Osteopaenia - a marker of low bone mass and fracture risk

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Abstract

Introduction

Absolute fracture risk is greatest for individuals with osteoporosis, more than half of these fractures arise from those with osteopaenia and normal bone mineral density, a probable consequence of greater numbers at risk in these categories. However, areal bone mineral density measurements used commonly in clinical practice do not detect differences in bone tissue properties, geometry and microarchitecture, contributing to bone strength. This critical review discusses osteopaenia as a marker of low bone mass and fracture risk.

Conclusion

Neuver technologies such as high-resolution peripheral computed tomography have the advantage of assessing trabecular and cortical components of bone separately. Quantifying these parameters and considering clinical risk factors that affect fracture risk independent of bone quantity and quality, may better discriminate between high and low-risk individuals, improving the decision-making for targeting appropriate interventions to reduce the public health burden of fractures.

Introduction

Defining osteopaenia and osteoporosis

For nearly three decades, areal bone mineral density (BMD) has been measured using either dual-photon absorptiometry or, more recently, dual-energy X-ray absorptiometry (DXA) as a marker of osteoporosis¹. DXA-derived BMD is calculated as the bone mineral content divided by the area of bone scanned. This two-dimensional representation of volumetric BMD is confounded by bone size and shape. Nonetheless, fracture risk increases with decreasing BMD, such that each standard deviation decrease in BMD is associated with a 1.5–3.0-fold increase in age-adjusted fracture risk².

BMD is a continuous variable, which approximates a normal distribution, and it is commonly categorised into normal BMD, osteopaenia and osteoporosis on the basis of nominal thresholds recommended by an expert panel of the World Health Organization³. Osteopaenia is the low bone mass category defined by BMD T-scores between −1.0 and −2.5. Using these cut-points, 16% of young normal women are defined as having osteopaenia and 5% have osteoporosis, but these individuals may make little, if any, contribution to the population burden fragility fracture. The osteopaenia threshold was based on data that derived a theoretical fracture threshold⁴, whereas the osteoporosis threshold was based on the prevalence of fracture among postmenopausal Caucasian women. Although these thresholds were devised for epidemiological purposes appropriate for Caucasian women, they have been widely adopted for clinical use in broader populations.

Almost half of women aged 50 years and older in Australia have osteopaenia (and 23% have osteoporosis corresponding to BMD T-score < −2.5)⁵. Although thresholds for describing men with normal BMD, osteopaenia and osteoporosis have not been defined, the gradient for fracture risk is similar for each standard deviation deficit in BMD for both sexes. Utilising similar T-score thresholds for men aged 50 years and older indicates that just over half have osteopaenia corresponding to BMD T-score from −1.0 to −2.5 (and 6% have osteoporosis, T-score < −2.5)⁶. As there is discordance in BMD between skeletal sites, such estimates depend on the site scanned, as well as the reference range used to determine T-scores⁷. However, while osteoporosis confers the greatest risk for fracture, fracture risk is not negligible in persons with more moderate deficits in BMD⁸–¹⁰. Age-standardised 5-year absolute fracture risk derived from total hip BMD at baseline for post-menopausal women in Australia are 30.8% (95%CI 22.0–39.6) for women with osteopaenia, 17.5% (95%CI 13.2–21.7) for women with osteoporosis and 7.2% (95%CI 3.7–10.7) for women with normal BMD⁹. The aim of this critical review was to explore osteopaenia as a marker of low bone mass and fracture risk.

Discussion

Fracture and BMD

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies. Population-based studies reveal that the burden of fracture arises, not from the relatively small, high-risk group with osteoporosis, but from the larger group with intermediate risk. Different studies have used different inclusion and exclusion criteria, defined low-trauma fractures in different ways and ascertained different combina-
is shown, together with the cut-off points for osteoporosis and osteopaenia (shaded Figure 1: indicating that most fractures arise from the group with osteopaenia. Data relate to post-

ing that absolute risk for the group with osteopaenia is intermediate between those with osteoporosis and normal BMD. The proportion of fractures arising from those with osteoporosis, osteopaenia and normal BMD is represented by columns shaded in black, indicating that most fractures arise from the group with osteopaenia. Data relate to post-menopausal Australian women.

