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ORIGINAL ARTICLE

Reproducibility of bone mineral density measurements using dual X-ray absorptiometry in daily clinical practice

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Abstract Bone mineral density (BMD) measurements are frequently performed repeatedly for each patient. Subsequent BMD measurements allow reproducibility to be assessed. Previous studies have suggested that reproducibility may be influenced by age and clinical status. The purpose of the study was to examine the reproducibility of BMD by dual energy X-ray absorptiometry (DXA) and to investigate the practical value of different measures of reproducibility in three distinct groups of subjects: healthy young volunteers, postmenopausal women and patients with chronic rheumatic diseases. Two hundred twenty-two subjects underwent two subsequent BMD measurements of the spine and hip. There were 60 young healthy subjects, 102 postmenopausal women and 60 patients with chronic rheumatic diseases (33 rheumatoid arthritis, 10 ankylosing spondylitis and 10 other systemic diseases). Forty-five patients (75%) among the third group were receiving corticosteroids. Reproducibility was expressed as the smallest detectable difference (SDD), coefficient of variation (CV), least significant change (LSC) and intraclass correlation coefficient (ICC). Sources of variation were investigated by linear regression analysis. The median interval between measurements was 0 days (range 0–7). The mean difference (SD) between the measurements (g/cm^2) was −0.0001 (±0.003) and −0.0004 (±0.002) at L1-L4 and the total hip, respectively. At L1-L4 and the total hip, SDD (g/cm^2) was ±0.04 and ±0.02, CV (%) was 2.02 and 1.29, and LSC (%) 5.60 and 3.56, respectively. The ICC at the spine and hip was 0.99 and 0.99, respectively. Only a minimal difference existed between the groups. Reproducibility in the three groups studied was good. In a repeated DXA scan, a BMD change, the least significant change (LSC) or the SDD should be regarded as significant. Use of the SDD is preferable to use of the CV and LSC because of its independence from BMD and its expression in absolute units. Expressed as SDD, a BMD change of at least ±0.04 g/cm^2 at L1-L4 and ±0.02 g/cm^2 at the total hip should be considered significant. This reproducibility seems independent from age and clinical status and improved in the hips by measuring the dual femur.

Keywords Chronic rheumatic diseases · Dual energy X-ray absorptiometry (DXA) · Healthy volunteers · Osteoporosis · Post-menopausal women · Reproducibility

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Introduction

Osteoporosis is a major public health problem [1, 2]. Bone densitometry has become the "gold standard" in its diagnosis, treatment evaluation and research. The WHO has established dual X-ray absorption (DXA) as the best densitometric technique for assessing bone mineral density (BMD) in postmenopausal women and based the definitions of osteopenia and osteoporosis on its results [3]. Recently, efficient therapeutic options for treatment of osteoporosis have been developed, which create possibilities of effective intervention. Therefore, screening for and treatment of osteoporosis are widely practiced in postmenopausal women and in people with an increased risk of osteoporosis because of underlying diseases (e.g., chronic rheumatic diseases especially when

treated by corticosteroids) [4, 5, 6]. It has also become more and more common to perform a second DXA measurement to monitor BMD status or the effect of therapeutic intervention. When a second measurement is performed on a patient, the clinician needs to distinguish between a true change in BMD and a random fluctuation related to variability in the measurement procedure. Evaluation of short-term variability is usually carried out through repeated BMD measurements performed over a short period of time. The reproducibility of DXA measurements is claimed to be good. Such variability is due to multiple causes, such as device errors, technician variability, patient movements and variation due to other unpredictable sources [7, 8, 9]. Data on potential sources of measurement variability show conflicting results. For example, BMD measurement error was independent of age in one study [10], whereas others found greater measurement error in older osteoporotic subjects [11].

