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POSITION PAPER

The need to distinguish intervention thresholds and diagnostic thresholds in the management of osteoporosis

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Abstract
This position paper of the International Osteoporosis Foundation (IOF) and the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) addresses the rationale for separate diagnostic and intervention thresholds in osteoporosis. We conclude that the current BMD-based diagnostic criteria for osteoporosis be retained whilst clarity is brought to bear on the distinction between diagnostic and intervention thresholds.

Keywords Definition · Diagnosis · Fracture risk · FRAX · Intervention thresholds · Osteoporosis

Introduction

The treatment gap in the management of patients at increased risk of fracture is well-characterised and persistent [1]. The reasons for this are many, but a major factor is the lack of awareness of the increased fracture risk by physicians and other healthcare professionals, as well as the patients themselves. For example, while the finding of a non-osteoporotic BMD (T-score > −2.5) may hinder consideration of treatment in someone at high risk for other reasons, the vast majority of undertreatment results from a lack of risk assessment (including BMD) and consideration of treatment in those at high risk in both primary and secondary care settings [2, 3]. Some have suggested that the latter fault lies with the definition of osteoporosis and have called for a rethink [4, 5]. This paper reports the result of

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a meeting of a working group of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), which, on behalf of ESCEO and the International Osteoporosis Foundation (IOF), reviewed the case for redefining osteoporosis.

Defining osteoporosis

The conceptual description of osteoporosis dates back nearly 30 years arising from an international consensus conference held in Hong Kong in March 1993, sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the European Foundation for Osteoporosis and Bone Disease (now the International Osteoporosis Foundation) and the American National Osteoporosis Foundation (now the Bone Health and Osteoporosis Foundation) [6]. Osteoporosis was described as: 'A systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture', a conceptual definition supported several years later by the NIH Consensus Development Panel on Osteoporosis [7].

The World Health Organization diagnostic criteria for osteoporosis were developed shortly thereafter, based on the measurement of bone mineral density (BMD). At that time, BMD was the only aspect of skeletal fragility that could be readily assessed in clinical practice, and thus formed the cornerstone for the operational definition of osteoporosis. Osteoporosis was defined as a BMD that was 2.5 standard deviations or more below the mean value of young healthy women, i.e. a T-score ≤ -2.5 SD [8, 9]. An important asset of the definition was that it provided a standardised description that allowed the comparison of osteoporosis prevalence across countries and regions, and secular trends. The term 'established osteoporosis' was coined to denote the same BMD criteria but in the presence of a prior fragility fracture. The criteria were subsequently updated and refined to remove the ambiguity of using multiple sites for BMD measurement, different reference values for calculating T-scores and to provide a definition for men aged 50 years or more [10]. The reference range for calculating the T-score in both men and women is the Third National Health and Nutrition Examination Survey (NHANES III) database for femoral neck measurements in White women aged 20–29 years [11] as recommended by the International Osteoporosis Foundation, the National Osteoporosis Foundation and the International Society of Clinical Densitometry [12–14]. The referents in women apply equally to men aged 50 years or more since the gradient of risk and the age-adjusted risk of hip fracture for any given BMD at the femoral neck is similar in both sexes [15–17]. The question arises whether the operational definition of osteoporosis should automatically also define the intervention threshold for management of patients in clinical practice.

Diagnostic criteria

The established role of BMD

The 1994 definition of osteoporosis rapidly won general acceptance, shown by its almost immediate use in clinical practice and research, and through its inclusion in medical reference books by 1995 [18]. A 2003 WHO report restated the 1994 standards, a powerful indication of their usefulness and acceptance: 'the cornerstone of diagnosis is the measurement of bone mineral density. Diagnostic thresholds offered by the WHO have been widely accepted' [19]. The WHO diagnostic criteria for osteoporosis were soon adopted as inclusion criteria for drug trials and subsequently seen as intervention thresholds. The use of BMD-based diagnostic criteria has been the basis for the registration of drugs by regulatory agencies including the Food and Drug Administration in the USA, the European Medicines Agency and Pharmaceuticals and Medical Devices Agency of Japan [20–23] and guidelines developed by the WHO [24].

Osteoporosis is a classic example of a continuously distributed risk factor (BMD) with a graded increase in risk of a remote outcome (fracture). The construct is similar to many non-communicable diseases such as hypertension, diabetes mellitus and hypercholesterolaemia. These disorders have been well served by definitions which select points on the distribution of the risk factor which are associated with unacceptable risks of the outcome (stroke, neuropathy and myocardial infarction, respectively). Any cut off value is somewhat arbitrary, but the prevalence of osteoporosis in the general population using the WHO definition is completely in accord with clinical expectations of the burden of the disorder [9]. Indeed, this was the rationale for the choice of the T-score threshold, and it is an appropriate one with which to assign the burden of disease both nationally and globally [8, 25–27]. This is currently a unique position for any musculoskeletal non-communicable disease.

