

# Digital vertebral morphometry performed by DXA: a valuable opportunity for identifying fractures during bone mass assessment

Patrícia Muszkat<sup>1</sup>, Marília Brasilio Rodrigues Camargo<sup>1</sup>,  
Barbara Santarosa Emo Peters<sup>2</sup>, Ilda Sizue Kunii<sup>1</sup>, Marise Lazaretti-Castro<sup>1</sup>

<sup>1</sup> Division of Endocrinology,  
School of Medicine, Federal  
University of São Paulo  
(Unifesp), São Paulo, SP, Brazil

<sup>2</sup> Department of Nutrition, Faculty  
of Public Health, University of São  
Paulo (USP), São Paulo, SP, Brazil

## Correspondence to:

Patrícia Muszkat  
Rua Brás Cardoso, 219  
04510-030 – São Paulo, SP, Brazil  
patymuszkat@hotmail.com

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## ABSTRACT

**Objectives:** To evaluate the usefulness of vertebral morphometry in identifying unreported vertebral fractures and correlate potential risk factors. **Subjects and methods:** Female patients above 45 years, postmenopausal for at least 2 years, diagnosed with osteoporosis and undergoing treatment for at least three months were considered eligible. All of them underwent bone densitometry and vertebral morphometry performed by concomitant DXA. The presence of fractures was defined between T7 and L4; only moderate and severe fractures were considered for analysis. All volunteers were submitted to laboratory tests, anthropometry and responded a questionnaire on their lifestyle habits and medical history. **Results:** Thirty two (17%) out of the 188 female patients presented with at least one vertebral fracture, among whom only 4 (12.5%) were previously aware of the fracture. The fractures were mainly located on the thoracic spine. Nine patients had severe fractures (28.1%), whereas 23 had moderate fractures (71.9%). On average, patients with fractures were 5 years older and weighed 5 kilograms less than those without fractures. The creatinine clearance was on average 9 mL/min less in patients with vertebral fracture. The assessment of vertebral fractures by morphometry is a fast, accurate and complementary method associated with low radiation exposure for identifying moderate and severe vertebral fractures. Predisposition to vertebral fractures does not depend solely on BMD. Arch Endocrinol Metab. 2015;59(2):98-104

## Keywords

Postmenopausal women; Genant; vertebral fracture; vertebral fracture assessment

## INTRODUCTION

Bone fractures are the main cause of morbidity and mortality associated with osteoporosis. Fractures of long bones, such as that of the proximal femur, are usually fall-related, causing severe pain and incapacity, which lead patients to seek for immediate medical care. Vertebral fractures, however, may occur without obvious trauma and be associated with nonspecific symptoms (1). Most spinal fractures are not clinically recognized at the time they occur: two out of three radiographically detected vertebral fractures are asymptomatic findings (1). A large proportion of symptomatic fractures are associated with mild pain that tends to disappear in two to three weeks. Even vertebral fractures associated with moderate to severe pain can remain undiagnosed, since there are several other conditions that cause back pain.

Vertebral fractures cause loss of stature; chronic pain; abuse and harmful use of anti-inflammatory and analgesic drugs; increased risk of falls; reduced lung capacity; sleep disorders; increased patient dependency on others; decreased appetite (2); which all markedly impair patients' medical condition and quality of life. Most vertebral fractures occur at an earlier age than hip fractures (3), which is an important early indicator of disease severity. The mortality rate 5 years after a vertebral fracture is 20% higher than expected for the same age (4). Additionally, vertebral fractures, even if asymptomatic, are predictors of increased risk of new fractures (5-11), therefore their identification is important for designing the clinical treatment.

Clinical studies have shown that the existing treatments for osteoporosis increase spinal BMD between 4-12% and decrease the rate of vertebral fractures by 40-70% (12-13). An early radiologic diagnosis, fol-

lowed by the appropriate treatment, aids in preventing new fractures (14). Therefore it is important to identify vertebral fractures as early as possible.

The vertebral fracture assessment (VFA) performed by digital morphometry during a dual-energy X-ray absorptiometry (DXA) bone densitometry scan is a great opportunity for detecting vertebral fractures, which, by and large, might remain clinically unrecognized, but that could have relevant clinical implications.

