The impact of US versus Indian BMD reference standards on the diagnosis of osteoporosis among South Asian Indians living in the United States

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Abstract

The relationship between bone mineral density (BMD) and fracture risk is not well-established for non-white populations. There is no established BMD reference standard for South Asians. Dual energy x-ray absorptiometry (DXA) was used to measure BMD at total hip and lumbar spine in 150 US-based South Asian Indians. For each subject T-scores were calculated using BMD reference values based on US white, North Indian and South Indian populations, and the resulting WHO BMD category assignments were compared. Reference standards derived from Indian populations classified a larger proportion of US-based Indians as normal than did US white-based standards. The percentage of individuals reclassified when changing between reference standards varied by skeletal site and reference population origin, ranging from 13% (95% CI, 7–18%), when switching from US-white- to North Indian-based standard for total hip, to 40% (95% CI, 32–48%), when switching from US white to South Indian reference values for lumbar spine. These finding illustrate that choice of reference standard has a significant effect on the diagnosis of osteoporosis in South Asians, and underscore the importance of future research to quantify the relationship between BMD and fracture risk in this population.

Introduction

Osteoporosis is a disorder of bone characterized by diminished density and altered microarchitecture, which results in heightened risk of fracture [1]. The de facto gold standard for the diagnosis of the disorder is bone mineral density (BMD) as measured by dual energy

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Conflict of Interest Statement
The authors have no financial interests that could influence the design, analysis, or conclusions of this study.

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x-ray absorptiometry (DXA) [2]. Because the relationship between BMD and fracture risk has not been well-characterized in non-white individuals, it is not obvious which reference range is most appropriate to define osteoporosis and osteopenia in these groups [3]. Some investigators support the application of the BMD threshold derived from premenopausal white women universally [2], while others suggest that BMD reference standards derived from a population that matches a given patient’s sex and ethnic background may be appropriate [4, 5]. Furthermore, densitometers report T-scores based on reference standards matched to the patient’s sex and, in the case of some manufacturers, race [3].

South Asians represent one fourth of the world’s population and a distinct genetic cluster [6]. There are nearly 2.8 million individuals of Indian origin residing in the United States [7]. The US population of this ethnic group is growing quickly, more than doubling between Census 1900 and Census 2000 [8]. Within the South Asian population, North and South Indians are genetically, culturally and linguistically distinct subgroups with differing disease predispositions [9,10].

The basis of using BMD, as measured by DXA, to diagnose osteoporosis hinges on the test’s ability to predict fracture risk [4]. However, only a few studies have investigated factors affecting BMD in Indians [11–15], and only one small case-control study has shown that low BMD is a risk factor for femoral fracture in Indians [16]. As it stands, the relationship between BMD and fracture risk has not been rigorously characterized in this ethnic group. Given this paucity of data, it is not possible to define diagnostic thresholds in South Asians with equivalent levels of fracture risk to the cut-points established for white women.

This study investigates whether the choice between reference standards derived from white Americans, North Indians, or South Indians affects diagnosis of osteoporosis and osteopenia in a sample of 150 South Asian Indians residing in California.

**Methods**

Between August 2006 and October 2007 we enrolled 150 South Asian Indian individuals in a population-based, cross-sectional pilot study called the Metabolic Syndrome and Atherosclerosis in South Asians Living in Americas (MASALA) study. The subjects were 50% female and ranged in age from 45 to 79 years. Recruitment methods, eligibility criteria, questionnaire and clinical measurements were based on the Multi-Ethnic Study of Atherosclerosis (MESA) [17,18]. Participants were recruited using a list of San Francisco Bay Area residents with South Asian Indian surnames purchased from a commercial mailing list company (Genesys Marketing System Group, Washington, PA). To be eligible, participants had to self-report Indian ancestry and be between 45 and 84 years of age. Those with known cardiovascular disease, as defined in MESA, were ineligible for the study [17,18]. In addition, we excluded individuals undergoing active cancer treatment, with impaired cognitive ability, life expectancy < 5 years, plans to move, residence in a nursing home, and those who spoke neither English nor Hindi.

BMD was measured in all participants at the lumbar spine (L1-L4, posterior-anterior) and total hip by fan-beam DXA (Hologic Discovery-Wi, Hologic Inc., Bedford, MA, USA).

**US White Reference Standards**

The US white total femur reference standard for this study are based on BMD data for non-Hispanic white US adults collected in the third National Health and Nutrition Examination Survey (NHANES III) [19]. This reference value is based on BMD measurements taken from 382 males and 409 females, age 20–29, using DXA (Hologic QDR 1000; Hologic Inc., Bedford, MA, USA). The total femur reference mean BMD was 0.942 g/cm² with a standard deviation
of 0.122 g/cm² for females, and 1.041 g/cm² with a standard deviation of 0.144 g/cm² for males [19].

