Prevalence of Vertebral Fractures in Children with Suspected Osteoporosis

Andreas Kyriakou[1], MD, Sheila Shepherd[1],PhD, Avril Mason[1], MBChB, S Faisal Ahmed[1], MBChB, MD, FRCPCH

Affiliations: [1] Developmental Endocrinology Research Group, School of Medicine, University of Glasgow, Royal Hospital for Children, 1345 Govan Road, Glasgow, G51 4TF, United Kingdom

Address correspondence to:

Professor S Faisal Ahmed, MBChB, MD, FRCPCH

Developmental Endocrinology Research Group

Royal Hospital for Children

1345 Govan Road, Glasgow, G51 4TF

Tel +44 141 451 5841

Fax +44 141 201 0837

faisal.ahmed@glasgow.ac.uk

Short title: Vertebral Fracture Assessment in Pediatrics

Abbreviations: VF – Vertebral fractures; VFA – Vertebral Fracture Assessment; BMD – Bone mineral density; BMC – Bone mineral content; DXA – Dual energy X-ray absorptiometry; BMI – body mass index; SDS – standard deviation score; LS – Lumbar spine; TB – total body; %CV – coefficient of variation; OR – odds ratio; VFI- Vertebral Fracture Index

Funding Source: No funding was secured for this study.

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

Conflict of Interest: The authors have no conflicts of interest to disclose.

Abstract

Objectives: To explore the prevalence and anatomical distribution of Vertebral Fractures (VF) in disease groups, investigated for primary and secondary osteoporosis, using Vertebral Fracture Assessment (VFA).

Study Design: VFA was performed independently by two non-radiologist observers, in 165 children (77 males, 88 females) as part of their investigation for osteoporosis. Vertebral bodies from T6 to L4 were assessed for VF using the Genant's scoring system. The common readings for the presence of a VF were used for evaluating the prevalence and anatomical distribution of VF.

Results: The median age of the subjects was 13.4 years (range, 3.6, 18). Of the 165 children, 24 (15%) were being investigated for primary bone disease and the remainder had a range of chronic diseases known to affect bone health. VF were identified in 38 (23%) children. The distribution of the VF was bimodal, with VF peaks centred at T9 and L4. Conditions associated with increased odds for VF were Inflammatory Bowel Disease (odds ratio, 3.3 [95% CI, 1.4, 8.0], P=0.018) and Osteogenesis Imperfecta (odds ratio, 2.3 [95% CI, 1.04, 5.8], P=0.022). Among children with VF, those with Duchenne's Muscular Dystrophy (P=0.015) and Osteogenesis Imperfecta (P=0.023) demonstrated higher number of VF than the other disease groups.

Conclusion: VFA identified the presence of VF, in a bimodal distribution, in both primary bone disease and chronic disease groups. VFA is a practical screening tool for identification of VF in children and adolescents at risk of fragility fractures.

Introduction

In young people, vertebral fractures (VF) are increasingly recognised as an important marker of primary and secondary osteoporosis, spanning diverse groups of chronic illness, in particular those treated with glucocorticoids.[1,2,3] VF by themselves are indicative of severe bone fragility irrespective of the reported bone mineral density (BMD)[4] and, in both adults and children, are associated with a significant risk of further vertebral and non-vertebral fractures.[5,6,7] Early identification of VF in children who are at risk of osteoporosis may influence the clinician's options for bone protection therapy, either through optimising nutrition and limiting exposure to glucocorticoids or initiation of specific therapies such as bisphosphonates, with a view to possible normalisation of vertebral morphology during the years of active bone growth.[8,9]

The identification of VF has been hampered by the availability of an imaging modality that provides adequate visualisation of the thoracic and lumbar spine, is readily available in all centres and is associated with suitably low levels of radiation exposure to allow for its use in screening and for repeated studies. Information gathered on VF anatomical distribution, from screening in different disease groups, and readability at each vertebral level could aid clinical assessment and inform the choice of imaging modality, respectively.

