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Original Article

Site-Specific Variation in the Classification of Osteoporosis, and the Diagnostic Reclassification Using the Lowest Individual Lumbar Vertebra *T*-score Compared with the L1–L4 Mean, in Early Postmenopausal Women

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Abstract. In this study we report first the concordance and variation in diagnostic osteoporosis classification using multiple skeletal site measurements compared with the lumbar spine only; and secondly, at the lumbar spine, the variation and diagnostic osteoporosis reclassification using the lowest individual vertebra *T*-score compared with the L1–L4 mean *T*-score. One hundred and fifty early postmenopausal women were evaluated as part of the recruitment for a multicenter osteoporosis prevention study. Bone mineral density (BMD) was restricted such that no more than 10% of the subjects had a lumbar spine BMD below 0.8 g/cm^2. Forty-seven per cent of the subjects were classified as having low bone mass (*T*-score $\leqslant -1.0$) at the lumbar spine, 63% at the mid-forearm, 39% at the distal forearm and 50% at the hip ($p<0.05$). The greatest proportion of subjects were categorized as osteoporotic at the lumbar spine, followed by the forearm and then the hip. Correlation between sites ranged from 0.57 to 0.60 ($p<0.01$). Eighty-one percent of the subjects had a significant difference between their highest and lowest individual lumbar vertebra *T*-score (defined as a difference outside the 90% confidence interval coefficient of variation *T*-score value). Using the lowest individual lumbar *T*-score, recategorized 33% of the subjects classified as osteopenic (based on the mean L1–L4 *T*-score) as osteoporotic, and 23% of those classified as normal as osteopenic ($p<0.05$). Of all four vertebrae, L2 had the highest *T*-score in 37.7% of the subjects (mean -0.3) and L4 the lowest in 61% (mean -1.5) (mean difference 1.2 units, 95% CI 0.7 to 1.7). The classification of osteoporosis varies according to skeletal site, with pronounced differences in the early menopausal population. *T*-scores are useful for characterizing subjects with the highest risk of osteoporosis but BMD and fracture risk must be recognized in a continuum. Individual *T*-scores of the lumbar vertebrae show wide variation in the absence of degenerative spinal disease or vertebral collapse and the use of the lowest, significantly different, individual lumbar vertebra *T*-score reclassified over half of the subjects in this study. This poses a great therapeutic dilemma in clinical practice, particularly if these fractures are at higher risk of future collapse.

Keywords: Osteoporosis classification; Postmenopausal women; Skeletal sites; *T*-score

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Introduction

In 1994 the World Health Organization (WHO) established reference criteria for the diagnosis of osteoporosis in adult women. A value of bone mineral density (BMD) or bone mineral content (BMC) above -1 standard deviation (SD) of the young adult mean

was defined as normal, between −1 and −2.5 SD as low bone mass or osteopenia, and below −2.5 SD as osteoporosis, which in the presence of one or more fragility fractures was classified as established osteoporosis. However, the report did not specify which site should be measured, although it acknowledged that measurements at the wrist would capture some but not all patients with osteoporosis while multiple-site measurements would increase the apparent prevalence of the disease [1].

Measurements of the skeleton at one site correlate with measurements made at other skeletal sites, correlation coefficients ranging from 0.5 to 0.8 [2,3]. The correlations are closer in the young healthy population than in patients with significant bone loss. This is due to variations in the rates of bone loss at different sites related to aging and accentuated at the time of the menopause [4]. However, non-concordance between sites has been reported in up to 50% of subjects [5].

In relation to the risk of fracture, a number of long-term prospective studies have shown that peripheral measurements can predict the risk of hip and spine fractures [6,7]; however, they cannot assess the risk of, for example, hip fracture as well as a measurement made at the hip itself [8]. Consequently, measurements of the hip are better predictors of the risk of hip fracture than measurements at any other skeletal site [9]. Discussions, however, continue regarding the validity of multiple-site measurements or single-site age-related measurements for predicting fracture risk at the various skeletal sites [10].

Vertebral deformities of the spine are a direct consequence of the biomechanical pattern of loading on the skeleton [11]. Hospital and population-based surveys concur that deformities occur most frequently at the mid-thoracic region (T7–T9) and the thoracolumbar junction (T12–L2), which are the most biomechanically compromised regions of the vertebral column [12]. Lumbar spine dual-energy X-ray absorptiometry (DXA) includes the L1–L4 vertebrae, of which fractures most commonly involve L1, followed by L4, L2 and then L3 [13]. No studies have examined the relationship between the BMD of these individual vertebrae and the risk of subsequent fracture, and furthermore whether, there is any preceding variation in the *T*-score of individual vertebrae which may thus predispose them to higher fracture risk, and may possibly be masked by the use of the mean L1–L4 *T*-score.