The use of prior fracture as a diagnostic threshold

In 2014, the National Bone Health Alliance Working Group proposed that the diagnosis of osteoporosis should be widened to include post-menopausal women and men age 50 years and over with hip fractures, with other low trauma fractures in the presence of osteopenia, and those with high fracture risk calculated using FRAX®, in addition to those meeting the WHO definition [4]. The notion of a prior fragility fracture as a diagnostic criterion was also proposed in 2020 [5].

The aims of the proposals, to target treatments to those at high risk of fracture and prevent more fractures, are laudable. The identification of patients with fracture for investigation, assessment and treatment is a well-established goal of clinical management in the vast majority of clinical guidelines worldwide [28]. The strategy is identical to that adopted for patients suffering myocardial infarctions or strokes. But the inclusion of multifactorial outcomes in diagnostic criteria for diseases is anachronistic; for example, it would be like suggesting that stroke, regardless of type or mechanism, should be included in the diagnosis of hypertension. Nonetheless, the proposal has arisen because of the failure of many clinicians and healthcare systems to identify and manage future fracture risk in patients who have already sustained fractures in whom undetected osteoporosis has also remained un-investigated and untreated [1, 29, 30]. This failure can be addressed, and is being addressed, without the need to alter the definition of osteoporosis [31–38].

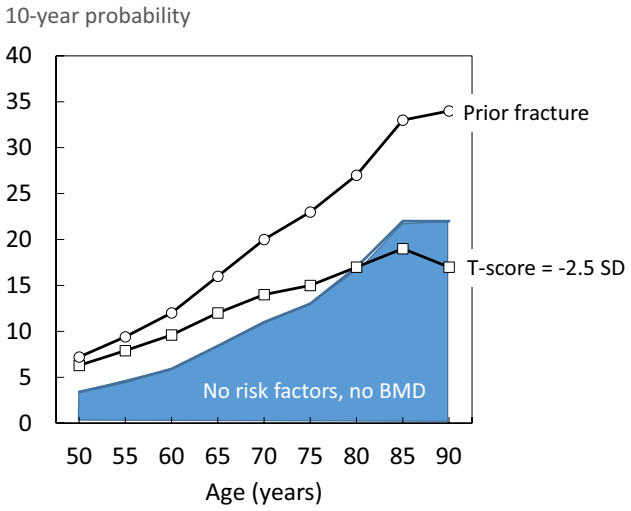

Fig. 1 10-year probabilities (%) of a major osteoporotic fracture for women from the UK according to a T-score of − 2.5 SD (open squares), or prior fracture (open circles) (BMI is set to 25 kg/m^2). [http://www.shef.ac.uk/FRAX]. Note the decreased probability after the age of 85 years due to the competing effect of mortality

Intervention thresholds

The limited role for BMD as an intervention threshold

While the use of the BMD threshold for the diagnosis of osteoporosis has advanced the development of effective agents in the management of osteoporosis, it is increasingly recognised as being less successful as an intervention threshold. Firstly, BMD alone is a poor screening tool in that most fractures in the community occur among individuals without BMD-defined osteoporosis [8, 39–41]. In the case of hip fractures, approximately 50% of cases will have osteoporosis so defined [42, 43]. Secondly, femoral neck BMD has a different prognostic significance at different ages [44] as shown previously for forearm BMD [45]. Indeed, with advancing age, a T-score of − 2.5 carries a fracture risk lower than that of many individuals of the same age and no clinical risk factors (Fig. 1). The explanation is that in the oldest old, there is a decrease in the probability of fracture because of the competing effect of death risk plus the decrease in T-score with advancing age so that a T-score − 2.5 is above average for the older population. Third, it is well established that fracture rates vary widely from country to country — much more so than can be explained by variations in BMD [43, 46] so that for any given fracture risk, the T-score will vary from country to country. The implication is that diagnostic thresholds (T-score ≤ − 2.5) are not equivalent to intervention thresholds (i.e. a level of FRAX probability) since the range of risk varies so markedly for any given BMD [44].

The use of the T-score as an intervention threshold and the sole gateway to therapy has also given rise to confusion. This problem has been exacerbated by the decision of certain healthcare systems to limit the reimbursement of treatment costs to those with a BMD T-score fulfilling the criteria for osteoporosis, despite being at high risk of future fracture in its absence [27, 47]. This is further exacerbated by a relative lack of easy and/or timely access to DXA resources in many healthcare settings. Finally, this situation has also been exacerbated by misleading and incorrect interpretations of clinical trial data that gave rise to a belief that osteoporosis treatments do not work in the absence of BMD-defined osteoporosis [48–52]. The use of BMD alone in determining intervention thresholds is demonstrably problematic.

