

Selecting patients for osteoporosis therapy: the new WHO paradigm



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'It has become clear that bone density, while valuable, may not be sufficient information to identify all patients at higher risk.'

With the development of a diverse therapeutic menu in osteoporosis, there is an increasing need to develop strategies for fracture risk assessment. This is to enable us to target treatments more effectively for those who need it and avoid unnecessary treatment for individuals at low risk of fracture.

In 1994, the WHO developed bone density diagnostic criteria, based on dual energy x-ray (DXA) measurements, using the concept of T scores; the number of standard deviations (SDs) above or below the average peak bone density in young adults. A T score between -1 and -2.5 was classified as osteopenia, -2.5 or lower was osteoporosis and -2.5 or lower with a fragility fracture was considered severe, established osteoporosis. Although only designed to be diagnostic criteria, T scores were interpreted by third-party payers and others to also be intervention thresholds.

For fracture prediction, DXA gives measurements that predict fracture with an increase in fracture risk of approximately 1.5–2 per SD decrease in bone mineral density (BMD) (the so-called gradient of risk) [1]. It has become clear that bone density, while valuable, may not be sufficient information to identify patients at higher risk. Recent studies have shown that up to half of the patients in the community with fractures have a baseline BMD above the WHO diagnostic threshold [2,3]. In the National Osteoporosis Risk Assessment (NORA), using peripheral bone density measurements, approximately half the osteoporotic fractures in the community occurred in women without osteoporosis. Although the relative risk of fractures in NORA was greater in women with T scores below -2.5, relative to the fracture risk of women with T scores of -1.0 to 2.5, there were far greater numbers of patients who were osteopenic. Similar results were found in the Study of Osteoporotic Fracture conducted by Wainwright and colleagues [3]. We can therefore conclude that, although BMD is highly specific, it is poorly sensitive.

Many women who will fracture in their lifetime will not be identified based on bone density assessment alone. If a treatment decision was based only on BMD using the WHO operational criteria of osteoporosis, approximately half of the postmenopausal women prior to fracture would not be considered for treatment. To explain these findings, we recognize the role of risk factors other than BMD. The most prominent of these include age and prior fracture. Kanis and colleagues have shown that for a given T score, the fracture probability increases significantly with age [4]. Thus, at the femoral neck, the risk of fracture with age varies markedly at the threshold of osteoporosis. With a T score of -2.5, at 50 years of age, the 10-year hip fracture probability is approximately 2% in women, but at 80 years of age is 12% with the same T score. Prior fracture is another important risk factor independent of BMD. If data from the placebo groups of the Fracture Intervention Trial (FIT) and Multiple Outcomes of Raloxifene Evaluation (MORE), the clinical trials of alendronate and raloxifene, are examined, patients with a prior history of vertebral fracture had an approximately fivefold increase in rate of vertebral fracture over the 3-year trial. In FIT, women with a prior vertebral fracture had an 8% risk of vertebral fracture in 3 years, while those without a prior vertebral fracture had a 1.6% risk [5,6]. Similarly, in the MORE trial, the risks were 12.7% in women with prior fracture and 2.5% in those without [7]. There are multiple clinical risk factors that are associated with increased fracture risk. These risk factors should be independent of BMD and modifiable by pharmaceutical intervention.

Recently, using meta-analyses of population-based cohorts from Europe, North America, Asia and Australia, the international validity of candidate clinical risk factors was examined by a WHO task force. Those factors that were validated included BMD at the femoral neck, low body mass index, age, a prior fragility fracture, glucocorticoid exposure, parental history of hip fracture, smoking, excessive alcohol intake and rheumatoid arthritis. These risk factors were then used to construct models of fracture probability. Other potential risk factors with less extensive

validation include BMD at the lumbar spine, bone markers, peripheral BMD, heel ultrasound and radiological vertebral fractures.

How do we use these validated risk factors? Current guidelines focus on the use of BMD as a criterion for intervention. For example, the National Osteoporosis Foundation (NOF) recommends treatment for postmenopausal women with T-scores below -2 or below -1.5 with risk factors [101]. However, these guidelines do not tell us how to integrate multiple BMD-independent risk factors, or how to detect osteoporosis with the use of clinical risk factors alone in situations where BMD is not available.

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Using the validated international risk factors, the WHO task force created models of probability of hip fracture and other osteoporotic fractures over a 10-year period. These models can be used globally to determine absolute fracture risk by using country-specific fracture rates. Intervention thresholds, or the risk above which intervention is worthwhile, will be country-specific, determined by gross domestic product per capita, priorities for healthcare and osteoporosis, and willingness to pay [8].

In North America, where there is universal recommendation for BMD screening, risk prediction will be improved by the addition of clinical risk factors in combination with BMD. As has been

pointed out by Ettinger and colleagues with the availability of information regarding absolute risk, we will continue to treat women with established osteoporosis with fracture. However, the new model will show the low absolute risk of osteoporotic fracture in early postmenopausal women with a low bone mass without risk factors, who may not need to be treated [9]. The model may also allow us to treat women at high risk without BMD. In the UK and Sweden, a 75 year old with fragility fracture can be treated without BMD.

What will be the impact of this new paradigm as osteoporosis clinicians? The WHO report is in review by the WHO over the next year. Once approved, a white paper will be published with the findings. Bone density manufacturers will develop software that will allow bone density technologists to ask patients about the international risk factors and enter their answers. As clinicians, in the near future we will most likely see our DXA machines continue to print out BMD and T scores, but we will also see numbers on the printout representing the absolute risk of hip and other osteoporotic fractures over the next 10 years. The DXA printout will not tell us who to treat. We will need to rely on new guidelines based on absolute fracture risk. For example, the NOF has developed a taskforce to rewrite the NOF guidelines based on absolute fracture risk.

In an era of limited health resources, we look forward to a future where we will target the increasingly diverse therapeutic menu in osteoporosis more effectively to those who need treatment and avoid unnecessary treatment for individuals at low risk of fracture.

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Website

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