Original Article

The Impact of GE Lunar vs ICMR Database in Diagnosis of Osteoporosis among South Indian Subjects

Karthik Balachandran, Adlyne Reena Asirvatham, Shriraam Mahadevan

Department of Endocrinology, Sri Ramachandra Medical College and Research Institute, Chennai, India

Abstract

Objective: To study the effect of choosing ICMR reference values on the classification of bone mineral density in Indian patients. **Design:** Retrospective analysis of Dual Energy X-ray absorptiometry (DEXA) and clinical data. **Patients:** Totally, 316 patients aged more than 65 years attending a tertiary care hospital in South India who underwent DEXA scan were included in the study. **Measurements:** DEXA scan at femoral neck and lumbar spine. **Results:** A total of 316 patients were studied. The mean age was 61.98 ± 7.66 years. There were 46.84% females and 53.16% males. The average BMI was 26.37 ± 4.51. Of these patients, 46 had history of hip fracture (14.55%). The adoption of the ICMR normative data resulted in a significant increase in T scores in both the hip (+0.51, $P < 0.05$) and the spine (+1.64, $P < 0.01$). The adoption of ICMR normative values, resulted in reduction of osteoporosis prevalence from 26.58% to 5.06%. **Conclusions:** There is a clinically significant reduction in diagnosis of osteoporosis with the adoption of ICMR reference standard. Clinicians should be recommended to use raw BMD values in gm/cm^2 in FRAX calculation and avoid the use of T scores, to avoid overestimation of fracture risk. If our results are replicated, the implications are enormous – Osteoporosis is currently being over diagnosed.

Keywords: DEXA, FRAX, ICMR reference, normative data, osteopenia, osteoporosis, reference standard

Introduction

Osteoporosis is defined by WHO as the T score of <= -2.5. T scores are not absolute numbers, but rather relative entities. Thus, a patient's T score depends not only her bone mineral density, but also on who we compare it with. The choice of the reference has an obvious impact on whether a patient will be classified as osteoporosis. If the reference standard is a population known to have higher areal bone mineral density owing to several factors (such as race, peak bone mass, stature, vitamin D status, etc.), it will result in a higher number of people being classified as having osteoporosis. The Caucasian reference database is derived from NHANES III Survey (National Health and Nutrition Examination Survey), a nationally representative sample in the United States of 14, 646 men and women. The data from this survey is used as the reference database in DEXA machines. Previous study by Shetty *et al*. showed good agreement between ICMR and the Hologic database. However, the baseline risk of the studied population was different and hence we decided to study the effect of adopting ICMR database as the reference on the diagnosis of osteoporosis.

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Materials and Methods

This was a retrospective study in which individuals who underwent BMD measurement and FRAX scoring at Sri Ramachandra Medical Centre, Chennai during the time period July 2016 to December 2017 were included. Men and women over 50 years of age with osteopenia and osteoporosis according to the WHO definition at one or more site were included in this study. Those who have already received treatment with US Food and Drug Administration (USFDA) approved drugs for osteoporosis were excluded. Height and weight were measured using standard medical scales. Femoral neck BMD and T-score were obtained from the DXA scanner. DXA was done using the same machine for all the subjects (GE Lunar Prodigy Advance enCORE™ Version 13.60). FRAX prediction values were calculated with

Address for correspondence: Dr. Shriraam Mahadevan, Department of Endocrinology, Sri Ramachandra Medical College and Research Institute, Chennai, India.
E-mail: mshriraam@gmail.com

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BMD (FRAX/BMD) and without BMD (FRAX) using FRAX India tool (https://www.sheffield.ac.uk/FRAX/tool.aspx). T scores were recalculated using ICMR normative data with the following equation (with ICMR normative value used for the BMD of young adult[1])

$$\frac{BMD_{patient} - BMD_{young\ adult}}{SD}$$

Statistical methods

Continuous variables are expressed as mean ± SD (standard deviation) and categorical variables are expressed as percentages. Comparison of Group means was done using Student's *t* test. The agreement between T scores (the standard Caucasian and the calculated T scores) was assessed with Bland Altman plot. The disagreement was quantified with weighted kappa (weighting -1 for complete agreement, 0.5 for partial disagreement and 1 for complete agreement). Correlation between the variables was tested using Spearman Correlation coefficient. Statistical analysis was done using Stata version 14.2.

Results

A total of 316 patients were studied. The mean age was 61.98 ± 7.66 years. There were 46.84% females and 53.16% males. The average BMI was 26.37 ± 4.51. Of these patients, 46 had history of hip fracture (14.55%). Table 1 shows the change in T scores with the adoption of ICMR database—at the spine and the hip.

The adoption of the ICMR normative data resulted in a significant increase in T scores in both the hip (+0.51, $P < 0.05$) and the spine (+1.64, $P < 0.01$). There was significant correlation between the standard and ICMR T scores at both the hip (0.98, $P < 0.001$) and the spine (0.99, $P < 0.001$). The agreement between T scores was plotted in a Bland-Altman plot, shown in Figure 1.

