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Editorial

Fracture Risk: A Role for Compact Bone

Over the last two decades cross-sectional studies have shown that a decreased bone mineral density (BMD) at any skeletal site is associated with an increased risk of fracturing [1–4]. This relationship between BMD and fracture reflects the documented association between bone mass and strength [5–7]. The integrated mass of compact and trabecular bone at the spine and femoral neck accounts for >80% of the variance in strength. Some critics have speculated that factors other than bone mass must be responsible for fractures, and that bone mass is merely a marker for falls or structural weakness [8, 9]. Recent longitudinal studies have confirmed that a low BMD, even at peripheral skeletal sites, predicts future fractures [10–13]. Most "risk factors" for fracture seem to operate through reducing bone mass and strength, thereby increasing the propensity to fracture. Risk factors account for a smaller portion of the variance in fracturing than BMD [14] and this role becomes negligible when they are considered in a multivariate analysis that includes a bone measurement. For example, body weight under 55 kg in postmenopausal white women increases the relative risk of fracture [15], but low weight is associated with a low BMD; when BMD is controlled, the increase of relative risk associated with low body weight is minimal. The same is true for risks like oligomenorrhea, immobilization, low calcium intake, family history, and corticosteroids. Muscular weakness and the tendency to fall are less highly associated with osteopenia, and account for some of the known independent effects of age on hip fracture.

The relative risk of fractures increases about twofold for every 1 SD decrease in BMD. Osteoporotic women average about 1.0–1.5 SD below age-matched controls in axial BMD; therefore they have a threefold higher relative risk of fracturing than their peers. However, such an analysis is misleading because the absolute risk, rather than the relative risk of fracture is critical. Older women have a fourfold higher risk than young women simply because osteopenia occurs in the so-called normal elderly. Consequently, the relative risk for osteoporotic women is improperly assessed against a background of already increased risk in age-matched controls; osteoporotic women have at least a tenfold higher risk than normal young women who are free from osteopenia or fracture.

Apparently, the mean BMD at fracture sites in patients with fractures is invariant with age, gender, and ethnic background. The usual spine BMD values found in osteoporotic patients with spine and trochanteric hip fractures is about 0.83 ± 0.15 g/cm^2 (using the University of Wisconsin calibration). The average femoral neck BMD in these same patients is about 0.65 ± 0.10 g/cm^2. The corresponding BMD values in cervical hip fractures are about 0.93 g/cm^2 for spine and 0.55 g/cm^2 for femoral neck [16]. The values are very similar in men and women, Asians and whites after adjustment for body weight. Note that against a background of osteoporotic spine fracture, the femoral neck BMD is reduced less (-1 SD versus -2 SD) than when compared to the BMD of older women who have no fractures (0.75 g/cm^2). It is very much reduced (-4 SD) compared to normal young women who have a femoral BMD of 1.00 g/cm^2 [17, 18]. One way of assessing the value of bone densitometry is by examining the attributable risk of fracture (the excess population risk associated with a particular factor). Against the background of older women without any fracture, about 80% or more of the attributable risk of fracture is associated with below-averaged BMD [18, 19]. In the total population of younger and older women, an even higher percentage of the attributable risk (95%) is associated with these low densities.

Still, important questions remain. Why do some individuals develop fractures with relatively high bone densities, yet others with profound osteopenia never fracture? Is this due to a structural abnormality, and if so, is this defect in trabecular or compact

bone? [9]. Most of the emphasis for the past 20 years has been on trabecular bone because its active metabolism leads to early and rapid changes in response to disease or to therapy. This is the most labile, but structurally least important area. Though trabecular osteopenia occurs with fracture, there has been no direct evidence, either *in vivo* or *in vitro,* of "structural fragility." Structural factors in trabecular bone (interconnection of trabeculae, accumulation of microfractures, trabecular wall thickness, and trabecular orientation) do not increase the prediction of bone strength *in vitro* beyond the predictability achieved by chemical analysis or densitometry alone. Increases of plate spacing and perforations, as well as loss of horizontal trabeculae, are compensated for by thicker vertebral trabeculae [20]. Trabecular structures tend to covary with density so they would not be expected to augment the already high strength prediction. In contrast, the role of compact bone in osteoporotic fracture remains unclear. Small changes in the amount of compact bone make a large difference in bone strength [21]. Both endosteal resorption and the increased porosity that occurs with aging (10% versus 5% in young normals) and with osteoporosis (15%) are possible factors in bone fragility [22–24]. Perhaps the structural weakness at fracture sites is in compact bone as much as in trabecular bone [25].

In this regard it is important to note that the density and rate of bone loss of trabecular bone is virtually identical in men and women [26–28]. It is difficult to reconcile the tenfold higher fracture rate of the spine and threefold higher rate of hip fracture in women with this absence of a gender difference. The ultimate load of whole vertebrae from women is about 30–50% lower than that in men [6, 7] but there is no significant difference in compressive strength of the trabecular bone [28]. Recent studies [27] have shown that women lose compact bone from the margin of the vertebral body itself but men do not. The maintenance of this compact shell undoubtedly contributes to strength and protects the vertebral body from fracture [25]. This explains why quantitative computed tomography (QCT) measures of trabecular density, even dual-energy determinations that halve the 20% error due to fat in marrow, explain only 20–40% of strength [29–31]; 80–85% is explained when the compact shell is also measured [6, 7, 25]. Does the same situation apply to the femur? Again, 80% of the variance in strength is accounted for by integral bone mass across the neck [5], however, trabecular density of the central trabecular region accounts for only 40–50% of strength [32–34]. Phillips et al. [35] showed that the section modulus of the cortical shell was critical to femoral strength. There are aging decreases of femoral BMD in women [17]; our own results suggest a somewhat lower bone loss in men. Again the loss of trabecular bone from the Ward's triangle is more similar in men and women than the overall bone loss, suggesting that compact bone is retained in men. If this is so, then both the population and biomechanical data support the hypothesis [36, 37] that loss of both compact bone and trabecular bone contribute to hip fracture.

More detailed studies will be necessary to outline the complex interplay of compact bone and trabecular bone at key fracture sites such as the proximal femur and the spine. It appears likely, however, that the interplay of these gross anatomical features may be more important than subtleties of trabecular bone structure in bone strength [20, 28]. New high-resolution computed tomography allows examination of the axial skeleton directly [38]; similar methods for the peripheral skeleton exist [39] but the relationship to axial sites needs to be demonstrated.

The possible import of compact bone on strength of the spine and proximal femur raises questions about the therapeutic approaches for the treatment of osteoporosis. Therapeutic agents that preserve or increase trabecular bone are of obvious import; many agents achieve this at least on a transient basis. On the other hand, agents may have to at least preserve compact bone to prevent spine and femur fractures. Estrogen has a positive effect on trabecular bone and a stabilizing effect on compact bone, so the usual 50–70% reduction in fracture rate is not unexpected. Calcium, even though it does not prevent loss of trabecular bone, may benefit compact bone, perhaps through reduction of porosity as much as through inhibition of endosteal resorption. If calcium reduces fracture rates it probably does so through its action on compact bone. Agents such as sodium fluoride or parathyroid hormone (PTH), which dramatically increase trabecular bone, seem to have less benefit than expected. Compact bone loss appears unaffected by fluoride and PTH, and perhaps strength is compromised by increased cortical porosity. If the hypothesized role of compact bone is correct, then these agents and newer agents, such as bisphosphonates, calcitonin, and vitamin D metabolites, must be shown to have a positive effect on compact as well as trabecular bone if femur and spine fractures are to be prevented.

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