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REVIEW

The clinical contribution of cortical porosity to fragility fractures

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Cortical bone is not compact; rather it is penetrated by many Haversian and Volkmann canals for blood supply. The lining of these canals are the intracortical bone surfaces available for bone remodeling. Increasing intracortical bone remodeling increases cortical porosity. However, cortical bone loss occurs more slowly than trabecular loss due to the fact that less surface per unit of bone matrix volume is available for bone remodeling. Nevertheless, most of the bone loss over time is cortical because cortical bone constitutes 80% of the skeleton, and the relative proportion of trabecular bone diminishes with advancing age. Higher serum levels of bone turnover markers are associated with higher cortical porosity of the distal tibia and the proximal femur. Greater porosity of the distal radius is associated with higher odds for forearm fracture, and greater porosity of the proximal femur is associated with higher odds for non-vertebral fracture in postmenopausal women. Measurement of cortical porosity contributes to fracture risk independent of areal bone mineral density and Fracture Risk Assessment Tool. On the other hand, antiresorptive treatment reduces porosity at the distal radius and at the proximal femoral shaft. Thus, porosity is a substantial determinant of the bone fragility that underlies the risk of fractures and may be a target for fracture prevention.

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Introduction

There is a need for new tools that can measure bone features to identify those at risk of fracture. This is because the majority of individuals who suffer a fracture do not have osteoporosis, but have osteopenia or normal areal bone mineral density (aBMD).[1,2] To address this lack of sensitivity, the World Health Organization (WHO) developed the Fracture Risk Assessment Tool (FRAX), which calculates the 10-year probability of a major osteoporotic fracture and hip fracture based on clinical risk factors with or without aBMD included.[3] However, although FRAX can include trabecular bone score, it does not take into account the cortical bone architecture, which is important for bone strength, particularly cortical porosity. Both trabecular and cortical bone are important determinants of bone strength, and a small increase in cortical porosity substantially reduces bone strength; and thus increases the risk of fracture.[4,5] Load sharing between the cortical shell and the trabecular core varies between sites and according to location within a site. In biomechanically tested cadaver proximal femurs, trabecular core was essential during a sideways fall.[6] However, in laboratory studies, fracture load decreased by only 7% after removal of the trabecular bone of the femoral neck, suggesting that cortical bone contributes over 90% to the fracture load and bone strength.[7]

Bone fragility is often reported as a condition characterized by the thinning and loss of trabeculae, and trabecular bone loss has dominated the research on bone fragility over many years.[8] Due to this focus, the role of cortical bone in the pathophysiology of bone fragility has been neglected,[9] despite the fact that 80% of the skeleton is cortical bone, and 80% of fractures in women over 65 years of age are non-vertebral.[10] The purpose of this review is to summarize some new results on the associations between *in vivo* measurement of cortical porosity and fracture risk, and the determinants of the variation in cortical porosity.

Definition and Measurement of Cortical Porosity

Cortical porosity is the average fraction of void volumes within the cortical bone volume.[8,11] Studies using high-resolution peripheral quantitative computed tomography (HR-pQCT) to quantify porosity (XtremeCT; Scanco Medical AG, Bruttisellen, Switzerland) present low values of porosity (between 1% and 15%) because of quantifying only porosity of the compact-appearing cortex[12–17] and only pores over 100 μm, although 60% of cortical pores are under 100 μm in diameter.[18–20] This threshold-based image analysis underestimates porosity by

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including only completely empty voxels and excluding the voxels containing both void and bone matrix.[11] Furthermore, direct measurements of cortical bone water content using deuterium oxide or dehydration experiments report a void volume between 15 and 40%, suggesting an under-reporting of porosity.[21–23] To avoid exclusion of voxels that contain both void volume and bone matrix, a new approach has been developed, taking into account this process of partial volume effect.[11]

