Different reference ranges affect the prevalence of osteoporosis and osteopenia in an urban adult Malaysian population

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Osteoporosis (OP) is defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture [1]. The term bone strength is used to include both bone mineral density (BMD) and bone quality. Although we cannot directly measure bone quality, BMD can be readily measured using dual-energy X-ray absorptiometry (DXA). The purpose of such assessments would be to identify those at risk of an osteoporotic fracture, and/or to determine in whom to start treatment. The World Health Organisation (WHO) defined OP as a BMD \( \leq -2.5 \) SD below the mean for healthy young women (ie, T-score \( \leq -2.5 \)) at any site (spine, hip or 1/3 radius), with the mean based on American Caucasian female data. This level would identify 30% of all postmenopausal women as having OP, of which more than half would have sustained a previous osteoporotic fracture [2]. Thus, OP can be diagnosed following a fragility fracture, or when there is a T-score of \( \leq -2.5 \) as measured by DXA [3].

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A group from the WHO Collaborating Center for Metabolic Bone Disease [4] and the International Osteoporosis Foundation (IOF) [5] have suggested that the femoral neck (FN) BMD measured with DXA to be used as the reference standard for diagnosing OP in both genders and all ethnic groups, using T-scores derived from the United States (US) National Health and Nutrition Examination Survey (NHANES) III database of Caucasian women aged 20–29 years. However, many studies have shown that there are ethnic differences in BMD [6,7]. Generally, Asian populations were found to have lower BMDs compared to Caucasian populations [8,9]. The BMD reference curves for Chinese women have been found to be lower compared to Japanese and Caucasian women. Chinese women had peak BMD at the lumbar spine (LS) and hip regions that were 2.7–7.9% lower than those of Japanese women and 0.5–7.2% lower than those of Caucasian women [10]. Even within the same country, the BMD of Cambodian, Laotian, and Vietnamese women in Rochester, Minnesota, US was found to be lower than those of Caucasian women living in the same area [11]. Thus, the mean BMD of a healthy young Asian woman would be lower than that of a Caucasian. As a result, if a Caucasian reference range is used, the T-score will be lower compared to a local country-specific reference range. Several other studies from Asian countries such as Korea [12], Thailand [13], and Vietnam [14] have shown that using a Caucasian/USA reference range leads to a higher incidence of OP.

This is the first study to examine the prevalence of OP and osteopenia (OPE) in a multi-ethnic Asian urban population in Malaysia, and to compare the change in prevalence with the use of a Caucasian, compared to an Asian, BMD reference range to determine the T-score.

### 2. Methods

#### 2.1. Study design and study location

A cross-sectional study was conducted in 3 selected residential areas in Puchong, Serdang, and Kajang, in the state of Selangor, Malaysia. Data were collected from June 2016 to August 2018.

#### 2.2. Subject sampling

All adults aged 45 and above from randomly selected addresses from the voters’ registry were invited to participate in this study. The selection of respondents used stratified random sampling with equal proportions. In addition, systematic random sampling was performed to select adequate respondents in each ethnic stratum. Research assistants distributed house-to-house brochures with details of the research project by hand. Potential subjects were screened when they called for an appointment. The inclusion criteria were those aged between 45 and 90 years and belonging to the Malay, Chinese or Indian ethnic groups. The exclusion criteria were subjects already diagnosed with OP, were taking/had taken medication for OP (including calcitriol or alfacalcidol), have a known secondary cause of OP, subjects with renal impairment (estimated glomerular filtration rate < 60 mL/min/1.73 m²), known to have or had metabolic bone disorders, malabsorption, thyroid disease, immobilization or taking other drugs which affected bone homeostasis (eg, corticosteroids, phenytoin, methotrexate, cyclosporine, oral contraceptive pill) or subjects who had a computed tomography scan in the past 1 year.

Eligible subjects were scheduled for a face-to-face clinical assessment and BMD measurement by DXA. The study protocol...
was approved by the Ethics Committee of Universiti Putra Malaysia, approval reference FPSK (FR16) P002 dated 9th May 2016. All subjects signed written informed consent.

2.3. Anthropometric parameters and BMD measurement

Anthropometric measurements, ie, height, weight, and body mass index (BMI), were performed for all subjects. The designated personnel measured the height of the subjects, who were required to stand barefoot on the base of the stadiometer. The weight of the subjects was also taken at the same time. The height was measured in centimetres (cm) and the weight in kilograms (kg) and recorded to the approximate value of one decimal point. Subsequently, the BMI was calculated as weight/height².

The DXA was performed using a HOLOGIC Discovery W densitometer (Hologic Corporation, Bedford, MA, USA) to measure the BMD of the lumbar spine (LS) that represented the mean value of L1 to L4, the left femoral neck (FN), and the left total hip (TH). The precision of the machine is ± 2%. A calibration using the phantom was done before the first scan of each clinic session. The reference populations used were the manufacturer’s White (Caucasian) and Asian (Japanese) population databases. BMD was classified into normal, OPe, and OP based on T-scores using the WHO classification [2]. A T-score greater than −1.0 was classified as normal, between −1 and −2.5 was classified as OPe, and less than−2.5 was classified as OP.

