Osteoporos Int (2003) 14: 110–115
DOI 10.1007/s00198-002-1321-z

ORIGINAL ARTICLE

Patient assessment using standardized bone mineral density values and a national reference database: implementing uniform thresholds for the reimbursement of osteoporosis treatments in Belgium

S. Boonen · J.-M. Kaufman · J.-Y. Reginster
J.-P. Devogelaer · on behalf of the Belgian Bone Club (BBC)

Received: 29 May 2002 / Accepted: 6 September 2002 / Published online: 17 January 2003

Abstract Dual-energy X-ray absorptiometry (DXA) devices from the three main manufacturers provide different bone mineral density (BMD) values, due in part to technical differences in the algorithms for bone mineral content (BMC) and area measurements and in part to the use of different manufacturer-derived reference databases. As a result, significant differences exist between Hologic, Lunar and Norland systems in the reported young normal standard deviation scores or *T*-scores. In a number of European countries, including Belgium, a *T*-score below −2.5 is one of the key criteria for reimbursement of osteoporosis treatments. This paper addresses the first attempt to implement a nationwide, uniform expression of BMD in patients, in order to harmonize drug reimbursement. To this end, measures were taken to implement a uniform expression of BMD in Belgian patients, by converting each manufacturer's absolute BMD to standardized BMD (sBMD) values and by establishing a single national reference range.

S. Boonen
Leuven University Center for Metabolic Bone Diseases and Division of Geriatric Medicine, Katholieke Universiteit Leuven

J.-M. Kaufman
Unit for Osteoporosis and Metabolic Bone Diseases, Ghent University Hospital

J.-Y. Reginster
Centre Universitaire d'Investigation du Métabolisme Osseux et du Cartilage Articulaire, State University of Liège

J.-P. Devogelaer (✉)
Arthritis Unit, Université catholique de Louvain, Belgium
E-mail: devogelaer@ruma.ucl.ac.be
Tel.: +32-2-7645390
Fax: +32-2-7645394

Present address: J.-P. Devogelaer
Service de Rhumatologie, UCL 5390, Saint-Luc University Hospital, Avenue Hippocrate 10, 1200 Brussels, Belgium

Introduction

Over the past decade, dual-energy X-ray absorptiometry (DXA) has emerged as the major tool in diagnosing osteoporosis and monitoring osteoporosis treatment. Recent technological advances in DXA technology have substantially enhanced the physician's ability to detect and manage the disease, but have also created a dilemma as physicians have attempted to compare results obtained on different devices (e.g., pencil-beam systems versus fan-array systems) from different manufacturers (e.g., Hologic versus Lunar) using different reference ranges (e.g., local versus US data).

The aim of the current study was to optimize the interpretation of bone mineral density (BMD) in Belgian patients by the use of standardized BMD values and by implementing a single reference range for all densitometers, in order to harmonize patient assessment and to provide uniform thresholds for the reimbursement of osteoporosis treatments in Belgium. The study was intended only to assess the peak bone mass and not to determine the postmenopausal bone loss. No measurement of *Z*-scores was considered. Over the past few years, US reference data for the hip have been generated from the NHANES III study [1, 2] and have been suggested to serve as a standardization platform [3]. As part of the current project, reference values were obtained from young normal Belgian women and these were compared with US reference ranges. In addition, measures were taken to implement a uniform expression of BMD in Belgian patients, by converting each manufacturer's absolute BMD to standardized BMD (sBMD) values [4, 5, 6, 7].

Subjects and methods

Subjects

A total of 340 healthy young-adult women were enrolled in 37 different clinical sites across Belgium. Participants had to be

Caucasian and between 25 and 35 years of age. The following exclusion criteria were applied before enrollment: (i) a history of medical conditions known to affect BMD, including diabetes, hyperthyroidism, hyperparathyroidism, intestinal resection, anorexia nervosa, rheumatoid arthritis, gastrectomy, and (ii) any current or prior use of drugs known to affect bone metabolism, including estrogens, corticosteroids, bisphosphonates and thyroxine, (iii) secondary amenorrhea of more than 6 months' duration, and (iv) a body mass index (BMI) exceeding 38 kg/m^2. Date of birth, height and weight were recorded.