The aims of this study were firstly to examine, in early postmenopausal women, the relationship between lumbar spine BMD *T*-score and the *T*-score of other skeletal sites in the classification of osteoporosis; secondly, to explore the variation in the individual lumbar vertebral BMD *T*-score; and, thirdly, to examine the effect of using the lowest individual lumbar vertebral BMD *T*-score compared with the mean of L1–L4 in reclassifying subjects with osteoporosis.

Subjects and Methods

Subjects

One hundred and fifty early postmenopausal women (aged 45–60 years) were evaluated as part of an international, multicenter, double-masked, randomized, placebo-controlled osteoporosis prevention study. Women were recruited by direct mailings, advertisements in the media or by telephone. Cohorts were derived using primary care deprivation ratings and included both urban and city populations. Women were at least 6 months postmenopausal, had a serum follicle stimulating hormone level above the upper third of the postmenopausal reference range and were in good general health as judged by medical history, physical examination and routine laboratory screening tests.

Subjects were excluded from the study if they had a past or present history of malignancy, a history of disease or treatment affecting bone metabolism, estrogen or progesterone therapy within 3 months of screening, prior bisphosphonate or fluoride therapy, and a body weight outside ±30% ideal weight. Enrolment was restricted so that no more than 10% of the subjects had a lumbar spine BMD of below 0.8 g/cm^2, in order to ensure that the majority of participants were not osteoporotic (as part of the multicenter study protocol).

Radiographs

Standardized anteroposterior and lateral thoracolumbar spine radiographs were performed in all subjects. For the anteroposterior film, patients were positioned supine, parallel to the longitudinal axis of the X-ray table. Alignment was checked by sighting at the head of the table, looking down to the patient's feet. Part positioning for the thoracic spine film included T2–T12 in the image, with the central ray positioned to the level of the seventh thoracic vertebra, and for the lumbar spine T12–S1, with the central ray to the level of the third lumbar vertebra. Collimation was adjusted direct to the spine to exclude unnecessary anatomy, and the images taken with patients held in fixed expiration. Care was taken to ensure T12 images were excluded on both the lumbar and thoracic images.

Similar techniques were performed for lateral image acquisition, with patients positioned in the left lateral position with the legs flexed for comfort and support. Both arms were placed at right angles to the anterior surface of the body and the elbows flexed for comfort. Supports were placed between the knees, ankles and under the knees to maintain the lateral position. Patient alignment was adjusted to ensure the mid-axillary plane of the body was in line with the middle of the table and that there was vertical superimposition of the shoulder and hips. All radiographs were performed by the same two radiographers to limit interobserver variability.

Films were graded independently by an experienced radiologist and a trained observer, masked to the BMD

value, for the presence of vertebral deformity, osteophytosis, end plate sclerosis and aortic calcification in the region L1–L4. Vertebrae were graded, using a visual semiquantitative technique on inspection of the lateral lumbar films, as: normal (grade 0), mildly deformed (grade 1; approximately 20–25% reduction in anterior, middle and or posterior height and reduction in area of 10%), moderately deformed (grade 2; approximately 25–40% reduction in any height and reduction in area of 20–40%) or severely deformed (grade 3; approximately 40% reduction in any height and area) [14]. No direct vertebral morphometric measurements were performed. Vertebral fractures were defined as deformities of grade 1 or greater and, where present, excluded that subject from the study.

Osteophytes were graded according to the classification by Orwoll et al. [15] as severe (grade 3; large osteophytes at three or four interspaces), moderate (grade 2; large osteophytes at one or two vertebral interspaces), mild (grade 1; small osteophytes at one or two vertebral interspaces) or none. End plate sclerosis was recorded as present (grade 3, involving 50% of the vertebrae; grade 2, involving 20–50% of the vertebrae, grade 1, intermediate between grade 2 and absence) or absent. Aortic calcification was recorded as being present (punctate or dense) or absent.

The intra-observer kappa statistic for vertebral sclerosis was 0.89 and the inter-observer kappa value 0.75. There were no subjects with vertebral deformities. Osteophytes and aortic calcification occurred too infrequently for the kappa statistic to be calculated.

Bone Mineral Density

BMD of the lumbar spine (L1–L4 mean, and individual values of L1, L2, L3 and L4), total hip, ultradistal forearm (UD forearm) and mid-forearm were measured by DXA (Hologic QDR 2000, Waltham, MA). Positioning of patients during absorptiometry and data analysis were standardized as were machine calibration and technician training.

