Bone mineral density

What normative data should we use to report Saudi female patients?

Ahmed M. Outif, *MSc, PhD,* ***Awatif A. Hendi,*** *MSc, PhD,* ***Abdulaziz A. Al-Dihan,*** *MD,* ***Safar S. Al-Ghamdi,*** *MSc, PhD.*

ABSTRACT

Objective: Despite the fact that the Kingdom of Saudi Arabia (KSA) was a pioneer in developing its bone mineral density (BMD) reference population (RP), BMD is still reported in most Saudi dual energy x-ray absorptiometry (DEXA) centers according to Lebanese RP. The aim of the current work was to assess the implication of using normal ranges other than Saudi female normal range in reporting BMD of Saudi female patients (SFP).

Methods: This study was conducted at the Security Forces Hospital, Riyadh, KSA. Three published Arabian female DEXA RPs were reviewed and statistically compared. The implication of using RPs other than Saudi female reference population (SFRP) in reporting SFP was assessed in 1653 patients who were reported according to SFRP, Lebanese female reference population (LFRP) and Kuwaiti female reference population (KFRP). All female patients' BMD data performed between June 1995 and July 2003 were included in the study.

Results: The 2 published SFRPs were comparable along most age decades. On the other hand, significant differences between SFRP and LFRP, and between SFRP and KFRP were noted. While the LFRP was lower than SFRP along most age decades, the KFRP was higher than the SFRP. The use of LFRP in reporting BMD values of SFP resulted in an overall false negative rate of 20%. The use of KFRP in reporting BMD values of SFP resulted in an overall false positive rate of 15%.

Conclusion: The current use of LFRP in reporting SFP should be discontinued and instead SFRP should be used. Further national studies are needed to reassure the Saudi RP and to resolve the differences between the current 2 SFRP at the second and fifth age decades.

Saudi Med J 2004; Vol. 25 (8): 1040-1045

Osteoporosis is a metabolic bone disease characterized by a reduction in bone strength, low bone mineral density (BMD) and an associated increase risk of fracture. Osteoporotic fractures are a major cause of excess mortality, morbidity and health, and social service expenditure in elderly people.[1,2] Thus, there is a need for a concerted public health strategy for the early diagnose of osteoporosis and the reduction of its effects. Bone mineral density is the most important predictor of osteoporotic fractures in asymptomatic patients and is widely used to diagnose osteoporosis and to assess its severity. There is a strong, relationship between BMD and osteoporotic fractures.[3,4] Changes in BMD are commonly used as an indicator of fracture risk. Depending on the BMD

From the Division of Nuclear Medicine (Outif), Security Forces Hospital, Department of Physics (Hendi, Al-Ghamdi), King Saud University, and the Department of Radiology (Al-Dihan), Riyadh Medical Center, Riyadh, *Kingdom of Saudi Arabia*.

Received 9th December 2003. Accepted for publication in final form 27th March 2004.

Address correspondence and reprint request to: Dr. Ahmed M. Outif, PO Box 3643, Riyadh 11482, *Kingdom of Saudi Arabia*. Tel. + 966 (1) 4774480 Ext. 2250. Fax. + 966 (1) 4764757. E-mail: ahmed_outif@yahoo.co.uk

measurement site and fracture location, each reduction in BMD of one standard deviation (SD) is associated with a 1.5 to 2.6 fold increase in the risk of fracture.[5,6] Several methods are available to measure BMD, but currently the most widely used technique is Dual Energy X-ray Absorptiometry (DEXA). This method has been assessed in many large clinical trials and used to characterize fracture risk in large epidemiological studies.[3-6] Bone density is determined genetically and it is higher in black than white and in men than in women,[7] accordingly the determination of whether a BMD value is normal depends upon its comparison with appropriate gender-specific reference values derived from a similar healthy population. In clinical practice, raw BMD values (in g/cm^2) are not used for assessing skeletal status and fracture risk. Instead, they are expressed in term of the number of SD above or below the young (20-40 years) population. Such a value is normally referred to as T-score. The World Health Organization (WHO) has established diagnostic criteria for diagnosing osteoporosis based on T-score values as follow:[8] T-score better than 1 indicates normal bone. T-score between 1 and 2.5 indicates osteopenia (decreased bone density). T-score less than 2.5 indicates osteoporosis. T-score less than 2.5 with a non-traumatic fracture indicates established osteoporosis. The WHO diagnostic criterion depends on having a set of BMD reference data (mean ± SD) for each skeletal site for the particular reference population (RP). For this reason, score can easily be adjusted upwards or downwards if an inappropriate RP is chosen. In the United States of America, it is estimated that over one million patients in the period 1989-1997 were misdiagnosed due to improper use of T-score.[9]

