

Influence of Different Reference Databases on Categorization of Bone Mineral Density: A Study on Rural Postmenopausal Women from Southern India

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Abstract

Background and Objectives: Currently available DXA (Dual energy X-ray Absorptiometry) scanners utilise bone mineral density (BMD) of Caucasian population to calculate T scores and categorise BMD. We studied the influence of various databases on classification of BMD in south-Indian postmenopausal women aged above 50 years. **Methodology:** This was a cross-sectional study. Hologic DXA scanner was used to estimate BMD at lumbar spine (LS) and femoral neck (FN). T scores of ≤ -2.5 , -2.4 to -1, -0.9 to +1 were diagnostic of osteoporosis, osteopenia and normal respectively. Three reference databases (Italian, Korean and north Indian) were used to recalculate T scores. The agreement ($\kappa = \text{kappa}$) between manufacturer provided database and the other databases was studied. The impact of different databases in diagnosing osteoporosis in subjects with FN fracture was assessed. **Results:** A total of 1956 postmenopausal women with mean (SD) age of 62 (4.3) years and 211 femoral neck (FN) fracture subjects with mean (SD) age of 68 (7.2) years were recruited. In subjects with fracture, osteoporosis at FN was found in 72% with Caucasian, 88% with North Indian, 56% with Italian, and 45% with Korean database. On comparing manufacturer provided database with the other population-specific reference, there was perfect agreement with north Indian ($\kappa = 0.81$ [FN], $\kappa = 0.82$ [LS]) and good agreement with the Italian database ($\kappa = 0.78$ [FN], $\kappa = 0.74$ [LS]). **Conclusion:** North-Indian database identified most of the participants with FN fracture as having osteoporosis and had perfect agreement with the manufacturer's database. Follow up studies will further validate the impact of utilizing this database in clinical practice.

Keywords: Osteoporosis, population-specific database, fracture

INTRODUCTION

Osteoporosis, a common metabolic bone disease is a significant cause of morbidity in postmenopausal women and elderly men. In India, a significant proportion of the population >50 years has osteoporosis and fragility fractures.^[1] Fragility fractures, especially of the femoral neck (FN) has been associated with mortality of about 10%–20%.^[2,3] Widely prevalent nutritional calcium and Vitamin D deficiency in developing countries like India also further contribute adversely to bone health.^[4] The gold standard for the diagnosis of osteoporosis is bone mineral density (BMD) measurement at lumbar spine, FN, and forearm by a dual-energy X-ray absorptiometry scan (DXA) and expressed as T-scores which is the number of standard deviations (SDs) of the patient's measured BMD from a reference peak BMD (PBMD) (mean BMD of gender-matched young adults). A T score ≤ -2.5 at any site is considered as

diagnosis of osteoporosis and a score between -1 and -2.5 as osteopenia.^[5]

The DXA Manufacturers (Hologic, GE Lunar, Norland) have incorporated Caucasian-based reference PBMD to calculate T scores.^[6] However, there seem to be wide variations in the attainment of PBMD based on ethnicity differences, genetic and environmental influences.^[7] Thus, the use of different reference databases may influence the diagnosis of osteoporosis, leading to either underdiagnosis or overdiagnosis of low BMD. There have been studies from few countries

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which estimated the PBMD which was specific to a particular ethnicity and utilized them as a reference population to derive T scores for the diagnosis of osteoporosis. Few studies have also looked at the differences in diagnosis of osteoporosis when manufacturer based versus ethnicity-specific reference BMD were used.^[8,9] Shetty *et al.* looked at the impact of using an Indian population-based database obtained from four cities (Hyderabad, Delhi, Lucknow, and Mumbai) versus Hologic database in classifying postmenopausal women into various categories (normal, osteopenia, and osteoporosis) and found that although agreement between them was good, a significant proportion of subjects with FN fracture were classified as osteopenia rather than osteoporosis when Indian reference database was used.^[10] Recently, Marwaha *et al.* published an age-specific BMD reference range for the Indian population using DXA scan in a healthy cohort of 2034 Indian women aged 18–85 years.^[11] There are other country-specific databases which could have either a positive or negative impact on the diagnosis of low BMD. Their influence in the diagnosis of osteoporosis in the Indian context has not been studied. Hence, we attempted to study the influence of three databases (North Indian, Italian, and Korean) versus manufacturer database on categorization of BMD of south Indian postmenopausal women into normal, osteopenia and osteoporosis at lumbar spine and FN and also studied the agreement between three databases and manufacturer database in the diagnosis of osteoporosis. We also looked at the impact of utilizing these databases in diagnosing osteoporosis in a cohort of postmenopausal women with recent FN fracture.

