

Reliability of Vertebral Fractures Assessment (VFA) in Children with Osteogenesis Imperfecta

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Abstract The aim of this study is to evaluate the diagnostic accuracy of vertebral fractures assessment (VFA) in comparison with conventional radiography in identifying vertebral fractures in children and adolescents affected by OI. On 58 patients (33 males, 25 females; age range 1–18 years; 41 children and 17 adolescents) with osteogenesis imperfecta (OI type I, $n = 44$, OI type III, $n = 4$; OI type IV, $n = 10$), lateral spine images by radiographs and by dual-energy X-ray absorptiometry (DXA) were acquired. For vertebral fracture diagnosis, plain radiographs were used as “gold standard” and VFA and morphometric X-ray absorptiometry (MXA) were performed. The visualized vertebrae were 738 (97.9 %) by radiographs and 685 (90.9 %) by DXA of a total of 754 vertebrae from T4 to L4. VFA and MXA identified, respectively, 129 (74 %) and 116 (66 %) of the 175 vertebral fractures detected by radiographs. Radiographs identified 36 patients with vertebral fractures, VFA 35 and MXA 41 (6 false positives). On a per vertebra basis, radiographs and VFA

had elevated agreement (93.9 %; k score 0.81, 95 % CI 0.76–0.86), that resulted slightly lower for MXA (90.6 %; k score 0.72, 95 % CI 0.65–0.78). VFA and MXA demonstrated high sensitivity (95.6 and 94.1 %, respectively) while specificity was 100 % for VFA and 90.6 % for MXA on a per patient basis; the agreement was excellent for VFA (98.3 %; k score 0.96, 95 % CI 0.89–1.03) and good for MXA (87.9 %; k score 0.73, 95 % CI 0.55–0.91). The diagnostic performance parameters resulted better for VFA (sensitivity 95.6 %; specificity 100 %; PPV 100 %; NPV 97.2 %), than for MXA (sensitivity 94.1 %; specificity 85.4 %; PPV 72.7 %; NPV 97.2 %). The results of our study demonstrate the reliability of VFA for diagnosis of vertebral fractures in children with OI suggesting its use as a more safe and practical alternative to conventional radiography.

Keywords DXA · VFA · Osteogenesis imperfecta · Vertebral fractures · Children

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Introduction

Osteogenesis imperfecta (OI) is a genetic disorder of connective tissue (type I collagen) characterized by increased bone fragility predisposing to multiple bone fractures and bone deformities [1]. Multiple vertebral fractures are frequently observed in children with OI, and are often of severe grading [2], developing therefore a progressive spinal deformity, in particular kyphoscoliosis, which causes worsened quality and shortened expectancy of life [3, 4].

Vertebral morphometry performed on lateral spine radiographs is the method commonly used to identify and quantify vertebral deformities in children with OI. As it has

been demonstrated in several studies [5–10] that bisphosphonate treatment may favor a normalization of vertebra morphology during the years of bone growth, accurate and early diagnosis of vertebral fractures in children with OI should be considered very important.

The radiation exposure limits the frequent use of vertebral morphometry by conventional radiography in the clinical patient care. At present, a novel method of acquiring the lateral images of the spine is available, using dual-energy X-ray absorptiometry (DXA) technology to allow vertebral fracture assessment (VFA) [11]. VFA has several advantages, which include a significantly lower radiation exposure dose (<20 μSv) than conventional radiography (300 μSv) and acquisition of the entire spine in a single image [12]. Moreover, as a result of the movement of the X-ray source together with the detectors (in the arm), being always perpendicular to the spine, there is a very slight magnification in the medio-lateral direction (due to the fan-beam) and no magnification in the cranio-caudal direction and therefore no magnification in vertebral heights.

Up to now, only one study [13] has been performed to evaluate VFA in children, in which the authors concluded that VFA is not suitable for pediatric use because of compromised visibility of vertebrae and poor diagnostic accuracy. Recent advances in VFA technology have improved image resolution [14] and several studies have demonstrated VFA to be reliable and accurate in detecting vertebral fractures in adults [15–17].

We hypothesized that the enhanced image quality would allow better visibility of vertebral bodies improving therefore sensitivity and specificity also in children.

The purpose of our study was to evaluate the diagnostic accuracy of VFA in comparison with conventional radiography in identifying vertebral fractures in children affected by OI.

