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Osteoporosis Diagnosis in Men: The T-Score Controversy Revisited

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Abstract Osteoporosis becomes common with aging in both sexes, but is often ignored in men. The 2013 International Society for Clinical Densitometry consensus conference endorsed a Caucasian female referent database for T-score calculation in men. This recommendation has generated controversy and concern. Accumulating data indicate that at the same DXA-measured body mineral density (BMD) (g/cm^2), men and women are at approximately the same fracture risk. With this point in mind, using the same database to derive the T-score in men and women is reasonable. As a result, a greater proportion of men who sustain a fragility fracture will have T-scores that are higher than they would if a male database were used; in fact, many men will fracture at T-scores that are "normal." This highlights the importance of diagnosing osteoporosis not just by T-score, but also by the presence of fragility fracture and/or by estimations of fracture risk as generated by tools such as the FRAX calculator. The practical consequences of this change in densitometric definition of osteoporosis in men should be monitored, including the proportion of men at risk identified and treated as well as defining the response to treatment in those assessed by this more comprehensive approach.

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Introduction

It is well known that the consequence of osteoporosis is fragility fracture [1]. These fractures increase with advancing age [2]. As they are more common in women, osteoporosis is often considered to be a disease of older women. However, the lifetime fracture risk for men age over the age of 50 is up to 30 % and approximately 30 %–40 % of all osteoporosis-related fractures occur in men [3, 4]. U.S. fracture incidence data published in 2014 validate this high risk in men; the incidence of wrist, humerus, spine, and hip fracture in Olmsted County Minnesota residents over age 50 is about 26,000/100,000 person years in women and about 16,000/100,000 person years in men [5]. Clearly, osteoporosis-related fractures occur in men with a frequency that makes it also a common event in this gender. Importantly, while fracture rates are declining in women in the US [5] and worldwide [6], no such decline was observed from 1989–1991 to 2009–2011 among men in the Rochester, Minnesota experience [5]. Although the reasons for this sex-difference need to be understood, men are likely to become an even greater proportion of the population who fractures, a point driven further by the marked increase in the numbers of older adults in the population [7].

Despite the existence of practice guidelines and effective therapies to reduce fracture risk in men [4, 8, 9, 10•] osteoporosis remains largely ignored in males. Indeed, following hip fracture the factor that is most strongly associated with being less likely to receive osteoporosis medications is male sex. Specifically, in the US Medicare population from 2001–2011, only 9 % of men (vs 30 % of women) received treatment within 1 year of sustaining a hip fracture [11]. It is staggering to realize that 90 % of men who sustain an osteoporosis-

related hip fracture do not receive osteoporosis treatment. Doubtlessly, multiple reasons exist for this inadequate recognition and treatment but one reason appears to be confusion and controversy surrounding the diagnosis of osteoporosis in men.

In this regard, a recent consensus conference endorsed use of a uniform Caucasian female referent database for T-score calculation in men [12]; a recommendation that is understandably controversial. The attention generated by this T-score controversy might become an opportunity to improve recognition of men at risk for fragility fracture. This review will provide a summary of T-score derivation; how using a female database will alter male T-scores and evaluate potential other approaches to improving recognition of men at increased risk for fracture.

T-Score History

DXA is generally considered to be the gold standard for BMD measurement. It would be clinically ideal, and consistent with other conditions such as lipid status and blood pressure, if BMD measurements could be reported numerically. However, for a variety of reasons including differences in X-ray energy generation, bone edge detection paradigms, and region of interest placement, BMD by DXA in g/cm^2 differs substantially among DXA manufacturers. This situation would be analogous to blood pressure measuring devices produced by different manufacturers yielding different blood pressure results. If all DXA instruments measured BMD identically, there would be no need for a T-score; unfortunately, this is not the case. To avoid confusion that would result from instrument specific numerical BMD cutpoint values, the T-score concept was suggested whereby each patient's value is compared with a young normative database generated on the same device [13].