The short-term coefficient of variation within subjects at the various skeletal sites, shown in Table 1, was calculated from two repeated measurements with repositioning, using the formula

$$\mathrm{CV}\% = \frac{\sqrt{\frac{\sum (a-b)^2 \times 100}{2n}}}{(\bar{a} + \bar{b})/2}$$

where a is a first measurement, b a second measurement, n = 490 subjects, and $\bar{a} + \bar{b}$ are mean values.

Table 1. Short-term coefficient of variation at the various skeletal sites

	Lumbar spine L1–L4	Total hip	Ultradistal forearm	Mid-forearm	Lumbar Spine			
					L1	L2	L3	L4
CV (%)	1.48	0.99	1.82	1.07	2.80	2.20	2.20	2.40

Table 2. Coefficient of variation for the L1–L4 mean and individual L1, L2, L3 and L4 vertebrae expressed in *T*-score units

	L1–L4 mean	L1	L2	L3	L4
CV (*T*-score units)	0.11	0.30	0.28	0.29	0.30

The CV for each individual lumbar vertebra was then expressed in *T*-score units. This was calculated by dividing the absolute SD in grams per square centimeter for each lumbar vertebra by the SD of the young normal range population (0.11 g/cm^2; derived from the user's manual, Hologic, MA, USA). This is shown in Table 2. Significant changes in *T*-score units were taken at the 90% confidence limit ($\pm$ 2 $\times$ CV). A similar method was used to calculate the CV expressed in *T*-score units for the L1–L4 mean. Thus, for example, it is possible to measure the BMD of L1 with a reproducibility of $\pm$0.3 *T*-score units. Differences between the CV in *T*-score units greater than 0.6 were considered significantly different (2 $\times$ the highest individual CV, i.e., either L1 or L4 in the case of this study).

The study protocol was approved by the Nottingham City Hospital Ethics Committee and all patients gave formal written consent.

Statistical Analysis

Analysis was performed using SPSS for Windows 8.0 software (SPSS, Chicago, IL). Results are presented as the mean $\pm$ SD. Groups were compared using one-way ANOVA (p<0.05) and Pearson's correlation coefficient calculated to the p<0.01 value.

Results

Patient characteristics are shown in Table 3. The mean (SD) age of the subjects was 54.5 $\pm$ 2.1 years (range 48–59 years), height 1.61 $\pm$ 0.06 m and weight 65.1 $\pm$ 10.1 kg. All 150 subjects had undergone a spontaneous menopause, but in 24 this had occurred before the age of 45 years (mean 40.4 $\pm$ 3.8 years) and 8 subjects had a body mass index (BMI) in the lower part of the normal range, mean BMI 18.9 $\pm$ 1.1 kg/m^2

Table 3. Patient characteristics

Characteristic	Mean (SD)
Age (years)	54.5 (2.1)
Age at menarche (years)	13.2 (2.7)
Age at menopause (years)	47.8 (4.9)
Years since menopause	4.5 (3.0)
Body mass index (kg/m^2)	25.1 (3.6)

Table 4. Bone mineral density at the various skeletal sites for the study population and (in square brackets) a normal population aged 55 years derived from the Hologic Reference Database

Skeletal site	BMD (g/cm^2)
Lumbar spine L1–L4	0.95 (0.13) [0.93 (0.11)]
Total hip	0.86 (0.11) [0.88 (0.12)]
Trochanter	0.66 (0.10) [0.65 (0.10)]
Femoral neck	0.74 (0.11) [0.75 (0.12)]
Distal radius and ulna	0.38 (0.05) [0.36 (0.07)]
Mid-radius and ulna	0.53 (0.05) [0.54 0.06)]

Values are mean (SD).

BMD at the various skeletal sites is shown in Table 4. The mean normal population BMD is shown in square brackets. There was no significant difference between our population BMD and that of the normal population.

The classification of osteoporosis, osteopenia and normal bone mass at the various skeletal sites is shown in Fig. 1. Forty-seven percent of the subjects were classified as having low bone mass ($T < -1.0$) at the lumbar spine, 63% at the mid-forearm, 39% at the UD forearm and 50% at the total hip ($p<0.05$).