Patients and Methods

Patients

We studied a sample of 58 patients (33 males, 25 females; 41 children and 17 adolescents, mean [\pm SD] age 9.7 ± 8.5 yrs, median age 7.0 yrs; first quartile–third quartile (Q1–Q3) of the age 3.2–11.0 yrs; age range 1–18 yrs) with OI (OI type I, $n = 44$, OI type III, $n = 4$; OI type IV, $n = 10$) referred to the Congenital Osteodystrophy Center, Department of Pediatrics. All patients were enrolled before beginning treatment with bisphosphonates.

In all patients, anthropometric data, spine images by conventional radiographs and by DXA technique and bone mineral density (BMD) measurements were acquired on the same day.

Spine Imaging

Conventional radiographs of the thoracic and lumbar spine in the anterior–posterior and left lateral projections were acquired by using a full digital radiographic system (Apollo DRF, Villa Medical Systems, Milan, Italy). For the lateral views, subjects were positioned on their left side with knees and hips flexed. Tube-to-film distance was set at 105 cm and the films were centered at T7 and L3 for the thoracic and lumbar views, respectively.

Lateral and posterior–anterior DXA images of the spine (from T4 to L4) were acquired using the Discovery A densitometer (Hologic, Inc., Bedford, MA, USA), leaving the patient in the supine position (with the scanner arm rotated through 90°). The spine fan-beam DXA images were acquired in high-definition, software version 4.3, using single-energy (SE) scan modes.

BMD Measurements

By the same scanner, postero–anterior scans of the lumbar spine (from L1 to L4) were also acquired to measure BMD using pediatric software (version 12.4, Hologic, Bedford, MA) for children aged 1–14 years and auto-low density software for adolescents aged 15–18 years (version 12.4, Hologic, Bedford, MA). Areal BMD results were converted to age- and sex-specific Z scores using data provided by the manufacturer.

To minimize the effect of bone size on BMD in growing individuals, mathematical model for correction of areal BMD for the poster-anterior depth of the vertebrae was used to obtain estimates of volumetric density, bone mineral apparent density (BMAD). BMAD was calculated with the formula $\text{BMAD } \text{g}/\text{cm}^3 = \text{bone mineral content}/\text{area}^{1.5}$ (where $\text{area}^{1.5}$ is the area times the square root of the area) [18].

Image Analyses

Two experienced skeletal radiologists evaluated independently on different days spinal radiographs and DXA images, each blinded to the other evaluation. All the adequately visualized vertebrae were analyzed to identify vertebral fractures using the visual semiquantitative assessment (SQ) method [19] both by conventional radiographs (SQ-RX) and by DXA images (VFA). According to SQ method, the readers visually identified fractures by reduction in anterior, middle, or posterior vertebral heights classifying the three types of vertebral fractures, wedge, crush, or biconcave, as mild (20–25 % reduction), moderate (25–40 % reduction), or severe (>40 % reduction). After independent evaluation of radiographs and DXA images, the readers re-evaluated the vertebrae with

discrepancy in the diagnosis, even in case of discrepancy in the grade of fracture.

The SQ-RX assessment obtained by the consensus of the readings by the two radiologists was used as “gold standard” for vertebral fracture diagnosis.

On DXA spine images, the Hologic QDR Physician’s Viewer software (version 7.02) performed vertebral morphometry placing six points in each vertebral body starting at L4 and continuing through the thoracic spine up to vertebra T4 to calculate the anterior (Ha), middle (Hm), and posterior (Hp) heights, and the ratios (Ha/Hp, Hm/Hp) of each vertebra. This automatic vertebral assessment performed by software was named morphometric X-ray absorptiometry (MXA). The software classified the vertebrae as normal or fractured estimating the extent of anterior or middle vertebral height reduction with respect to posterior height according to SQ criteria by Genant [19] (Fig. 1) Each automatic vertebral morphometry was reviewed by a trained clinician who corrected manually the wrong point placement.

Statistical Analysis

Data were analyzed by means of a personal computer implemented with dedicated software (SPSS 18). To evaluate the concordance between the three techniques, we calculated the percent agreement and Cohen’s kappa coefficient (concordance index) [20] while, to assess the diagnostic reliability of VFA and MXA as compared to SQ-RX, we

calculated sensitivity, specificity, positive (PPV), and negative (NPV) predictive values.

Results

In Table 1, the anthropometric characteristics and densitometric values of the 58 patients with OI (Types I–III–IV) enrolled are reported.

The visualized vertebrae were 738 (97.9 %) in the conventional radiographs and 685 (90.9 %) in the DXA images of a total of 754 vertebrae from T4 to L4.

