

Bone Structure and Fracture Risk: Do They Go Arm in Arm?

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Fracture incidence varies markedly among racial and ethnic groups.^(1–5) Hip and nonvertebral fractures are consistently highest among whites, lowest among those of African descent and intermediate among Asians.^(1–3) Specifically, age-adjusted hip fracture incidence ranges from a low of 1 per 100,000 person-years in black women in Nigeria to a high of 421 per 100,000 person-years in white women in Norway, respectively.⁽⁶⁾ Variation in vertebral fracture incidence by ethnicity is less well established,⁽¹⁾ although the incidence of clinical vertebral fractures is at least as high in Asians as whites.⁽⁵⁾ An improved understanding of the mechanisms underlying these variations in fracture rates may provide insight for identifying those at greatest risk for fracture and potentially identify novel targets for intervention.

Some of the ethnic-related variation in fracture rates is explained by differences in bone mineral density (BMD).^(2,7) However, even after accounting for differences in BMD by ethnicity, fracture rates differ. For example, at every level of BMD, black women have a lower risk of nonvertebral fracture than white women.⁽³⁾ Furthermore, despite having the lowest BMD values, postmenopausal Asian Americans have a lower risk of nonvertebral fracture than white, Hispanic, black, and Native American women.⁽²⁾ All together, these observations suggest that mechanisms other than differences in BMD are responsible for differences in fracture rates. This may be so because BMD measurements do not quantify some of the factors that contribute to bone strength, such as bone tissue properties, morphology, and microarchitecture.⁽⁸⁾ Indeed, relatively little is known about race- and ethnicity-related differences in these characteristics because until recently, there were no tools to assess bone structure adequately in vivo.^(9,10)

In this month's *JBMR*, Walker and colleagues use high-resolution peripheral computed tomography (HR-pQCT) to compare bone microarchitecture at the distal radius and tibia in postmenopausal Chinese-American and white women.⁽¹¹⁾ These results extend previous work showing that premenopausal Chinese women have smaller bone cross-sectional area but

increased cortical and trabecular thickness and greater cortical density at both the distal radius and the distal tibia.^(12,13) In the current study, 29 Chinese-American and 68 white postmenopausal women were evaluated. Areal bone mineral density (aBMD) at the spine, hip, and radius was measured using dual-energy X-ray absorptiometry (DXA), and bone microstructure at the distal radius and tibia was assessed using HR-pQCT. As expected, the Chinese-American women were shorter and weighed less than the white women. Surprisingly, however, aBMD was similar between the two groups at all skeletal sites. Postmenopausal Chinese-American women had approximately 10% smaller bone cross-sectional area but 5% to 6% higher cortical density and 16% to 18% higher cortical thickness than whites. Chinese-American women also had fewer trabeculae at the distal radius and fewer but thicker trabeculae at the distal tibia compared with whites. Differences in bone cross-sectional area were attenuated somewhat after adjusting for the shorter stature and lower weight of the Chinese-American women, whereas differences in cortical and trabecular thickness were largely unaffected. The net result of these differences in bone morphology, evaluated by finite-element analysis (FEA), showed similar compressive stiffness in the two groups, suggesting that the smaller cross-sectional area in Chinese-American women was compensated for by their increased cortical and trabecular thicknesses.

The study provides novel insights into differences in bone structure by ethnicity, yet several issues should be considered when interpreting the results, including (1) the modest sample size, (2) the limitations of HR-pQCT measurements and assumptions used for derivation of some microarchitecture features, and (3) lack of information on tissue material properties. The authors examined a relatively small convenience sample of only 29 Chinese-American subjects who were, on average, 2 years younger and tended to be closer to the menopause than the white women. After adjusting the analyses for age and body mass index (BMI), the strength of some of the ethnicity-related differences was attenuated, although most of the differences

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remained significant. Considering the HR-pQCT measurements, it is important to note that whereas trabecular density and trabecular number are measured directly, trabecular thickness and separation are derived using histomorphometric methods assuming a platelike architecture.⁽¹⁴⁾ Although the same algorithm is applied to both groups, it is not known whether trabecular architecture is represented with similar accuracy by a platelike architecture in Chinese-American versus white women. In addition, the cortical thickness was assessed using the manufacturer's standard algorithm, which does not measure cortical thickness directly but rather calculates it by dividing the mean cortical volume by the periosteal surface. Given the smaller periosteal perimeter in the Chinese-American women, cortical thickness may have been overestimated using this approach. Newer algorithms for assessing cortical thickness and porosity^(15–17) may provide better estimates of race- and ethnicity-related differences in the cortical compartment. Further, given the resolution of the HR-pQCT images (82- μm^3 isotropic voxel size), it is difficult to know whether the increased cortical density in the Chinese-American women was due to increased cortical tissue mineral density and/or reduced intracortical porosity.

