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Peak Bone Mass, Bone Loss and Risk of Fracture

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Abstract. Both peak bone mass and bone loss contribute to subsequent fracture risk. Other variables such as architectural abnormalities, microdamage, geometric properties, and trauma probably contribute as well. Until the contribution of these other potentially important risk factors can be quantified, it will be difficult to determine precisely the relative importance of peak bone mass and subsequent bone loss in the etiology of fractures.

Keywords: Bone loss; Bone mass; Fractures

An important question which remains to be answered definitively is the relative contributions of peak bone mass and bone loss to the development of low bone mass later in life with its attendant fractures. This question, however, is more complex than it first appears. The timing of peak bone mass and both the timing and rates of bone loss may differ depending on skeletal site, and therefore the relative contributions of these factors to fracture susceptibility probably differ depending on the fracture of interest. For example, the peak incidence of vertebral fractures precedes that of hip fractures, and there must be a correspondingly briefer period of bone loss before these often asymptomatic fractures occur. In addition, however, bone loss may affect the structural properties of vertebral bodies more severely than it does these properties in the femoral neck. As discussed below, these and other problems complicate the answer to the question regarding the relative contributions of peak bone mass and bone loss to fracture risk.

Fracture pathogenesis is complex and other factors in addition to low bone mass play a role in the development of these fractures. Until these factors can be measured and their contributions to fracture development calculated, it will be difficult to determine the exact role of peak bone mass and especially bone loss in the development of those fractures. Low bone mass is, however, clearly an important determinant of fracture risk. When tested in vitro, up to 80% of the strength of bone can be accounted for by its mass [1]. Prospective studies have indicated that a 1 SD decrease in bone mass can account for a 50%–100% increase in the risk of all non-spine fracture [2–4], and a 1 SD difference in bone mass in the femoral neck is associated with a relative risk of 2.6 (i.e. a 160% increase in risk) for subsequent hip fracture [5]. However, other factors may also be responsible for increased fragility of the skeleton, and their contribution may be important in risk assessment. Moreover, skeletal fragility fractures require both diminished skeletal integrity and exposure to trauma at the site of fracture. While this trauma is usually referred to as 'minor,' the strength of the young adult femoral neck, for example, is inadequate to withstand the forces which result from an unprotected fall from standing height. In fact, the energy in a typical fall may exceed by a factor of 10 that needed to fracture an unprotected hip [6]. Soft tissue covering the greater trochanter, protective reflexes and other non-skeletal factors undoubtedly modify the risk of suffering osteoporotic fractures. A better understanding of these influences will clarify the roles of peak bone mass and bone loss in fracture etiology.

Among other potential skeletal influences on fracture risk, architectural abnormalities are a likely contributor to increased fracture risk. These are known to occur [7], particularly in the trabecular architecture of the vertebral bodies, and the resultant loss of connectivity in trabeculae clearly leads to a structure weakened beyond what could be attributed to the loss of bone mass. Horizontal connecting trabeculae seem to disappear first, weakening the remaining structure due to the lack of stability of vertical struts in their absence [8]. However, such abnormalities cannot be assessed non-invasively at present and thus their quantitative contribution to fracture risk is unknown. These architectural changes are associated with bone loss, and thus bone mass measurements, which detect the diminished skeletal fragility. However, several studies suggest there may be an additional contribution possible from these architectural changes. When individuals of similar bone mass (trabecular bone volume) with and without vertebral fractures are compared, those with fractures have more trabecular abnormalities [9]. In addition, several studies have shown that individuals with prevalent fractures are more likely to have subsequent fractures than those without

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fractures but with similar amounts of bone [10]. Data have also recently been presented which demonstrated that women with rapid bone loss, independent of bone mass, had increased vertebral but not radial fracture incidence [11]. The implication of this finding is that rapid bone loss, which may lead to perforation of trabeculae, can result in architectural abnormalities which disproportionately affect the strength of vertebral bodies. Development of technology (possibly ultrasound) to assess prospectively these abnormalities along with bone mass measurements will allow a quantitation of their additional contribution to fracture risk.

Bone, like other materials, is subject to fatigue damage and such microdamage can be found on biopsies [12,13]. However, these changes cannot be non-invasively quantitated so that their contribution to fracture risk is not known and may indeed vary from fracture site to site [14], even within an individual. Furthermore, although bone suffers fatigue damage it also repairs such damage, and the extent to which damage accumulates or differs between those with and without fractures, or interacts with other factors involved in fracture etiology, is also unknown.

Geometric aspects of the skeleton can also contribute to fracture risk, especially for the femoral neck but perhaps for other fractures as well. It has been shown that hip axis length may contribute to fracture risk [15] independently of bone mass, increasing the risk of both femoral neck and trochanteric fractures by approximately 70%–90% for each standard deviation increase in length [16]. Other geometric properties of the femoral neck, including its length, could explain the lower femoral neck fracture incidence in Japanese compared with Caucasians which occurs despite the lower femoral neck bone mass in the Japanese [17]. Intuitively, a longer hip axis [16] or femoral neck length [17] might be thought to contribute to a longer lever arm, and therefore greater bending forces when exposed to trauma, but this may not be the case. Much of the variability in the hip axis length measurements is in the pelvic thickness [16] and femoral neck length has yet to be shown to contribute to fracture risk. Thus, femur geometry, although almost certainly important, is complex and will require further research before an understanding of its role in fracture etiology is clear.