The quality of the images was compromised in the upper thoracic spine (T4–T7) where all the unanalyzable vertebrae in the standard radiographs (16) and in the lateral DXA images (69) were localized. Hence, in the T8–L4 region all the vertebrae (100 %) were adequately visualized by both techniques.

In Table 2, fracture assessment with the three techniques is reported. VFA identified 129 (74 %) of the 175 vertebral fractures detected by SQ-RX. In Table 3, the number of patients diagnosed as having none, one, or multiple vertebral fractures is reported: 36 by SQ-RX, 35 by VFA and 41 by MXA. Considering SQ-RX as gold-standard MXA classified 6 patients incorrectly as having fractures (false positives). False negatives by VFA and MXA regarded exclusively mild vertebral fractures (38/100 and 39/100, respectively) and moderate vertebral fractures (8/59 and 10/59, respectively), while all severe vertebral fractures (16/16) by SQ-RX were correctly identified likewise by VFA and MXA. Among false negatives by VFA and MXA, 20 were included in the 69 unreadable vertebrae by DXA technique (Fig. 2).

In Table 3, the number of patients diagnosed as having none, one, or multiple vertebral fractures is reported; both VFA and MXA identified 35 (97.2 %) of the 36 patients with vertebral fractures by SQ-RX (Table 3), but MXA

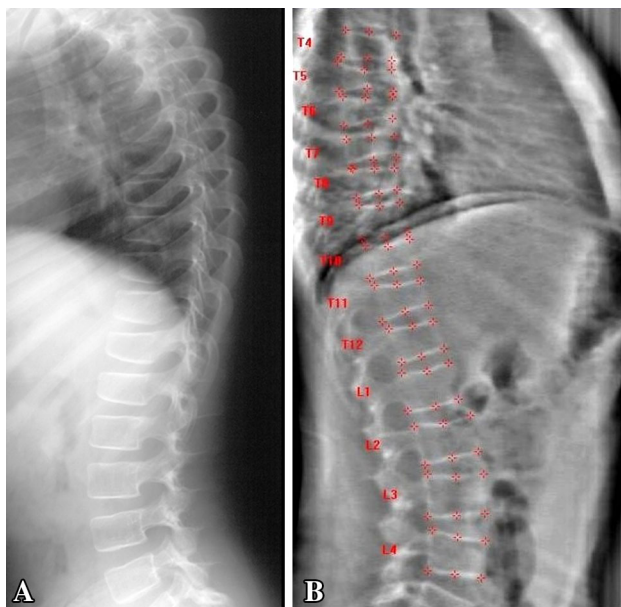


Fig. 1 A 5-year-old child with osteogenesis imperfecta type III. Lateral radiograph (a) and lateral DXA image with computerized morphometry (MXA) (b) show multiple vertebral fractures at the same levels (T5, T6, T7, T8, T9, T10, T11)

Table 1 Anthropometric characteristics and densitometric values (mean \pm SD) of patients with OI Type I–III–IV

	Mean \pm SD
Age (years)	9.7 \pm 8.5
Height (cm)	120.3 \pm 28.2
Weight (kg)	29.7 \pm 17.7
Lumbar spine densitometry (L1–L4)	
BMC (g)	15.30 \pm 11.55
Projection area (cm ²)	28.70 \pm 12.73
BMD (g/cm ²)	0.459 \pm 0.187
BMD (z score)	–2.5 \pm 1.3
BMAD (g/cm ³)	0.091 \pm 0.028

Table 2 Number and grading of vertebral fractures assessed by the three different techniques

Method	Normal	Any fracture	Mild fracture	Moderate fracture	Severe fracture	Not analyzed
SQ-RX	563	175	100	59	16	16
VFA	556	129	62	51	16	69
MXA	559	126	61	49	16	69

classified also 6 patients incorrectly as having fractures (false positives).

On a per vertebra basis, agreement and concordance index assessed by kappa statistics between SQ-RX and VFA were elevated (93.9 %; *k* score 0.81, 95 % CI 0.760–0.863) and slightly lower but still good for MXA (90.9 %; *k* score 0.72, 95 % CI 0.65–0.78). When considering also the grading of vertebral deformity the agreement was likewise very good (agreement: 98.5 %; *k* score: 0.87, 95 % CI 0.84–0.90). Assuming SQ-RX as gold standard, we calculated the diagnostic performance parameters demonstrating high sensitivity for both VFA and MXA (95.6 and 94.1 %, respectively) while specificity was

100 % for VFA and was lower for MXA (90.6 %), that classified as fractured 10 normal vertebrae.

