. Information regarding the location of a microcrack or apoptotic osteocytes can be readily signaled to a nearby point on the surface to initiate removal and repair by remodeling [25]. This spatial configuration — a large surface area makes the bone matrix accessible to being remodeled while the small bone matrix volume fashioned as a trabecular plate makes that plate vulnerable to perforation by the negative BMU balance.

A larger trabecular surface area was not associated, or only weakly negatively associated, with higher remodeling markers suggesting that the surface in this compartment is ample so that differences in trabecular surface area between individuals contribute little to differences in trabecular remodeling between individuals; trabecular surface area accounted for under 3% of the variance in remodeling markers. In addition, remodeling upon trabecular surfaces and upon endocortical surfaces, may be driven less by geometric factors than the proximity to, and composition of, the marrow environment with osteoclast precursors and RANKL expressed by the lining cells forming the roof of the bone remodeling compartment [14,15]. Remodeling is more active adjacent to hematopoietic than to fatty marrow. As the appendicular skeleton does not have much hematopoietic marrow, the trabecular bone at these sites may be turned over more slowly than at the central sites [26].

Cortical bone has a low internal surface/volume ratio. Of the total endosteal surface area available to initiate remodeling in the iliac crest biopsies, similar proportions envelop trabecular (54%) and cortical bone (46%, of which 13% is endocortical and 33% is intracortical) [27,28]. However, as cortical bone volume is greater than trabecular bone volume, there is less intracortical surface *per unit* cortical bone matrix volume so most points within this large bone matrix volume are distant from a surface. Interstitial bone, which comprises about 30% of cortical bone volume [3], is distant from the centrally placed haversian canals within osteons, and so is less susceptible to being remodeled. It has a higher tissue mineral content making it more prone to microdamage which is less readily signaled to an intracortical or endocortical surface.

Thus, differences between individuals in the intracortical surface area may contribute to differences in initiation of remodeling from person to person, and so contribute to differences in remodeling intensity and structural decay after menopause. Intracortical surface (and intracortical porosity) accounted for about 4–11% of the variance in remodeling markers in individuals, and higher intracortical surface was associated with an increment in remodeling about half that seen across menopause. Postmenopausal women with high intracortical surface had the highest remodeling markers. The endocortical surface area was not independently associated with remodeling markers after accounting for the contribution of the other surface; a feature consistent with the view that most of the cortical thinning and remodeling is intra- rather than endocortical in origin [26].

Even though a higher proportion of the trabecular than cortical bone matrix volume is turned over annually, the slower loss of a larger volume of cortical bone is the source of 70% of all of the bone lost from adulthood to old age at the distal radius [29]. In that study, in subjects between 50 and 65 years, equal amounts of bone were lost from cortical and trabecular compartments of the distal radius. In this study of women aged between 40 and 61 years, we report greater deficits in cortical than trabecular bone mass across menopause at the distal tibia and equal deficits in bone mass at cortical and trabecular regions at the distal radius challenging the notion that bone loss after menopause is “predominantly” trabecular, at least in the appendicular metaphyseal region [30]. Indeed, Riggs et al. report a substantial decline in cortical vBMD after menopause [31]. Whether this notion applies to the axial skeleton is in need of reappraisal as no studies have examined the magnitude of bone loss from cortical and trabecular components of the vertebral body. Further work is needed to determine whether cortical bone loss precedes menopause as reported for trabecular bone [32].

This study has the following limitations. First, it is cross-sectional; whether surface facilitates remodeling, the reverse or both remains to be determined. Second, estimates of surface area were validated in vitro, not in vivo. The surface areas are likely to be underestimated in cortical bone because the resolution of HR-pQCT is 82 μm. Advances in software are available to quantify intracortical porosity below this resolution [33]. Most porosity (that forms the intracortical surface) is below this, so both surface area and intracortical porosity

are likely to be underestimated; the smaller intracortical than trabecular surface area reported here probably reflects this limitation. While we report greater deficits in cortical than trabecular bone in post- compared to pre-menopausal women, the deficits in trabecular bone are likely to be underestimated and are probably actually greater because we did not correct for cortical trabecularization which results in cortical fragments being erroneously measured as 'trabecular' bone (26). Finally, remodeling markers are the result of the total amount of bone matrix remodeled across all sites, and so probably reflects the remodeling of the cortical compartment (80% of bone) more than the trabecular compartment (20% of bone).

Within these limitations, we infer that the spatial configuration of bone – its surface/volume ratio, particularly of the larger cortical volume of bone – is likely to contribute to the intensity of remodeling; the larger the surface, the greater the accessibility of the bone matrix volume to being remodeled, the smaller the volume, the greater the vulnerability to structural decay by that remodeling. Thus, quantifying the structural design of bone; its cortical dimensions and porosity, the intracortical, endocortical and trabecular surface areas is likely to contribute to a better understanding of the susceptibility to bone loss and vulnerability of bone to being decayed by this bone loss. Assessment of fracture risk, and treatment allocation and monitoring is likely to be assisted by knowledge of the structural configuration of bone. Microstructure can now be measured in vivo and is likely to improve identification of women at risk for skeletal structural decay and those protected from it after menopause thereby assisting in the rational allocation of therapy. A high cortical porosity and therefore a large intracortical surface may predict fracture risk with greater sensitivity and specificity. These traits are measurable in daily clinical practice. While cortical porosity is held to be the result of bone loss, we speculate that it may be also, in part, the cause of it.

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