Finally, trauma, especially that associated with falling, plays an important role in many fractures, particularly those of the femur [18]. It should also be noted that fractures of the vertebral bodies are probably not truly atraumatic. It has been shown that numerous common forces, including lifting objects, sneezing, coughing and others, can result in forces on the spine which exceed the strength of osteoporotic vertebral bodies [18]. Until the contributions of all these variables – architectural abnormalities, fatigue damage, geometry and trauma – can be determined, it will be difficult to ascertain precisely the contribution of bone loss alone to subsequent fracture risk. This reflects the fact that bone loss may be correlated with many of these factors, and may increase or decrease in importance depending on whether the bone loss results in architectural abnormalities, occurs in those who later experience trauma, or many other factors.

Peak bone mass and bone loss each contribute to low bone mass found later in life and it is obvious that the contribution of bone loss will increase as people age. Nevertheless, peak bone mass makes an important contribution and small changes in peak bone mass could make large differences in fracture risk in the population. Given that fracture risk changes between 50% and 150% for each standard deviation difference in bone mass (depending on the skeletal site measured), even relatively small increases in peak bone, say 0.5 SD, would be expected substantially to reduce the age-adjusted fracture rates. This relatively small amount of bone is approximately equal to the difference in adult bone mass between those who report consuming milk at every meal during childhood and those who report rarely or never consuming milk during this period [19]. Although it remains to be proven by clinical trials, observational data suggest that numerous environmental influences during growth might result in 0.5 SD differences in peak adult bone mass, including exercise, aspects of diet, and negative influences such as prolonged amenorrhea or anorexia nervosa.

We have examined longitudinal measures of radial bone mass made on various samples of postmenopausal women. The influence of bone loss increased with age so that by age 70 years both the peak bone mass and loss contributed equally to bone mass in the radius [20]. Bone loss is probably an important determinant of fracture risk, but other factors associated with bone loss such as development of microarchitectural abnormalities and microdamage could be contributing as well as bone loss itself. In the only study so far published, loss was not found to contribute independently to non-vertebral fractures [21], but the question has not been definitively answered. Some individuals lose bone at a more rapid rate than others and this rapid rate may persist in some of these individuals over a period of years [22]. Such rapid loss could result in trabecular damage and additional risk of fracture above that contributed by the loss of bone alone. It is also possible that even relatively short periods (2–3 years) of rapid bone loss might contribute to perforation of trabeculae and thus to increased fracture incidence. Long-term studies of bone loss from the spine and hip have yet to be published due primarily to the more recent availability of techniques to measure these sites.

The relative contribution of peak bone mass and bone loss can only be determined with further studies. What is the clinician to use now as criteria for intervention? A practical approach may be suggested. A measurement of bone mass would be made only when intervention to prevent bone loss was contemplated. Most commonly this would be at menopause to consider intervention with hormone replacement. But other forms of therapy are under development for which similar criteria could be applied. If the measurement was greater than 1 SD above the mean for young normals, no further measurement would be needed and no intervention undertaken. If the measurement was lower than 1 SD below the mean for young normals, intervention would be recommended (provided no contraindications were present). Several approaches to those within 1 SD of the mean could be suggested. Bone

mass measurement might be repeated in 1–3 years. This would depend on the expected magnitude of bone loss and the precision of the instrument. The period of time between initial and subsequent measurement should be shorter for those with lower bone mass. However, bone would be lost during that period of time. Since markers of bone turnover can be used to predict subsequent loss [22], one or several markers could be measured and if turnover were high, intervention would be indicated. Specific protocols must be developed, defining: (1) what markers are to be used, (2) when measurements are to be made, and (3) at what concentration of a specific marker intervention would be indicated. Other variables which contribute independently of bone mass, e.g. geometric properties such as femoral neck length, might also aid in making decisions among this group.

It must be stressed that effective therapies to reduce fracture risk depend upon prevention of bone loss. Once a patient's bone mass is low there is little that can be done to reverse this. Hormone replacement therapy, currently approved bisphosphonates and calcitonin may all result in short-term, small increments in bone mass (2% or so), but beyond this their effectiveness depends on the preservation of what bone mass is present at the initiation of therapy. It is also important to note that factors such as cigarette smoking, family history and presence of other diseases may also influence fracture risk and other interpretations of bone mass data.

Which site to measure for the most effective risk assessment has not been determined. All sites seem to give a relatively similar assessment for risk for all subsequent fractures. However, measurement of the femoral neck was shown in one study to give a better assessment of risk of subsequent femoral neck fracture [5]. Another study showed similar trends but no significant differences among sites in prediction of hip fractures [23]. Since hip fracture is the fracture of major public health concern, assessment at this site may best serve public interest. However, there is limited access to hip measurement and any site measured will serve for all fractures. A problem of misclassification also exists, since some individuals with low bone mass at one measured site have relatively normal measurements at other sites [24]. Multiple measurements could be made, but this would substantially increase the cost of the risk assessment with unproven benefits in fracture risk prediction. Perhaps the approach outlined above will suffice, since those whose measurements at one site are not as low as at another site would probably fall in the intermediate zone (± 1 SD from the mean of young normals) and subsequent measurement of bone mass or of markers would be done.

Peak bone mass and bone loss both contribute to fracture risk. Bone loss is only one of the factors associated with aging that contributes to risk and quantitative assessment of other factors such as the development of architectural abnormalities and microdamage is needed to improve our ability to determine the individual at highest risk of fracture in order to intervene before fracture occurs.

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