Measurement of BMD by dual energy X-ray absorptiometry (DXA) is central to the comprehensive skeletal health assessment of children with increased risk of fracture, both children presenting with suspected primary bone disorders and children with potential secondary bone disease including those associated with chronic inflammatory disorders, chronic immobilisation, endocrine disturbance, cancers and therapies with adverse effects on bone health.[2] Vertebral Fracture Assessment (VFA) is the assessment of lateral spine images acquired by DXA to detect VF. VFA may prove to be a valuable screening tool for osteoporosis, particularly in the presence of normal bone density[10] and has recently been shown

to be an accurate and reproducible method for assessing vertebral morphometry in children.[11] Preliminary data has highlighted its clinical utility in young people with Inflammatory Bowel Disease and Anorexia Nervosa.[12,13] The purpose of this study was to investigate the role of VFA in estimating the prevalence and the anatomical distribution of VF in children and adolescents undergoing routine clinical assessment for osteoporosis.

Methods

Study population

The study cohort consisted of 165 consecutive children and adolescents (77 males, 88 females) who had a DXA BMD measurement at the Royal Hospital for Children, Glasgow, as part of their clinical evaluation for suspected or previously diagnosed osteoporosis, between July 2013 and May 2014. It has been standard practice from 2013 onwards for all patients to have both BMD and VFA performed. 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.[14,15]

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) (Figure 1A). The subject was placed in the left lateral decubitus position with hips, knees and shoulders bent at 90 degrees. As outlined previously, reference data were used to calculate a predicted and a percentage predicted bone area for age and sex.[16,17] 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, 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%.

Vertebral Fracture Assessment By DXA

Lateral spine images were analysed independently by two non-radiologist observers (AK, SS), who performed VFA in all 165 subjects. 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 (Figure 1B). From these points, the software (Encore Version 13) 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, as either no fracture or VF, according to the extent of any height reduction as expressed by the reduction in height ratios using the scoring system developed by Genant: No fracture (grade 0) if the reduction in any height ratio was ≤20%, VF (inclusive of grade 1-3) if a height ratio reduction was greater than 20%.[18] Interobserver agreement in vertebral readability was 94% (kappa, 0.73 [95% CI, 0.68, 0.73]). Interobserver agreement for the presence of a VF of any severity, in per-vertebra analysis was 99% (kappa, 0.85 [95% CI, 0.79, 0.91]). In 20 children, VFA was compared to an assessment of lateral vertebral morphometry on a lateral spine x-ray (LVM). 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]). When analysis was based on the VF grading, agreement was lower and reached

88% with kappa score being 0.55 (95% CI, 0.40, 0.68). Agreement on per person basis between the two methods reached 95% (kappa, 0.88 [95% CI, 0.72, 1.0]).[11]

Statistics

Analyses were conducted using SPSS 20 (SPSS Inc, Chicago). Population characteristics are expressed as median (range) for continuous variables, while categorical variables are expressed as the value (percentage frequency). Comparison between groups was performed by Mann-Whitney U test and Kruskal-Wallis test for continuous variables and by Chi-square test or Fisher's exact test for categorical variables. All tests were two-sided and $P < 0.05$ was considered significant. The common readings for the presence of a VF from the two observers were used for evaluating the prevalence of VF in the population in total and in relation to the underlying chronic disease, and for determining the anatomical distribution of VF. Odds ratios (OR) were used to compare the relative odds of the occurrence of VF on a vertebral level, with the odds of a VF occurring on the rest of the vertebral levels from T6-L4, and for the evaluation of the influence of the underlying condition on the occurrence of VF. To overcome the obstacle of the variability in the number of the vertebrae per subject that were included in analysis for the estimation of the number of vertebral deformities in each subject in whom VF were identified, we used the Vertebral Fracture Index (VFI) = (VFn / Vtotal) × 100, where VFn was the number of VF in a subject and Vtotal was the total number of vertebrae from T6 to L4 of the subject that were included in analysis.

Results

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 SDS was -0.25 (-5.6, 3.8), median BMI SDS was 0.06 (-4.6, 3.6), median TB BMC for bone area SDS was -0.1 (-1.3, 3.3) and median LS BMC for bone

area SDS was -0.3 (-2.7, 1.6). Of this cohort of 165, 24 (15%) had been investigated for Osteogenesis Imperfecta. The remaining 141 (85%) 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), Coeliac Disease (n, 6), haematologic malignancies (n, 6) and other chronic conditions, including metabolic and liver disease (n, 11), autoimmune disorders (n, 9), and other (n, 22) (Table 1).

