Osteopaenia - a marker of low bone mass and fracture risk

JA Pasco\textsuperscript{1,2*}, MA Kotowicz\textsuperscript{1,2}

Abstract
Areal bone mineral density is commonly categorised into normal bone mineral density, osteopaenia and osteoporosis on the basis of nominal thresholds recommended by the World Health Organization. However, bone mineral density is a continuous variable and there is a strong association between lower bone mineral density and greater risk for fracture. Fracture risk is not negligible in persons with moderate deficits in bone mineral density. Although absolute fracture risk is greatest for individuals with osteoporosis, more than half of the fractures arise from those with osteopaenia, and even normal bone mineral density, a probable consequence of greater numbers of individuals 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, which contribute to bone strength. Newer technologies such as high-resolution peripheral computed tomography have the advantage of assessing trabecular and cortical components of bone separately, in addition to geometric characteristics of the skeleton. 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. This would improve the decision-making for targeting appropriate interventions, either lifestyle or medication, 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 osteoporosis\textsuperscript{1}. 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 risk\textsuperscript{2}. 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 Organization\textsuperscript{3}. 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 corresponding to BMD T-score < −2.5\textsuperscript{3}. 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). 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-scores\textsuperscript{6,7}. However, while osteoporosis confers the greatest risk for fracture, fracture risk is not negligible in persons with more moderate deficits in BMD\textsuperscript{8–10}. Age-standardised 5-year absolute fracture risk derived from total hip BMD at baseline for postmenopausal women in Australia are 30.8% (95%CI 22.0–39.6) for women without osteoporosis, 17.5% (95%CI 13.2–21.7) for women with osteopaenia and 7.2% (95%CI 3.7–10.7) for women with normal BMD\textsuperscript{9}.

Fracture and BMD
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-
Figure 1: The distribution of bone mineral density (BMD) at the total hip for women is shown, together with the cut-off points for osteoporosis and osteopaenia (shaded in grey). Absolute risk for fracture (%) is represented by the unshaded columns, indicating 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 postmenopausal Australian women.

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 as 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.
as the GOS Fracture Risk (FRISK) Score\textsuperscript{17,22} and the Garvan algorithm\textsuperscript{23}, respectively. The GOS FRISK estimated 10-year probability of low-trauma fractures at the hip, spine, forearm and humerus, whereas the Garvan predicted 5- and 10-year probability of fragility fractures of the hip, spine, wrist, humerus, hand, scapula, clavicle, pelvis, lower limb and sternum. The FRAX includes multiple clinical risk factors, whereas both the GOSFRISK and Garvan utilise fewer risk factors (Table 1). The FRAX did not include falls because these data were not consistently collected across the multiple population-based studies from which the data were derived\textsuperscript{14}. The purpose of developing such models is to provide clinically useful tools to better identify, with high sensitivity and specificity, individuals in the population who are at greatest risk for fracture.

**Bone microarchitecture and structure**
The observation that age and previous fracture independently increase the risk for fracture\textsuperscript{8,17} is consistent with the notion that increasing age\textsuperscript{24} and fragility fracture\textsuperscript{45} 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\textsuperscript{26}. To be strong, bones need to be stiff enough to withstand deformation under loading, yet adequately elastic to absorb energy during compression and tension\textsuperscript{27}. 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\textsuperscript{26,29}.

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\textsuperscript{50}. 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\textsuperscript{23}. These women were defined as having osteoporosis or osteopenia 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 osteoporosis with the BMD measurement being spuriously increased by artefact. The apparent greater micro-architectural deterioration among those women with osteopenia 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\textsuperscript{24,33} and that this could explain the high proportion of non-

### 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>Age</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>Weight</td>
</tr>
<tr>
<td>Previous fracture</td>
<td>Previous fracture</td>
<td>Previous fracture</td>
</tr>
<tr>
<td>Falls</td>
<td>Falls</td>
<td>Falls</td>
</tr>
<tr>
<td>Parent fractured hip</td>
<td>Current smoking</td>
<td>Oral glucocorticoid use</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Other secondary causes of osteoporosis*</td>
<td>Alcohol 3 or more units per day</td>
</tr>
</tbody>
</table>

* Chronic liver disease, untreated hypogonadism, prolonged immobility, organ transplantation, type 1 diabetes, thyroid disorders, gastrointestinal disease.
vertebral fractures that occur with ageing at predominantly cortical sites.

In an Australian study of 185 female twin pairs aged 40–61 years, postmenopausal women were found to have higher levels of remodeling markers that were associated with larger intracortical surface area rather than with the progressively diminishing trabecular surface area. 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 interest

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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Critical review