On a per patient basis, the agreement with X-rays was excellent for VFA (98.3 %; *k* score 0.96, 95 % CI 0.89–1.03) and good for MXA (87.9 %; *k* score 0.73, 95 % CI 0.55–0.91). The performance diagnostic parameters resulted better for VFA (sensitivity 95.6 %; specificity 100 %; PPV 100 %; NPV 97.2 %), than for MXA (sensitivity 94.1 %; specificity 85.4 %; PPV 72.7 %; NPV 97.2 %). Results per vertebra and per patient basis are reported in Table 4.

The 36 patients with vertebral fractures identified by SQ-Rx had BMD and BMAD values significantly lower with respect to patients without vertebral fractures (BMD 0.305 ± 0.101 vs 0.467 ± 0.094 , $p < 0.001$; BMAD 0.072 ± 0.028 vs 0.096 ± 0.016 , $p < 0.001$).

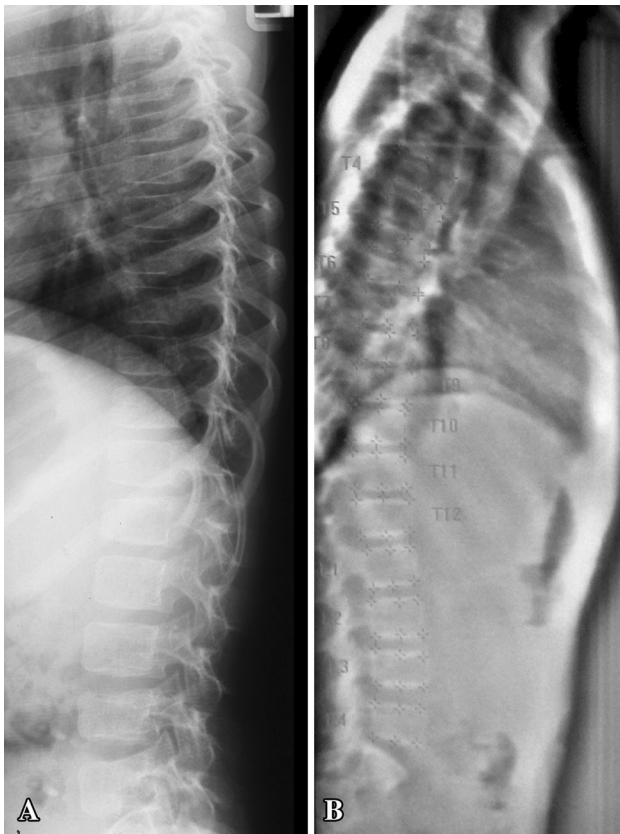


Fig. 2 A 6-year-old child with osteogenesis imperfecta type III. Lateral radiograph (a) shows vertebral fracture at T6 level that was missed by computerized morphometry (MXA) (b) because of poor quality of DXA image at upper thoracic level

Discussion

Our results demonstrated the good diagnostic accuracy of VFA in children and adolescents with OI types I, III, IV.

In fact, most vertebrae (90.9 %) were adequately visualized in VFA images. The clinical impact of the 69 unreadable vertebrae by VFA was minimal because most of them (57) were localized at T4 level, a rare location for isolated fracture.

Similarly to adult patients [21, 22], the visibility of the vertebrae by VFA in these pediatric patients was adequate at T8–L4 level where all the vertebrae were readable whereas it was slightly compromised at T4–T7 level, where only 77 % of them were adequately visualized. The lower spatial resolution of DXA images with respect to conventional radiographs emphasizes the deleterious effect on the quality image due to the presence of the ribs, the lung parenchyma, and diaphragmatic movements, producing images of poor quality at the upper thoracic level. VFA and MXA missed 26 and 34 % of vertebral fractures, respectively. About 40 % of the undiagnosed vertebral fractures by VFA and MXA were included among the unreadable vertebrae. This misdiagnosis had poor clinical relevance for VFA that correctly diagnosed 35/36 patients with vertebral fractures identified by SQ-RX with a high sensitivity (95.3 %) on a per patient basis. In fact, most children with

Table 3 Number of patients diagnosed as having none, one, or multiple vertebral fractures with the three different techniques

Patients	Without vertebral fracture	With vertebral fractures	With 1 fracture	With >1 fractures
SQ-RX	22 (37.9 %)	36 (62.1 %)	10 (17.2 %)	26 (44.8 %)
VFA	23 (39.6 %)	35 (60.3 %)	11 (19.0 %)	24 (41.4 %)
MXA	17 (29.3 %)	41 (70.7 %)	15 (25.9 %)	26 (44.8 %)