The T-score is defined as the difference between a patient's BMD and that of a young normal population divided by the standard deviation of the young normal population as follows: T-score = (patient BMD – young normal mean BMD)/standard deviation of the young normal population. It is apparent that the young normal values could profoundly alter the T-score. For example, using a young normal population with a lower average BMD will "improve" the calculated T-score. Despite such issues, defining osteoporosis using the T-score by the World Health Organization (WHO) was a great advance [14]. Since fracture is strongly related to reduced bone mass and because risk is related on a continuum to BMD, the level of risk as defined by the T-score was a key moment in the field. While the original WHO classification was intended for a population-based prevalence approach, it led to a diagnostic classification of osteoporosis based on risk of fracture. Thus, the T-score concept led to the diagnosis of osteoporosis with the cutpoint set at ≤ -2.5. This unintended consequence, nevertheless, became an important advance because it permitted the diagnosis of osteoporosis before fracture occurred.

However, it has long been apparent that T-scores use is associated with issues, including different T-score values at various skeletal sites (lumbar spine, hip, distal 1/3 radius) and reliance on a normal population and the standard deviation of that population as noted above [15, 16]. Recognizing these problems, standardization on the NHANES database for T-score calculation was advocated and adopted [17, 18].

T-Score Derivation in Men

Until recently, separate gender-specific databases were used to derive the T-score, and thus, a different absolute BMD in g/cm^2 to define osteoporosis in men vs women. It seems logical to relate a man or woman's BMD to the normative database of young normal men or women at peak bone mass. Peak bone mass as measured by DXA is greater in men than women, because of larger bone size in men and the fact that the 2-dimensional depiction of BMD (g/cm^2) by DXA is heavily influenced by bone size.

On most densitometers to this day, BMD T-scores in men are derived by comparison with a male young normal population. Since the young normal male population has a higher average BMD, a given T-score using the male referent database will be associated with a higher absolute bone density in g/cm^2 than when a female referent is used. However, if fracture risk of men and women is similar at the same BMD, then use of sex-specific databases would not be appropriate [19]. Indeed, data have accumulated (reviewed briefly below) that incident fracture risk at the same DXA-measured femoral neck BMD is very similar between men and women. As a result, the International Osteoporosis Foundation has recommended use of female young normal data to derive femoral neck T-scores in men [20], a position previously endorsed by the International Society for Clinical Densitometry (ISCD) [21]. The question of normative database to utilize for T-score calculation was revisited at the ISCD Position Development Conference in 2013 from which the recommendation to continue use of NHANES III data as the reference standard for femoral neck and total hip T-score derivation was reaffirmed as follows: "*A uniform Caucasian* (*non-race adjusted*) *female reference database should be used to calculate T-scores for men of all ethnic groups*" [12]. What are the data to support this conclusion?

Briefly, evidence continues to accumulate that fracture risk in men and women is similar at the same DXA-measured BMD [22–24]. For example, in the Rotterdam study, hip fracture risk at a given femoral neck BMD does not differ by sex [25]. Similarly, in the EPOS study, at the same spine BMD, the risk of incident vertebral fracture is similar in men

and women [26]. Consistent with this, men and women were found to have similar absolute risk for vertebral and all fractures at the same BMD [27, 28]. However, not all studies find that men and women fracture at the same absolute BMD. Indeed, overlap, with similarity, but not identity, has been reported [27, 29, 30]. In summary, it appears that at the same DXA-measured BMD, men and women are at approximately the same fracture risk. As such, use of the same database to derive the T-score is reasonable. Indeed, if all bone densitometers measured BMD the same, this approach would simply be endorsing use of a single number to define disease. This is hardly a revolutionary concept, in that hypertension, for example, does not have diagnostic cutpoints that differ by sex.

It is not necessarily intuitive that men and women should fracture at the same BMD. Is it in fact plausible that the BMD to fracture risk relationship could be the same in men and women when it is widely appreciated that DXA-measured peak BMD is higher in males? This apparent paradox can be conceptualized as noted in Fig. 1A, B. Briefly, the higher DXA-measured BMD in men is simply due to larger bone size, not greater volumetric density. Quantitative computed tomography (QCT) studies document both that male bones are larger than women and that the volumetric BMD (g/cm^3) is comparable with, or even lower, in males. This larger bone size in men is present at both the lumbar spine and femoral neck [31] and persists even after adjustment for body size [32, 33]. Thus, it is correct that BMD as measured by DXA is higher in men than in women, because of larger bone size. As larger (male) bone size conveys greater strength, it is necessary that a greater loss of bone will need to occur in men to reach the DXA-measured BMD of women. Interestingly, it appears that this is the case, as when men (mean age 66.6) and women (mean age 61.0) are matched for DXA-measured femoral neck BMD, on QCT men have lower volumetric BMD and higher bone area resulting in similar values for bone strength as assessed by finite element analysis (Fig. 1B) [34••]. In summary, DXA "compensates" for the larger male bone size by requiring a lower amount of bone mineral to be present such that the estimated bone strength is comparable when the BMD in grams/cm^2 is equivalent. The tide has thus turned to advocating a uniform female database for the diagnosis of osteoporosis in men, based upon the T-score. Implementation of this into routine clinical care will require a software update, an option that is either currently available or likely to be available in the near future (personal communication - Hologic and GE Lunar).