BMD measurements

BMD values (g/cm^2) were measured by DXA at the lumbar spine (L2–L4 and L1–L4) and the hip (femoral neck and/or total hip region). In Belgium, DXA scanners are available from three manufacturers (Hologic, Lunar and Norland). In 181 women (recruited in 13 centers), BMD was measured using equipment from Hologic (6 QDR-1000, 1 QDR-1500, 2 QDR-2000, 4 QDR-4500), Lunar instruments were used to assess BMD in 120 women in 13 centers (7 DPX-L, 5 DPXplus, 1 DPX-IQ), and in 39 women from 4 centers, measurements were obtained on Norland densitometers (XR26 MK2 Quick Scan). Posteroanterior (PA) lumbar spine and hip BMD were measured using standard procedures specified by each manufacturer for scanning and analysis. All machines were calibrated by the individual manufacturers and quality controls performed according to their standards. The coefficient of variation for the precision of BMD measurements was less than 1% as measured on the European spine phantom (ESP; QRM, Erlangen, Germany).

Table 1 Baseline characteristics of the study population($n = 340$)

	Mean ± SD (SEM)	Range
Age (years)	29.6 ± 3.2 (0.17)	24–36
Height (cm)	166.5 ± 6.3 (0.35)	152–193
Weight (kg)	61.8 ± 9.0 (0.50)	44–112
BMI (kg/m^2)	22.2 ± 2.7 (0.15)	17–38

Calculation of standardized BMD

Standardized BMDs were calculated using previously established cross-calibration equations, providing results in internationally accepted utilization units [4, 5, 6, 7]. The formulas are given in Appendix B.

Statistical analysis

All data were expressed as mean ± SD. Mean BMD values and thresholds were compared using Student's *t*-test. All statistical tests were two-sided, and comparisons were considered significant at a *p* value of 0.05 or less.

Results

Table 1 shows the baseline characteristics of the study population. The BMD values of the subjects are presented in Tables 2 and 3 (lumbar spine) and Table 4 (total hip). At both sites, the BMD values in the Belgian (BBC) reference population were not statistically different from the (US) reference ranges provided by the manufacturers, except for the spine BMD values from Norland which were slightly but significantly lower in the Belgian population.

To discriminate the manufacturer-specific BMD values from the sBMD values, the former values were expressed by convention in grams per square centimeter and the latter in milligrams per square centimeter. According to the formula of Genant et al. [4], at the lumbar spine (L2–L4) sBMD (average based on Hologic, Lunar and Norland values) was 1140 ± 112 mg/cm^2 (mean ± SD) in the BBC reference population and 1155 ± 113 mg/cm^2 in the US reference population, respectively (NS). According to the formula of

Table 2 Lumbar spine (L2–L4) BMD values of normal young females according to the various manufacturers

Manufacturer	L2–L4 BMD (g/cm^2)		Difference	L2–L4 sBMD (mg/cm^2) according toGenant et al. [4]		Difference	L2–L4 sBMD (mg/cm^2) according to Hui et al. [5]		Difference
	Belgian reference population (BBC)	US reference population	*p*	Belgian reference population (BBC)	US reference population	*p*	Belgian reference population (BBC)	US reference population	*p*
Hologic	1.056 ± 0.108	1.079 ± 0.110	NS	1133 ± 108	1160 ± 110	NS	1129 ± 107	1156 ± 110	NS
Lunar	1.215 ± 0.121	1.200 ± 0.120	NS	1157 ± 121	1143 ± 120	NS	1154 ± 148	1140 ± 112	NS
Norland	1.035 ± 0.109	1.080 ± 0.110	003	1114 ± 106	1162 ± 110	003	1108 ± 106	1152 ± 113	004
Global	(–)	(–)		1140 ± 112	1155 ± 113	NS	1136 ± 111	1149 ± 113	NS