In the absence of an NHANES based lumbar spine reference standards, we used the manufacturer’s reference curves (Hologic Inc., Bedford, MA, USA) for Caucasian men and women for the US white lumbar spine (L1-L4, anterior posterior) standards. The reference means were 1.047 g/cm² and 1.091 g/cm² for women and men respectively, with a standard deviation of 0.110 g/cm² for both sexes [communication with manufacturer].

**North Indian Reference Standard**

The North Indian total femur reference standards are taken from a study of normative bone mineral density conducted in Lucknow, Uttar Pradesh, India by Makker et al in 2007 [20]. Reference standards from this study are based on 114 women and 85 men, age 20–30, whose total hip BMD was measured using a fan-beam densitometer (Lunar Prodigy, GE Healthcare, Madison, WI, USA). The BMD reference means for women and men were 0.904 g/cm² and 1.101 g/cm² with standard deviations of 0.092 g/cm² and 0.133 g/cm² respectively [20]. Because Makker et al measured lumbar spine BMD laterally rather than in an posterior-anterior fashion, we were unable to use their data as a North Indian lumbar spine reference standard.

**South Indian Reference Standard**

The South Indian total hip and lumbar spine (L1-L4, posterior-anterior) reference standards were based on a study of normative bone mineral density conducted at Apollo Hospital in Chennai, Tamil Nadu, India. Participants were enrolled between 2004 and 2006 and included individuals working in various intuitions, family members of hospital employees, and families of patients visiting the hospital for reasons unrelated to bone health. Fan-beam DXA (Hologic Explorer, Hologic Inc., Bedford, MA, USA) was used to obtain BMD measurements. Total hip and lumbar spine reference standards from this study are based on 76 women and 84 men in the 20–29 age group. The total hip BMD reference mean was 0.808 g/cm² for women and 0.880 g/cm² for men, with standard deviations of 0.116 g/cm² and 0.108 g/cm² respectively. Lumbar spine reference means for women and men were 0.932 g/cm² and 0.967 g/cm² respectively, with standard deviations of 0.109 g/cm² for both sexes.

**Comparison of Reference Standards**

Densitometers manufactured by Hologic Inc. were used to measure the BMD of US-based South Asian subjects in the MASALA study, and to establish the white and South Indian reference standards [19], while a GE Lunar densitometer was used to collect the data on which the North Indian standard was based [20]. Because densitometers built by different manufacturers tend to produce systematically different results [21], we used equations established by the International Committee for Standards in Bone Measurement (ICSBM) to convert the BMD measurements of MASALA subjects to the equivalent values for a Lunar densitometer, thereby enabling the use of the North Indian reference standard [22,23]. The following equation, based on Lu et al [23], was used:

$$BMD_{\text{lunar}} = 1.0402 \times BMD_{\text{Hologic}} + 0.0382$$

We then calculated T-scores using reference standards derived from US whites, North Indians and South Indians according to following equation:

$$T - \text{score} = \frac{BMD_{\text{subject}} - BMD_{\text{reference}}}{SD_{\text{reference}}}$$
where BMD\text{reference} and SD\text{reference} are mean BMD and standard deviation calculated from reference data and BMD\text{subject} is the BMD of the study participant. T-scores resulting from each reference standard were used to classify subjects according to WHO criteria for BMD [2]:

1. Subjects with T-score \leq -2.5 were considered to have osteoporosis
2. Subjects with -2.5 < T-score \leq -1 were classified as having osteopenia
3. Subjects with T-score > -1 were regarded as having normal BMD.

The designation of osteopenia is used in this article to be consistent with WHO recommendation, although it is noteworthy that the International Society for Clinical Densitometry (ISCD) considers “low bone mass” to be a preferable label for individuals in this T-score range [24].

The BMD categories assigned to subjects under each reference standard were cross tabulated, and the percentage of subjects with discordant classifications was calculated for each pair of comparable standards (with 95% confidence intervals). In addition we calculated the mean change in T-score (with 95% confidence intervals) associated with switching reference standards. Fisher exact tests were used to assess if either gender or older age were associated with discordant classification between North Indian, South Indian, or US white reference standards. Student’s t-test was employed to assess difference between mean BMD between US-based South Asian subjects of North and South Indian heritage. Wilcoxon-Mann-Whitney test was used to compare the age distribution of male and female subjects. Statistical analysis was carried out using SAS 9.2 (SAS Institute Inc, Cary, NC, USA).