StrAx1.0 software is a non-threshold-based approach (StraxCorp Pty Ltd, Melbourne, VIC, Australia) that automatically selects attenuation profile curves, and segments the bone into the compact-appearing cortex, transitional zones, and trabecular compartment in high-resolution CT images[11,24,25] as well as in low-resolution CT images.[26,27] Bone is segmented by analyzing ~3600 consecutive overlapping profiles around the perimeter of each cross-sectional slice.[11] Local bone edges are identified as the beginning and end of the rising and falling S-shaped portions of the density profile curve that has two plateaus: one corresponding to the compact-appearing cortex and one corresponding to the trabecular compartment.[11] Between these plateaus is a descending S-shaped curve or transition between the two plateaus, which is called the transitional zone.[11] StrAx quantifies porosity as the average void volume fraction of all voxels within the total cortex; this is not only the porosity of the compact-appearing outer part of the cortex but also the porosity of the transitional zone in the inner part of cortex. Moreover, StrAx includes porosity of both the completely empty voxels, as well as voxels containing void and mineralized bone matrix.[11] Conversely, porosity quantified using this software for analysis of HR-pQCT images[24,25] or low-resolution CT images,[26] is higher than porosity reported with other methods.[11] Porosity of the compact-appearing cortex is ~35% and that of the transitional zones is ~60%, and the average porosity of the total cortex (compact-appearing plus transitional zones) is 43%, respectively.[26] StrAx software does not quantify the size and number of pores, but the proportion of porosity (emptiness) regardless of the size of the pores.

As illustrated in the StrAx profile curves, there is a gradual change in attenuation from the outer to the inner part of bone.[11] Bone is a continuous structure, with no sharp cutoff between cortical and trabecular bone.[11] It is therefore a challenge to separate the cortical bone from the trabecular bone. Moreover, trabecularized cortical fragments of the inner cortex look similar to trabecular bone.[8] Taking the transitional zone into account by using the non-threshold-based method avoids misclassification of trabecularized cortex as trabecular bone.[8] Accuracy of porosity measurements at distal radius and tibia using HR-pQCT images with a voxel size of 82 μm was validated against μCT images of cadaver specimens with a voxel size of 19 μm as the gold standard.[11] Zebaze *et al.*[11] also assessed accuracy of porosity quantified at the proximal femur in HR-pQCT images, against scanning electron microscopy (s.e.m.) images of specimens collected at 2.5 μm resolution as the gold standard. The agreement (R^2) between HR-pQCT and these gold standards for quantification of porosity ranged from 0.87 to 0.99.[11] The in vivo and ex vivo precision error was <4.0%.[11] Accuracy of porosity measurements using clinical CT images with a voxel size of 740 μm was validated by testing agreement with HR-pQCT measurements with a voxel size of 82 μm.[26,27] The agreement (R^2) between CT and HR-pQCT for quantification of porosity at the same femoral subtrochanter site ranged from 0.86 to 0.96.[26,27] The coefficients of variation for porosity of each cortical compartment were between 0.3 and 2.3%.[26] Thus, StrAx1.0 software provides accurate and reliable measurements of cortical porosity.

Cortical Porosity and Fragility Fracture

The first study to demonstrate that cortical porosity of the distal tibia measured *in vivo* using HR-pQCT was associated with fracture included 345 women between 40 and 61 years of age, and 93 of them had at least one fracture at any site.[24] Images of the distal tibia and distal radius were obtained using HR-pQCT (voxel size of 82 μm)[24] and analyzed using StrAx1.0 software.[11] As many of the fractures occurred during childhood, greater porosity may be established during growth. A larger medullary area relative to the total area of the distal tibia was also associated with fracture, reflecting greater excavation on the endocortical surfaces relative to periosteal apposition, with enlargement of the medullary area relative to the total area in wider bones.

Moreover, in a case-control study of 68 postmenopausal women with fractures and 70 controls, cortical porosity of the distal radius, quantified *in vivo* using HR-pQCT images (voxel size of 82 μm) and StrAx software, was associated with forearm fracture.[25] Also in a nested case–control study of 211 fracture cases and 232 controls, cortical porosity of the proximal femur quantified *in vivo* using low-resolution clinical CT (voxel size of 740 μm) and StrAx1.0 software, was associated with non-vertebral fractures in postmenopausal women.[26] The increased risk of fracture was independent of aBMD and FRAX in both studies.[25,26] Increasing porosity increases odds for fracture,[14,24,25] and treatment reduces porosity at the distal radius and at the proximal femoral shaft in postmenopausal women.[27–29] It is therefore reasonable to conclude that porosity is a substantial determinant of the bone fragility that underlies risk of fractures.

As most fractures occur in individuals with osteopenia, it is of clinical interest that cortical porosity of the distal radius is associated with forearm fractures, and cortical porosity of the proximal femur is associated with non-vertebral fractures, especially in women with osteopenia.[25,26] Furthermore, and more significantly, this holds for those with normal aBMD, who are often regarded as being at a low risk for fractures (**Figure 1**).[26] Conversely, cortical porosity was not significantly associated with fractures in women with osteoporosis, which may be due to a lack of statistical power.[26] Although 92% of women with forearm fracture and osteoporosis had high porosity of the distal radius,[25] only 39% of women with non-vertebral fracture and osteoporosis had high porosity of the femoral subtrochanter.[26] Due to the small sample size of women with osteoporosis in both these studies, larger studies are needed to address the question of whether porosity is captured by the diagnostic aBMD threshold for osteoporosis (*T* score < -2.5), or whether a measurement of porosity is an independent risk indicator of fracture in those who have osteoporosis.