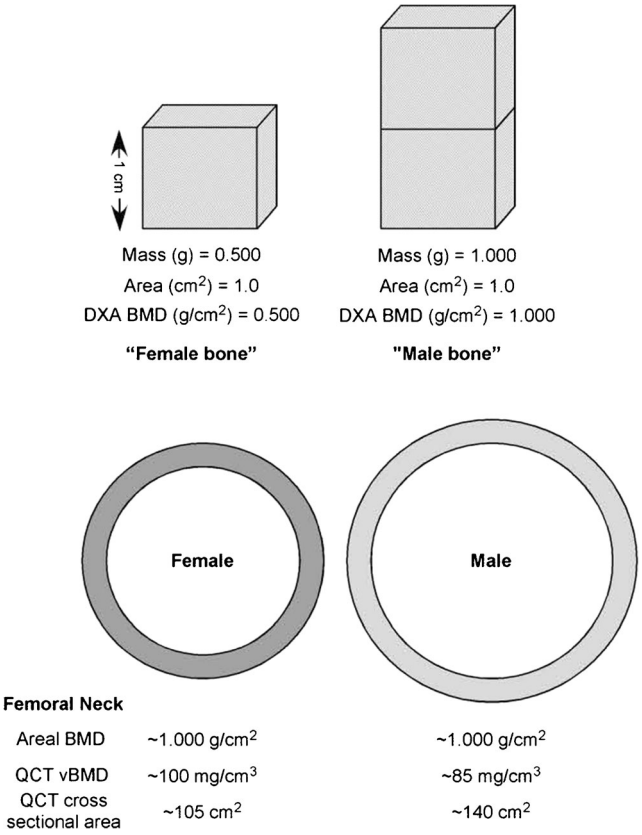

Fig. 1 **A**, Larger bone size leads to higher BMD as measured by DXA. This concept is illustrated here using hypothetical bone cubes of 1 cm^3 that have identical mass (0.5 grams) and volumetric BMD (0.500 grams/cm^3.) While not drawn to scale (male bones are not necessarily twice the size of female bones) this illustrates the concept that the additional depth present in larger "male" cubes on the right leads to a higher BMD as measured by DXA. **B**, At the same femoral neck area BMD, men and women have similar bone strength. Illustrated here using data adapted from Srinivasan et al [34••] are male and female bones matched for areal BMD. Bone strength, as estimated by finite element analysis, is similar due to the larger male bone size being offset by lower volumetric BMD. BMD, bone mineral density

T-Score Derivation in Men: Reasons Not to Change

Existing data and biomechanical rationale support the conclusion that the fracture risk for men and women are similar at the same DXA-measured BMD. Nonetheless, some have argued that the male normative database should continue to be used. Pragmatically, it can be suggested that changing to a female database will cause confusion for patients and providers as use of a female database will improve T-scores in men by a variable amount. As such, patients could change diagnostic categories from osteoporosis to osteopenia, or osteopenia to normal, with no change in BMD but rather the database. Recent data from the Geelong Osteoporosis study illustrates this point [35••]. In this report, 619 men aged 60–93 were followed for up to 9 years after BMD measurement and fractures were recorded. Using the Australian male referent database at the femoral neck, 207 had normal BMD, 357 were osteopenic, and 55 were osteoporotic. Using the female referent database at the same site, the numbers shift away from the osteoporotic classification; the percentage of normal subjects increased by 75 % while the percentage of osteoporotic subjects fell by 40 %. As such, with a female database, the

proportion of men who fractured despite normal BMD values shifted markedly with many men fracturing despite normal BMD. This point brings up vexing issues such as how one should diagnose osteoporosis in men before the fracture occurs, if the majority of men who subsequently sustain an osteoporotic fracture will have normal BMD by DXA using the female referent. Perhaps we should reconsider how to classify osteoporosis itself. It does not truly matter what the T-score is in a man who sustains a fragility fracture because he has osteoporosis. The clinical event, namely the fragility fracture, defines the disease perhaps even more importantly than the T-score (see below). It is apparent that approaches to optimally identify individuals who will sustain fragility fractures prior to the event are needed.