These problems arise because BMD captures the likelihood of fracture incompletely. There is an appropriate analogy with several other multifactorial outcomes, such as stroke and hypertension. Blood pressure is continuously distributed in the population (as is BMD), and hypertension is an important cause of stroke (high specificity). But a majority of individuals with stroke are normotensive (low sensitivity) [53]. These considerations raised the question as to whether addition of other risk indicators could further improve the sensitivity of a risk assessment algorithm and hence the development of fracture risk prediction models. Available online risk engines include the Garvan fracture risk calculator [54], QFracture® [55, 56] and FRAX [57–59]. Of these, FRAX is the most widely used [60]. A fundamental difference between FRAX and other risk models is that the parameters of risk differ (incidence vs. probabilities for FRAX) so that comparative data are not readily interpreted [61].

The use of prior fracture as an intervention threshold

In many countries, intervention thresholds have been based not only on the T-score for BMD but also on the presence of a prior fragility fracture [25, 28, 62–65]. These strategies seem intuitively sound since they cover the operational definition of disease and/or its clinical expression. For example, the NOF in the US recommends BMD assessment in postmenopausal women, and treatment is advised in those with a T-score of ≤ -2.5 SD. Treatment is also recommended in women with a prior spine or hip fracture [64]. In Europe, postmenopausal women with a fragility fracture are generally considered eligible for treatment [63, 66, 67]. In contrast to BMD, a prior fracture confers an increased risk over all ages (see Fig. 1) reflecting the fact that future skeletal failure is more likely in those who have already experienced skeletal failure. Once again, the approach is entirely aligned with management of other chronic conditions where disease-related outcomes mandate consideration and use of interventions to reduce future risk of recurrence. There is increasing evidence that the implementation of fracture liaison services though campaigns such as Capture the Fracture can improve access to better management and treatment leading to reductions in future fractures [32, 68, 69].

Use of FRAX probability as an intervention threshold

Recently, the advent of risk assessment algorithms indicates that prevention of fractures is better targeted based on fracture probability or risk using multiple risk factors rather than on BMD alone [70–72]. FRAX, currently available in 78 territories, is the most widely used fracture risk assessment tool, and it is incorporated into a large number of assessment guidelines [28, 73], recommended by the Committee for Medicinal Products for Human Use (CHMP) [21] and approved by the National Institute for Health and Care Excellence (NICE) [74].

Several guidelines that use FRAX have recommended that a fixed probability threshold be used as an intervention threshold. Examples include a 20% 10-year probability of a major fracture in Canada and the USA, and a 15% probability in Japan and Sweden [62, 64, 65, 75]. The National Bone Health Alliance recommended that postmenopausal women and men aged 50 years or more should be diagnosed with osteoporosis if they have 10-year FRAX probability of hip fracture $\geq 3\%$ or the 10-year probability of major osteoporotic fracture $\geq 20\%$ in individuals with osteopenia [4]. The criteria followed the NOF guidelines with some minor modifications. Quite apart from the dubious validity of confusing a risk factor (which may or may not be included in the risk score) together with the risk score and the outcome itself, there is the added complication that individuals diagnosed with osteoporosis through different routes, for example BMD T-score, fixed FRAX threshold and prior fracture, could have markedly different fracture probabilities.

A problem with the use of fixed thresholds alone arises in the proportion of the population eligible for treatment. The impact of using different intervention threshold has been explored for postmenopausal women in Japan [76]. At high thresholds e.g., $\geq 20\%$ fracture probability, very few women under the age of 60 years would ever attain this threshold (less than 1%). On the other hand, if a less stringent threshold were chosen, say 10%, then approximately 5% of women at the age of 50 years would exceed this threshold, and a majority of women over the age of 65 years would be eligible, and the treatment threshold would be exceeded in 50% of all postmenopausal women. Both scenarios are contrary to current clinical practice.