The precision error is usually expressed as the coefficient of variation (CV) [12, 13, 14], which is the ratio of the standard deviation (SD) to the mean of the measurements, although several other statistics to express reproducibility exist, such as the smallest detectable difference (SDD). The SDD represents a cut-off that can be measured in an individual and is usually considered more useful than the CV in clinical practice. Despite the abundance of publications on BMD variability in different patient groups, no data comparing DXA measurement reproducibility between healthy young subjects, postmenopausal women and patients with chronic rheumatic diseases are available on short-term BMD variability. Therefore, we investigated short-term variability, the practical significance of different measures of variability and the sources of variability in these three clinical situations: healthy young volunteers, postmenopausal women and patients with chronic rheumatic diseases.

Material and methods

Subjects

Two hundred and twenty-two subjects were recruited in one center. For 4 months in 2004 (September to December), 222 patients had BMD measurement of the lumbar spine and femur twice. The interval between the two DXA measurements varied between 1 h and 7 days (a change in BMD was not expected during this interval). There were three distinct groups: 60 young healthy subjects, 102 postmenopausal women and 60 patients with chronic rheumatic diseases (33 rheumatoid arthritis, 17 ankylosing spondylitis, 10 miscellaneous rheumatic diseases, 3 scleroderma, 3 Sjoegren's disease, 3 systemic lupus and 1 polymyositis). Forty-seven patients (78.3%) among the third group were receiving corticosteroids (mean duration: 4.6 years).

Methodology of BMD measurement

All BMD measurements were performed on a Lunar Prodigy Vision machine (General Electric Inc.). The DXA scans were obtained by standard procedures supplied by the manufacturer for scanning and analysis. The compare feature was used for the second scan. No records were kept of difficulties observed in the positioning of patients. Plain X-rays documenting the presence of arthritic changes were not used. Daily quality control was carried out by measurement of a Lunar phantom. At the time of the study, phantom measurements showed stable results. The phantom precision expressed as the CV (%) was 0.08. The BMD measurements were carried out by two experienced technicians. Patient BMD was measured at the lumbar spine (L1-4; anteroposterior projection) and the femurs (dual femur). The mean result of the measure of the two femurs (total hip) was used. When the two BMD measurements were made on the same day, the patient was completely repositioned after the initial measurement. T and Z scores were calculated using the reference population provided by the manufacturer. In the T score, the patient's BMD value is expressed as SD as compared with the mean BMD of a reference population of young adults. For Z score calculation, the patient's BMD is compared with the mean BMD of people of the same sex and age and also expressed as SD. ΔBMD and the ΔT score were calculated by subtracting the results of the second measurement from the results of the first. The range of the difference in BMD as a percentage was calculated by dividing the difference between the first (a) and the second (b) measurement by the mean of those two figures, giving the fraction of difference between the two measurements as compared with the mean of the two measurements. The normally distributed variables are presented as mean (SD).

Precision

The measurement error was calculated using Bland and Altman's 95% limits of agreement method [15]. Other methods used to evaluate reliability and agreement are also described. These are the CV and the intraclass correlation coefficient (ICC). Precision expressed according to Bland and Altman's 95% limits of agreement method gives an absolute and metric estimate of random measurement error, also called SDD. In this case, where there are two observations for each subject, the standard deviation of the differences (SD_{diff}) estimates the within variability of the measurements. Most disagreements between measurements are expected to be between limits called "limits of agreement," defined as $d \pm z_{(1-a/2)}\ SD_{diff}$ where d is the mean difference between the pairs of measurements, and $z_{(1-a/2)}$ is the 100(1-a/2)th centile of the normal distribution. The value d is an estimate of the mean systematic bias of measurement 1 to measurement 2; d is expected to be 0 because we do

not assume a true change in BMD to occur during the interval between the two BMD measurements. Defining a to be 5%, the limits of agreement are $+1.96SD_{diff}$ and $-1.96SD_{diff}$. Thus, about twice the standard deviation (SD) of the difference scores gives the 95% limits of agreement for the two measurements by the machine. A test is considered to be capable of detecting a difference, in absolute units, of at least the magnitude of the limits of agreement. The CV, the most commonly presented measure for BMD variability, is the SD corrected for the mean of paired measurements. CV, expressed as a percentage, was calculated as:

$$CV(\%) = \left\{ \sqrt{\left[\sum (a-b)^2/2n \right] / (Ma+Mb)/2} \right\} \times 100 \quad (1)$$

where a and b are the first and the second measurement, Ma and Mb are the mean values for the two groups, and *n* is the number of paired observations. For two point measurements in time, a BMD change exceeding $2\sqrt{2}$ times the precision error of the technique is considered a significant change (with 95% confidence). Gluer et al. called this smallest change that is considered statistically significant "the least significant change" (LSC) [16]. In the current study, the LSC (%) was computed for the different BMD measurement sites. In these calculations the precision error is expressed as the CV (%). The ICC equals variance between patients divided by variance between patients plus variance between measurements. The value of the ICC ranges from 0 to 1, 1 representing perfect reliability of the measurement.

Analysis of sources of variability

We used multiple linear regression analysis to study the causes of the observed variation in BMD. Demographic variables, for example, age (years) and body mass index (BMI) (kg/m^2), and BMD variables, such as area (cm^2) of BMD measurement, were included as sources of BMD variability, that is, possible confounders that need correction. Statistical analysis was carried out using SPSS, version 11.5 (SPSS, Chicago, Ill.).

Results

Patient characteristics

The BMD measurements of 222 subjects (51 males (28.3%)/171 females) were collected during the recruitment period. There were 60 healthy young volunteers (30 males (50%)/30 females), 102 postmenopausal women and 60 patients with chronic rheumatic disease [21 males (35%)/30 females]. Table 1 shows the characteristics of the study population. The mean (SD) age of the study population was 47.0 (15.1) years (20–80). Their mean (SD) height was 161.4 (9.5) (139–187) cm and their mean (SD) weight 70.8 (13.0) kg (40–115). The mean (SD) BMI was 27.4 (5.5) kg/m^2 (14.7–43.0). The interval between the first and the second spine and hip DXA ranged between 0 and 7 days, with a median of 0 days.

Table 2 shows the BMD data and the derived T and Z score data for each measurement site. The mean (SD) difference between the first and the second measurement (g/cm^2) was −0.0001 (±0.003) at L1–4 and −0.0004 (±0.002) at the total hip. The mean (SD) T scores of the first measurement were −1.25 (1.45) and −0.56 (1.24) at L1–4 and total hip, respectively.

Variability

Table 2 presents the results of the various methods of calculating variability for the two most frequently used measurement sites. Figures 1 and 2 show the scatter plots of the difference between the two measurements against their mean for the lumbar spine and total hip. The horizontal lines in these graphs show the mean of the differences and the limits of agreement. When Bland

Table 1 Characteristics of the study population

	Healthy young volunteers $n=60$	Post-menopausal women $n=102$	Chronic rheumatic disease $n=60$	Total study population $n=222$
Age years, m (SD)	28.2 (5.5)	58.1 (7.0)	47.1 (12.8)	47.0 (15.1)
(Range)	(20–40)	(40–80)	(20–79)	(20–80)
Sex: M (%)/F	30 (50)/30	0 (0)/102	21 (35)/39	51 (23.0)/171
Weight: kgs, m (SD)	69.9 (11.0)	72.0 (13.0)	69.6 (14.4)	70.8 (13.0)
(Range)	(46–100)	(40–110)	(47–115)	(40–115)
Height: cm, m (SD)	169.0 (8.4)	156.0 (6.3)	162.9 (9.5)	161.4 (9.5)
(Range)	(150–187)	(139–169)	(144–185)	(139–187)
BMI: kg/m^2, m (SD)	24.5 (3.4)	29.6 (5.4)	26.4 (5.7)	27.4 (5.5)
(Range)	(17.1–31.7)	(18.7–43.0)	(14.7–41.7)	(14.7–43.0)
Tobacco consumption				
Current *n* (%)	12 (20)	1 (1)	11 (18.3)	24 (10.8)
Quantity (pack/years)	6.7	18	19.5	13.0
Corticosteroids *n* (%)	0 (0)	0 (0)	47 (78.3)	47 (78.3)
Years (range)	0 (0)	0 (0)	4.6 (1–15)	4.6 (1–15)