The aim of the current study is to assess the prevalence of moderate and severe vertebral fractures identified by vertebral morphometry performed during DXA bone densitometry scans and its relation to the possible risk factors for osteoporosis in a population of postmenopausal patients being treated for osteoporosis at the outpatient clinic of metabolic bone diseases at the Department of Endocrinology, Federal University of São Paulo.

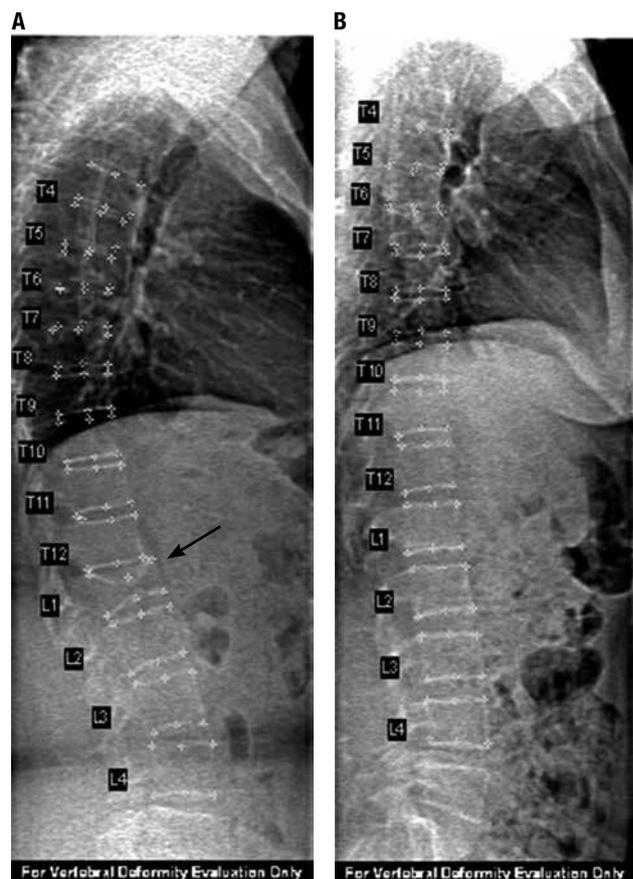
## PATIENTS AND METHODS

Two hundred and five women diagnosed with osteoporosis and registered in the database of patients being followed up at the outpatient clinic of metabolic bone diseases, at the school-hospital from Escola Paulista de Medicina (Unifesp), took part in this study. The patients were invited to participate in the study either by telephone or in-person contact during their appointments in 2009. Data collection took place between June and December 2009. Eligible patients were aged 45 years or older, postmenopausal for at least two years, diagnosed with osteoporosis at some point, and receiving treatment for at least three months. The criteria used for diagnosing osteoporosis were those proposed by the World Health Organization (WHO): the patients with a T-score less than or equal to -2.5 in their lumbar spine, femoral neck and/or total femur bone densitometry scans were classified as osteoporotic. The official guidelines of the Brazilian Society for Clinical Densitometry, as published on the official website of this entity, were followed.

The current study received approval from the Research Ethics Committee at Unifesp (ERB n. 0839/08). All of the participating patients signed a voluntary informed consent form.

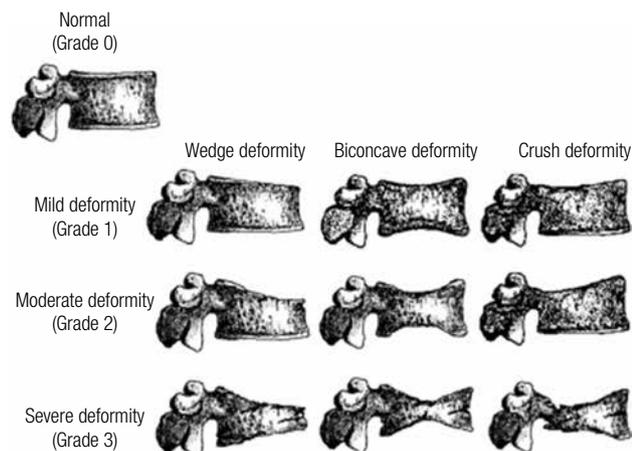
All of the patients underwent bone densitometry scans in a Discovery A equipment (Hologic®, Bedford, MA, USA, software version 12.3) for assessing bone mass; body fat mass; lean body mass; and vertebral frac-