Cortical Porosity Improves Identification of Women with Fracture

Using femoral neck aBMD (*T* score threshold < -2.5) enabled identification of only 9% of 211 women with non-vertebral

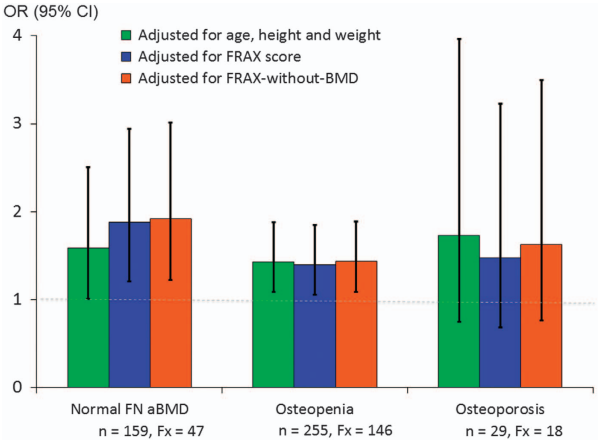

Figure 1 Odds ratio (OR) and 95% confidence interval (CI) for non-vertebral fracture per each standard deviation (s.d.) higher cortical porosity, in postmenopausal women with normal femoral neck areal bone mineral density (FN aBMD), osteopenia and osteoporosis. FRAX, fracture risk assessment tool; Fx, number with fracture. With the permission of Springer. (Ahmed *et al.*[24]).

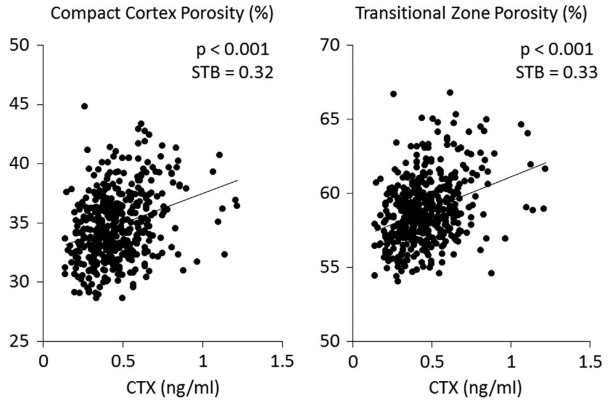

Figure 2 Femoral subtrochanteric porosity of the compact appearing cortex, and transitional zone, as a function of C-terminal cross-linking telopeptide of type I collagen (CTX). The standardized beta coefficients (STB) are adjusted for age, height, weight and fracture status in linear regression analysis. With the permission of Elsevier. (Shigdel *et al.*[29]).

fracture, and the FRAX (threshold >20%) identified 21%; furthermore, cortical porosity (threshold >80th percentile) of the femoral subtrochanter enabled identification of 29%.[26] Measurement of high cortical porosity identified 26% additional women with fracture than identified by using the osteoporosis threshold, and 21% additional women with fracture than by using the FRAX threshold.

Cortical porosity of the femoral subtrochanter was also associated with increased risk of non-vertebral fracture independent of FRAX-without-BMD.[26] In hospitals where DXA machines are not available for measurement of aBMD, CT is usually available, and rather than using FRAX-without-BMD alone, combining this with a measurement of porosity enabled identification of 19% additional women with fractures than the 25% identified by FRAX without BMD alone.[26] It is therefore likely to improve identification of women at risk for fracture, as the measurement of porosity captures elements of fracture risk that are only partially captured by the aBMD or FRAX, with and without aBMD.[26]

A tradeoff for cortical porosity thresholds at the 75th, 80th and 90th percentiles is reported with a sensitivity of 34, 29, and 16%, and specificity of 83, 88, and 95%, respectively.[26] Further work is needed to determine the optimal threshold for cortical porosity. The sensitivity for fracture improved from 21 to 43% when a measurement of cortical porosity of the femoral subtrochanter was combined with FRAX; however, 57% of the fracture cases were not identified by either of these thresholds (cortical porosity >80th percentile or FRAX >20%). Thus, improving sensitivity for fracture remains a challenge that may be met by measuring other structural properties in combination with fall characteristics.