In the Kingdom of Saudi Arabia (KSA) 2 RP[10,11] were published by 2 independent investigators; however, none of the 2 has gained interest, and T-score is currently reported according to Lebanese RP,[12] which is available on most DEXA machines. The aims of the current study were to compare the 2 published Saudi female reference populations (SFRPs) with the Lebanese female reference population (LFRP) and Kuwaiti female reference population (KFRP)[13] and to assess the implication of using either the LFRP or the KFRP as a reference for reporting BMD results of the Saudi female patients (SFP).

Methods. The current work was conducted at the Division of Nuclear Medicine/Security Forces Hospital, Riyadh, KSA and was divided into 2 phases as follows:

1) In the first phase, all the published Arabian RPs were reviewed using the free PubMed medical search engine[14] as well as the references of the recruited papers. The published RPs of Arab countries (KSA,[10,11] Lebanon,[12] and Kuwait[13]) were then statistically assessed for any differences maybe found between their mean BMDs along all age decades (10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79 years). The statistical z-values of the combinations of each 2 RPs were assessed for each age decade and site of interest using the equation:[15]

$$z = \frac{(\bar{x}_1 - \bar{x}_2)}{[(\sigma_1^2/n_1) + (\sigma_2^2/n_2)]^{1/2}} \quad (1)$$

Where $\bar{x}_1$ and $\bar{x}_2$ are the means of the 2 RPs (samples), σ_1 and σ_2 are the SD of the 2 RPs and n_1 and n_2 are the samples size (number of subjects) of the 2 RPs. The significance level was set at 0.01 and z-values >2.58 were considered significant and considered too large to be accounted for by chance.

2) In the second phase of this study, the implication of using RPs other than SFRP in reporting BMD values of the SFP was assessed. For this part of the study, we reviewed all Saudi female DEXA scans performed in our hospital during the period from June 1995 to July 2003. A total of 1653 female patients were reviewed. The BMD results of these patients were grouped into 10-years age cohorts (or decades) ranging from 30 (4th decade) to 80 (8th decade) years old. The BMD of all patients were determined using Lunar DPX-L version 4.7B system and the manufacture's standard protocol. Measurement sites were the proximal left femur and the L2-L4 lumbar vertebra. Quality assurance/calibration procedures were performed in accordance with the manufacture's recommendations.

The manufacture's recommended procedures for patient positioning and processing were strictly followed.[16] Briefly, for the proximal femur scan, the patient was placed in the supine position and the left leg was held in slight internal rotation such that the femoral neck is placed in horizontal plane and the leg movement is minimized. The foot brace provided by the manufacture was used to support the feet in the desired position. In the case of lumbar spine scan, the patient was placed in a supine position with the 2 legs raised on the 30 cm foam support block provided by the manufacture. The support block helps separate vertebrae and straightens the lower back. The scans were processed, in most cases, automatically by the computer. Manual corrections of the edgemarks or region of interest (ROI) were only performed in unusual anatomy or when the computer generated ROI or edgemarks were for any reason, judged by the technologist inaccurate. The T-score values for both lumbar spine (L2-L4) and femoral neck were

calculated using both the SFRP[10] and the LFRP[12] and the following equation:

$$\text{T-score} = (\text{BMD} - \text{YN})/\sigma \qquad (2)$$

Where BMD is the measured BMD, and YN and σ are the mean and SD of the young normal population according to either SFRP or LFRP. YN was considered to be the peak-mean BMD of each RP. The T-score of each site of interest (spine and femoral neck) was reported separately according to the above-mentioned WHO criteria. The calculated T-scores using SFRP and LFRP were then compared and the implication of using LFRP in reporting BMD values of the SFP was assessed. The percentage of false positive and false negative resulted from the use of LFRP for each site of interest was reported for each age decade. Similar approach was also used to assess the implication of using KFRP in reporting SFP.