The T-score "improvement" resulting from shifting to a female database differs by skeletal site and densitometer used [36], but for Hologic and GE densitometers, it is generally less than 0.5 T-score [37•]. Nevertheless, as noted above, this change may alter the T-score based diagnostic classification. If we continue to rely upon the T-score as our primary risk assessment tool for diagnosis, then it is likely that fewer men will receive osteoporosis treatment prior to the fracture. This negative outcome will compound the problem of underrecognition of osteoporosis in men. As we have noted, only about 10 % of men who sustain a hip fracture receive treatment. Given these points, it is apparent that other factors besides BMD need to be considered in men if we are to have an accurate metric to determine fracture risk. The above really highlights this controversy.

What is "Osteoporosis" in Men?

Historically, a T-score diagnosis of osteoporosis was the sole indication that medical treatment should be initiated. If that were still true, how T-scores are derived would be critical. However, this is no longer the case, because we are now using risk stratification that takes into account clinical risk factors plus BMD to determine who should be treated [38]. One very important criterion is the fragility fracture. While it seems self-evident that someone with a fragility fracture has osteoporosis, we need to emphasize the point, that a fragility fracture alone is an acceptable definition of osteoporosis. Thus, we can make a diagnosis of osteoporosis by either the T-score or the fragility fracture. Another very important step in the diagnostics of osteoporosis is recognition of overall fracture risk through risk assessment tools such as FRAX [39••]. This approach takes into account known risk factors for fracture including (but not requiring) bone mineral density. If estimating fracture risk using the T-score can make the diagnosis of osteoporosis, then it is logical to extend this concept to risk as determined by other risk factors in addition to the T-score. Using this approach, more men with "osteopenia" and even men with normal BMD should be considered for treatment.

The good news is that therapeutic guidelines are increasingly using overall fracture risk assessment, not just the T-score, to define the therapeutic intervention threshold. An example of this approach is the Canadian guidelines, which recommend that pharmacologic therapy be offered to those at high risk (defined as ≥ 20 % probability of major fracture over 10 years) and also considered for those at moderate risk (between 10 % and 20 %) [40]. Similarly, in the UK, the National Osteoporosis Guideline Group (NOGG) uses estimated risk to define the intervention threshold [41]. Briefly, the NOGG approach suggests that fragility fracture defines an indication for treatment; as such, the intervention threshold at each age is defined as the calculated risk equal to that of a person with a prior fracture. As calculated risk progressively rises with age, so does the intervention threshold [41]. A similar approach is being advocated for Europe [42]. This approach has intuitive appeal because it, in fact, extends the concept of diagnosing and intervening based on fracture risk, which was originally defined only by the T-score. With such an approach, the therapeutic intervention level increases with advancing age. This might be considered a clinical stumbling block, however, directly linking fracture calculators to an intervention tool (as is the case with FRAX and the NOGG guidance) allows straightforward clinical application. While such an approach may seem complicated at first blush, it seems self-evident that therapy should be directed toward those at highest risk, as defined by a composite of risk factors, not just the T-score. Importantly, the cost-effectiveness of interventions based on this approach, namely overall fracture probability, establishes generic alendronate as cost effective when the 10-year risk exceeds 7.5 % [42, 43]. A few examples, as shown in the Table 1, demonstrate such an approach. Consider a 55-year old man with a femoral neck T-score of -2.2 (female referent) and, thus, osteopenia, or, alternatively, a T-score of -2.5 (male referent) and, thus, osteoporosis. The absolute bone density is the same and thus, on the basis of BMD, fracture risk is identical whatever the T-score. Another example in Table 1 is that of a 70 year-old man for whom treatment (based on T-score alone) would be indicated if a male, but not female database were used. However, regardless of T-score, the risk factor of his age in the FRAX calculation leads a recommendation for therapy. The important distinction between the first two examples is age, which makes him a candidate for treatment even though the T-score using the female referent would not. Other examples of men in whom treatment would or would not be indicated using only the T-score cut point of -2.5 with either the male and female database are shown in the Table 1. In these other examples, one can appreciate the importance of utilizing other risk factors, besides the T-score, in determining who should receive treatment. With this formulation, therefore, the T-score