Given that many guidelines in Europe, North America and elsewhere recommended treatment in the absence of information on BMD in women with a previous fragility fracture, a translational approach suggests that the intervention threshold in women without a prior fracture can be set at the age-specific fracture probability equivalent to women with a prior fragility fracture [77, 78]. As expected, this threshold rises with age (see Fig. 1); for example, the threshold rises from a 10-year probability of 7% at 50 years to 27% at 80 years in the UK. In other words, the intervention threshold is set at the 'fracture threshold' and has the added advantage of being independent of cost-effectiveness approaches to threshold setting that can rapidly be outdated by reductions in drug costs. This approach to intervention thresholds, first adopted by the National Osteoporosis Guideline Group (NOGG) for the UK [79], is now widely used in Europe, the Middle East and Latin America [59, 66, 80–86]. It is a direct consequence of age-specific thresholds that the probability at which treatment is recommended differs as it is country-specific, though varies little in the western world [46]. For example, the fracture probability in women with a prior fracture in the five major EU is highest in the UK and lowest in Spain. The difference between countries is most evident at younger ages and becomes progressively less with advancing age [87]. In Europe, the proportion of men and women above this threshold varies little from 11 to 13%. The merits of this approach are that it embraces both primary and secondary prevention of fracture and that it can be readily applied to all countries, races and ethnicities regardless of the availability of BMD. In countries with a more conservative approach, the threshold can be uplifted, say by 10 or 20%. Conversely, an intervention threshold can be downward adjusted where a more liberal approach is desired. Finally, a hybrid approach incorporates an age-dependent threshold up to the age of 70 years and a fixed threshold thereafter [63, 79].

Conclusion

The low rate of treatment in patients who have sustained a fragility fracture appears to underlie the recent calls for a change in the diagnostic criteria for osteoporosis, but there is little evidence that this alone would improve management in such patients. The WHO BMD-based, operational definition of osteoporosis is analogous to that employed successfully for the use of continuously distributed clinical risk variables in the management and prevention of other multifactorial outcomes such as myocardial infarction (by defining hypercholesterolaemia) and stroke (by defining hypertension). It has yielded a regulatory framework in the USA, EU and elsewhere which has permitted the development of an enviable armamentarium of therapeutic interventions.

The confusion appears to arise because of the erroneous merging of diagnostic and intervention thresholds. The example used for the basis of the paper by Paskins and colleagues illustrates this clearly, namely a 76-year-old woman with a recent vertebral fracture [5]. Here, the diagnosis is one of fragility fracture, which like a diagnosis of myocardial infarction or stroke should initiate a course of interventions, including pharmacological agents, to reduce future risk of recurrence. The need for a parallel diagnosis of BMD-defined osteoporosis serves to delay and indeed limit access to treatment, particularly where the result is misinterpreted, possibly fuelled by previous views that the treatments do not work in the absence of BMD-defined osteoporosis [48, 49]. Importantly, there is increasing evidence that the implementation of fracture liaison services though campaigns such as Capture the Fracture can improve access to better management [32].

It is widely recognised that BMD alone for fracture risk assessment is less sensitive than risk assessment algorithms such as FRAX that incorporate risk indicators in addition to BMD. It is certainly relevant to question the need for diagnostic criteria when the field is moving towards risk-based assessment and intervention, including adjustments to FRAX and guidance thresholds to distinguish high risk from very high risk to optimise the use of anabolic agents [67, 88–91]. These developments will inevitably decrease the clinical utility of the T-score, but they will, however, take time to implement into routine clinical practice. Notwithstanding, current diagnostic criteria will remain of value in quantifying the burden of disease and the development of strategies to combat osteoporosis in the foreseeable future.

It is hard to argue that operational BMD-based definition is anything other than a seminal event of positive significance in osteoporosis-related healthcare, and there appears little possible (or indeed intellectually sound) reason to argue for a change [92]. Those suggesting an alteration to the diagnostic criteria for osteoporosis would do well to consider the implications of such an approach if it were to be adopted more widely. Would they really be happy with diagnosing hypertension purely on the basis of a stroke or myocardial infarction? In our view, the proposal is intellectually constrained, inadequately justified and may well inappropriately reflect the pressures of reimbursement-led healthcare.

We recommend that the BMD-based definition of osteoporosis be retained whilst further clarity is brought to bear on the distinction between diagnostic and intervention thresholds as has been successfully managed in cardiovascular disease [93].

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Declarations

Conflict of interest JA Kanis led the team that developed FRAX. He was also the Chair of the WHO Technical report that provided the operational definition of osteoporosis.
EV McCloskey has received consultancy/lecture fees/grant funding/honoraria from AgNovos, Amgen, AstraZeneca, Consilient Healthcare, Fresenius Kabi, Gilead, GSK, Hologic, Internis, Lilly, Merck, Novartis, Pfizer, Radius Health, Redx Oncology, Roche, SanofiAventis, Servier, Synexus, UCB, Viiv, Warner Chilcott, I3 Innovus and Unilever.
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B Dawson-Hughes is on the Data Safety Monitoring Board of AgNovos, outside the submitted work.
S Maggi declares no conflict of interest.
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