Results. ***First phase (Statistical comparison).*** The literature review revealed 4 RPs (2 Saudi,[10,11] 1 Lebanees[12] and 1 Kuwaiti[13]). As the ultimate aim of the current work was to answer the question: What RP should be used in reporting BMD values of SFP? We were very fortunate to find that 2 independent studies were previously conducted to develop Saudi RP. These 2 RPs were first compared to decide whether there is any significant difference between their means and if they both represent the same general population. The results of this statistical comparison (calculation of z-value) along all age groups (decades) are tabulated in the second and third columns of **Table 1** for both the femoral neck and spine (L2-L4) regions. No significant difference was noted between the means of the 2 SFRPs along most age decades. Only at the second age decade (age 10-19 years) for both sites of interests, and at the fifth age decade (age 40-49 years) for the spine region, significant differences between the 2 SFRPs were noted. It was also noted (**Figure 1**) that the BMD measured by Ghannam et al[11] at the spine area is higher than that measured by El-Desouki[10] at the same site along all age decades. On the other hand, the mean BMD measured by Ghannam et al[11] at the femur area oscillates about that measured by El-Desouki[10] at the same site. As no important statistical significant difference between the 2 Saudi RPs, and as Ghannam et al[11] admitted to some sort of selectivity in their sample and that their sample may not be representative of the average Saudi female, the RP developed by El-Desouki[10] was employed for comparison with the other non-Saudi RPs. **Table 1** summarizes the results of the statistical comparison between the SFRP and LFRP. It is clear that the significant difference was noted between the mean BMDs of the SFRP and LFRP along most of the age decades (**Table 1**). Only at the third and sixth age decades for both femur and spine sites, and at the fifth age decade for the spine area insignificant differences between the SFRP and LFRP were noted. The mean BMD of the Saudi women is consistently higher than that of the Lebanese along most age decades (**Figure 1**). Only at the eighth age decade for both sites of interest and at the seventh age decade for the spine area were the main BMD of the Saudi females less than that of Lebanese females (**Figure 1**).

The sixth and seventh columns fo **Table 1** summarizes the result of the statistical comparison between the SFRP and KFRP. It is indicated that the Saudi women have significantly lower BMD values along most age decades compared to Kuwaiti women. Only at the seventh age decade insignificant differences between the 2 RPs was noted. The mean BMD of the Saudi women is consistently lower than that of the Kuwaiti women (**Figure 1**). The mean normal BMD values of the Saudi women are on average 20% lower than their Kuwaiti counterpart at the spine region and 6% at the femur region.

Second phase (assessment of the implication of using either LFRP or KFRP in reporting SFP. In this phase, 1653 SFP were retrospectively reviewed. The results of this review are summarized in **Table 2** for each site of interest and decade. The use of LFRP resulted in 21% collective false negative for the femoral region and 20% collective false negative for the spine region. On the other hand, the use of KFRP resulted in 19% collective false positive for the femoral region and 11% collective false positive for the spine region.

Table 2 also summarizes the per-decade accuracy results for each RP and site. The false negative results associated with the use of LFRP in reporting spine region of SFP ranging from 18% (for the fifth age decade) to 22% (for the sixth age decade). In the case of femoral region, the use of LFRP resulted in per-decade false negative ranging from 14% (for the fourth age decade) to 27% (for the seventh age decade). On the other hand, the per-decade false positive associated with the use of KFRP in reporting femoral region of SFP ranging from 14% (for the eighth age decade) to 24% (for fourth age decade). For the spine region, the use of KFRP in reporting SFP resulted in per-decade false positive ranging from 8% (for the seventh age decade) to 17% (for the fifth age decade).

Discussion. Despite the presence of 2 previous attempts to develop Saudi RP, BMD of the Saudi population remains reported (in many centers) according to the Lebanese RP provided by LUNER DEXA systems. We have recently conducted a survey of 10 nuclear medicine centers in Riyadh