Table 1 Treatment decision is affected by T-score database and also by use of fracture risk to define therapeutic intervention threshold

Patient	FN BMD	FN T (male)	Treat? [a]	FN T (female)	Treat? [a]	FRAX 10-year risk	Treat? [b]
55 y, no risk factors	.730	-2.6	Yes	-2.2	No	7.7/1.8	No
70 y, no risk factors	.730	-2.6	Yes	-2.2	No	9.9/3.2	Yes
75, no risk factors	.730	-2.6	Yes	-2.2	No	10/4.2	Yes
75, FH hip fx, smoker	.730	-2.6	Yes	-2.2	No	28/23	Yes
75, FH hip fx, smoker	.800	-2.1	No	-1.7	No	22/17	Yes
80, FH hip fx, ETOH	.910	-1.2	No	-0.9	No	19/14	Yes

FN Femoral neck; *BMD* Bone mineral density; *FH* Maternal or paternal history of hip fracture; *ETOH* Alcohol use

[a] Assuming that treatment is recommended at a T-score ≤ -2.5

[b] Assuming that treatment is recommended at a 10-year risk of ≥ 20 % for major and ≥ 3 % for hip fracture

Note: FRAX calculations using US Caucasian male, 180 pounds, height 69 inches

becomes, in a way, subservient to the composite of other risk factors that are incorporated into a risk assessment algorithm.

Redefining What We Mean by the Term: "Osteoporosis"

The diagnosis of osteoporosis should be made on the basis of risk or prior fragility fracture [38, 39••]. With this approach, the terminology and treatment of osteoporosis succumbs to the notion of risk; if the patient is at elevated risk, then the patient should be treated. We have returned to the definition of osteoporosis as originally defined by the T-score, but now, it encompasses the totality of risk, not just the T-score. While this approach makes sense, there must be evidence that men deemed eligible for treatment will respond to available agents. Indeed, most treatment studies in men have used a male normative database, and subjects responded to treatment if they had a T-score ≤ -2.5 or < -2 plus a prior fragility fracture. There are no studies documenting that men with high fracture risk by FRAX respond to current therapy [44], although a study of denosumab in men on androgen deprivation therapy for prostate cancer included men with relatively good BMD values [45]. The treated men had fewer morphometric vertebral fractures.

Finally, risk factors beyond BMD and even beyond FRAX are involved in fracture risk. An area that deserves more consideration, in this regard, is the loss of muscle mass/strength with age, a phenomenon known as sarcopenia that is attaining increased recognition. Loss of muscle strength increases risk of falls, a virtual prerequisite for hip fracture. Indeed, more men and women sustain hip fractures when they have sarcopenia as defined by reduced muscle mass [46, 47]. Carrying this thought one step further, potentially future medications designed to prevent hip fractures might be effectively directed toward improving muscle mass and function [48]. As a practical clinical matter today, this concept necessitates consideration of falls risk and muscle strengthening, as well as the traditional risk factors, as essential elements of what is considered "osteoporosis" care.

Conclusions

Recognition that men and women fracture at about the same BMD as measured by DXA makes scientific sense and has been adopted by medical and scientific organizations with planned implementation of a single normative database for T-score calculation by DXA manufacturers. However, DXA should be used as only one part of the determination of whether a man should be treated for osteoporosis. While it is important that more men who have suffered an osteoporotic fracture be identified and treated, fracture risk should be determined, ideally, before the fracture. Thus, factors beyond DXA must be incorporated into the assessment, and treatment should be provided. The research agenda should include studies to determine that current and future therapies lower fracture risk in men identified by this more comprehensive approach.

Compliance with Ethics Guidelines

Conflict of Interest N. Binkley has received consultancy fees or funding from Merck Sharp & Dohme, Lilly, and Amgen.

R. Adler and J. P. Bilezikian declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent All studies by the authors involving animal and/or human subjects were performed after approval by the appropriate institutional review boards. When required, written informed consent was obtained from all participants.

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- •• Of major importance

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