METHODOLOGY

This was a cross-sectional study in healthy ambulatory rural south Indian women conducted over a period of 18 months at a tertiary care center (January 2016 to June 2017). The study was approved by the Institutional Review Board. Consecutive ambulant postmenopausal women (>50 years of age) from rural south India were recruited into the study. We also included a cohort of hospital based patients (admitted during this period) who had sustained hip fracture ($n = 211$) following a trivial fall (<2 weeks duration). Weight in kilogram was recorded using an electronic scale and standing height in centimeter was measured with a stadiometer. The formula of weight (kg)/height in meter^[2] was used to calculate body mass index (BMI). Blood samples were collected in fasting state for the measurement of serum calcium ($n = 8.3\text{--}10.4$ mg/dL), phosphorus ($n = 2.5\text{--}4.5$ mg/dL), albumin ($n = 3.5\text{--}5.0$ g/dL), creatinine ($n = 0.6\text{--}1.4$ mg/dL), and 25-hydroxyvitamin D ($n = 30\text{--}75$ ng/mL). BMD at the lumbar spine and FN was assessed with Hologic QDR 4500 Discovery A DXA scan. Daily QC was performed with a phantom provided by the manufacturer and machine was calibrated, and if the value was within the normal range, then only BMD examination of the study participants was conducted. A coefficient of variation of 2% was noted at both sites over the study period. In FN fracture subjects, BMD measurement was done within 1 week following surgery and unininvolved hip was

used for assessment. Hologic machine used National Health and Nutrition Examination Survey (NHANES) (USA-based reference data) to calculate T scores. We also recalculated T scores based on reference data provided by North Indian study, Italian population, and Korean PBMD.^[11-13] Overall, we used three databases to recalculate T scores which were done using the following formula:

$$\text{Subject T score} = \frac{\text{BMD of the subject } (\text{g/cm}^2) - \text{reference BMD}}{\text{SD } (\text{g/cm}^2)}$$

The categorization of T scores into Normal (+1 to −1), osteopenia (between −1 and −2.5) and osteoporosis (≤ -2.5) was as per the world health organization (WHO) guidelines.

Statistics

The continuous variables were expressed as mean and SD. Student's *t*-test was used to compare the means of continuous variables. BMD categories were expressed as proportions. Agreement between two databases was expressed as kappa. The kappa values were categorised as nil to fair (0–0.40), 0.41–0.65 as moderate, 0.66–0.80 as good, and 0.81–1 as almost perfect agreement. A value of $P < 0.05$ was considered statistically significant.

RESULTS

A total of 1956 ambulatory rural South Indian postmenopausal women and 211 FN fracture patients were included in the study. The baseline characteristics of the study participants are shown in Table 1. Women with FN fracture were significantly older with lower mean BMI, and lower 25(OH) vitamin D levels when compared to ambulatory postmenopausal women ($P < 0.05$). Vitamin D deficiency (<20 ng/ml) was seen in more than half of the study population (52% in ambulatory women and 59% in the fracture group).