### Results

The median age for both men and women enrolled in this study was 56.3 years (p = 0.67). The median body mass index (BMI) was 24.8 kg/m\textsuperscript{2} for women and 25.9 kg/m\textsuperscript{2} for men. The majority of the sample (84%) reported North Indian heritage, though mean BMD at did not differ between North and South Indian subjects at either the total hip (p = 0.82) or lumbar spine (p = 0.76).

The sex-specific prevalence rates of osteoporosis and osteopenia of the total hip and lumbar spine resulting from the use of BMD reference standards derived from US white, North Indian and South Indian populations are reported in Table 1. The use of either Indian reference standard increased the proportion of South Asian Indians whose BMD was categorized as normal.

Cross tabulations of BMD category assignment are shown in table 2 for each pair of comparable reference standards. Switching from US white to South Indian reference values led to increased T-scores and reclassification of 19% (95% CI, 14–25%) of participants at the total hip and 40% (95% CI, 32–48%) at the lumbar spine. Using North Indian rather that US white reference standards resulted in higher T-scores and reclassification of 13% (95% CI, 7–18%) of subjects. Substituting the South Indian standard in place of the North Indian one resulted in 7% (95% CI, 3–12%) of study participants being reclassified from osteopenic to normal at the total hip. No participants were reclassified in the other direction. Neither gender nor older age affected the likelihood of an individual’s BMD being reclassified when changing reference standards (p > 0.2 for all).

Using the South Indian reference standard in place of one based on US whites led to a mean increase in total hip T-score of 1.39 (95% CI, 1.32–1.45) in men and 1.13 (95% CI, 1.12–1.14) in women, and an increase in lumbar spine T-score of 1.13 (95% CI, 1.13–1.13) in men and
1.05 (95% CI, 1.04–1.05) in women. Substituting North Indian-based reference standards for those based on US whites increased mean total hip T-scores by 0.96 (95% CI, 0.87–1.05) in female participants and 0.66 (95% CI, 0.63–0.68) in men. The use of a South Indian rather than the North Indian reference standard increased the mean total hip T-score of male participants by 0.73 (95% CI, 0.67–0.78) and female subjects by 0.17 (95% CI, 0.09–0.24).

Discussion

This study demonstrates that the choice of reference standard affects T-scores and, consequently, the apparent rates of osteoporosis and osteopenia in a sample of South Asian Indians in the US. Compared to reference values based on US whites, Indian-based standards more frequently classified US-based South Asian Indians as having normal bone density levels at the total hip and lumbar spine. The use of Indian reference standards reclassified up to 40% of subjects to a BMD category better than that assigned using US white-based values.

Compared to North Indian reference values, the use of South Indian standard produced higher T-scores in our sample, resulting in the reclassification of 7% of subjects. Due to the absence of a North Indian lumbar spine reference standard we were unable to determine if this difference between North and South Indian reference standards persists at the spine. It is notable that while total hip reference standards based on South and North Indian populations differed, US-based South Asian Indians had similar mean BMD irrespective of Northern or Southern origin ($p = 0.82$ for total hip; $p = 0.76$ for lumbar spine). This seemingly contradictory finding may reflect socioeconomic, environmental, and lifestyle differences between Indians who remain in India and those who emigrate. Alternatively, this data may suggest that the difference in mean BMD between North and South Indians seen among younger adults may decrease with age.

The effect of employing Indian-based reference standards on T-scores and BMD classification in South Asian Indians seen in our study concurs with an earlier finding that using Indian-based reference standard lowers the apparent prevalence of osteoporosis in Indians [20]. The difference between reference values derived from North Indian and South Indian populations is in accordance with the observation that these groups are genetically distinct [9,10].

The results of this study should be considered in light of several significant limitations. Most importantly, the absence of data detailing the prospective relationship between BMD and fracture risk in South Asians makes it impossible to determine what standard is most appropriate for clinical use. If the lower BMD values seen in young, apparently healthy South Asians predispose them towards pathologically low bone density in older age, the use of Indian-based standards will tend to misclassify as normal individuals who are actually at high risk for fracture. However, if the lower mean BMD seen in South Asians results from factors that do not predispose South Asians to increased fracture risk, the use of US white-based reference values will lead to false positive diagnoses of osteoporosis. A further factor complicating the interpretation of this study is the unanswered question of whether US-based South Asians are sufficiently similar to South Asians on the Indian subcontinent to justify the use of reference standards derived from this population, or whether a “westernizing” effect might invalidate such a comparison. While this study fails to provide a definitive answer, it clearly illustrates that given current knowledge the interpretation of DXA results in this population is not at all clear. This study highlights the need for prospective research to uncover the relationship between BMD and fracture risk in non-white populations.

