Original Article

Monitoring of Dual-Energy X-ray Absorptiometry Measurement in Clinical Practice

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Abstract

Bone densitometry has become the ''gold standard'' in osteoporosis diagnosis and treatment evaluation. It has also become more and more common to perform a second dual-energy X-ray absorptiometry (DXA) measurement to monitor bone mineral density (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. The reproducibility of DXA measurements is claimed to be good. Such variability is due to multiple causes, such as device errors, technician variability, patients' movements, and variation due to other unpredictable sources. The precision error is usually expressed as the coefficient of variation (CV). However, several other statistics to express reproducibility exist such as the smallest detectable difference (SDD) or the least significant change (LSC). 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. 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 (g/cm^2). At each measurement center, the SDD must be calculated from in vivo reproducibility data. The choice of the optimum time and site for performing follow-up scans depends on the ratio of the expected BMD treatment effect to the precision of the measurements.

Key Words: Bone mineral density; dual-energy X-ray absorptiometry; reproducibility.

Introduction

Osteoporosis is a worldwide major public health problem *(1,2)*. Bone densitometry has become the ''gold standard'' in its diagnosis and treatment evaluation. With its advantages of high precision, short scan times, low radiation dose, and stable calibration, dual-energy X-ray absorptiometry (DXA) has been established by the World Health Organization (WHO) as the technique of reference for assessing bone mineral density (BMD) in postmenopausal women and for basing 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 with corticosteroids) *(4–6)*. Moreover, BMD measurement is needed to select patients for osteoporosis treatment, as there is no proof that drugs for osteoporosis (other than hormone replacement therapy [HRT]) are beneficial in women with clinical risk factors for fractures but normal BMD values.

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. The reproducibility of DXA measurements is claimed to be good. Such variability is due to multiple causes, such as device errors, technician variability, patients' movements, and variation due to other unpredictable sources *(7–11)*.

The precision error is usually expressed as the coefficient of variation (CV) *(12–14)*, which is the ratio of the standard deviation (SD) to the mean of the measurements; however, several other statistics to express reproducibility exist, such as the smallest detectable difference (SDD) or the least significant change (LSC). 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.

Methods of Bone Mineral Density Reproducibility Measurement

Precision errors are evaluated by performing repeated scans on a representative set of individuals to characterize the reproducibility of the technique. Most published studies examine the short-term precision error, which is based on repeated measurements of each subject performed during a time period of no more than 2 weeks. During such a short period, no true change in BMD is expected.

The Coefficient of Variation

The CV, the most commonly presented measure for BMD variability, is the SD corrected for the mean of paired measurements. The CV, expressed as a percentage, is calculated as CV (%) $= (\sqrt{((\sum(a-b)^2/2n))}/((Ma+Mb)/2) \times 100$ where a and b are the first and second measurements, Ma and Mb are the mean values for the two groups, and n is the number of paired observations.

Reproducibility is far better for BMD measurement than for most laboratory tests. Reproducibility expressed by the CV is usually 1–2% at the spine on anteroposterior images and 2–3% at the proximal femur in individuals with normal BMD values; the difference between the two sites is ascribable to greater difficulties with repositioning and examining the femur as compared with the spine. However, these data obtained under nearly experimental conditions may not apply to everyday clinical practice. Reproducibility depends heavily on quality assurance factors, including tests to control the quality and performance of the machine, as well as the experience of the operator. Assessment of machine performance requires daily scanning of a phantom that may be anthropomorphic or not, followed by calculation of the in vitro CV, which serves to evaluate short-term and long-term performance and to detect drift in measurement accuracy. However, these in vitro data do not necessarily reflect in vivo reproducibility, which should be evaluated at each measurement center. Measurements are obtained either 3 times in each of the 15 patients or twice in each of the 30 patients, and the CV (m/θ) is calculated from the mean (m) and standard deviation (θ) of these repeated measurements. The CV is expressed as a percentage and depends on mean BMD values *(6)*. The standard deviation reflects measurement error, which is a characteristic of machine performance and is independent from the value measured.

The Least Significant Change

For two point measurements in time, a BMD change exceeding $2\sqrt{2}$ times the precision error (PE) of a technique is considered a significant change (with 95% confidence); the corresponding change criterion has been termed the "least significant change" (LCS). The LSC = $2.8 \times$ PE, where PE is the largest precision error of the technique used (or more easily the CV expressed in percentage). This smallest change that is considered statistically significant is also expressed in percentage *(15)*.