Values are mean ± SD, NS not significant

Table 3 Lumbar spine (L1–L4) BMD values of normal young females according to the various manufacturers

Manufacturer	L1–L4 BMD (g/cm^2)		Difference	L2–L4 sBMD (mg/cm^2) according toGenant et al. [4]		Difference	L2–L4 sBMD (mg/cm^2) according to Hui et al. [5]		Difference
	Belgian reference population (BBC)	US reference population	*p*	Belgian reference population (BBC)	US reference population	*p*	Belgian reference population (BBC)	US reference population	*p*
Hologic	1.027 ± 0.112	1.047 ± 0.110	NS	1104 ± 108	1126 ± 110	NS	1101 ± 108	1123 ± 110	NS
Lunar	1.189 ± 0.149	1.180 ± 0.120	NS	1132 ± 121	1124 ± 120	NS	1129 ± 121	1121 ± 120	NS
Norland	NA	NA	NA	NA	NA	NA	NA	NA	NA
Global	(–)	(–)		1115 ± 114	1125 ± 115	NS	1112 ± 113	1122 ± 115	NS

Values are mean ± SD, NS not significant, NA not available

Table 4 Total hip BMD values of normal young females according to the various manufacturers

Manufacturer	BMD (g/cm^2)		Difference	sBMD (mg/cm^2) according to Hanson et al. [6]		Difference	sBMD (mg/cm^2) according to Lu et al. [7]		Difference
	Belgian reference population (BBC)	US reference population	*p*	Belgian reference population (BBC)	US reference population	*p*	Belgian reference population (BBC)	US reference population	*p*
Hologic	0.928 ± 0.121	0.939 ± 0.122	NS	940 ± 120	953 ± 124	NS	941 ± 120	952 ± 122	NS
Lunar	1.009 ± 0.123	1.000 ± 0.122	NS	957 ± 122	948 ± 116	NS	956 ± 123	948 ± 122	NS
Global	(–)	(–)		946 ± 121	951 ± 122	NS	945 ± 122	949 ± 122	NS

Values are mean ± SD, NS not significant, NA not available

Hui et al. [5], the respective values of sBMD at the lumbar spine (L2–L4) were 1136 ± 111 mg/cm^2 and 1149 ± 113 mg/cm^2 for the global BBC and US values, respectively. These numbers did not differ significantly from each other, and the simpler formula of Genant et al. [4] was used for the standardization. At the total hip, according to the formula of Hanson et al. [6], sBMD values (based on Hologic and Lunar only) were 946 ± 121 mg/cm^2 and 951 ± 122 mg/cm^2 in the BBC and US reference populations, respectively (NS). According to the formula of Lu et al. [7], the respective values were 945 ± 121 and 951 ± 122 mg/cm^2, also not statistically different from each other, nor from the former values.

Based on the WHO criteria, thresholds were calculated corresponding to standardized BMD values 2.5 SD below the average peak bone density. At both the lumbar spine and total hip, thresholds based on the BBC and the US normal values were similar (Table 5). At the hip, standardization is complicated, because femoral neck BMD is measured by differing algorithms, according to the manufacturer (Table 6). The standardization, if it is possible, would be based on a cross-calibration. This does not offer complete statistical guarantees; the agreement coefficient kappa will be weak [8]. If we accept these small discrepancies, the values for femoral neck can be expressed according to the formulas of Lu et al. [7] and/or Simons et al. [8] in order to normalize femoral neck BMD towards Norland values.