2.4. Plain radiograph assessment of the lumbar spine

The antero–posterior and lateral lumbar spine radiographs were taken with the patient in the erect position using a portable X-ray machine (Toshiba 25 KW Radiography System, Tokyo, Japan). The radiation exposure was 40–80 mAs and 70–80 kVp depending on the body habitus of the subjects. The diagnosis of a vertebral fracture was made using a semi-quantitative technique, based on the Genant classification of vertebral fractures in OP [15]. A morphometric fracture was diagnosed based on a greater than 25% reduction in the anterior, central, and/or posterior segment height of the vertebra relative to the adjacent vertebra accompanied with a reduction in the area.

2.5. Statistical analysis

Analysis was performed using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp, Armonk, NY, USA). As all data were normally distributed, mean and standard deviation (SD) were used for the continuous variables. One way ANOVA, t-tests and chi-square tests were used to determine association between variables. A P value of < 0.05 was considered to be statistically significant.

3. Results

BMD was measured in 386 subjects. A total of 342 subjects were studied after 44 subjects who were found to have vertebral fractures were excluded. There were 222 females (64.9%) and 120 males (35.1%). The mean age of the group was 59.68 (SD: 8.89) years. The majority of the subjects were of the Chinese ethnic group (45.9%), followed by Indian (31.3%), and Malay (22.8%). The characteristics of subjects are shown in Table 1. Blood tests performed showed normal full blood counts, renal, liver, and bone profiles for the subjects (data not shown).

In Malaysia, when analyzing BMD measured by DXA, it is recommended that race-specific reference ranges are used when available [16]. As there is no Malaysian reference range, the manufacturer’s Asian reference range is normally used to calculate the T- and Z-scores in the DXA printouts. As shown in Table 1, mean T-scores were significantly lower in females compared to males at the LS and FN but not TH when the Asian reference range was used. When the White (Caucasian) range was applied to the data, the mean T-scores were significantly lower in females compared to males in all 3 sites. Mean T-scores were significantly lower at each site in both males and females when the Asian T-scores were compared to Caucasian T-scores (T test P ≤ 0.001 at LS, FN and TH).

Based on the Asian reference range, there were 140 (40.9%) subjects with OPe and 48 (14.0%) with OP. After applying the Caucasian reference range, there were 152 (44.4%) subjects with OPe and 79 (23.1%) with OP. This represented an 8.6% (12/140) increase in subjects with OPe and a 64.6% (31/48) increase in subjects in OP. Overall, 75 (21.9%) subjects had their diagnostic status changed. The proportion of male and female subjects in each BMD category based on the Caucasian or Asian range is shown in Table 1. In addition, there was a significant increase in the percentage of subjects with OP in both males and females when the Caucasian reference range was applied, compared to using the Asian reference range (chi-square P = 0.044 in males and P = 0.017 in females).

Table 2 shows the prevalence of normal, osteopenic and osteoporotic BMD in the 3 ethnic groups in Malaysia using the Asian and Caucasian reference ranges. There was an increase in the prevalence of OP when the Caucasian reference range was used compared to the Asian reference range in all 3 ethnic groups, but this was only significant in Chinese (chi-square P = 0.151 in Malay, P = 0.024 in Chinese, and P = 0.093 in Indian).

4. Discussion

The WHO defined OP on the basis of a value for BMD 2.5 SD or more below the young female adult mean (T-score less than or equal to −2.5 SD) based on DXA measurements [2].

For the purpose of standardization of research studies on OP, it was decided by WHO [4] and IOF [5] that the recommended reference range is the NHANES III reference database for FN measurements in Caucasian women aged 20–29 years, for both women and men. The International Society for Clinical Densitometry (ISCD) advises to use a uniform Caucasian (non-race adjusted) female normative database for women and men of all ethnic groups [17], which is similar to the other 2 organizations. In the discussion from the paper from Kanis and colleagues [4], they mention that differences in BMD in different regions of the world only vary by approximately 1 SD. These small variations in BMD between populations therefore appear to be substantially less than variations in fracture risk. For example in China and India, hip fracture risk is lower than in Europe or the US [18], despite generally lower BMD in Asia [8–10]. They conclude that in view of the disparity between population fracture risk rates and BMD, it is uncertain whether reference ranges drawn from local populations would be of any added value. This is especially true if the local population BMD data is not linked to robust fracture risk data.

The mean BMD of the young healthy reference group used for the calculation of the T-score is related to the achievement of peak bone mass in the population. Studies in Asian populations have shown that BMD at peak bone mass can be lower [19,20] or occur at a lower age than in Europe or the US [18], despite generally lower BMD in Asia [8–10]. This would be another reason that the T-scores would be different depending on the reference range used.