The prevalence of osteoporosis at the lumbar spine and FN with manufacturer database (NHANES) was 39% and 22%,

Table 1: Baseline characteristics

Parameter	Mean \pm SD		<i>P</i>
	Healthy women ($n=1956$)	Women FN fracture ($n=211$)	
Age (years)	62 \pm 4.3	68 \pm 7.2	0.001
BMI (kg/m ²)	23.6 \pm 3.2	21 \pm 4.4	0.001
Serum corrected calcium (mg/dL)	9.2 \pm 0.4	9.3 \pm 0.6	NS
Serum phosphate (mg/dL)	3.8 \pm 0.2	4.0 \pm 0.3	NS
Serum creatinine (mg/dL)	0.9 \pm 0.2	1.1 \pm 0.2	NS
Serum 25(OH) Vitamin D (ng/ml)	21 \pm 4.2	17 \pm 6.4	0.001

FN: Femoral neck, NS: Not significant, BMI: Body mass index, 25(OH) Vitamin D: 25-hydroxy Vitamin D

respectively. There was a significantly ($P < 0.05$) greater proportion of participants diagnosed with osteoporosis at lumbar spine (45%) with Italian database and at FN with North Indian database (33%) when compared to other databases [Tables 2, 3 and Figures 1, 2].

In subjects with FN fracture, osteoporosis at FN was found in 72% with NHANES, 88% with North Indian, 56% with Italian, and 45% with Korean database [Figure 3]. On comparing manufacturer provided database with the other population-specific reference, there was perfect agreement with North Indian ($\kappa = 0.81$ for FN and $\kappa = 0.82$ for LS) databases, good agreement with the Italian ($\kappa = 0.78$ for FN and $\kappa = 0.74$ for LS) and the agreement was found to be lower with the Korean database ($\kappa = 0.6$).

DISCUSSION

This is the first Indian study to compare the various country based databases (NHANES, Italian, North Indian, and Korean) for the diagnosis of osteoporosis in a large cohort of south Indian rural postmenopausal women. Patients with FN fracture were older with a lower BMI and lower Vitamin D levels when compared to healthy controls. More than half of them had Vitamin D deficiency.

Overall, 40% and 20% had osteoporosis at the lumbar spine and FN, respectively, when Hologic (NHANES) reference database was used. A large number of participants were diagnosed to have osteoporosis at lumbar spine when Italian database was used, and a greater proportion of subjects were diagnosed with osteoporosis at FN when North Indian reference database was used. A perfect agreement was seen between the North Indian database and NHANES database for the diagnosis of osteoporosis at both sites. Most of the participants with FN fracture were diagnosed with having osteoporosis when North Indian database was used.

Table 2: Prevalence of osteoporosis and osteopenia at lumbar spine based on various databases

Site	Databases			
	NHANES, n (%)	North India, n (%)	Italian, n (%)	Korean, n (%)
Osteoporosis	762 (39)	626 (32)	880 (45)	405 (21)
Osteopenia	762 (39)	802 (41)	548 (28)	778 (40)
Normal	432 (22)	528 (27)	528 (27)	773 (39)

Table 3: Prevalence of osteoporosis and osteopenia at femoral neck based on various databases

Site	Databases			
	NHANES, n (%)	North India, n (%)	Italian, n (%)	Korean, n (%)
Osteoporosis	430 (22)	645 (33)	312 (16)	174 (9)
Osteopenia	1018 (52)	939 (48)	900 (46)	796 (41)
Normal	508 (26)	372 (19)	744 (38)	986 (50)

The prevalence of osteoporosis in this study is similar to earlier reported studies.^[14,15] When considering the population of India >50 years (>100 million), a significant proportion will

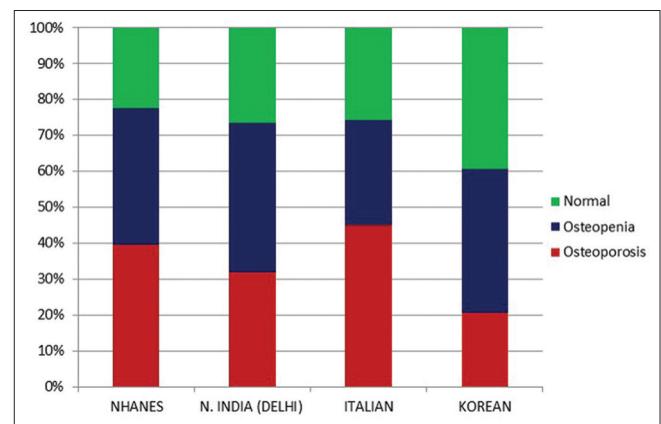


Figure 1: Categorization of bone mineral density at lumbar spine using different databases