The greatest proportion of subjects were classified as osteoporotic at the lumbar spine, followed by the forearm and then the hip. Within the same 12 subjects classified as osteoporotic at the spine, 3 were also osteoporotic at the total hip (8 osteopenic, 1 normal), 3

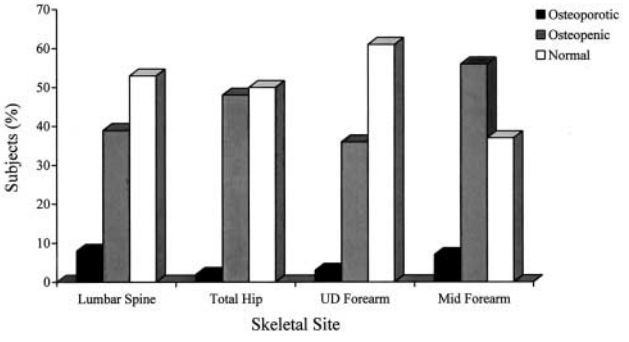

Fig. 1. Classification of osteoporosis according to skeletal site.

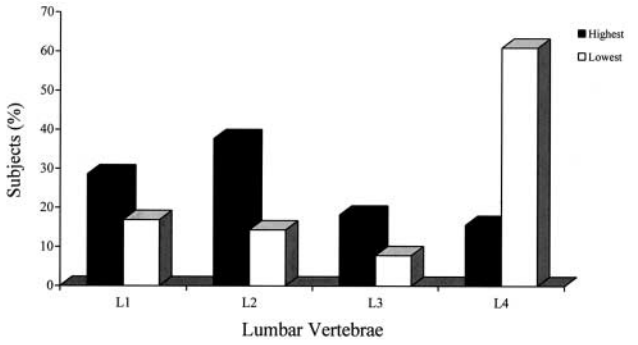

Fig. 2. Distribution of lumbar vertebrae with the highest and lowest *T*-scores (mean difference $\geqslant 0.6$ *T*-score units between each vertebra).

osteoporotic at the UD forearm (6 osteopenic, 3 normal) and 5 osteoporotic at the mid-forearm (5 osteopenic, 2 normal). Only 5 of the 150 patients had a *T*-score of equal to or less than -2.5 at all skeletal sites. The correlation between the lumbar spine and various skeletal sites were: total hip 0.59, UD forearm 0.57 and mid-forearm 0.60 ($p<0.01$).

At the lumbar spine 81% of the subjects had a *T*-score unit difference of more than 0.6 between their highest and lowest individual vertebrae. In this group, the L1–L4 mean *T*-score categorized 9% of the subjects as osteoporotic, 43% as osteopenic and 48% as normal. Using the lowest, significantly different, individual vertebral *T*-score, reclassified 33% of the osteopenic subjects as osteoporotic, and 23% of the normal subjects as osteopenic. This reclassified overall 23% of the study group as osteoporotic, 40% as osteopenic and 37% as normal.

The distribution of the vertebrae with the highest and lowest *T*-scores is shown in Fig. 2. Of all four vertebra, L2 had the highest *T*-score in 37.7% of the subjects, (mean -0.3) and L4 lowest in 61% (mean -1.5) (mean difference 1.2 units, 95% CI 0.7 to 1.7). Six percent of the subjects were found to have mild osteophytosis (grade 1) with the remainder being normal; 9% of the subjects had end plate sclerosis (grade1), 2.2% had minimal aortic calcification and there were no prevalent vertebral fractures.

Discussion

This study demonstrates that the classification of osteoporosis in early postmenopausal women is dependent on the site of BMD measurement. The prevalence of low bone mass varied from 39% when classified at the distal forearm, to 50% when classified at the total hip. The greatest proportion of subjects were categorized as osteoporotic at the lumbar spine, followed by the forearm and then the hip.

These results are consistent with previous studies [16–18], but in contrast to the study by Feyerabend et al. [5], who reported a non-concordance rate in the region of 50%. Rates of bone loss vary according to skeletal site

and are related to aging, but accelerated at the time of the menopause [4]. The effects of the menopause peak within the first 4–8 years and have a predilection for trabecular bone [19,20]. All the subjects in this study were within the early menopause, in which the effects of estrogen deficiency may not have had the time to express their maximal detrimental skeletal effects. Similarly, the study population was of a young age group and thus the long-term effects of aging may have had little impact. As with other studies we observed a modest correlation between BMD at the lumbar spine and other skeletal sites [2,3].