The Smallest Detectable Difference

The measurement error can be calculated using Bland and Altman's 95% limits of agreement method *(16)*. Precision expressed by this method gives an absolute and metric estimate of random measurement error, also called SDD. In this case, in which there are two observations for each subject, the standard deviation of the differences (SD_{diff}) estimates within variability of the measurements. Most disagreements between measurements are expected to be between limits called "limits of agreement" defined as d $\pm$ $z_{(1-\alpha/2)}$ SD_{diff} where d is the mean difference between the pairs of measurements and $z_{(1-\alpha/2)}$ is the $100(1-\alpha/2)$th percentile of the normal distribution. The value "d" is an estimate of the mean systematic bias of measurement 1 to measurement 2. The value "d" is expected to be 0, because a true change in BMD is not assumed to occur during the interval between the two BMD measurements. Defining "α" to be 5%, the limits of agreement are +1.96 SD_{diff} and −1.96 SD_{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.

Clinical Implications of Bone Mineral Density Reproducibility Measurement

In clinical practice, two absolute values (g/cm^2) have to be compared, rather than two percentages (T-scores). When serial measurements are obtained in a patient, only changes greater than the LSC (in %) or the SDD (in g/cm^2) can be ascribed to treatment effects. Smaller changes may be related to measurement error.

We recently studied the in vivo short-term variability of BMD measurement by DXA in three groups of subjects with a wide range of BMD values: (1) healthy young volunteers, (2) postmenopausal women, and (3) patients with chronic rheumatic diseases (most of them taking corticosteroids). In all studied subjects, reproducibility expressed by different means was good and independent from clinical and BMD status. Thus, the clinician interpreting a repeated DXA scan of a subject should be aware that a BMD change exceeding the LSC is significant, in our center 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 *(17)*. Indeed, it has become standard to perform repeated DXA measurement in postmenopausal women to monitor efficacy of treatment

(18,19) and in patients with chronic rheumatic diseases in which a high prevalence of bone loss has been demonstrated *(20–22)*, 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 *(7–9)*. However, two studies showed variability data more in line with our results. In Ravaud et al.'s *(11)* 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. Eastell *(23)* showed an LSC (%) of 5.4 at the lumbar spine and 8 at the total hip, respectively, in osteoporotic postmenopausal women. It has been suggested that the varying results of reproducibility studies may be explained by the "population" investigated, as 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 *(24)*. However, our study failed to show better variability (expressed as CV [%]) in young healthy volunteers *(17)*. Another reason advocated was that osteoarthritis in postmenopausal women may contribute to poorer variability than found in healthy young subjects. The SDD values found in our study were comparable with the figures presented by Ravaud et al. *(11)*. In the first group of postmenopausal women (mean age: 53 yr) 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, mean age: 80 yr), these figures were 0.04 and 0.04, respectively. In Lodder et al.'s *(9)* study of 95 women (mean age: 59.9 yr), 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 who were studied tended to be lower than the values in the postmenopausal women (Table 1). 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 (Fig. 1).

It has been shown that reproducibility expressed using the SDD is independent of the BMD value, whereas reproducibility expressed using the CV or the derived LSC depend on the BMD value. Ravaud et al. *(11)* reported that using SD, the values of the cut-offs are 0.024 g/cm^2 at the spine, 0.030 g/cm^2 at the femoral neck, 0.020 g/cm^2 at the greater trochanter, and 0.021 g/cm^2 at the total hip for postmenopausal women aged ≤70 yr, and the values of the cut-offs for postmenopausal osteoporotic women aged >70 yr are 0.040 g/cm^2, 0.033 g/cm^2, 0.033 g/cm^2, and 0.038 g/cm^2 at the spine, femoral neck, greater trochanter, and total hip, respectively. Using CV, cut-offs vary depending on the BMD level. In postmenopausal women aged >70 yr for a BMD level between 0.600 g/cm^2 and 1.000 g/cm^2 the cut-offs derived from CV vary between 0.015 g/cm^2 and 0.024 g/cm^2, 0.024 g/cm^2 and 0.041 g/cm^2, 0.018 g/cm^2 and 0.030 g/cm^2, and 0.015 g/cm^2 and 0.025 g/cm^2 for the spine, femoral neck, greater trochanter, and total hip, respectively. In postmenopausal osteoporotic women aged >70 yr for the same range of BMD level, cut-offs vary between 0.031 g/cm^2 and 0.051 g/cm^2,

