Vertebral Morphometry: Repeat Scan Precision Using the Lunar Expert-XL and the Hologic 4500A. A Study for the ‘WISDOM’ RCT of Hormone Replacement Therapy

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Abstract. On radiation safety grounds there is concern about the morbidity attributable to routine radiographs of the spine for the identification of new fractures in large-scale trials of fracture prevention. However, the role of the potentially safer low-radiation-dose technique of vertebral morphometry performed by third generation dual-energy X-ray absorptiometry equipment requires evaluation for use in clinical trials. We have therefore investigated the short-term inter-scan imprecision as well as the imprecision attributable to different-day analyses by the same operator and differences in analyses by different operators. The volunteer subjects were participants in a pilot study for a randomized controlled trial of hormone replacement therapy (Women’s International Study of long Duration Oestrogen after Menopause, WISDOM). Each subject had two morphometric X-ray analysis scans separated by 2–4 weeks. Exclusions were women with densitometrically defined osteoporosis, as defined by the WHO criterion, and women with a body mass index exceeding 30.9 kg/m². On average, the women were 58.7 years of age and had bone mineral density values in the lumbar spine which were about 0.7 SD units higher than a reference US female age-matched population. Scans were assessed from vertebrae T7 through L4. In the study there were no clinically significant differences in performance between the Hologic QDR 4500A and the Lunar Expert XL equipment. Between-scan imprecision was significantly worse than imprecision attributable to reanalysis of the same scan by a different operator or the same operator after an interval. Vertebral level had an effect on measurement uncertainty, especially at the level of the diaphragm and at T7. Coefficients of variation, expressed as percentages of mean values, were better for absolute height measurements than for height ratios, ranging from 1.75% to 3.40% for the three heights measured on three separate machines and from 2.34% to 4.11% for the two height ratios. These results compared favorably with the equivalent figures from a parallel study of morphometry precision undertaken using standard lateral radiographs of the thoracic and lumbar spine (3.1–3.6% and 3.8–3.9%, respectively). We conclude that in trials of prevention therapy in women (or men) selected for not having osteoporosis, low-dose vertebral morphometry using the Hologic 4500A, the Lunar Expert XL or similar equipment is preferable on safety grounds to the classical technique based on standard radiographs, although conventional radiology may still be required in those with prevalent or incident deformities to exclude causes other than osteoporosis. The place of this low-dose technique in trials performed on patients with osteoporosis requires further study.

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Introduction

Vertebral fractures are associated with a high morbidity [1] and are a strong independent risk factor for subsequent fracture [2,3]. Accurate identification of prevalent and incident vertebral fractures is of central importance in epidemiologic studies and in the assessment of interventions for osteoporosis, but definition of vertebral fracture has proved problematic [4,5]. Qualitative assessment of vertebral deformities is inaccurate because of significant inter- and intra-individual variations in vertebral dimensions, and in recent years a number of morphometric approaches have been devised in which individual vertebral heights in the lumbar and thoracic spine are compared with vertebra-specific data from a reference population [5–7].

Traditionally, vertebral morphometry has been applied to lateral radiographs of the spine obtained using conventional radiography; however, this approach has several disadvantages, including the high radiation dose involved [8] and distortion and magnification of the image. The recent development of dual-energy X-ray absorptiometers which employ a fan-beam system has provided a means by which images of the spine of adequate quality can be produced at much lower radiation doses [9,10]; in addition, distortion and magnification of the image can be eliminated by means of a centerline scan which enables a constant distance to be maintained between the X-ray tube and the spine during the scan.

The feasibility of this approach, known as morphometric X-ray analysis (MXA), is now well established but there are few published data on the reproducibility of measurements. This is particularly important in determining the suitability of the method for clinical trials and is also required for calculation of the sample size necessary to demonstrate significant treatment effects on vertebral fracture. In this study we have examined the reproducibility of vertebral height measurements obtained by MXA in healthy postmenopausal women participating in a trial of hormone replacement therapy using the Hologic QDR 4500 and the Lunar Expert-XL dual-energy X-ray absorptiometers. We have compared the precision values obtained with those reported for conventional X-ray morphometry.

Materials and Methods

Subjects

The subjects were participants in the feasibility studies for a long-term randomized controlled trial of hormone replacement therapy – ‘WISDOM’ (Women’s International Study of long Duration Oestrogen after Menopause) – and had been recruited for the trial through general practices in the Medical Research Council General Practice Research Framework. One hundred and eighty-five women (mean age 58.7 years, range 46–68 years) from general practices close to one of three British scanning centers: Solihull (center 1); Addenbrooke’s Hospital, Cambridge (center 2); and Guys and St Thomas’s Hospitals, London (center 3) were approached. The ethics review committees at all three centers approved the study prior to starting. Women with a body mass index (BMI: weight in kg/height in meters²) greater than 30.9 or with clinical evidence of spinal scoliosis were excluded. All participants gave informed written consent before inclusion in the study. At the first visit each woman had an anteroposterior spine bone mineral density (BMD L1–L4) and a vertebral morphometry (MXA) measurement. After a 2- to 4-week interval the MXA measurement was repeated. The BMD measurements were analyzed and reported locally. Women with a BMD more than 2.5 SD below the young US adult mean were referred to their primary care physician.

Equipment

Two of the centers used a Hologic QDR4500A (Hologic, Waltham, MA). A centerline scan was done in turbo mode followed by a 14 min high-definition lateral scan (single and dual energy protocol). The subjects were instructed to exhale fully and then to breathe shallowly. The scans were analyzed using software version 8.17. The third center used a Lunar Expert-XL (Lunar, Madison, WI). A 37 s 5 mA fast lateral scan was performed in under 40 s. Subjects were asked to exhale fully and then hold their breath. The data was acquired using software version 1.63 and analysis was performed with v.1.64.

The MXA images were sent to Cambridge for centralized analysis. Both single-energy and dual-energy images were used in the analysis of the Hologic scans, depending on which gave the greater clarity in defining the vertebral body outlines. The Lunar scan images were dual energy and contrast was optimized to give the maximum gray levels for each scan. Further image enhancement was undertaken with the image analysis tools and filters before point placement. No ‘Compare’ facility was available with the Lunar software at the time this work was done.

Intra-operator Precision

The intra-operator precision was evaluated using the results from a single fully trained operator and based on the scans from Cambridge and Solihull. Vertebrae from T7 to L4 were analyzed three times by the operator, who each time remained masked to the previous analyses. The re-analyses were performed after intervals of approximately 22 days (center 2) and 76 days (center 1).