In this study, we found that the prevalence of OP significantly increased in both males and females when a Caucasian reference range was applied; the prevalence of OP increased from 7.5% to 15.8% in males and from 17.6% to 27.0% in females when the Asian and Caucasian reference range were applied, respectively. This was associated with a consistent reduction in the mean T-scores at all
measured sites. This is similar to several other Asian studies, which have shown that using a Caucasian database in Asian patients will lead to an increase in the diagnosis of OP. In a study from Thailand looking at women aged between 40 and 80 years, the number of women with OP increased when the USA reference range from the DXA machine was used compared to a local Thai population database [13]. This increase was seen in all age groups and also both at the LS and FN. For example, the prevalence of OP at the FN in 60–64 year olds increased from 20.1% using a Thai reference range to 52.6% using the USA reference range. A study from Vietnam that examined BMD in men and women between the ages of 18–89, found that in those over the age of 50, the proportion of subjects with OP increased when the DXA machine reference range was used compared to the Vietnamese reference range [14]. The number of subjects with FN OP increased from 28.6% to 43.7% in women and from 10.4% to 29.6% in men when the DXA machine reference range was used compared to the Vietnamese reference range, respectively. This is similar to our study showing increased prevalence of OP in both men and women using the DXA machine (Caucasian) reference range. However, not all studies have shown that the non-local reference range leads to an increased diagnosis of OP. In a study from Korea, when they compared OP prevalence based on using the NHANES reference compared to the Korean reference range they found that the prevalence of OP in men was less when the NHANES reference was used, but increased in women [12]. Another factor in this discussion is that even within Asia itself, there are differences in the BMDs of different populations. A study from Korea compared the prevalence of OP based on the Japanese reference standard given in the DXA machine and the local Korean reference ranges, and found that the prevalence varied depending on gender and site [21]. Thus, even in countries that are geographically close together, there is a difference in BMD and hence T-scores. Similarly, in a study from Sri Lanka, it was found that the Asian BMD reference values provided by the DXA machine manufacturer was lower than the BMD values found in their cross-sectional randomly sampled community survey [20]. Therefore, as long as the diagnosis of OP is based on a T-score value of ≤ −2.5, with the implication that it is a treatment threshold, the reference range used to calculate the T-score remains important. Using a reference range that increases the prevalence of OP would mean potentially many more people being treated, thus raising the spectre of over-treatment.

This study has also provided information on the prevalence of OP and OPe in the community in a multi-ethnic Malaysian population. There have only been a handful of previous studies. In a similar study looking at an urban population, the prevalence of OP was 8.4% in males and 16.1% in females [22], comparable to our results of 7.5% in males and 17.6% in females. However, the investigators used a Singapore reference range to calculate the T-scores. Our study also shows that the Chinese have the highest proportion of OP, 22.3% using the Asian database, out of the 3 ethnic groups. This is slightly higher than the prevalence of 15.8% found in a study from Malaysia that used a Singapore reference range [23]. The higher prevalence of OP in the Chinese in Malaysia was also shown in a study published in 2005 that did not specify which reference range that was used to calculate the T-score. In that study, the prevalence of FN OP was highest in the Chinese, 24.8%, followed by Malay, 14.8%, and Indian, 9.1% [24], a pattern similar to our study. This lower BMD in the Chinese may be a factor in the increased risk of hip fractures found in the Malaysian Chinese population [25].

There are a few limitations to this study. Firstly, our population may not be fully representative of the Malaysian population in terms of the ethnic breakdown of the subjects. We had 20.2% (76/386) Malay, 40.7% (157/386) Chinese, and 27.7% (107/386) Indian subjects. This is a higher proportion of Chinese and Indian subjects compared to the population in the state of Selangor, where the proportion of ethnic groups were 54.1% Malays, 24.0% Chinese, and 11.2% Indians [26]. Further studies will be needed to fully examine the BMD distribution in Malays. In addition, because we specifically wanted to look at a healthy population, we excluded those who already had a diagnosis of OP, or were on treatment for OP. This may have led to an under-estimation of the prevalence of OP and OPe. However, in just looking at healthy subjects, we eliminated the possible effect of treatment on increasing BMD, which may have reduced the prevalence of OP and OPe.

5. Conclusions

In a healthy Malaysian urban population aged 45 to 90, 14.0% had OP and 40.9% had OPe. Application of a Caucasian reference range increased the number of subjects with OP to 23.1% and those with OPe to 44.4%, with 21.9% of subjects having changed BMD diagnostic category. Overall, we found that Caucasian T-scores are lower than Asian T-scores in both males and females, and this result was consistently present in the 3 ethnic groups studied. Thus the use of a White (Caucasian) reference range rather than an Asian population specific reference range would lead to a higher rate of diagnosing OP, which can potentially lead to over-treatment.

CRediT author statement

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Conflicts of interest

The authors declare no competing interests.

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