The ideal BMD measurement site would be the one that gave the greatest gradient in fracture risk and lowest risk of diagnostic misclassification, in addition to accuracy and precision. Unfortunately no ideal site exists and discussions continue around the diagnostic validity of a single measurement in contrast to multiple sites for the assessment of fracture risk. In the elderly, this problem is partly resolved in that hip fractures are the most serious consequence of osteoporosis, in relation to both patient morbidity and health-economic burden. Measurements at the hip predict hip fracture better than measurement at any other skeletal site and, furthermore, measurements at the spine may not accurately reflect skeletal integrity because aortic, sclerotic and osteophytic calcification may falsely elevate BMD [14,21]. However, many women are referred for BMD assessment in the early years after the menopause, in order to make informed decisions about hormone replacement therapy. Since bone loss is more prominent in this age population at trabecular sites, it seems sensible to opt for a spinal or distal forearm measurement. Further long-term follow-up studies in this age group are necessary to assess the validity of multiple-site in relation to single-site measurements for prediction of fracture risk, particularly with respect to vertebral and distal forearm fractures.

Site-specific assessment is further complicated when the BMD cutoff that defines osteoporosis is examined more closely. The *T*-score value that identifies most osteoporotic patients with high sensitivity and specificity has been controversial for many years and it is well recognized that considerable overlap exists between subjects using the WHO definition, accentuated by variations in the precision and accuracy of the various measurement sites. Furthermore, it is now established that a gradient of fracture risk exists with decreasing BMD [22,23] and for every 1 SD decrease in BMD, there is a 1.5- to 2-fold increase in fracture risk [24,25].

At the lumbar spine, this is accentuated further by the variation in the individual vertebra *T*-scores, as demonstrated in this study. It is recognized that the precision error in measuring one vertebra is much greater than measuring the L1–L4 mean, although 81% of the subjects were still found to have a *T*-score unit difference between the highest and lowest lumbar vertebra outside the 90% confidence interval. Using the lowest individual vertebral *T*-score reclassified over half the study subjects as osteoporotic. Posterior facet joint degeneration, osteophytes or the presence of vertebral collapse may falsely elevate BMD in an older population but such changes are not common in a younger population as shown here. This poses a real therapeutic problem in clinical practice where, in the absence of spinal disease or vertebral collapse, one or two vertebrae may have a low *T*-score that is masked by the mean L1–L4 *T*-score which classifies the patient as being within the normal range, even though they are at higher risk of fracture.

L4 had the lowest *T*-score of all four vertebrae in 61% of the subjects, followed by L1, L3 then L2. Assuming equal loading forces on the lumbar spine, it may be perceived that this vertebra is at higher risk of fracture. Davies et al. [13] showed at the lumbar spine a higher prevalence of L1 fractures, followed by L4, L3 and then L2. It is known that vertebral bodies are primarily subjected to compressive forces, with superimposed bending in the sagittal plane and torsion about the vertical plane. About half this compressive load in the upright position results from the tension in the muscles and ligaments required to maintain the erect posture, with the other half from body weight. This load is markedly increased during routine activities, while stooping to lift a load produces strains in the lumbar vertebra up to 10 times the load lifted, most prominent at L1. This may explain the differences in the distribution of vertebrae with the lowest *T*-scores and the subsequent distribution of fractures. It may therefore be perceived that an L1 vertebrae with a low BMD may be at much greater risk of fracture in comparison to an equivalent lumbar vertebra of the same *T*-score.

Limitations in this study are, however, recognized. Enrolment was restricted such that not more than 10% of the subjects had a lumbar spine BMD of less than 0.8 g/cm^2. The prevalence of osteoporosis will thus be much lower than in the normal population. Nevertheless, the study conclusively demonstrates the variability in lumbar spine *T*-scores. Furthermore, subjects were recruited by direct mailings, advertisements in the media or by telephone, and although cohorts were derived using primary care deprivation ratings and including both urban and city populations, some selection bias is recognized.

In summary, bone densitometry can be used to identify the individual ‘at risk’; however, it needs to be recognized that osteoporosis is not a densitometry diagnosis but a disease, namely the presence or history of a low-trauma fracture. In a sense this is an artificial problem created by the fact that a respected body, the WHO, declared that a *T*-score below -2.5 is tantamount to a diagnosis of osteoporosis. The difficulty remains as to which *T*-score to use, compounded by the fact that the risk of fracture is related to BMD in a continuum rather than a specific cutoff value. The cutoff one uses is thus essentially artificial; nevertheless the WHO criteria have been widely accepted and are useful, in particular at sites where measurements have been shown to predict solid fractures, namely the spine and total hip.

Fracture prediction from other sites that can be measured may never be available; however, with respect to the lumbar vertebrae there is wide variation in the *T*-score between individual vertebrae. Further long-term follow-up studies are necessary to determine whether vertebrae with a lower score are at higher risk of subsequent fracture.

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