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A critical appraisal of vertebral fracture assessment in paediatrics☆

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ABSTRACT

Purpose: There is a need to improve our understanding of the clinical utility of vertebral fracture assessment (VFA) in paediatrics and this requires a thorough evaluation of its readability, reproducibility, and accuracy for identifying VF.
Methods: VFA was performed independently by two observers, in 165 children and adolescents with a median age of 13.4 years (range, 3.6, 18). In 20 of these subjects, VFA was compared to lateral vertebral morphometry assessment on lateral spine X-ray (LVM).
Results: 1528 (84%) of the vertebrae were adequately visualised by both observers for VFA. Interobserver agreement in vertebral readability was 94% (kappa, 0.73 [95% CI, 0.68, 0.73]). 93% of the non-readable vertebrae were located between T6 and T9. Interobserver agreement per-vertebra for the presence of VF was 99% (kappa, 0.85 [95% CI, 0.79, 0.91]). Interobserver agreement per-subject was 91% (kappa, 0.78 [95% CI, 0.66, 0.87]). Per-vertebra agreement between LVM and VFA was 95% (kappa 0.79 [95% CI, 0.62, 0.92]) and per-subject agreement was 95% (kappa, 0.88 [95% CI, 0.58, 1.0]). Accepting LVM as the gold standard, VFA had a positive predictive value (PPV) of 90% and a negative predictive value (NPV) of 95% in per-vertebra analysis and a PPV of 100% and NPV of 93% in per-subject analysis.
Conclusion: VFA reaches an excellent level of agreement between observers and a high level of accuracy in identifying VF in a paediatric population. The readability of vertebrae at the mid thoracic region is suboptimal and interpretation at this level should be exercised with caution.

1. Introduction

The finding of one or more vertebral fractures (VFs) is indicative of severe bone fragility irrespective of the reported bone mineral density (BMD) [1] and, in adults, is associated with a significant risk of further vertebral and non-vertebral fractures [2–4]. In recent times the high prevalence of VF has been recognised as an important clinical consequence not only in children and adolescents with primary bone disease [5] but also in those with secondary osteoporosis [6,7] and their importance as a sign of osteoporosis in this population has been highlighted by the International Society for Clinical Densitometry [1].

The majority of VFs are clinically silent and their prevalence may be much higher when active surveillance methods are employed [8–11]. However, the practice of identifying VF in the paediatric population is at an early stage, with a lack of consensus on methodology. Early identification of VF may not only be useful for identifying bone fragility but may also guide initiation of bone protective therapy especially since there is evidence for normalization of vertebral morphology [12,13]. The availability of a relatively non-invasive but reliable method for diagnosing VF would also be valuable for population-based epidemiological studies as well as longitudinal studies.

Vertebral fracture assessment (VFA) detects VF by the assessment of lateral spine images acquired by dual energy X-ray absorptiometry (DXA), thus reducing the radiation exposure [14]. In adults with osteoporosis, VFA is often considered to be comparable to spinal radiographs and is increasingly used for integrated assessment of BMD and VF status [15,16]. More recently, in children with osteogenesis imperfecta, VFA has been shown to be comparable to spinal radiographs in diagnosing VF [17]. As the assessment of vertebral morphometry enters into routine practice in children, there is a need to study the use of VFA in this population. The purpose of this study was to evaluate the clinical utility of VFA in paediatrics by investigating the readability, reproducibility, and accuracy of identifying VFs in a group of children and adolescents undergoing routine clinical assessment for osteoporosis.

2. Methods

2.1. Study population

The study cohort consisted of 165 children and adolescents (77 males, 88 females) who had a DXA BMD measurement at the Royal

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Hospital for Sick Children, Glasgow, as part of their clinical evaluation for suspected or previously diagnosed osteoporosis, between July 2013 and May 2014. Anthropometric measurements, height and calculated body mass index (BMI), were obtained on the day of the DXA visit, and converted to standard deviation scores (SDS) using 1990 UK standards [18,19].

2.2. Image acquisition and BMD measurement

Lateral images of the thoracic–lumbar spine were obtained following BMD measurement of the lumbar spine (LS, L2–L4) and total body (TB), using Lunar Prodigy (GE Medical Systems, Waukesha, Wis., USA). The subject was placed in the left lateral decubitus position with hips, knees and shoulders bent at 90°. As outlined in previous studies, reference data were used to calculate a predicted and a percentage predicted bone area for age and sex [20,21]. The reference data allowed for a comparison of the actual Bone Mineral Content (BMC) of the individual with the predicted BMC of a subject of the same sex and bone area from which the percentage predicted BMC (ppBMC), expressed as an SDS (BMC SDS) could be calculated. The percent coefficient of variation (%CV) of the device, calculated on repeated measurement of a phantom, is <1%. The individual %CV, calculated on repeated measurement of the lumbar spine in anteriorposterior view, in a group of 24 children, is <2.1%.