Another limitation of this study is that the Indian-based reference standards were derived from cross-sectional studies which may not adequately reflect their source populations. However, since both studies relied on ambulatory volunteers, it is likely that the samples were healthier

J Clin Densitom. Author manuscript; available in PMC 2011 October 1.
than the populations from which they were drawn, and that any resulting bias would decrease the observed difference between US white- and Indian-based reference values. Another limitation of this study is that the North Indian reference standards were collected on a GE-Lunar densitometer, while all other BMD measurements were acquired using Hologic machines. The equations recommended by the International Committee for Standards in Bone Measurement (ICSBM) [22] that were used to adjust for inter-manufacture differences have been shown to produce BMD discrepancies of less than 6% which are not systematically biased [23]. A further constraint of this study is that subjects were recruited using a commercially available calling list of South Asian surnames, resulting in possible selection bias. Consequently BMD values of subjects enrolled in this study may not accurately reflect those of US-based South Asians in general, and should not be used as a reference database.

In conclusion, this study demonstrates that the choice of reference standard used to calculate T-scores and classify BMD values may affect the diagnosis of osteoporosis in South Asians. Currently, the appropriate interpretation of DXA results is unclear for this group. Further research is required to determine the quantitative relationship between BMD and fracture risk in order to establish diagnostic thresholds in this population.

Acknowledgments

The MASALA study was funded by K23 HL080026-01, the University of California, San Francisco Research Evaluation and Allocation Committee, and by NIH/NCRR UCSF-CTSI Grant Number UL1 RR024131-01. We are grateful to Noam Jacob and Justine Suzanne Jones for their critical reading of this manuscript.

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**Table 1**

Prevalence of osteoporosis and osteopenia in South Asian Indians, age 45-79, residing in the United States using BMD reference standards from US whites, South Indians and North Indians

<table>
<thead>
<tr>
<th>Sex, Age</th>
<th>Total Hip</th>
<th>Lumbar Spine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>US White</td>
<td>South Indian</td>
</tr>
<tr>
<td><strong>Females, count (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages (n = 75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>53 (71)</td>
<td>70 (93)</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>20 (27)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>2 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Males, count (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages (n = 75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>61 (81)</td>
<td>72 (96)</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>14 (19)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
Comparisons of agreement between US white, North Indian, and South Indian reference standards in the diagnosis of osteoporosis and osteopenia in South Asian Indians residing in the United States

| Table 2 |
|------------------|------------------|
| **A. Total Hip, US White versus South Indian** | **B. Total Hip, US White versus North Indian** |
| Count (%) | Count (%) | Count (%) | Count (%) |
| **Normal** | **Osteopenia** | **Osteoporosis** | **Normal** | **Osteopenia** | **Osteoporosis** |
| US White | 114 (76) | 0 (0) | 0 (0) | 114 (76) | 0 (0) | 0 (0) |
| Osteopenia | 28 (19) | 6 (4) | 0 (0) | Osteopenia | 18 (12) | 16 (11) | 0 (0) |
| Osteoporosis | 0 (0) | 1 (1) | 1 (1) | Osteoporosis | 0 (0) | 1 (1) | 1 (1) |
| % reclassified \( b \) = 19% (95% CI, 14–25%) | % reclassified = 13% (95% CI, 7–18%) |
| Mean T-score difference \( c \) = 1.26 (95% CI, 1.22–1.30) | Mean T-score difference = 0.81 (95% CI, 0.75–0.86) |

| **C. Total Hip, North Indian versus South Indian** | **D. Lumbar Spine, US White versus South Indian** |
| Count (%) | Count (%) | Count (%) | Count (%) |
| **Normal** | **Osteopenia** | **Osteoporosis** | **Normal** | **Osteopenia** | **Osteoporosis** |
| South Indian | 132 (88) | 0 (0) | 0 (0) | North Indian | 75 (50) | 0 (0) | 0 (0) |
| Osteopenia | 10 (7) | 7 (6) | 0 (0) | Osteopenia | 46 (31) | 11 (7) | 0 (0) |
| Osteoporosis | 0 (0) | 0 (0) | 1 (1) | Osteoporosis | 0 (0) | 14 (9) | 4 (3) |
| % reclassified = 7% (95% CI = 3–12%) | % reclassified = 40% (95% CI = 32–48%) |
| Mean T-score difference = 0.45 (95% CI = 0.38–0.51) | Mean T-score difference = 1.09 (95% CI, 1.08–1.09) |

\( a \) Due to rounding error percentages may not sum to 100%, and individual percents of reclassified individuals may not sum to the total % reclassified.

\( b,c \) % reclassified and mean T-score difference are, respectively the percentage of individuals whose BMD category assignment changed, and mean change in T-score, that resulted from switching between a given pair of reference standards.