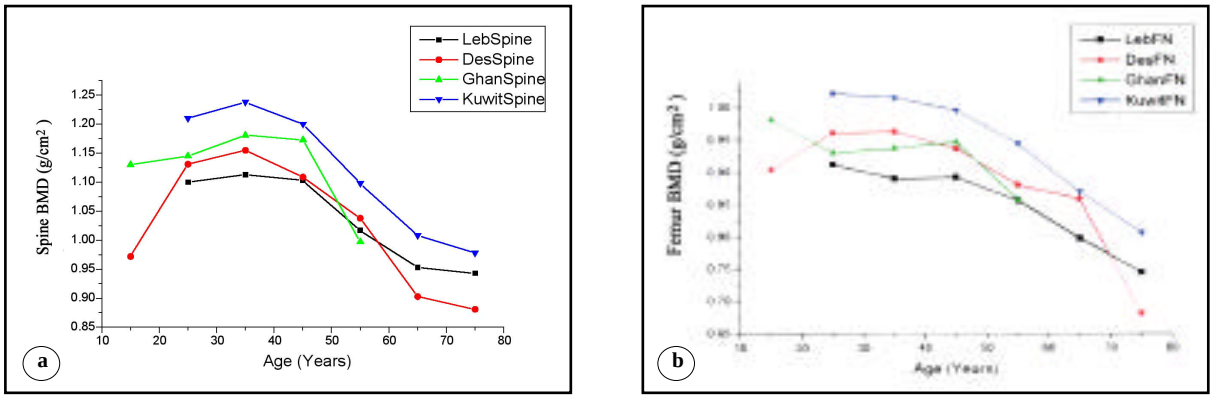

Figure 1 - Comparison of bone mineral density (BMD) values of **(a)** the spine and **(b)** femur for the 2 Saudis,[10,11] Lebanese,[12] and Kuwaiti[13] female reference populations. Leb - Lebanese, Des - El-Desouki study, Ghan - Ghannam et al study, Kuwit - Kuwaiti, FN - femoral neck.

Table 1 - Statistical comparison (calculation of z-value) between the 2 Saudi (El-Desouki[10] and Ghannam et al[11]) studies, the Lebanese (L),[12] and the Kuwaiti (K)[13] female reference populations.

Age decade (range)	D versus G z-value		D versus L z-value		D versus K z-value	
	FN	Spine	FN	Spine	FN	Spine
2nd (10-19)	- 2.83*	- 4.8*	-	-	-	-
3rd (20–29)	1.76†	- 0.14†	2.31†	1.78†	- 2.77*	- 4.47*
4th (30–39)	2.00†	- 1.83†	6.03*	3.20*	- 3.57*	- 5.05*
5th (40–49)	- 0.83†	- 3.40*	4.09*	0.47†	- 4.93*	-6.56*
6th (50–59)	1.21†	1.22†	2.51†	1.86†	- 5.20*	- 5.13*
7th (60–69)	-	-	6.01*	- 3.48*	- 0.81†	- 1.12†
8th (70-79)	-	-	- 5.04*	- 3.61*	- 5.43*	- 3.99*

D - El-Desouki study, G - Ghannam et al study, FN - femoral neck, *significant, †not significant.

Table 2 - Assessment results of the implication of using Lebanese and Kuwaiti reference population in reporting BMD of the Saudi female patients.

Age decade (range)	N	Use of Lebanese reference population		Use of Kuwaiti reference population	
		Femoral neck F-ve n (%)	Spine F-ve n (%)	Femoral neck F+ve n (%)	Spine F+ve n (%)
4th (30–39)	156	22 (14)	29 (19)	38 (24)	23 (15)
5th (40–49)	272	51 (19)	49 (18)	53 (19)	46 (17)
6th (50–59)	597	103 (17)	129 (22)	113 (19)	59 (10)
7th (60–69)	451	120 (27)	93 (21)	82 (18)	38 (8)
8th (70-79)	177	42 (24)	36 (20)	25 (14)	21 (12)
Total	**1653**	**338 (21)**	**336 (20)**	**311 (19)**	**187 (11)**

F-ve - false negative rate, F+ve - false positive rate, BMD - body mass index

city and found that 6 centers use Lebanese RP, 2 centers use American RP, and 2 centers do not know what RP they use in reporting their BMD patients. The ultimate aim of the current work was to search the best RP that can be used to report BMD of SFP. To achieve this goal, all the published Arabian female normal DEXA populations were reviewed and statistically compared. Apart from the second age decade (age 10-19 years) in both sites of interest (femoral neck and spine) and the fifth age decade (age 40-49 years) in the spine region, the 2 SFRPs[10,11] were found to be comparable and may represent similar populations. The difference between the 2 published SFRPs during the second and the fifth decades maybe attributed to differences in the diet and lifestyle of the subjects used in both samples. These differences were indeed mentioned by the authors of the second Saudi reference range[11] who indicated that most of their samples were recruited from their hospital staff who might have more westernized lifestyle. These differences between the 2 SFRPs may not affect the actual calculation of T-score, as T-score is usually calculated using the peak BMD and neither of the 2 decades in question represent peak value in both RPs. As no significant difference between the 2 SFRPs and as the second SFRP[11] was based on selective data and as such may not be representative of the average Saudi female, the first SFRP[10] is regarded from now on as the SFRP.