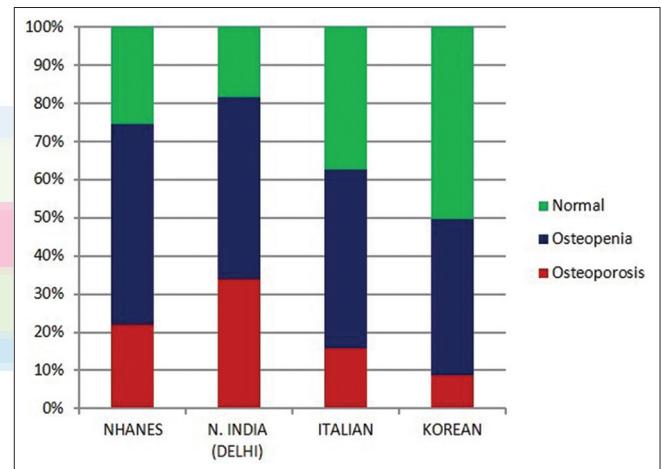


Figure 2: Categorization of bone mineral density at femoral neck using different databases

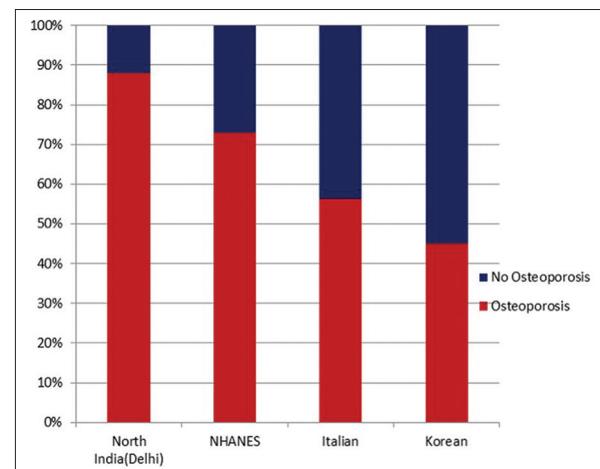


Figure 3: Diagnosis of osteoporosis at femoral neck in fracture subjects with utilization of different databases

be diagnosed as having osteoporosis.^[16] A higher prevalence of osteoporosis has been reported from the Indian subcontinent when compared to studies from other ethnicities and it has been noted that there were geographic and ethnic disparities in the occurrence of osteoporotic fractures.^[12,17-20] Most of the Indian studies used manufacturer Caucasian reference population database (peak bone mass) to calculate T scores. Ethnicity-specific database has been established and used in some countries to diagnose osteoporosis.^[12,13,19,21] There have been studies describing the impact of using ethnicity-specific reference on the prevalence of osteoporosis.^[9,22]

A Swedish study had shown a two-fold increase in prevalence in osteoporosis as per the WHO criteria when Swedish reference database was used due to high peak bone mass in this population as compared to manufacturer provided the database.^[22] A decreased prevalence of osteoporosis in women was observed when using a new diagnostic reference data from the Korean population as compared with the reference data provided by the manufacturer of the DXA device.^[12] Significant differences in the PBMD at various sites among the Chinese, Japanese, and Caucasian women, which has been shown to influence the prevalence of osteoporosis in a study by Wu *et al.*^[23] Overall, a low PBMD, when compared to Caucasian population, has been reported in Indian studies. Two recent studies found that an Indian population-based database underestimated the diagnosis of osteoporosis.^[10,24] In a study by Shivane *et al.*, PBMD in Indian females was found to be 14%–20% lower than US-based reference standard and height and weight were the significant predictors of bone mass.^[25] Patni noted that reference BMD of their study population was 1.5–2 SD lower than the reference Western population.^[26]