The values are summarized in Table 7. Indeed, if we only take into account the DXA values of total hip BMD, users of the Norland apparatus could be baffled, because former Norland apparatus does not provide values for the total hip region. For Hologic and Lunar users, however, the total hip region can be more accurately used (Table 4). As can be seen from Table 7, the values are not statistically or clinically significantly different from each other. If we compare the number of volunteers with a BMD *T*-score lower than −2.5, 2 patients only had a manufacturer value of osteoporosis at the spine according to the WHO rules, versus the same 2 patients after standardization. At the total hip also, no shift in diagnostic category was observed before and after standardization for the *T*-score category ≤ −2.5.

Discussion

Because of differences in calibration and bone-edge detection algorithms, the absolute values obtained on equipment from Hologic, Lunar and Norland can differ markedly. Because of this, there has been a great deal of interest in developing a standardized BMD to which all DXA results could be converted, regardless of which manufacturer's densitometer was used. Over the past decade, the International Committee for Standards in Bone Measurement approved formulas for converting each manufacturer's absolute BMD to a sBMD [4, 5, 6, 7]. In a joint effort with the BBC to harmonize patient assessment in Belgium, the three major manufacturers of DXA devices agreed to provide the sBMD values as part

Table 5 Standardized BBC thresholds for reimbursement at the lumbar spineand total hip (corresponding to *T*-score −2.5)

	sBMD (mg/cm^2)							
	Based on BBC reference data			Based on US reference data			Difference	
	According to Genant et al. [4]	According to Hui et al. [5]	Difference *p*	According to Genant et al. [4]	According to Hui et al. [5]	Difference *p*	BBC Vs US [4]	BBC Vs US [5]
Lumbar spine								
L2–L4	860	858	NS	872	867	NS	NS	NS
L1–L4	830	830	NS	837	836	NS	NS	NS
	According to Hanson et al. [6]	According to Lu et al. [7]		According to Hanson et al. [6]	According to Lu et al. [7]			
Total hip	643	640	NS	645	644	NS	NS	NS

Table 6 Femoral neck BMD values of normal young females according to the various manufacturers

Manufacturer	Belgian BMD (g/cm^2)	Manufacturer's (US) reference data (NHANES III)	Difference *p*
Hologic	0.834 ± 0.107	0.849 ± 0.111	NS
Lunar	0.989 ± 0.145	0.980 ± 0.120	NS
Norland	0.903 ± 0.087	0.950 ± 0.120	NS

Table 7 Standardized BBC thresholds for reimbursement based on femoral neck BMD (corresponding to T-score −2.5)

	sBMD (mg/cm^2)							
	Based on BBC reference data			Based on US reference data			Difference	
Value	According to Lu et al. [7]	According to Simmons et al. [8]	Difference p	According to Lu et al. [7]	According to Simmons et al. [8]	Difference p	BBC Vs US [7]	BBC Vs US [8]
Mean values	914 ± 155	915 ± 115	NS	926 ± 117	929 ± 117	NS	NS	NS
T-scores −2.5	627	628	NS	634	637	NS	NS	NS

of the bone density report, based on these equations. By convention, the value for the sBMD is multiplied by 1000 to convert it to milligrams per square centimeter, rather than reporting it as grams per square centimeter, in order to readily distinguish this value from the non-standardized value.

The choice of a reference range is important for the accurate categorization of patients, as too is the estimate of the variance around the mean value [9, 10]. An inappropriate reference range for peak BMD may result in identification of an incorrect proportion of subjects with osteoporosis at DXA. In the creation of reference databases, each manufacturer has utilized a different sample of the (US) population. The SD (upon which the T-score is based), which is calculated for the values from any given sample, varies from sample to sample. As a result, significant differences exist between Hologic, Lunar and Norland systems in the reported young normal standard deviation scores or T-scores [11, 12, 13]. This discrepancy is not only caused by differences in the normal populations, but also by differences in statistical methods used to determine the young normal mean and standard deviation [13]. With the development of the cross-calibration equations between manufacturers [4], it became possible for the proximal femur data from NHANES III [1, 2] to be adopted as a common femur database for manufacturers (even though the data were obtained solely on Hologic DXA devices). However, T-scores at the lumbar spine are still calculated from manufacturer-derived databases.