Table 2 Reproducibility of BMD (g/cm2) measurement in healthy young volunteers, post-menopausal women and patients with chronic rheumatic diseases. *LS* lumbar spine; *TH* total hip; *mean difference* mean of the difference between the first and the second BMD measurement; *SD difference* SD of the difference between the first and the second BMD measurement; *SDD* smallest detectable difference (g/cm^2); *CV* coefficient of variation (%); *LSC* least significant change (%); *ICC* intraclass correlation coefficient. SD difference and SDD are rounded off to two decimal places in the text of the article

	Healthy young volunteers $n = 60$		Post menopausal women $n = 102$		Chronic rheumatic disease $n = 60$		Total population study $n = 220$	
	LS	TH	LS	TH	LS	TH	LS	TH
BMD: g/cm^2								
1st measure: m (SD)	1.152 (0.116)	1.062 (0.116)	0.944 (0.159)	0.878 (0.122)	1.005 (0.177)	0.922 (0.167)	1.017 (0.176)	0.940 (0.154)
2nd measure: m (SD)	1.159 (0.114)	1.061 (0.116)	0.942 (0.160)	0.877 (0.122)	1.001 (0.175)	0.925 (0.168)	1.017 (0.178)	0.940 (0.154)
T score								
1st measure: m (SD)	−0.150 (0.992)	0.402 (0.963)	−1.820 (1.328)	−1.016 (1.014)	−1.390 (1.442)	−0.745 (1.312)	−1.252 (1.452)	−0.560 (1.240)
2nd measure: m (SD)	−0.105 (0.979)	0.375 (0.970)	−1.841 (1.354)	−1.022 (1.023)	−1.432 (1.431)	−0.737 (1.323)	−1.261 (1.472)	−0.567(1.245)
Mean difference: m (SD) (Systematic bias)	−0.0071 (±0.005)	−0.0001 (±0.003)	0.0015 (±0.004)	0.0006 (±0.002)	−0.0042 (±0.006)	0.0027 (±0.004)	−0.0001 (±0.003)	−0.0004 (±0.002)
SD (random measurement error)	0.0206	0.0111	0.0180	0.0109	0.0230	0.0146	0.0205	0.0121
SDD (g/cm^2)	±0.0403 (−0.047–0.033)	±0.0218 (−0.022–0.022)	±0.0353 (−0.037–0.034)	±0.0213 (−0.022–0.021)	±0.0450 (−0.049–0.041)	±0.0286 (−0.031–0.026)	±0.0403 (−0.040–0.040)	±0.0237 (−0.024–0.023)
CV (%)	1.78	1.05	2.29	1.58	1.91	1.24	2.02	1.29
LSC (%)	4.94	2.90	6.35	4.38	5.29	3.44	5.60	3.56
Random effects ICC(95% CI)	0.98 (0.96–0.98)	0.99 (0.99–0.99)	0.99 (0.98–0.99)	0.99 (0.99–0.99)	0.99 (0.99–0.99)	0.99 (0.99–0.99)	0.99 (0.99–0.99)	0.99 (0.99–0.99)

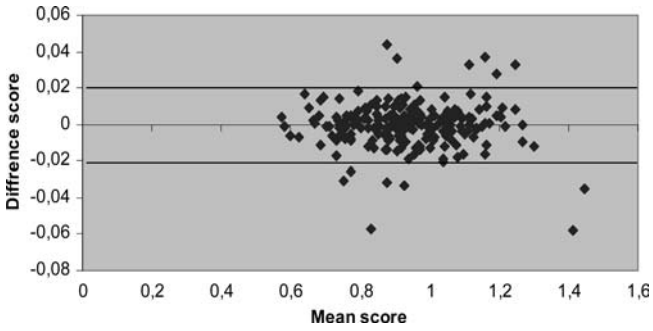

Fig. 1 *Graph* of the difference score against the mean score of the total hip BMD measurements (g/cm^2) in the study population. The outermost (*solid*) lines represent the SDD