Marwaha *et al.* have recently published a normative data for women for Northern India and derived standardized BMD reference data (peak bone mass) which could represent a larger cohort of healthy Indian women.^[11] In our study, we used this data to recalculate T scores and most of the FN fracture subjects were correctly identified as having osteoporosis when this North Indian database was used. It should be noted that available reference databases for BMD from India have included a significant proportion of participants with Vitamin D deficiency. 96% of participants in the north Indian database had Vitamin D deficiency.^[11] The mean 25-hydroxyvitamin D was 13.6 ± 10 ng/ml in healthy controls of Indian council of medical research reference database.^[10]

Osteoporosis and fragility fractures, especially of the hip, are associated with significant morbidity and mortality, especially in postmenopausal women. A mortality of 20% has been reported in participants >60 years.^[3] Overall, a study by Dhanwal *et al.* found an incidence of 159 hip fractures per 100,000 population/year in Indian women >50 years.^[27] When considering the number of postmenopausal women in India, a significant proportion of them have osteoporosis which predisposes them to an increased risk of fragility fracture. Thus, the importance of using an appropriate

database is vital to correctly identify the individuals at risk.^[21] Across all ethnicities, a low BMD is a consistent risk factor for fractures. Ethnicity and race seem to influence the risk of fracture in addition to factors such as age, gender and lifestyle.^[28,29] Although BMD is one of the important factors which will predict fracture, there are other composite indices of bone strength such as weight, height, and differences in hip geometry like longer hip axis length that can influence the bone morphology irrespective of ethnicity impacting the incidence of the fractures.^[30,31] In our study, the impact of using different databases has shown that a variable proportion of FN fracture participants were appropriately identified as having osteoporosis. The implication of using an appropriate database is that it would correctly identify the at risk subjects, who could then be started on anti-osteoporotic treatment even before the occurrence of the fracture.

Early diagnosis and treatment with either anti-resorptive or anabolic agent in addition to ensuring adequate calcium and Vitamin D nutrition decreases the incidence of fragility fractures. Hypovitaminosis D is widely prevalent in India in all age groups and it is quite essential that Vitamin D deficiency is treated adequately, especially in postmenopausal women and elderly men with osteoporosis who are candidates for anti-osteoporotic treatment.^[32-34] Prospective interventional studies have shown a risk reduction of 40%–50% in fracture incidence after 2–3 years of starting treatment with anti-osteoporotic medications.^[35] In the Indian context, treatment of osteoporosis is cost-effective as these drugs are freely available and most of the high-risk population can afford them. Furthermore, such treatment would reduce the morbidity, mortality, and the financial burden associated with osteoporosis and consequent fragility fractures. Finally, it should be borne in mind that ethnicity-specific databases may be influenced by the interplay of many factors such as genetics, level of physical activity, and nutritional status of participants included in the reference population.^[36] This also may have an impact on BMD categorization even in south Indian populations, especially when north Indian database is used to define osteoporosis. However, north Indian database is probably ethnically closest available database to the population from south India for categorization of BMD and thus will serve as a useful alternative to Caucasian database till robust reference data from south India is made available. Further longitudinal studies are needed in the Indian context to study the impact of using this Indian database to diagnose and treat osteoporosis on the reduction of incidence of fragility fractures.

CONCLUSION

A significant proportion of rural Indian postmenopausal women had osteoporosis. Recently, derived North Indian database correctly identified most of the participants with FN fracture as having osteoporosis and had a perfect agreement with the manufacturer's database. This database could be potentially used in the Indian setting to categorize T-scores and initiate treatment for osteoporosis. Follow-up studies will further validate

the impact of utilizing this database in clinical practice to decide the initiation of treatment and its effect in preventing fractures.

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Conflicts of interest

There are no conflicts of interest.

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