In an attempt to avoid inconsistencies and to provide a uniform basis for patient assessment in Belgium, we established a single national reference population. One of the goals of our study was to examine whether any discrepancy exists with respect to the mean BMD values and respective standard deviations between our subjects and US reference populations (including NHANES III). In various European studies, a high percentage of subjects appeared to be erroneously classified as osteoporotic when US reference range T-scores were used [14, 15, 16], suggesting that individual populations should use their own reference range T-scores to avoid misdiagnoses of osteoporosis. These results apparently contrast with the findings of our study in Belgium, demonstrating similar peak BMD values and standard deviations in US reference populations and our subjects. Only in Norland BMD values of the lumbar spine was there a slight difference in favor of US values. This discrepancy might be explained by the low numbers of volunteers tested on Norland machines. Accordingly, we observed less than 2% of misdiagnosis of osteoporosis in Belgian young women when using US reference range T-scores, both at the total hip region and at the lumbar spine.

The primary objective of our analysis was to provide a uniform basis for the reimbursement of osteoporosis treatments in Belgium. BMD values obtained before and after standardization in Belgian and US women do not differ significantly from each other either statistically or clinically. There is no clinical relevance in the small changes observed. In women with DXA-documented osteoporosis, antiresorptive agents such as alendronate [17], raloxifene [18], risedronate [19] and salmon calcitonin [20] have been demonstrated to reduce fracture risk. In a number of countries, including Belgium, a T-score below −2.5, which is the WHO operational definition of osteoporosis [21], is one of the key criteria for reimbursement. However, thresholds for reimbursement—as defined in our study—may or may not indicate an absolute need for treatment in individual patients. The indication for therapy should be modulated by clinical factors [22]. Although there is a strong association between BMD and the likelihood of fracture [23], other factors may influence fracture risk as well. For a proportion of women who are labeled as osteoporotic, the risk of a fracture during their remaining lifetime could theoretically be sufficiently low that treatment would not be appropriate. Conversely, many women who do not reach the threshold of "osteoporosis" according to the WHO definition might have other risk factors and circumstances that would justify treatment. This is always the case in any pathologic condition, in which the risk of complications is never an all-or-none phenomenon. Whatever the pertinence of this discussion, the fact remains that the strongest association between bone fragility and the clinical and operational diagnosis of osteoporosis rests on bone mass measurement.

Clearly, our objective to harmonize patient assessment and drug reimbursement in Belgium will fail if strict quality control procedures are not observed at densitometry sites. Such procedures are crucial to the generation of accurate, precise and comparable bone density data. Central quality control with circulating phantoms would help to determine the validity of the data in individual centers.

Our analysis has a number of limitations. As indicated, we acknowledge that fracture risk depends on life expectancy and other factors, as well as bone density. There is no absolute *T*-score value that necessarily leads to fracture and therefore to the absolute need for treatment. Information about a woman's BMD must be combined with other risk factors, as well as with information about the effectiveness, inconvenience, side effects, risks and costs of the treatment considered [22]. Moreover, the data presented are cross-sectional and deal with peak BMD in a young healthy population. Extrapolation of these findings to longitudinal models of bone loss with advancing age should always be appreciated with caution [16]. Finally, there is still the possibility that results for any individual patient may differ substantially from the collective because the standardized thresholds reported are based on an average study population [4]. The question of what constitutes the true normal population remains. As for the NHANES III values, the currently defined BBC values for the female young normal mean and standard deviation for DXA systems are based on measurements in a relatively small number of women in the young normal range. To expect a sample of several hundred women to accurately represent the young normal BMD and standard deviation of the population as a whole may be unreasonable [13].

We conclude that it is important that different segments of the community are given the same message concerning the prevalence, incidence and epidemiology of osteoporosis. There is thus a strong case for standardization. The data presented here provide the first attempt to implement a nationwide, uniform expression of BMD in patients, in order to harmonize drug reimbursement.