0.038 g/cm^2 and 0.063 g/cm^2, 0.043 g/cm^2 and 0.071 g/cm^2, and 0.038 g/cm^2 and 0.063 g/cm^2 for the same bone sites. Consequently, to express variability on a percentage basis using CV leads to underestimating variability in patients with low BMD and overestimating variability in patients with high BMD *(11)*. Previous reports in the literature, as well as the data of Ravaud et al.'s *(11)*, Lodder et al.'s *(9)* and ours *(17)* (Table 1), demonstrate that absolute precision errors derived from SD are constant across a wide range of BMD values and are independent of the level of BMD. Because of therapeutic consequences, the clinician should be especially careful in judging an apparent BMD change in patients with osteoporosis. Influence of age on BMD reproducibility is controversial. Previous studies have suggested that BMD measurement errors were independent of age, and some studies even suggested that SDD may vary in extreme ages (i.e., children and the elderly) probably because of age-related factors other than BMD. However, a few data exist for reproducibility of DXA in women >70. Ravaud et al.'s *(11)* data, as well as the data of Fuleihan et al. *(12)*, and Maggio et al. *(10)* show that the measurement error is greater in older osteoporotic subjects. Several factors, such as difficulties in repositioning, could explain the increase of measurement error in this kind of patient. Therefore, 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 with all previous publications about DXA reproducibility, we found that our center had better results for the hip BMD variability than the lumbar spine. This is because our study was the first to use the mean measure of the two femurs (i.e., the dual femur). In this study, we showed that in a group of young healthy volunteers the SDD was ±0.0218 g/cm^2 when both femurs were measured, whereas it was ±0.0339 g/cm^2 when only one femur was measured. Thus, these results enhance to encourage the use of the measurement of both hips to improve the reproducibility of DXA at this site *(17)*.

Although the variability as expressed by the CV, 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.

In summary, reproducibility of BMD measurement by DXA in different kinds of patients (i.e., postmenopausal women, patients with chronic rheumatic diseases, the elderly, and so forth) as expressed by different means is good at a group level. However, the clinician must remain aware that an apparent BMD change in an individual patient may represent a precision error. At each measurement center, the

Table 1
Comparison of BMD Measurement Reproducibility Evaluation in Two Studies Including Various Groups of Patients

| | El Maghraoui et al. *(17)* | | | | | | Lodder et al. *(9)* | | | |
| | Healthy young volunteers (n = 60) 28.2 ± 5.5 yr | | Postmenopausal women (n = 102) 58.1 ± 7.0 yr | | Chronic rheumatic diseases (n = 60) 47.1 ± 12.8 yr | | Post menopausal women (n = 95) 59.9 ± 8.1 yr | | Children (n = 23) 11.2 ± 1.3 yr | |
	LS	TH	LS	TH	LS	TH	LS	TH	LS	TH
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)	−0.001 (±0.05)	−0.0004 (±0.04)	−0.0009 (±0.02)	−0.003 (±0.03)
SD (random measurement error)	0.0206	0.0111	0.0180	0.0109	0.0230	0.0146	0.0238	0.0184	0.0088	0.0116
SDD (g/cm^2)	±0.0403	±0.0218	±0.0353	±0.0213	±0.0450	±0.0286	±0.0466	±0.0361	±0.0172	±0.0228
CV (%)	1.78	1.05	2.29	1.58	1.91	1.24	1.92	1.59	0.84	1.19
LSC (%)	4.94	2.90	6.35	4.38	5.29	3.44	5.43	4.50	2.38	3.37
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 (0.98–0.99)	0.99 (0.99–0.99)	0.99 (0.99–1.00)	0.99 (0.99–1.00)

Note: Mean difference, mean of the difference between the first and second BMD measurement; SD difference, SD of the difference between the first and second BMD measurement.