Prevalence of vertebral fractures

Of the 1815 vertebrae from T6 to L4 in 165 patients, 1528 vertebrae (84 %) were readable by both observers and of these, 22 vertebrae were further excluded as the observers disagreed on the presence of a VF. The remaining 1506 vertebrae were included to estimate the prevalence of VF in the cohort and to investigate the anatomical distribution of VF. The median number of vertebrae per subject that were included in analysis was 10 (range 5, 11). Of the 165 subjects, 38 (23 %) were found to have a total of 67 fractures. Of them, 26 (68 %) had a single VF, 6 (16 %) manifested 2 fractures, 2 (5 %) had 3 VF, 1 (2.6 %) had 4 VF, 2 (5 %) had 5 VF and 1 (2.6 %) had 9 fractures. Those with VF did not differ significantly from the subjects without VF in age, sex distribution, height SDS, BMI SDS, TB BMC for bone area SDS and LS BMC for bone area SDS (Table 2).

Anatomical distribution

The distribution of VF along the spine from T6 through L4, the proportion of VF among the number of vertebrae included in analysis and the odds ratios for the presence of a fracture at each vertebral level are presented in Figure 2. Of the 38 subjects with VF, 13 (34 %) had VF only in the thoracic region, 17 (45 %) had VF only in lumbar spine and 8 had (21 %) VF located in both sites. The proportion of VF among the normal vertebrae did not differ between the

thoracic and the lumbar spine (P=0.08). Two major peaks were present when the anatomic distribution was examined: a peak centred at T9 (P=0.033) and a peak centred at L4 (P=0.042).

Prevalence of VF in Disease groups

The fracture prevalence in disease groups is presented in Figure 3. Conditions associated with increased odds for VF included Inflammatory Bowel Disease (odds ratio, 3.3 [95% CI, 1.4, 8.0], p=0.018) and Osteogenesis Imperfecta (odds ratio, 2.3 [95% CI, 1.04, 5.8], p=0.022). Among patients with VF, those with Duchenne's Muscular Dystrophy (P=0.015) and Osteogenesis Imperfecta (P=0.023) demonstrated higher VFI than the other disease groups.

Discussion

VF are evident not only in children and adolescents with primary bone disease but also in those with chronic disease. The purpose of this study was to determine the prevalence and anatomical distribution of VF in a contemporary cohort of children and adolescents, using VFA as part of their clinical evaluation for suspected or previously diagnosed osteoporosis. This study highlights the prevalence of VF as a complication of chronic disease, as VFA has identified the presence of abnormal vertebral morphology not only in children and adolescents with primary bone disease but also in a fifth of those with conditions associated with secondary osteoporosis. In this study, we found an increased risk for VF in those with Osteogenesis Imperfecta and Inflammatory Bowel Disease. In addition, amongst the children in whom VF were identified, those with Osteogenesis Imperfecta and Duchenne's Muscular Dystrophy were more likely to have multiple VF. We also identified the presence of VF in other disease groups undergoing evaluation of bone health including Anorexia Nervosa, Cystic Fibrosis and malignancy, albeit at a lower prevalence. These results are perhaps not surprising as there have been previous reports in a variety of disease groups in childhood and adolescence of abnormal vertebral morphology, both at diagnosis and throughout their disease course and both before

and following glucocorticoid exposure, suggesting contributory roles for disease and treatment related factors in the development of VF.[7,12,20,21,22,23,24]

The bimodal distribution of VF along the spine from T6 to L4 in our pediatric population is similar to the distribution reported in the literature of other chronic disease groups with increased risk of osteoporosis, with vertebral deformities occurring in both the thoracic spine and the lumbar spine.[7,12,21,24,25,26,27,28,29,30] The peak prevalence of VF at T9 and L4, across all disease groups described, questions the relative role of disease or glucocorticoid use versus the biomechanics of the pediatric spine. Fracture distribution in children may be related to the shape of the immature spine, both lesser thoracic kyphosis and lumbar lordosis as compared to the adult spine, leading to differences in fracture locations. The readability of vertebrae at mid thoracic level, may be sub-optimal[11,28,31], and therefore, the fracture prevalence rate may be even higher in this region.