2.3. Vertebral fracture assessment by DXA

Lateral spine images were analyzed independently by two non-radiologist observers (AK, SS), who performed VFA in all 165 cases. Before commencing the VFA analysis, the observers defined a common protocol for point placement on each vertebral body. Each observer manually identified six landmarks corresponding, to the four corners and the midpoints of the endplates, respectively, of each adequately visualised vertebral body starting at L4 and continuing through the thoracic spine (TS) up to T6. From these points, the software measured the anterior, middle and posterior heights and calculated the anterior:posterior height ratio and the middle:posterior height ratio within a vertebral body. The observers also calculated the posterior:posterior height ratio when comparing vertebrae above or below the one under examination. The vertebral bodies were classified according to the extent of any height reduction as expressed by the reduction in height ratios using the scoring system developed by Genant: grade 0 (no fracture) if the reduction in any height ratio was ≤20%, grade 1 (mild VF) if a height ratio reduction was from 20% to 25%, grade 2 (moderate VF) if the decrement was 25% to 40%, and grade 3 (severe VF) if a height ratio reduction exceeded 40% [22].

2.4. Lateral vertebral morphometry (LVM) on lateral spine X-ray

Complete lateral imaging of the TS and LS using standard radiographic procedures was available in 20 subjects as part of their routine medical care. These 20 subjects, in whom a lateral spine X-ray was performed, had so on the basis of clinical symptomatology (12 subjects), or because of finding on clinical examination of the spine of tenderness (4 subjects) or suspected scoliosis (4 subjects). Only radiographs obtained within 2 months from the day the lateral spine DXA image was obtained were included. The images were assessed by one of the observers who performed the VFA but independently from the VFA, the reader being blinded to the individuals' identity, clinical characteristics, diagnosis, BMD results, and to the evaluation of the VFA. Lateral vertebral morphometry (LVM) was assessed on digitized images (Picture Archiving and Communication System (PACS), GE Systems, Milwalkee, Wis). The six landmarks were identified at the silhouette of each adequately visualised vertebral body from T6 through L4, corresponding to the four corners of the body and the midpoints of the endplates. The point-to-point distances were measured using a digital calliper for anterior, middle and posterior heights. Height ratios were calculated of each vertebral body and classified as normal or mild, moderate or severe VF as described earlier.

2.5. Statistics

Analyses were conducted using SPSS 20 (SPSS Inc, Chicago). Population characteristics are expressed as median (range) for continuous variables, whilst categorical variables are expressed as the value (percentage frequency). For continuous and categorical variables, comparison of groups was performed by Mann–Whitney test and Chi-square test or Fisher's exact test, respectively. Spearman's correlation coefficient was used to assess the association between variables. All tests were two-sided and $p < 0.05$ was considered significant.

Vertebral readability on VFA was evaluated by calculating the frequency of readable vertebrae by each observer and by both observers. The per-vertebra readability was determined for each vertebral level and for all vertebrae from T6 to L4. For the evaluation of readability at the subject level, good visibility by observers was defined as ≥10 out of 11 vertebrae from T6 to L4 adequately visible for the assessment of vertebral morphology. Agreement between observers utilising VFA was assessed for each readable vertebra (per-vertebra agreement) and for each subject (per-subject agreement). The per-vertebra agreement for the presence and for the grade of the VF was determined at each vertebral level and for all levels from T6 to L4 combined. The overall agreement, beyond that expected by chance alone between observers was expressed as a percentage of full agreement for the presence of a VF and for grade of the VF and as Cohen's kappa coefficient and associated 95% confidence intervals (CI). The criteria described by Landis and Koch [23] were used for qualitative interpretation of the agreement: almost perfect (kappa, 0.81–1.00), substantial (kappa, 0.61–0.80), moderate (kappa, 0.41–0.60), fair (kappa, 0.21–0.40), slight (kappa, 0.00–0.20) or poor (kappa, <0.00). The ability to detect vertebral fracture on lateral spinal images acquired by DXA in comparison to conventional radiographs was also evaluated by kappa statistics. The diagnostic value of VFA was assessed by calculating sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with conventional radiographs as the gold standard. Calculation of these parameters was performed using binomial logistic regression.

3. Results

3.1. Study population's characteristics

The median age of the 165 subjects at the time of the DXA image acquisition was 13.4 years (range, 3.6, 18), median height Z score was −0.25 (−5.6, 3.8), median BMI Z score was 0.06 (−4.6, 3.6), median TB BMC for bone area Z score was −0.1 (−1.3, 3.3) and median LS BMC for bone area Z score was −0.3 (−2.7, 1.6). Of this cohort of 165, 28 (17%) had been investigated for primary bone disease including osteogenesis imperfecta (n, 24), previous frequent fractures (n, 3) and bilateral femoral head osteonecrosis (n, 1). The remaining 137 (83%) children had a range of chronic diseases known to affect bone health including anorexia nervosa (n, 35), inflammatory bowel disease (n, 25), cystic fibrosis (n, 15), Duchenne's muscular dystrophy (n, 12), metabolic and liver disease (n, 11), autoimmune disorders (n, 9), endocrine abnormalities (n, 7), haematologic malignancies (n, 5) and other chronic conditions (n, 18).

3.2. Readability of DXA lateral spine images

Assuming a possible total of 1815 vertebrae, from T6 through to L4 (ie 11 vertebrae per subject) in 165 subjects, 1625 (90%) were adequately visualised by one observer, 1541 (85%) by the other observer and 1528 (84%) by both observers to permit assessment of morphology.