Abbr: BMD, bone mineral density; CI, confidence interval; CV, coefficient of variation (%); ICC, intraclass correlation coefficient; LS, lumbar spine; LSC, least significant change (%); M, mean; SD, standard deviation; SDD, smallest detectable difference (g/cm^2); TH, total hip.
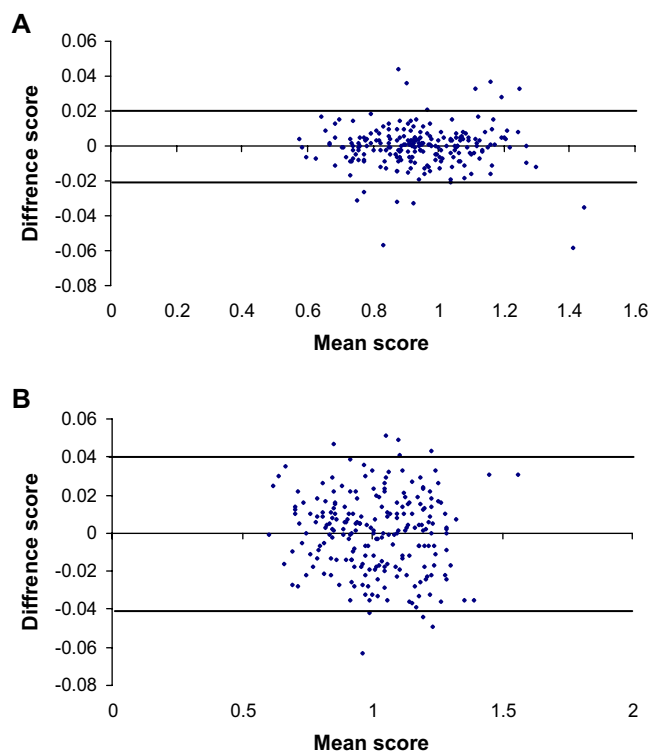
Fig. 1. Graph of the difference score against the mean score of the total hip (A) and the lumbar spine (B) bone mineral density (BMD) measurements (g/cm^2) in our center *(17)* using the Bland and Altman method. The outermost (solid) lines represent the smallest detectable difference (SDD).

SDD should be calculated from in vivo reproducibility data. In clinical practice, the SDD should be used to estimate the significance of observed changes, in absolute values.

Other Factors Influencing DXA Monitoring

The first factor is the time interval between two measurements in the same patient, which must be long enough to allow occurrence of a change greater than the SDD or the LSC. Therefore, it depends on the expected rate of change in BMD measurement, which varies according to whether the measurement site is composed predominantly of trabecular or of cortical bone, and the reproducibility of BMD measurement at that site. Thus, in clinical practice, a treatment-induced BMD increase can only be detected in general after 2 years. However, in patients receiving long-term steroid therapy, the changes in BMD may be so important that they can be detected at 1 year. Thus, although the spine may not be the best site for the diagnosis of osteoporosis, given the high prevalence of spinal degenerative disease, it is the most sensitive site for detecting changes in a period of time. However, our study showed that measurement of both femurs (called "dual femur" in Lunar machines [General Electric Inc., Madison, WI]) increases the reproducibility at this site.

In another side, the changes in BMD measurements are influenced by the ability of osteoporosis treatments to increase the BMD at the different skeletal sites. For some treatments such as teriparatide and the more potent bisphosphonates, statistically significant changes in spine BMD occur on time scales of 1 to 2 years in the majority of patients, although for other treatments, such as raloxifene, the changes are often not large enough to be statistically significant. Thus, with the exception of HRT, treatment dosages cannot be adjusted on the basis of BMD changes. Moreover, there is no proof that repeating BMD measurements improves compliance, as most patients discontinue anti-resorptive medications after a few months because of administration constraints, side effects, cost of medications, or lack of interest.