Acknowledgements The authors are grateful for logistic support from Hologic Inc., Lunar Corporation and Norland Corporation and to Drs. Bersou, Blockeel, Boutsen, Casaer, Coolen, Crombez, De Boeck, de Buisseret, Delval, Dorny, Dumont, Dwelshauwer, Gaudissart, Geusens, Goethals, Gomez, Grégoire, Hendrickx, Jacques, Lamberigts, Lenaeerts, Louis, Mertens, Milet, Pornel, Raeman, Remans, Temmerman, Troch, Vancleynenbreugel, Van Laere, Van Meerbeek, Van Wanghe and Verbeek for recruiting and assessing subjects. S.B. is senior clinical investigator of the Fund for Scientific Research—Flanders, Belgium (FWO—Vlaanderen).

Appendixes

Appendix A: The executive board of the Belgian Bone Club

The executive board of the Belgian Bone Club consists of the following investigators: Jean-Jacques Body, MD, PhD (Université Libre de Bruxelles), Steven Boonen, MD, PhD (Katholieke Universiteit Leuven), Marc E. De Broe, MD, PhD (University of Antwerpen), Jean-Pierre Devogelaer, MD (Université catholique de Louvain), Jean-Marc Kaufman, MD, PhD (Rijks Universiteit Gent), Jean-Yves Reginster, MD, PhD (Université d'Etat de Liège), Jan Remans (Genk) and Serge Rosenberg, MD, PhD (Université Libre de Bruxelles).

Appendix B: Various formulas used to standardize the BMD values

Lumbar spine sBMD (mg/cm^2)

– *Genant et al.* [4]

Hologic: LS BMD=$(1.0755\times BMD_H)\times 1000$

Lunar: LS BMD=$(0.9522\times BMD_L)\times 1000$

Norland: LS BMD=$(1.0761\times BMD_N)\times 1000$

– *Hui et al.* [5]

Hologie: LS BMD=$[1.0550\ (BMD_H-0.972)+1.0436]\times 1000$

Lunar: LS BMD=$[0.9683\ (BMD_L-1.100)+1.0436]\times 1000$

Norland: LS BMD=$[0.9743\ (BMD_N-0.969)+1.0436]\times 1000$

Total hip sBMD (mg/cm^2)

– *Hanson et al.* [6]

Hologic: TH sBMD=$1.008\times BMD_H+6$

Lunar: TH sBMD=$979\times BMD_L-31$

Norland: TH sBMD=$1012\times BMD_N)+26$

– *Lu et al.* [7]

Hologic: TH sBMD=$[(0.006+1.008)\times BMD_H]\times 1000$

Lunar: TH sBMD=$[(-0.031+0.979)\times BMD_L]\times 1000$

Norland: TH sBMD=$[(0.026+1.012)\times BMD_N]\times 1000$

Femoral neck sBMD (mg/cm^2)

– *Lu et al.* [7]

Hologic: FN sBMD=$[(0.019+1.087)\times BMD_H]\times 1000$

Lunar: FN sBMD=$[(-0.023+0.939)\times BMD_L]\times 1000$

Norland: FN sBMD=$[(0.006+0.985)\times BMD_N]\times 1000$

– *Simmons et al.* [8]

Hologic: FN sBMD=$[(1.031\times BMD_H)+0.058]\times 1000$

Lunar: FN sBMD=$[(0.961\times BMD_L)-0.037]\times 1000$

Norland: FN sBMD=$BMD_N\times 1000$

References

1. Looker AC, Wahner HW, Dunn WI, et al. Proximal femur bone mineral levels of US adults. Osteoporos Int 1995;5:389–409.
2. Looker AC, Wahner HW, Dunn WL, Calvo MS, Harris TB, Heyse SP, et al. Updated data on proximal femur bone mineral levels of US adults. Osteoporos Int 1998;8:468–489.
3. Kanis JA, Glüer C-C for the Committee of Scientific Advisors, International Osteoporosis Foundation. An update on the diagnosis and assessment of osteoporosis with densitometry. Osteoporos Int 2000;11:192–202.