and Altman's 95% limits of agreement method was used, the mean of the difference scores approached zero, reflecting no systematic bias between measurements (the 95% CI included zero difference). In this method, random measurement error is expressed as SD of the difference scores. Twice this value approaches the 95% limits of agreement. Thus, for the total hip the SDD in BMD measurements based on two BMD values with a short interval is 0.02 g/cm^2. The SDD at the spine was 0.04 g/cm^2. The CV (%) was 1.29 at the total hip and 2.02 at the spine. The LSC (%) was 3.56 and 5.60 at the total hip and at the spine, respectively.

Therefore, in an individual subject a BMD change at the total hip can be considered significant if the change between the measurements exceeds the SDD (expressed in absolute units) of 0.02 g/cm^2 or the LSC (expressed as percentage) of 3.56%. Reliability expressed by ICC was 0.99 with narrow 95% confidence intervals at all measurement sites.

Discussion

This study shows the in vivo short-term variability of BMD measurement by DXA in three groups of subjects with a wide range of BMD values: healthy young volunteers, postmenopausal women and patients with chronic rheumatic diseases (most of them taking corticosteroids). In all studied subjects, the reproducibility expressed by different means is good. The clinician interpreting a repeated DXA scan of a subject should be aware that a BMD change exceeding the LSC is significant, here arising from a BMD change of at least 3.56% at the total hip and 5.60% at the spine. Expressed as SDD, a BMD change should exceed 0.02 g/cm^2 at the total hip and 0.04 g/cm^2 at the spine before it can be considered a significant change. Despite the many publications on BMD variability in different patient groups, there are not any studies to our knowledge comparing short-term BMD variability between large groups of healthy young volunteers, postmenopausal women and patients with chronic rheumatic diseases. Indeed, it has become usual to perform repeated DXA measurement in this kind of patients: in postmenopausal women to monitor the efficacy of treatment [17, 18, 19] and in patients with chronic rheumatic diseases where the high prevalence of bone loss has been demonstrated [20, 21], especially when long-term corticosteroid therapy is used. In the reports published, variability is usually expressed as CV, and the figures for short-term variability are lower than the ones we found [7, 8, 9]. However, three studies showed variability data more in line with our results [9, 10, 11]. In the Ravaud et al. study, two samples of healthy ($n = 70$) and elderly ($n = 57$) postmenopausal women showed a CV (%) of 0.9 and 1.8, respectively, at the spine, and of 0.9 and 2.3, respectively, at the total hip [11]. Eastell showed an LSC (%) of 5.4 at the lumbar spine and 8 at the total hip, respectively, in osteoporotic postmenopausal women [22]. It has been suggested that the varying results of reproducibility studies might be explained by the "population" investigated; a phantom and healthy young subjects are likely to show more favorable variability than postmenopausal women, possibly in part because of easier positioning for measurement. The current study failed to show better variability, expressed as CV (%), in young healthy volunteers. Another reason advocated was that osteoarthritis in postmenopausal women may contribute to poorer variability than found in healthy young subjects. Besides, the majority of the studies mentioned had small patient samples, giving less precise results. Alternative measures of variability are the SDD and ICC. The Bland and Altman plots show between measurement differences [15]. The scatter plots of the current data show a random distribution of values, indicating the absence of a relationship between the measurement error and the true BMD value, as estimated by the mean of the two measurements. The SDD values found in the adult patients were slightly higher than the figures presented by Ravaud et al. [11]. In the first group of postmenopausal women (mean age 53 years) they describe, the SDD was 0.02 (g/cm^2) at the total hip and 0.02 at the lumbar spine. In the second group described, women with a mean age of 80 years, these figures were 0.04 and 0.04, respectively. In the