tures (digital morphometry – Figure 1). The analyzed sites were lumbar spine, femur and whole body. Vertebral fracture assessment was performed in the same unit, immediately after the densitometry scans, with the patient in supine position and rotation of the unit arm for image acquisition. The assessment of vertebrae was conducted by placing 6 points on each vertebral body (on the anterior, medial and posterior portions of both the upper and lower parts of each vertebra). The software was used for calculating the anterior, medial and posterior heights of each vertebra, which allowed for the determination of the vertebra's deformity type and degree according to the Genant method (Figure 2). Such method classifies a fracture according to its severity, each vertebra being assigned a score: 0, if there is no fracture; 1, 2 or 3, if the fracture is mild, moderate or severe, respectively. In mild fractures, the reduction in height of the anterior, medial and posterior portions is 20-25%; in moderate fracture; it is 25-40%; and in severe fractures, higher than 40%. Moderate to severe vertebral fractures between T7 and L4 vertebrae were considered for analysis. All of the 188 VFA images



**Figure 1.** Example analysis of morphometric assessments comparing a severe biconcave fracture at L1 (A) and normal morphometry (B).

were also evaluated by the semi quantitative method, in which the vertebrae deformity is graded only by visual inspection. Furthermore, 20 VFA images (10 of each group) were randomly assigned for two blinded physicians for a semiquantitative analysis to evaluate the presence or absence of a moderate or severe fracture between T7 and L4.



**Figure 2.** Schematic diagram of the semi-quantitative grading system for vertebral fractures: reproduced from Genant and cols. (15).

## Analytical methods

### Laboratory parameters

All patients had blood samples collected for measuring PTH; carboxy-terminal telopeptide of type I collagen (CTX); 25-hydroxyvitamin D (25OHD); creatinine; alkaline phosphatase activity (AP); total calcium (Ca); phosphorus (P); amino-terminal propeptide of type I collagen (PINP). Additionally, urine was also collected for measuring calcium (UCa) and creatinine (UCr) in the isolated samples. Ca, P and UCa were measured by an automatized colorimetric method. Both UCr and serum creatinine were measured by a kinetic colorimetric method. Clearance of creatinine (CrClear) was estimated by applying the Cockcroft-Gault equation (16). The UCa/UCr ratio was calculated. AP was measured by an enzymatic method (Olympus AU640 analyzer, USA). CTX, PINP and PTH were measured using commercially available kits (chemiluminescence, Roche, Elecsys 2010 analyzer, USA). For CTX, the intra- and inter-assay coefficients of variation (CV) were 4.6 and 4.7%, respectively; for PINP, the CVs were 1.8 and 2.7%, respectively; and for PTH, the CVs were 3.0 and 3.5%, respectively. 25OHD was measured by chemiluminescence (DiaSorin, Liaison analyzer, USA), with intra- and inter-assay CVs at 1.62 and 5.61%, respectively.

### Anthropometric data

Body mass and height were measured using a digital scale and a wall stadiometer. Body mass index (BMI) was calculated as the ratio between body mass (kg) and the square of height (m<sup>2</sup>).

### Questionnaire

The patients responded questions on their age; lifestyle habits (smoking habits and alcohol consumption); comorbidities (*diabetes mellitus*, specifically); fracture history dating to any time in their life or specifically after age 45; and current medications. Patients were classified as smokers or non-smokers; those who denied current smoking habits were considered as non-smokers.