In addition to bone size, morphology, and microarchitecture, variations in bone tissue material properties also may contribute to differences in fracture risk by ethnicity. However, relatively little is known about variations in the mechanical properties of bone tissue with age, ethnicity, or disease largely owing to the challenge of measuring these properties in vivo. The introduction of novel methods for in vivo assessment of bone tissue properties⁽¹⁸⁾ may provide additional insights in this area.

These limitations aside, a critical question is whether the observed differences in skeletal morphology account for the lower rates of wrist and hip fractures in Asian versus white women.^(1–3,19) Fractures occur when the forces applied to a bone exceed its strength. Thus factors related both to bone strength and to skeletal loading theoretically could influence ethnicity-related differences in fracture incidence. Although this study did not study subjects with and without fractures, several cross-sectional studies have shown that deteriorated bone architecture and/or reduced FEA-estimated bone strength at the distal radius or tibia is associated with a history of fragility fracture.^(20–28) In particular, individuals with a history of fracture have decreased trabecular bone density and cortical thickness,^(21,22,24–28) providing evidence that the increased cortical thickness seen in Chinese-American women could contribute to their lower fracture rates. In this study, Chinese-American and white postmenopausal women had similar FEA-estimated bone strength values. Yet, despite the same bone strength, the Chinese-American women likely still would have lower forearm fracture risk than the white women because a lower force would be applied to their wrists following a fall owing to their smaller stature and lower body weight. Moreover, it is possible that decreased fall incidence in Asians compared with whites^(29,30) also contributes to their lower fracture rates. In sum, the differences in bone morphology reported by Walker and colleagues⁽¹¹⁾ are consistent with the lower risk of wrist fractures reported in Asian women, but the contribution of nonskeletal factors to ethnicity-related differences in fracture also may play

an important role. Furthermore, this study focused exclusively on the appendicular skeletal, leaving open the question of whether the pattern of increased cortical density and thickness seen in Chinese-American women at the distal radius is also present at the proximal femur, possibly contributing to their lower risk of hip fracture.

Fracture risk increases with age; thus an important factor in understanding differences in fracture rates is whether ethnicity-related differences in bone morphology seen in premenopausal women^(12,13) are maintained after the menopause. Heterogeneity of bone loss at the menopause is widely accepted, with “fast” and “slow” losers observed.⁽³¹⁾ However, the factors that contribute to variation in rates of bone loss and structural deterioration during the menopause are poorly understood. The Study of Women Across the Nation (SWAN) reported that Japanese and Chinese women had greater declines in spine BMD than white or African-American women during the menopause.⁽³²⁾ Do changes in bone microstructure follow the same ethnicity-related patterns as BMD? Taken together with their previous report in premenopausal women,⁽¹²⁾ Walker and colleagues' current findings⁽¹¹⁾ provide preliminary insight into this question. They report that premenopausal Chinese-American women have *higher* trabecular density than white women, whereas postmenopausal Chinese-American women tend to have *lower* trabecular density than white women. In contrast, the increased cortical thickness seen in Chinese-American premenopausal women is preserved in postmenopausal women. These findings suggest that there may be preferential loss of trabecular bone and relative preservation of cortical bone in Chinese-American women. These observations are far from definitive given that they were drawn from two small cross-sectional studies, but they do raise important questions about possible contributions of race or ethnicity to compartment-specific patterns of bone loss following the menopause.

What are the physiologic mechanisms underlying the observed ethnicity-related differences in skeletal structure? How do possible differences in the rates of bone modeling and remodeling contribute to the observed differences in bone size and structure? In SWAN, serum osteocalcin and urinary cross-linked *N*-telopeptide of type 1 collagen (NTX) were highest in white and black and lowest in Asian premenopausal and early perimenopausal women.⁽³³⁾ The lower bone turnover rate in pre- and perimenopausal Asian women is consistent with less endocortical resorption leading to the greater cortical thickness and density seen in Chinese-American women^(12,13) but is counter to the increased rate of bone loss seen at the menopause. Clearly, further studies are needed to better delineate the factors that contribute to acquisition and maintenance of trabecular and cortical bone structure among all ethnicities.

In the United States, population growth is fastest among those who self-identify as nonwhite.⁽³⁴⁾ Moreover, given the predictions of increased fractures among societies worldwide,⁽³⁵⁾ further study of the material and structural determinants of fracture risk in multiethnic populations is urgently needed. The article by Walker and colleagues⁽¹¹⁾ adds to our knowledge in this area and raises a number of key questions that will guide future research directions. Prospective fracture studies with bone

morphology and structure measurements are needed to translate these observations to better management of patients. Improved understanding of skeletal fragility in all ethnicities will improve identification of those at greatest risk and motivate novel interventions for prevention of fractures based on specific structural deficits.

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