The first part of the current study revealed significant differences between SFRP, LFRP, and KFRP along most age decades. The LFRP is significantly less than SFRP especially at young age groups (20-40 years), which is used clinically for T-score calculation. As such, it is expected that using LFRP in reporting SFP will result in high false negative rate (diseased patient diagnosed as normal). On the other hand, the KFRP is significantly higher than SFRP along most age decades, and as such, the use of KFRP in reporting SFP is expected to result in high false positive rate (normal individuals diagnosed as diseased ones). Indeed these statistical speculations were confirmed in the second part of the current study. The use of LFRP in reporting SFP was found to yield some 20% overall false negative rate. On the other hand, the use of KFRP was found to result in some 15% overall false positive rate. Furthermore, the per-decade false negative and false positive rates associated with the use of either LFRP or KFRPs are also in good agreement with the results of the statistical analysis part of the current study summarized in **Table 1**.

It is very important to note that the current study suffer the limitation that the use of equation 1 in the calculation of z-values requires a sample size of at least 30 patients. This condition was not satisfied at some age decades of the studied RPs. In particular, equation 1 may not be applicable to the second and the eighth age decades. This limitation however does not affect the important results and conclusions of the current study, namely that of the false positive and false negative rates, as these 2 decades are not used in the actual calculation of T-score. Another statistical equation is available for sample size less than 30; however, this equation requires parameters that were not published by the authors of the investigated RPs.

In conclusion, the current study made it clear that due to the statistical differences between the SFRP, LFRP and KFRP, and the high false negative and false positive rates associated with the use of LFRP and KFRP, neither of these 2 RPs should be used in reporting SFP. In particular, the current use of LFRP in reporting SFP should be discontinued and instead, the SFRP developed by El-Desouki[10] should be used. Furthermore, national studies are needed to establish an accurate Saudi RP and to resolve the current differences between the 2 Saudi RPs along the second and the fifth decades.

Acknowledgment. The authors would like to thank Mr. Abdulaziz Al-Theeb from the Information Technology Department, Security Forces Hospital, Riyadh, Kingdom of Saudi Arabia for providing them with the list of all DEXA patients used in the current study.

References

1. Cooper C. Epidemiology and definition of osteoporosis. In: Compston JE, editor. Osteoporosis. New perspectives on causes, prevention and treatment. London (UK): Royal Collage of Physicians of London; 1996. p. 1-10.
2. Chrischilles EA, Butler CD, Davis, CS, Wallace RB. A model of lifetime osteoporosis impact. ***Arch Intern Med*** 1991; 151: 2026-2032.
3. Kanis JA and the WHO Study Group. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: Synopsis of a WHO Report. ***Osteoporos Int*** 1994; 4: 368-381.
4. Lips P. Epidemiology and predictors of fractures associated with osteoporosis. ***Am J Med*** 1997; 103: 3S-11S.
5. Cummings SR, Black D. Bone mass measurement and risk of fracture in Caucasian women: a review of findings from prospective studies. ***Am J Med*** 1995; 98: 24S-28S.
6. Kanis JA, Devogelaer JP, Gennari C. Practical guide for the use of bone mineral measurements in the assessment of treatment of osteoporosis: a position paper of the European Foundation for osteoporosis and bone disease. ***Osteoporos Int*** 1996; 6: 256-261.
7. Silverman SL, Medison RE. Decreased incidence of hip fracture in Hispanics, Asians, and Black: California Hospital discharged data. ***Am J Public Hlth*** 1988; 78: 1482-1483.
8. World Health Organization: Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. WHO technical report series No. 843. Geneva: WHO; 1994.

9. Mazess RB. Bone mineral density and T-scores. ***Osteoporos Int*** 1997; 7: 238-240.
10. El-Desouki M. Bone mineral density of spine and femur in the normal Saudi population. ***Saudi Med J*** 1995; 16: 30-35.
11. Ghannam NN, Hammami MM, Bakfeet SM, Khan BA. Bone mineral density of the spine and femur in healthy Saudi females: Relation to vitamin D status, pregnancy and lactation. ***Calcif Tissue Int*** 1999; 65: 23-28.
12. Maalouf G, Salem S, Sandid M, Attallah P, Eid J, Saliba N et al. Bone mineral density of the Lebanese reference population. ***Osteoporos Int*** 2000; 11: 756-764.
13. Dougherty G, Al-Marzouk N. Bone density by dual-energy X-ray absorptiometry in health Kuwaiti women. ***Calsif Tissue Int*** 2001; 68: 225-229.
14. PubMed Medical Research. Available from http://www.ncbi.nlm.nih.gov/PumMed/
15. Freund JE. Modern elementary statistics. 5th ed. Englewood Cliffs (NJ): Prentice-Hall Inc; 1979. p. 276–279.
16. LUNAR DPXTM. Series operator's manual. Software version: 4.6, Document Version: 9/98B, Part Number 6756. Available from http://www.bonedensitometers.com/