The ICMR T scores were used to classify the patients as normal, osteopenia and osteoporosis according to WHO criteria. The resulting reclassification is shown in the Table 2 (overall change, including spine T scores for defining osteoporosis).

The adoption of the ICMR normative data, resulted in significant change in classification. The adoption of ICMR normative values, resulted in reduction of osteoporosis prevalence from 26.58% to 5.06%. The effect of change in reference data on classification is shown in Figure 2.

The agreement in classification was assessed by weighted kappa statistic. The weightage was 1 for complete agreement and 0.5 for partial agreement and 0 for disagreement. For example, if the ICMR T scores resulted in normal and the standard T scores resulted in osteopenia, a score of 0.5 will be given. A score of zero will be given if there is complete disagreement between the two classifications. As is seen in the Table 2, no patient who was classified as osteoporosis by ICMR was classified as normal or osteopenia in the standard

Table 1: Change in T scores after adoption of ICMR normative data

Variable	Mean	SD	Δ T score
Hip T score	-1.39	1.03	Not Applicable
Hip T score (ICMR)	-0.88	1.0	+0.51
Spine T score	-1.26	1.54	Not applicable
Spine T score (ICMR)	0.38	1.0	+1.64

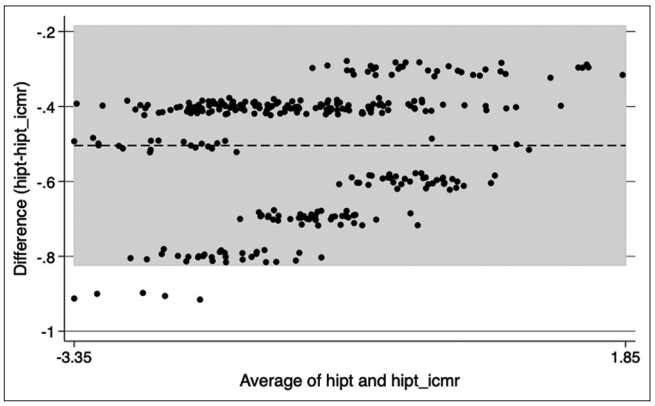

Figure 1: Bland Altman plot showing agreement between Caucasian and Indian Hip T scores. (hipt - Caucasian T scores, hipt_icmr - T scores derived from ICMR data)

classification. However, 48.5% of patients classified as normal by ICMR data were classified as osteopenia by the standard system and the 4.3% patients were classified as osteoporotic.

The weighted kappa was 0.389 ($P < 0.05$), considered "fair" by Koch and Landis classification.

Discussion

Our study shows that adoption of ICMR standards results in significant reduction in patients being classified as osteoporosis. There is no substantive change in this classification whether Lunar data are used as such or when standardized using published equations.[2]

In a study by Noon *et al*.,[3] the application of US reference data resulted in a higher T score in UK women. The discrepancy was more marked in the spine (+0.61 T score) than the hip (+0.42 T score). In the largest Indian study to evaluate the impact of adoption of ICMR database till date, Shetty *et al*. showed that 23.5% of the people classified as osteoporosis by the Hologic database, were reclassified as having osteopenia by the ICMR database. However, Shetty[4] *et al*. found that an almost perfect agreement existed between the Hologic and ICMR database (kappa – 0.82). While agreement between databases with kappa statistic is a valid measure, for the practicing clinician the pressing question is the reclassification/misclassification rate. In other words, what proportion of patients will be reclassified if reference database X is used instead of Y? The previous Indian studies on the topic,[4,5] have considered the reclassification occurring with the use

Table 2: Effect of adopting ICMR reference database on patient classification

Bone Status (by Caucasian normative data)	Bone Status (by ICMR normative data)			Total
	Normal	Osteopenia	Osteoporosis	
Normal	77	0	0	77
Osteopenia	79 (out of 155 classifed as normal by Caucasian normative reference)	76 (out of 155 classified as osteopenia by Caucasian normative reference)	0	155
Osteoporosis	7 (out of 84 diagnosed as osteoporosis by Caucasian normative reference)	61 (out of 84 diagnosed as osteoporosis by Caucasian normative reference)	16 (out of 84 diagnosed as osteoporosis by Caucasian normative reference)	84
Total	163	137	16	316