Table 4 Diagnostic agreement of VFA and MXA with the standard SQ-RX method

Indices	Per vertebra		Per patient	
	VFA	MXA	VFA	MXA
Agreement	93.9 %	90.85 %	98.3 %	87.9 %
<i>k</i> score	0.81	0.71	0.96	0.73
95 % CI	0.76–0.86	0.65–0.78	0.89–1.03	0.55–0.91
Sensitivity	73.7 %	66.3 %	95.6 %	94.1 %
Specificity	100 %	95.2 %	100 %	85.4 %
PPV	100 %	92.1 %	100	72.7
NPV	92.4 %	90.4 %	97.2	97.2
False positive	0	10	0	6
False negative	46	59	1	1

OI had multiple vertebral fractures, distributed along the thoracic and the lumbar spine and therefore patients were easily and correctly diagnosed.

These data show that VFA could be used as a diagnostic pre-screening tool, as most children with prevalent vertebral fractures would be correctly referred for radiography to confirm the diagnosis.

Unlike VFA, MXA performed automatically using the software Hologic QDR Physician's Viewer, had a high sensitivity (94.1 %) on a per patient basis but a lower specificity (85.4 %) and a worse agreement with SQ-RX (87.9 %); resulting in seven misdiagnosed patients, one fractured and six normal. In fact, MXA is a quantitative method based on measurement of vertebral heights to diagnose vertebral fractures and therefore it is unable to discriminate between true vertebral fracture and non-fracture vertebral deformities, in particular the so-called "short vertebral height" (SVH), resulting in more false positives and negatives [23].

VFA has higher diagnostic accuracy of MXA because it allows to rule out non-osteoporotic deformities by means of a prior accurate visual assessment of all vertebrae followed by evaluation of grading of the true vertebral fractures using a semiquantitative approach.

In the unique previous study performed to evaluate the diagnostic accuracy of VFA in vertebral fracture diagnosis in children [13], the authors reported that VFA identified only 20 % of vertebrae classified as fractured by SQ

assessment of conventional radiographs, missing even moderate fractures. So they concluded that, because of compromised visibility of the upper thoracic spine and poor diagnostic accuracy, VFA is not suitable for pediatric use.

In our study a high percentage of the vertebral fractures detected by SQ-RX were correctly identified by VFA (74 %) and by MXA (66 %).

These results may be due to several reasons.

First, improved DXA technology to acquire spine images in high-definition, resulted in a better visualization of the vertebrae, even in the upper thoracic spine.

Moreover, the use of an upgraded version of Hologic QDR Physician's Viewer software (version 7.02) allowed a better analysis of vertebrae to identify a higher percentage of vertebral fractures with respect to the previous study [13].

The adequate experience of skeletal radiologist may be another reason for the improved sensitivity and specificity of VFA in our study [14].

Finally, the improved diagnostic performance of VFA may have been favored by the high prevalence of vertebral fractures in the enrolled children and adolescents affected by OI.

In spite of the advancement in technology, lower spatial resolution of DXA images with respect to conventional radiography does not enable VFA to identify all vertebral fractures.

Nevertheless, VFA is able to identify with a good diagnostic accuracy almost all children with vertebral fractures as well as in adult population [24].

So we believe that VFA is a very useful and safe technique for evaluation of children with OI, that generally had multiple vertebral fractures, distributed along the entire spine. Up to now published data in children with OI are limited to identification of vertebral fractures only in the lumbar tract [6, 9, 10, 25]. Using VFA the entire spine can be adequately visualized by low dose radiation identifying also thoracic vertebral fractures. Furthermore VFA is a practical method allowing the combined assessment of BMD and vertebral fracture status. In conclusion, VFA can be proposed as a more safe alternative for conventional radiography to identify vertebral fractures in children with OI.

Conflict of interest Dr. Minisola reports personal fee from Abiogen Pharma, personal fee from Amgen, personal fee from Bruno Farmaceutici, personal fee from Chiesi Farmaceutici, personal fee from Eli Lilly, personal fee from Italfarmaco SpA, personal fee from Mediolanum Farmaceutici, personal fee from Merck Sharp & Dohme, personal fee from Novartis, personal fee from Pfizer, outside the submitted work. The other authors have no conflict of interest to declare.

Human and Animal Rights and Informed Consent The parents of all the children's and adolescent's gave written informed consent prior to the inclusion in the study. The protocol was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and was approved by the "Sapienza" University of Rome Ethics Committee.

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