Principally, BMD is used as a surrogate marker for the fracture risk, yet BMD increases do not reliably reflect a reduction in the fracture risk. Although bisphosphonates, raloxifene, and HRT have not been compared in the same study, they seem to produce comparable reductions in the risk of vertebral fractures of approximately 30–50%, whereas BMD changes differ markedly across medications. Studies have shown that BMD gains explain only a small proportion of the vertebral fracture risk reduction: 28% with risedronate *(25)*, 16% with alendronate *(26)*, and 4% with raloxifene *(27)*. It has been suggested that the percentage of BMD change may be related to the change in the relative risk of fracture *(28)*. In one study, a linear relationship was found between these two parameters, but a 1% increase in spinal BMD was associated with only a 3% decrease in the relative risk of vertebral fracture *(26)*. For peripheral fractures, in contrast, the risk reduction is clearly related to the BMD gain *(29)*. Common sense indicates that a BMD increase during treatment should be preferable to a BMD decrease. However, recent data showing that the fracture risk may decrease despite a reduction in BMD have been reported *(30)*. It has also been shown that the fracture risk was more heavily dependent on BMD at baseline than on BMD changes during treatment *(31)*.

Conclusion

Serial BMD measurements can be used to monitor current anti-resorptive treatments (bisphosphonates or raloxifene). However, adequate quality-control procedures must be used *(32)*. Measurement error must be considered when evaluating serial assessments. A clear understanding of the interpretation of serial measurements and the statistical principles impacting their interpretation is necessary to determine whether a change is real and not simply random fluctuation. It is inadequate to simply use the manufacturer's default precision error, which may underestimate the precision error in the clinical setting. Thus, every center should calculate its own precision error from in vivo reproducibility data. International societies interested in osteoporosis diagnosis and management such as the International Society for Clinical Densitometry or the International Osteoporosis Foundation should add to their guidelines at least two recommendations about DXA monitoring highlighted in this article: (1) the measurement of both hips improves the reproducibility at this site and (2) DXA

measurement centers should determine and use the individual SDD. Indeed, the use of the SDD is preferable to the use of the CV and LSC because of its independence from the BMD level and its expression in absolute units. The exact definition and advices for the measure and use of these parameters in clinical practice should be clearly explained. It is clear that the choice of the optimum site for performing follow-up scans depends on the ratio of the BMD treatment effect to the precision of the measurements. The larger the ratio, the more statistically significant will be the likelihood of the observed changes *(33)*. Actually, all data demonstrate agreeable results that the spine is the optimum site. In clinical practice, BMD measurements have to be spaced at least two yr apart. The main goal of serial BMD measurement is to check that no further bone loss has occurred; estimation of BMD gains is the secondary objective. This should be explained to the patients, many of whom expect to recover normal BMD values.