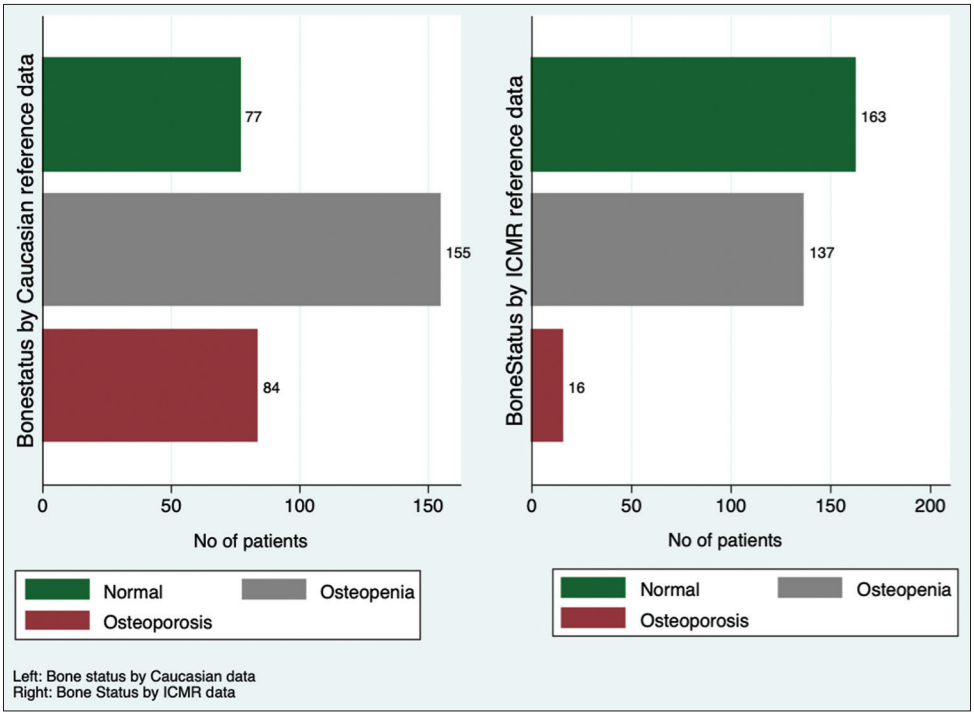

Figure 2: Reclassification of diagnosis after adoption of ICMR reference data

of ICMR database as a case of misclassification. However, in the absence of a gold standard, we believe it would be prudent to avoid making such judgements about the reclassification.

Shetty *et al*., show that 23.5% people with osteoporosis who had a hip fracture were reclassified as osteopenic. Since most fractures occur in the osteopenic range, the fact that the Hologic database "correctly" classified them as osteoporotic, cannot be used as a proxy measure to invalidate the ICMR classification. The reason between the discrepancy in the prevalence of DEXA measured osteoporosis and the low incidence of fractures in Indian population is unknown. Hitherto it has been attributed to factors other than BMD measurement/classification. The suggested remedy is the use of fracture risk stratification engines like FRAX. Due to differences in risk of fracture and cost of fracture, the intervention thresholds are not uniform across the world. Indeed, there are no well-defined intervention thresholds for FRAX score in India.

In this backdrop, BMD adds value in the form of substantial gains in the predicted gradient[6] of risk. Thus, BMD provides additional information about the probability of risk, that cannot be gleaned from clinical risk factors alone. This added advantage with BMD can be potentially blighted if there is a significant discrepancy between the fracture risk predicted by T scores alone when compared to fracture risk predicted by FRAX.

The parsimonious use of FRAX first approach[7] is an alternative to BMD measurement in resource poor settings. The addition of BMD to FRAX results in reclassification predominantly in those close to the intervention threshold. The clinical implication is that BMD measurements are most useful for those with an intermediate fracture risk. For the same reason, the effect of using a different reference standard (such as the ICMR database) would be most marked in patients with intermediate risk. Shetty *et al*. studied a population that included the extremes of predicted probability

of fracture (community dwelling people with low risk and patients with previous hip fracture, a high-risk group). Due to this dichotomy in the fracture risk of the underlying cohort, it is possible that the study by Shetty *et al*. might have underestimated the degree of reclassification that occurs with the use of ICMR database, even though hospital-based patients were also included. No subgroup analysis of the data pivoted on "fracture risk" was available. This is especially important since the utility of BMD testing is maximum in those with intermediate risk[8]—not those with the highest or lowest risk, since the patients at extremes of risk are unlikely to be reclassified by the addition of BMD testing to their treatment algorithm. This makes it important to study patients with wide array of basal risk of fracture (preferably intermediate risk) to see the effect of changing reference database. Our study, though hospital based, involves a patient group with a wider range of fracture risk to assess the impact of the use of ICMR database. Singh *et al.*,[5] in a hospital-based study, found significant reclassification with the use of ICMR database.

Conclusions

Our study shows that there is a clinically significant reduction in diagnosis of osteoporosis with the adoption of ICMR reference standard. In the absence of a gold standard, this reclassification should not be ignored. A suggested workaround is the use of FRAX, which unfortunately uses a proprietary risk engine. In this situation, clinicians should be recommended to use raw BMD values in gm/cm2 in FRAX calculation and avoid the use of T scores to avoid overestimation of fracture risk. If our results are replicated, the implications are enormous – the overdiagnosis of osteoporosis.

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Conflicts of interest

There are no conflicts of interest.

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