Clinical predictors of incident VF in rheumatic disorders treated with glucocorticoids include active disease in the preceding 12 months, longer duration and higher average daily dose of glucocorticoid therapy, greater increases in BMI SDS and decreases in BMD SDS.[21] In the current study, BMC was not a predictive factor for VF. A similar disconcordance between BMD measures and VF has been reported in children with primary bone disease and in children with chronic illness,[12,13,28,30,32,33,34,35] suggesting that BMD SDS can be higher than −2.0 despite a significant vertebral fracture history in high-risk children.[4] This could either reflect the limitations of DXA in measuring true bone density in children, or that abnormal bone geometry, micro-architecture and differences in rates of bone turnover are more important contributors of bone fragility. It is still possible that the relationship of BMD SDS and vertebral fractures exists but not with the arbitrary cut-off of <-2.0.[32] Substantial variation has been described when different pediatric reference data have been used to generate LS BMD SDS

from a single absolute BMD value, such that the proportion of children falling below the diagnostic threshold BMD SDS -2 ranged from 15% to 48%. Therefore, clinical decisions regarding management of bone health should not be based on DXA BMD measurement alone.[4] However, direct comparison between studies is difficult because of differences in population characteristics, observers' experience, DXA devices, software variability and the variable morphometric methods used to identify vertebral deformities.

In the majority of descriptions of VF in the context of chronic disease groups, the identified VF have largely been asymptomatic.[7,21,24,36,37] The STOPP trial has largely informed strategies for monitoring children both before and following glucocorticoid treatment and would suggest that surveillance for VF should continue for at least four years following exposure of glucocorticoids with the highest incidence of VF in the first 12 months from initiation of treatment. Given the significant prevalence of VF in children and adolescents shown in this study, screening for VF should be considered in those who would be at risk for fragility fractures. VFA, as a screening tool, will allow the early identification of VF irrespective of the presence of symptoms.

The clinical significance of mild deformities in children is currently unknown and may represent changes associated with normal development or other normal variants, particularly in the thoracic region where vertebrae naturally have a greater posterior than anterior height (normal wedging). However, any reduction in height would not be expected to exceed 20%, the threshold set for identification of VF.[25,38] Interestingly, the VF distribution of all grades of fracture is similar, which suggests that mild deformities are true fractures rather than normal variants.[26,27] Longitudinal assessments with VFA will clarify the significance of these deformities, whether fractures or normal variants, by monitoring their evolution over time, and

prospective studies will contribute to our better understanding in the need and the effectiveness of any intervention as well as informing best practice in spinal surveillance.

Conventional radiographs are currently the reference standard modality for the diagnosis of VF. A key limitation of this study is the lack of corroborative lateral spine x-ray, such that the VF detected by VFA could not be confirmed with spinal x-rays, and the degree to which height reductions identified with VFA are true VF remains unknown in our cohort. Another limitation is the diversity of our study cohort, variable ages and numbers in each disease group, which represents the entirety of the clinical workload during the time period studied. Thus, our observations of relative frequencies and odds ratios for VF in disease groups apply only to the convenience sample studied, and further evaluation with larger numbers of individuals in each group is warranted to define prevalence. We have previously reported that the agreement between the two modalities for the grade of the VF was not optimal.[11] The limitations of any quantitative morphometric technique, whether it is based on DXA images or conventional radiographs, should also be recognised. Point placement in vertebral morphometry is a subjective decision that will vary between different observers and will always be dependent on their level of experience and training. Although visual interpretation of the images is also subjective,[39] the qualitative assessment from an experienced radiologist can better differentiate true fractures from other vertebral anomalies. Nevertheless, our study reflects a real clinical setting, thereby showing the practical utility of VFA by technical staff who may not have advanced training in radiology.

In conclusion, VFA used in this setting as a complement to BMD measurement in children and adolescents identified a high prevalence of VF in both primary bone disease and chronic disease groups at risk of secondary osteoporosis, thus advocating the routine use of VFA, as an adjunct to existing screening investigations, in children with suspected osteoporosis.

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Figure Legends

Figure 1. (A) Lateral images of the thoracic–lumbar spine were obtained using dual energy X-ray absorptiometry (Lunar Prodigy) (B) Vertebral Fracture Assessment: 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 up to T6 (software Encore Version 13).

Figure 2. Anatomical distribution of vertebral fractures. Two major peaks are present: a peak centered at T9 (P=0.033) and a peak centered at L4 (P=0.042).

VF, vertebral fracture

Figure 3. Prevalence and odds ratios of vertebral fractures in disease groups.

VF, Vertebral Fracture; VFI, Vertebral Fracture Index