4. Genant HK, Grampp S, Glüer CC, Faulkner KG, Jergas M, Engelke K, et al. Universal standardization for dual X-ray absorptiometry: patient and phantom cross-calibration results. J Bone Miner Res 1994;9:1503–1514.
5. Hui SL, Gao S, Zhou X-H, Johnston CC, Lu Y, Glüer CC, et al. Universal standardization of bone density measurements: A method with optimal properties for calibration among several instruments. J Bone Miner Res 1997;12:1463–1470.
6. Hanson J. Standardization of femur BMD. J Bone Miner Res 1997;12:1316–1417.
7. Lu Y, Fuerst T, Hui S, Genant HK. Standardization of bone mineral density at femoral neck, trochanter and Ward's triangle. Osteoporos Int 2001;12:438–444.
8. Simmons A, Simpson DE, O'Doherty MJ, Barrington S, Coakley AJ. The effects of standardization and reference values on patient classification for spine and femur dual-energy X-ray absorptiometry. Osteoporos Int 1997;7:200–206.
9. Löfman O, Larsson L, Toss G. Bone mineral density in diagnosis of osteoporosis. J Clin Densitom 2000;3:177–186.
10. Simmons A, Simpson DE, O'Doherty MJ, Barrington S, Coakley AJ. The effects of standardization and reference values on patient classification for spine and femur dual-energy X-ray absorptiometry. Osteoporos Int 1997;7:200–206.
11. Pocock NA, Sambrook PN, Nguyen T, Kelly P, Freund J, Eisman JA. Assessment of spinal and femoral bone density by dual X-ray absorptiometry: comparison of Lunar and Hologic instruments. J Bone Miner Res 1992;7:1081–1084.
12. Laskey MA, Crisp AJ, Cole TJ, Compston JE. Comparison of the effect of different reference data on Lunar DPX and Hologic QDR-1000 dual-energy X-ray absorptiometers. Br J Radiol 1992;65:1124–1129.
13. Faulkner KG, Roberts LA, McClung MR. Discrepancies in normative data between Lunar and Hologic DXA systems. Osteoporos Int 1996;6:432–436.
14. Valimaki MJ, Karkkainen M, Lamberg-Allardt C, et al. Exercise, smoking and calcium intake during adolescence and early adulthood as determinants of peak bone mass. BMJ 1994;309:230–235.
15. Ahmed AIH, Blake GM, Rymer JM, Fogelman I. Screening for osteopenia and osteoporosis: do the accepted normal ranges lead to overdiagnosis? Osteoporos Int 1997;7:432–438.
16. Gürlek A, Bayraktar M, Ariyürek M. Inappropriate reference range for peak bone mineral density in dual-energy x-ray absorptiometry: implications for the interpretation of T-scores. Osteoporos Int 2000;11: 809–813.
17. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures. Results from the Fracture Intervention Trial (FIT). JAMA 1998;280:2077–2082.
18. Ettinger B, Black D, Mitlack B, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene. Results from a 3-year randomized clinical trial. JAMA 1999;282:637–645.
19. Reginster J-Y, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Osteoporos Int 2000;11:83–91.
20. Chesnut CH, Silverman S, Andriano K, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the Prevent Recurrrence of Osteoporotic Fractures (PROOF) Study. Am J Med 2000;109:267–276.
21. WHO. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Geneva: WHO, 1994.
22. Eddy DM, Johnston CC, Cummings SR, Dawson-Hughes B, Lindsay R, Melton LJ, et al. Osteoporosis: review of the evidence for prevention, diagnosis, and treatment and cost-effectiveness analysis. Osteoporos Int 1998;8 (Suppl. 4):S1–88.
23. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 1996;312:1254–1259.