Bone Turnover Markers, Cortical Porosity, and Fracture

All factors that influence bone loss do so through their effects on the bone remodeling process that continuously breaks down old and damaged bone and replaces this with new bone matrix.[30] This process is a surface phenomenon that occurs on all inner bone surfaces: the intracortical surface lining the Haversian and Volkmann canals, the endocortical surface between the cortex and marrow cavity, and the trabecular surface on either side of the trabecular plates. Bone loss is caused by the negative balance between bone resorption and bone formation within each of the bone multicellular units (BMU) and by the remodeling rate.

Serum levels of bone turnover markers (BTM), procollagen type I N-terminal propeptide (PINP) and C-terminal cross-linking telopeptide of type I collagen (CTX) reflect the rate of bone remodeling. Each standard deviation (s.d.) increasing PINP and CTX is associated with changes as follows: 0.27–0.33 s.d. higher porosity within each of the cortical compartments, 0.13–0.18 s.d. thinner cortices and 0.10–0.14 s.d. larger bone size of the femoral subtrochanter after accounting for age, height and weight in linear regression analysis (all $P<0.05$), as shown for CTX and porosity in **Figure 2**.[31] These changes were inferred to be produced by increased intracortical and endocortical remodeling and periosteal apposition. The more porous and thinner cortices were shifted further outward around a larger bone. As increasing bone size increases cross-sectional moment of inertia (CSMI) and resistance to bending,[32] the increased odds for fracture with increasing bone turnover suggests that the positive effect of larger bone size on bone strength does not offset the negative impact of higher porosity and thinning of cortices produced by increased bone remodeling.[24,31,33–35]

This first evidence of association of *in vivo* measurements of proximal femur cortical porosity from clinical CT images with bone remodeling activity as reflected by PINP and CTX[31] confirm a previously reported association between distal tibia cortical porosity with PINP and CTX.[36] Cortical bone loss is the result of unbalanced and accelerated intracortical remodeling on the surfaces formed by the many canals traversing cortical bone.[37] As more bone is resorbed than replaced at each BMU, focal enlargement of the canals occurs and canals coalesce, forming giant pores, as shown in biopsies from the proximal femur in women with hip fractures.[38] Deterioration of bone architecture produces bone fragility not only by trabecular perforation and loss of trabeculae, but also by increased porosity and cortical thinning;[8,34,38,39] both trabecular and cortical bone are important determinant of bone strength.[4] Trabecular bone is lost more rapidly, so that the relative

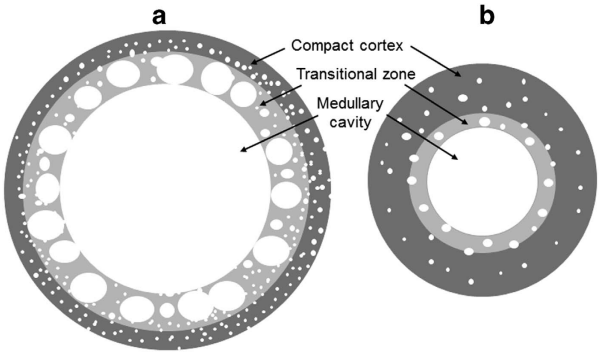

Figure 3 For two tubular bones, (**a**) had a larger total cross-sectional area (TCSA) than (**b**), larger medullary cavity, larger total cortical CSA (Compact cortex + Transitional zone), larger transitional zone CSA as a proportion of TCSA, but smaller compact cortex CSA as a proportion of TCSA, and higher porosity within each of the cortical compartments. With the permission of John Wiley and Sons. (Shigdel *et al.*[33]).

proportion of trabecular bone diminishes with advancing age. Although cortical bone loss accelerates with aging, and many non-vertebral fractures occur at sites containing a greater proportion of cortical bone.[8]

Higher levels of PINP and CTX are associated with larger total cross-sectional area (CSA) of the femoral subtrochanter.[31,35] In adolescents, increasing CTX is associated with larger mid-tibial bone size, and is suggested to persist into later life.[40] The reason for this may be that genetic factors account for most of the variance in BTM and bone size.[41,42] In women with larger bones built by increased bone modeling and remodeling during growth, a persisting greater periosteal apposition, intracortical, and endocortical resorption may create a double hazard after menopause, when increased remodeling intensity generates a greater void volume with substantially more remodeling surfaces.[36]