References

1. El Maghraoui A, Koumba BA, Jroundi I, Achemlal L, Bezza A, Tazi MA. 2005 Epidemiology of hip fractures in 2002 in Rabat, Morocco. Osteoporos Int 16:597–602.
2. Bono CM, Einhorn TA. 2003 Overview of osteoporosis: pathophysiology and determinants of bone strength. Eur Spine J 12(Suppl 2):S90–S96.
3. Kanis JA, Johnell O, Oden A, Jonsson B, De Laet C, Dawson A. 2000 Risk of hip fracture according to the World Health Organization criteria for osteopenia and osteoporosis. Bone 27:585–590.
4. Yeap SS, Hosking DJ. 2002 Management of corticosteroid-induced osteoporosis. Rheumatology (Oxford) 41:1088–1094.
5. Maricic M, Gluck O. 2004 Densitometry in glucocorticoid-induced osteoporosis. J Clin Densitom 7:359–363.
6. El Maghraoui A. 2004 Corticosteroid induced osteoporosis. Press Med 33:1213–1217.
7. Phillipov G, Seaborn CJ, Phillips PJ. 2001 Reproducibility of DXA: potential impact on serial measurements and misclassification of osteoporosis. Osteoporos Int 12:49–54.
8. Nguyen TV, Sambrook PN, Eisman JA. 1997 Sources of variability in bone mineral density measurements: implications for study design and analysis of bone loss. J Bone Miner Res 12:124–135.
9. Lodder MC, Lems WF, Ader HJ, et al. 2004 Reproducibility of bone mineral density measurement in daily practice. Ann Rheum Dis 63:285–289.
10. Maggio D, McCloskey EV, Camilli L, et al. 1998 Short-term reproducibility of proximal femur bone mineral density in the elderly. Calcif Tissue Int 63:296–299.
11. Ravaud P, Reny JL, Giraudeau B, Porcher R, Dougados M, Roux C. 1999 Individual smallest detectable difference in bone mineral density measurements. J Bone Miner Res 14:1449–1456.
12. Fuleihan GE, Testa MA, Angell JE, Porrino N, Leboff MS. 1995 Reproducibility of DXA absorptiometry: a model for bone loss estimates. J Bone Miner Res 10:1004–1014.
13. Rozenberg S, Vandromme J, Neve J, et al. 1995 Precision and accuracy of in vivo bone mineral measurement in rats using dual-energy X-ray absorptiometry. Osteoporos Int 5:47–53.
14. Nguyen TV, Eisman JA. 2000 Assessment of significant change in BMD: a new approach. J Bone Miner Res 15:369–372.
15. Gluer CC. 1999 Monitoring skeletal changes by radiological techniques. J Bone Miner Res 14:1952–1962.
16. Bland J, Altman D. 1986 Statistical methods for assessing agreement between methods of clinical measurement. Lancet i: 307–310.
17. El Maghraoui A, Do Santos Zounon AA, Jroundi I, et al. 2005 Reproducibility of bone mineral density measurements using dual X-ray absorptiometry in daily clinical practice. Osteoporos Int 16:1742–1748.
18. Johnson SL, Petkov VI, Williams MI, Via PS, Adler RA. 2005 Improving osteoporosis management in patients with fractures. Osteoporos Int 16:1079–1085.
19. Kanis JA, Devogelaer JP, Gennari C. 1996 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. The Scientific Advisory Board and the Board of National Societies. Osteoporos Int 6:256–261.
20. El Maghraoui A, Borderie D, Edouard R, Roux C, Dougados M. 1999 Osteoporosis, body composition and bone turnover in ankylosing spondylitis. J Rheumatol 26:2205–2209.
21. Maillefert JF, Aho LS, El Maghraoui A, Dougados M, Roux C. 2001 Changes in bone density in patients with ankylosing spondylitis: a two-year follow-up study. Osteoporos Int 12:605–609.
22. El Maghraoui A. 2004 Osteoporosis and ankylosing spondyltis. Joint Bone Spine 71:573–578.
23. Eastell R. 1996 Assessment of bone density and bone loss. Osteoporos Int 6(Suppl):3–5.
24. Glüer CC, Blake G, Lu Y, Blunt BA, Jergas M, Genank HK. 1995 Accurate assessment of precision errors: how to measure the reproducibility of bone densitometry techniques. Osteoporos Int 5:262–270.
25. Li Z, Meredith MP, Hoseyni MS. 2001 A method to assess the proportion of treatment effect explained by a surrogate endpoint. Statist Med 20:3175–3188.
26. Cummings SR, Karpf DB, Harris F, et al. 2002 Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. Am J Med 112:281–289.
27. Sarkar S, Mitlak BH, Wong M, Stock JL, Black DM, Harper KD. 2002 Relationship between bone mineral density and incident vertebral fracture risk raloxifene therapy. J Bone Miner Res 17:1–10.
28. Wasnich RD, Miller P. 2000 Antifracture efficacy of antiresorptive agents are related to changes in bone density. J Clin Endocrinol Metab 85:231–236.
29. Hochberg MC, Greenspan S, Wasnich RD, Miller P, Thompson DE, Ross PD. 2002 Changes in bone density and turnover explain the reductions in incidence of non-vertebral fractures that occur during treatement with antiresorptive agents. J Clin Endocrinol Metab 87:1586–1592.
30. Watts N, Geusens P, Barton IP, Felsenberg D. 2005 Relationship between changes in BMD and nonvertebral fracture incidence associated with risedronate: reduction in risk of nonvertebral fracture is not related to change in BMD. J Bone Miner Res 20:2097–2104.
31. Hochberg MC, Ross PD, Black D, et al. 1999 Larger increases in bone mineral density during alendronate therapy are associated with a lower risk of new vertebral fractures in women with postmenopausal osteoporosis. Arthr Rheum 42:1246–1254.
32. Roux C, Garnero P, Thomas T, Sabatier JP, Orcel P, Audran M, Comité Scientifique du GRIO. 2005 Recommendations for monitoring antiresorptive therapies in postmenopausal osteoporosis. Joint Bone Spine 72:26–31.
33. Blake GM, Fogelman I. 2002 Dual energy x-ray absorptiometry and its clinical applications. Semin Musculoskelet Radiol 6:207–218.