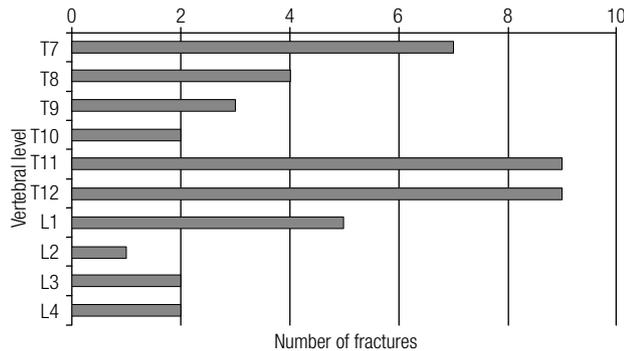
### Statistical analysis

The Statistical Package for the Social Science (SPSS) version 19.0 (SPSS Inc., Chicago, Illinois, EUA) was used for conducting the statistical analysis. All variables were subjected to the Kolmogorov–Smirnov test to assess the normality of data distribution. Independent Student's t-test was used for comparing the anthropometric, laboratory and densitometric data obtained for the two groups (with and without fractures). The associations among categorical variables were evaluated by using the chi-squared test and  $p < 0.05$  was considered significant. Agreement between observers was calculated using percentage of agreement and the  $\kappa$  statistic:  $\kappa = (p_o - p_c) / (1 - p_c)$ , where  $p_o$  = the proportion of units in which the judges agreed; and  $p_c$  = the proportion of units for which agreement is expected by chance (17).

## RESULTS

Among the 205 patients selected for taking part in the study, 3 were deceased and 14 were not interested. Thus, data were obtained from a total of 188 patients, of which 32 (17%) presented with at least one moderate or severe vertebral fracture, and among whom only 4 (12.5%) the fracture had been previously diagnosed. Most patients (87.5%) were not aware of the presence of fractures and no description of vertebral fractures was found in their medical records, so, such information was unknown even by their doctors. Six (18,7%) out of these 32 patients had more than one vertebral fracture, with one patient presenting with 4 fractures. Among the 4 patients who were previously aware of the existing fracture, 3 presented with more than one vertebral fracture.

The fractures were mainly located on the thoracic spine, with 56% of the cases occurring at the T11 and T12 vertebrae (9 involving each one of these), as can be seen in figure 3. As for fracture severity, we found 9 patients with severe fractures (28.1%) and 23 with moderate fractures (71.9%). The semiquantitative analysis showed the same results.



**Figure 3.** Distribution of vertebral fractures.

There was an agreement of 95% with the first blinded physician reading of the exams regarding the presence or absence of moderate or severe vertebral fracture and of 100% with the second one. The  $\kappa$  statistic showed a  $\kappa = 0,9$  for the first blinded physician and a  $\kappa = 1,0$  for the second one.

The results obtained from the anthropometric measurements, laboratory tests and densitometry scans from patients with and without vertebral fractures (VF) assessed by VFA are shown in tables 1 and 2. The only statistically significant data between groups were age; clearance of creatinine; body fat mass; and total body mass. There were no other statistically significant differences for any parameters evaluated.

Considering the 188 participants, patients age varied between 48 and 86 years (mean age of 68). In the group of patients with vertebral fractures (VF), the mean age was 5 years more than that in the group of patients without VF. On average, patients with VF weighted 5 kg less than those without fractures. CrClear was on average 9 mL/min less in patients with vertebral fracture. In the group of patients with VF, 16 (50%) patients had CrClear less than 60 mL/min, whereas in the group of patients without fractures that figure amounted to 52 (33.3%). Total body composition scans of patients with fractures showed on average 2,633 g fat and 3,992 g total mass less when compared to patients without fracture.

**Table 1.** Comparison of anthropometric and laboratory characteristics between the two groups: patients with and without vertebral fractures, as detected by digital morphometry performed by DXA