There are modest but significant associations of BTM with fracture in women and men.[43–46] Still, there have been uncertainties over the use of BTM in routine clinical practice to assess fracture risk because of inter- and intra-individual variability.[47,48] Although a recent study suggested that BTM also reflect cortical bone architecture in addition to fracture risk,[31] further studies are needed to evaluate the independent role of BTM in fracture risk prediction. Higher cortical porosity and thinner cortices were independently associated with increased odds for fracture (odds ratio 1.71; 95% confidence interval (CI) 1.38–2.11 and 1.79; 95% CI 1.44–2.23, respectively, both $P<0.05$) after adjustment for age, height and weight using logistic regression analysis.[35] Surprisingly, a larger external bone size increased the odds for fracture, but this association vanished after adjustment for cortical porosity, suggesting that porosity mediated the risk of fracture.[35]

Associations of Cortical Porosity and Other Bone Architectural Features

Women with higher body weight have thicker cortices and larger bone external size at the femoral trochanter (standardized beta coefficients (STB) 0.22–0.17, $P<0.001$), suggesting that periosteal apposition displaces the thicker cortex further outward around a larger perimeter.[35] They also tended to have lower levels of BTM (STB -0.10, -0.17, $P<0.10$), with a relatively smaller transitional zone area (STB -0.15, $P<0.01$), and thus a relatively larger compact cortical area and increased CSMI (STB 0.22–0.28, $P<0.001$). These associations are suggesting that reduced intracortical and endocortical resorption results in thicker cortices so that cortical architecture is better preserved. Thus, women with greater weight exhibited improved bone strength, which may be due to the increased bone size produced by periosteal apposition and due to reduced intracortical and endocortical resorption making the cortex thicker. Thicker cortices in obese women than in normal-weight women have been reported using HR-pQCT.[49] Cortical thickness increased similarly by increasing body weight and body mass index (BMI) within a range for weight and BMI of 44–110 kg and 18–43 kg m^{-2}, respectively.[35] Thicker cortices with increasing weight and BMI may partly explain lower risk of hip fracture with increasing weight and BMI.[50] However, the relationships between BMI and fracture risk vary by fracture site.

Increasing age and height are associated with larger bone size, larger medullary cavities, and greater strength, as reflected by a higher CSMI (STB 0.31–0.53, $P<0.001$).[35] However, with greater age, height, and especially with larger bone size, the porosity increases (STB 0.58, $P<0.001$) and the cortex becomes relatively thinner (STB -0.67, $P<0.001$), as illustrated in **Figure 3**.[35] In postmenopausal women, BTM did not increase with age, but taller women, and particularly those with larger bone sizes, had higher levels of BTM (STB 0.14–0.22, $P<0.05$). This is in agreement with a previous report[40] and partly explains why there is a higher risk of fracture in taller women who, on average, have larger bone size.[24]

The significance of the present work is that bone architecture is measured *in vivo* at the proximal femur, a common site of the most serious fragility fracture.[26] Moreover, bone architecture is quantified using minimally invasive imaging technology and a non-thresholding method that automatically segments the bone region into the compact-appearing cortex, transitional zones, and trabecular compartment, and measures the architecture within each of the cortical compartments.[11] Previous studies of bone architecture and cortical porosity have primarily been based on histomorphometric assessment of bone biopsy specimens or pQCT assessment of peripheral bone sites. However, one limitation is that the femoral subtrochanteric site contains little trabecular bone, so its association with fracture could not be studied.[26] Another limitation is that finite element analysis is not performed for calculation of strength estimates,[50] and the trauma involved is not accounted for in the statistical analysis of the data in the clinical studies of *in vivo* measurements of cortical porosity that are presented here.[26,31,35] Although femoral neck aBMD and cortical porosity at the femoral subtrochanter are inversely correlated ($r=-0.37$, $P<0.01$),[27,51] both of these bone traits are statistically independently associated with fracture risk (both $P<0.01$).[26] The clinical implications of these results are that these two bone traits capture some shared elements of bone strength as well as independent elements that are associated with fracture risk.[26]

Conclusion

Increasing levels of bone turnover markers are associated with higher cortical porosity and thinner cortices, which are two bone architectural features that predispose for fracture. Increasing cortical porosity is a risk factor for non-vertebral fracture

independent of aBMD and FRAX, and measurement of cortical porosity improves identification of women with fracture. Development of a new FRAX accounting for porosity may become a useful tool, to determine which patients need treatment for bone fragility. Further research is needed to identify the best combination of risk factors to improve the sensitivity for fracture using cortical porosity, FRAX, or other risk factors to predict fractures in prospective studies.

Conflict of Interest

The author declares no conflict of interest.

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