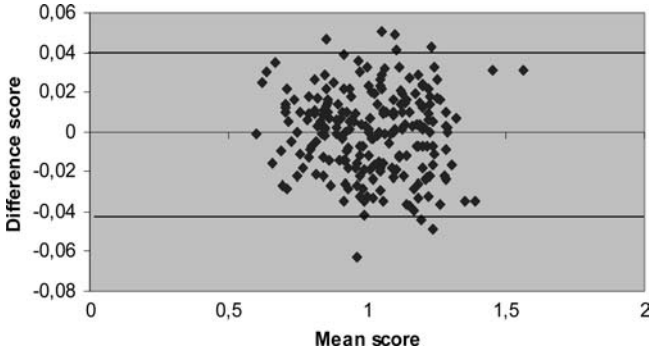

Fig. 2 *Graph* of the difference score against the mean score of the lumbar spine BMD measurements (g/cm^2) in the study population. The outermost (*solid*) lines represent the SDD

Lodder et al. [9] study (95 women, mean age 59.9 years), the SDD was 0.04 (g/cm^2) at the total hip and 0.05 at the lumbar spine. The SDD values of the children studied in this study tended to be lower than the values in the postmenopausal women. Using the SDD, one can state that a (BMD) change larger than the figure found is a true (BMD) change in 95% of the cases. The characteristics of the Bland and Altman method thus allow direct insight into the variability of the measurement under study. Previously published reports, as well as the current data, show that reproducibility expressed in absolute units (SDD) is independent of the BMD value. Reproducibility expressed as a percentage (CV) and the derived LSC, however, depend on the BMD value. Because of therapeutic consequences, the clinician should be especially careful in judging an apparent BMD change in patients with osteoporosis. The use of the SDD in the evaluation of an apparent BMD change gives a more conservative approach than the use of the CV at low BMD. Because of its independence from the BMD level and its expression in absolute units, the SDD is a preferable measure for use in daily clinical practice as compared with the CV and the derived LSC.

In contrast to all previous publications about DXA reproducibility, we found better results for the hip BMD variability than the lumbar spine. This is due to the fact that our study is the first to use the mean measure of the two femurs (dual femur). We tested and confirmed this hypothesis by measuring the SDD of the DXA measurement in the left hip alone in the first group (healthy subjects). It was ± 0.0339 vs. ± 0.0218 for both hips (data not shown). Thus, these results encourage the use of the measurement of both hips to improve the reproducibility of DXA at this site.

The ICC found in all of the groups was high, indicating good overall reproducibility of BMD measured by DXA. However, it is important to note that a large variability between patients automatically increases the ICC. The ICC and the Bland and Altman method yield complementary information; the presence of systematic bias cannot be found by estimating ICC. Although the variability as expressed by the ICC, and especially the SDD, is reassuring, showing good short-term variability at group level, the wide range of the differences in BMD and the derived T scores indicates considerable individual differences between two consecutive BMD measurements in some patients. The range in ΔT scores, for example, indicates that in some patients the diagnosis, based on the diagnostic thresholds of the WHO, would change owing to the measurement variability.

Our study showed that reproducibility is independent from age, BMD value and clinical status. However, no conclusion can be drawn from our study about DXA reproducibility in the elderly. Indeed, our study population was younger than those in the previously published series (only 20 patients were older than 65 years).

The figures show that at our center the favorable variability values presented in the literature cannot be reproduced in daily practice in postmenopausal women and/or patients with chronic rheumatic diseases. Thus, for optimal clinical decision-making, individual centers should establish the reproducibility figures based on routine DXA measurements in different patient groups.

In conclusion, the reproducibility of BMD measurements by DXA in postmenopausal women and patients with chronic rheumatic diseases expressed by different means is good at a group level. This reproducibility seems independent of age and clinical status. However, the clinician must remain aware that an apparent BMD change in an individual patient may represent a precision error. The measurement of both hips improves the reproducibility at this site and then should be recommended. In daily practice, centers should determine the individual SDD based on SDs. Indeed, the use of the SDD is preferable to the use of the CV and LSC because of its independence from BMD level and its expression in absolute units.

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