Equations of fractures as the outcome. Based on proximal femur BMD from a population-based cohort study of 616 postmenopausal Australian women followed for 5.6 years, 26.9% of radiologically confirmed fractures arose from women with osteoporosis and 73.1% from women without osteoporosis (56.5% from women with osteopaenia and 16.6% from women with normal BMD measured at the total hip).

Similarly, in a cohort study of 149,524 postmenopausal white women enrolled in National Osteoporosis Risk Assessment (NORA) from primary care practices in the United States and followed for 12 months after baseline assessment using BMD measurements obtained from a variety of peripheral devices (heel, finger or forearm), 18% of self-reported fractures arose from women with osteoporosis and 82% from women without osteoporosis (52% from women with osteopaenia and 30% from women with normal BMD).

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Fracture risk assessment

Various models for predicting fracture have been developed that involve BMD in conjunction with clinical risk factors with an aim of improving risk stratification, particularly within the large group with moderate bone deficits categorised as osteopaenia. The World Health Organization collaborating centre developed the FRAX algorithm as a tool based on clinical risk factors, with and without BMD, using primary data from multi-national prospective cohort studies. The FRAX estimates 10-year probability of hip fractures and major osteoporotic fractures (including fractures of the hip, spine, humerus and wrist).

In Australia, data from two population-based studies, the GOS and the Dubbo Osteoporosis Epidemiology Study independently combined BMD and clinical risk factors to generate fracture risk assessment tools known a consequence of larger numbers of women at risk of fracture in these groups (Figure 1).

However, the risk for fracture is multi-factorial. Many clinical risk factors for fracture operate through reduced BMD; however, others act independent of BMD. Increasing age contributes independently to the risk of fracture; for the same BMD, the risk of fracture varies by a factor of 8–10 between women aged <45 years and 80 years and older. Even though the majority of individuals who sustain a fragility fracture do not have a prevalent fracture (this proportion is 75% among women with osteopaenia), a prior fracture independently doubles the risk of subsequent fracture; women with osteopaenia and a prevalent fracture are at comparable risk to those with osteoporosis on BMD criteria. Low body mass index is recognised as a risk factor for fracture that is essentially independent of age and sex, but dependent on BMD. Falls independently increase the risk of fracture.

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The observation that age and structure (Bone microarchitecture and magnetic resonance imaging that include high-resolution peripheral quantitative computed tomography (pQCT) and magnetic resonance imaging that have the advantage of simultaneously assessing trabecular and cortical components of bone separately, in addition to geometric characteristics of the peripheral skeleton) are markers for greater material or structural deterioration in bone, not quantified by BMD. Bone morphology and microarchitecture contribute to the breaking strength of bone. To be strong, bones need to be stiff enough to withstand deformation under loading, yet adequately elastic to absorb energy during compression and tension. Recently developed technologies for assessing bone structure include high-resolution peripheral quantitative computed tomography (pQCT) and magnetic resonance imaging that have the advantage of simultaneously assessing trabecular and cortical components of bone separately, in addition to geometric characteristics of the peripheral skeleton.

In a matched case-control study of postmenopausal French women, 101 cases with fragility fracture over 13 years of follow-up were matched with fracture-free controls. Vertebral and non-vertebral fractures were associated with low volumetric BMD and structural deterioration of trabecular and cortical bone as assessed by high-resolution pQCT at the distal radius and tibia, independent of areal BMD. Cases had decreased trabecular volume, cortical thickness, trabecular number and trabecular thickness. Similarly, in another study using high-resolution pQCT, osteoporotic women had lower density, cortical thickness and increased trabecular separation than osteopaenic women. Among osteopaenic women, those with fracture had lower trabecular density and more heterogeneous trabecular distribution. These women were defined as having osteoporosis or osteopaenia based on measurements of BMD at the lumbar spine or proximal femur. The lower T-score was used to categorise subjects. A proportion of those with BMD in the osteopaenic range at the lumbar spine, alone, are likely to have had osteopaenia with the BMD measurement being spuriously increased by artefact. The apparent greater micro-architectural deterioration among those women with osteopaenia and fracture may therefore have been related to miscategorisation.

The pQCT assessment of the ultradistal radius in the United States shows that the structural basis for the observed decrease in trabecular volume differs between men and women. With ageing, women undergo loss of trabeculae with an increase in trabecular separation, whereas men start with thicker trabeculae and experience less age-related microstructural damage. Because decreases in trabecular number substantially affect bone strength, this finding may explain, at least in part, the protection men have against age-related increases in distal forearm fractures. More recent findings suggest that development of intracortical porosity may play an important role in compromising bone strength and that this could explain the high proportion of non-

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Table 1. Clinical risk factors incorporated into the fracture risk prediction models, FRAX\textsuperscript{19,20}, Garvan\textsuperscript{23} and FRISK\textsuperscript{17,22}.

<table>
<thead>
<tr>
<th>FRAX</th>
<th>Garvan</th>
<th>FRISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD femoral neck</td>
<td>BMD femoral neck or weight</td>
<td>BMD femoral neck</td>
</tr>
<tr>
<td>Age</td>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Gender</td>
<td>(Women only)</td>
</tr>
<tr>
<td>Weight, height (or BMI)</td>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>Previous fracture</td>
<td>Previous fracture</td>
<td>Previous fracture</td>
</tr>
<tr>
<td>Falls</td>
<td>Falls</td>
<td></td>
</tr>
<tr>
<td>Parent fractured hip</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral glucocorticoid use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other secondary causes of osteoporosis*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol 3 or more units per day</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Chronic liver disease, untreated hypogonadism, prolonged immobility, organ transplantation, type 1 diabetes, thyroid disorders, gastrointestinal disease.

BMD, bone mineral density; BMI, body mass index; FRISK, Fracture Risk.
vertebral fractures that occur with ageing at predominantly cortical sites\textsuperscript{24}.

In an Australian study of 185 female twin pairs aged 40–61 years, postmenopausal women were found to have higher levels of remodelling markers that were associated with larger intracortical surface area rather than with the progressively diminishing trabecular surface area\textsuperscript{31}. Identification of intracortical, endocortical and trabecular bone surface area are beyond the resolution of contemporary DXA analysis and are, therefore, not accounted for using BMD from DXA.

**Conclusion**

Fragility fractures pose a considerable health burden to the community. Effective strategies to reduce the burden of fractures depend on the development of preventive measures to target lifestyle or pharmacological interventions, based on identification of individuals at risk. The burden of fractures arises, not from the relative few with severely low BMD identified as osteoporosis, but from those with mild to moderate bone deficits. Individuals with osteopenia are commonly not treated because there is a lack of data relating to anti-fracture therapies in this group and, based on post hoc analyses from osteoporosis clinical trials, the numbers needed to treat are too large to be economically feasible if the whole group is to be considered. Yet, over half of the fractures in the population arise from this group. Those at highest risk for fracture within this group need to be identified and evidence-based treatment strategies developed to reduce the public health burden of fractures.

Improved risk stratification may be achieved by quantifying factors that contribute to bone strength, such as bone morphology and microarchitecture, which are properties beyond the resolution of conventional densitometry by DXA. It needs to be demonstrated that such predictors of risk are amenable to reduction with osteoporosis therapies and that anti-fracture treatment reduces fracture risk before recommendations are deemed appropriate. Furthermore, non-bone risk factors, that are amenable to modification, also need to be considered.

**Conflict of interests**

Julie Pasco has received speaker fees from Amgen, Eli Lilly and Sanofi-Aventis and funding from the Geelong Region Medical Research Foundation, Barwon Health, Perpetual Trustees, the Dairy Research and Development Corporation, The University of Melbourne, the Ronald Geoffrey Arnott Foundation, ANZ Charitable Trust, the American Society for Bone and Mineral Research, Amgen (Europe) Gmbh and the National Health and Medical Research Council (Australia).

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**Abbreviations list**

BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; FRISK, Fracture Risk; GOS, Geelong Osteoporosis Study; NORA, National Osteoporosis Risk Assessment; pQCT, peripheral quantitative computed tomography.

**References**


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