	Patients without fractures (156) Mean $\pm$ SD	Patients with fractures (32) Mean $\pm$ SD	P (t-test)
Age (years)	67 $\pm$ 9	72 $\pm$ 8	0.010*
Body mass (kg)	60.2 $\pm$ 10.8	55.9 $\pm$ 7.6	0.032*
Height (cm)	152.9 $\pm$ 6.3	151.1 $\pm$ 4.8	0.113
BMI (kg/m <sup>2</sup> )	25.7 $\pm$ 4.1	24.4 $\pm$ 2.9	0.107
Age of menopause onset (years)	45.3 $\pm$ 6.5	47.4 $\pm$ 6.7	0.113
P1NP (ng/mL)	28.2 $\pm$ 22	22.6 $\pm$ 13	0.172
CTX (ng/mL)	0.19 $\pm$ 0.18	0.18 $\pm$ 0.15	0.648
PTH (pg/mL)	56 $\pm$ 23	57 $\pm$ 28	0.833
25OHD (ng/mL)	24.3 $\pm$ 13.8	26.1 $\pm$ 10.6	0.494
Creatinine (mg/dL)	0.78 $\pm$ 0.21	0.78 $\pm$ 0.18	0.989
CrClear (mL/min)	68.5 $\pm$ 20.9	59.8 $\pm$ 16.0	0.028*
Ca (mg/dL)	9.3 $\pm$ 0.4	9.3 $\pm$ 0.5	0.811
P (mg/dL)	3.5 $\pm$ 0.4	3.5 $\pm$ 0.5	0.922
AP (U/L)	67.6 $\pm$ 34.0	59.3 $\pm$ 14.4	0.175
UCa/UCr	0.09 $\pm$ 0.06	0.10 $\pm$ 0.09	0.268

\* Statistically significant data.

**Table 2.** Comparison of body composition and bone mineral density results between the two groups: patients with and without vertebral fractures, as detected by digital morphometry performed by DXA

	Patients without fractures (156) Mean $\pm$ SD	Patients with fractures (32) Mean $\pm$ SD	P (t-test)
Lumbar spine BMD	0.737 $\pm$ 0.111	0.720 $\pm$ 0.132	0.441
Lumbar spine T-score	-2.8 $\pm$ 1.0	-2.9 $\pm$ 1.2	0.440
Femoral neck BMD	0.648 $\pm$ 0.100	0.623 $\pm$ 0.086	0.200
Femoral neck T-score	-1.8 $\pm$ 0.8	-2.0 $\pm$ 0.7	0.216
Total femur BMD	0.744 $\pm$ 0.108	0.714 $\pm$ 0.110	0.147
Total femur T-score	-1.6 $\pm$ 0.89	-1.8 $\pm$ 0.9	0.173
Total body BMD (g)	0.914 $\pm$ 0.083	0.887 $\pm$ 0.076	0.092
Total body T-score	-2.1 $\pm$ 0.9	-2.4 $\pm$ 0.8	0.092
Body fat mass (g)	21627.9 $\pm$ 6945.5	18994.3 $\pm$ 5275.4	0.044*
Lean body mass (g)	37208.7 $\pm$ 4544.5	35945.9 $\pm$ 3670.9	0.142
Lean body mass + BMC	38741.4 $\pm$ 4656.4	37383.4 $\pm$ 3767.7	0.124
Total body mass	60369.4 $\pm$ 10661.3	56377.7 $\pm$ 6952.4	0.044*
% fat	35.0 $\pm$ 6.1	33.2 $\pm$ 6.3	0.140

According to their questionnaires, no patient reported relevant alcohol consumption; 11.7% were current or past smokers, 42.5% of them presented with at least one fracture after age 45, diabetes was reported by 19%, but the distribution of these factors were not different between the groups with and without VF. Previous or current use of glucocorticoids were reported by 11 (5,8%), but none of them in the fractured group.

Considering patients' current treatment, besides calcium and cholecalciferol supplementation (according to the diet), most of them ( $n = 142$ , 75.5%) were using bisphosphonates at the time the assessment was performed; 16 (8.5%) were receiving raloxifene; 2 (1.06%) were being treated with teriparatide; 28 (14.8%) were receiving only calcium and/or cholecalciferol supplementation, with no significant difference between the groups.

## DISCUSSION

The aim of this study was to assess the applicability of digital morphometry performed by VFA in detecting previously undiagnosed vertebral fractures in a population comprised of osteoporosis patients receiving treatment on an outpatient basis. The results showed that morphometry was able to detect moderate or severe vertebral fractures in 17% of such patients, in 87.5% of whom the fracture was unknown. In other words, approximately 1 out of 7 patients receiving regular specialized treatment on an outpatient basis presented with an unknown vertebral fracture. In a study by Jager and cols., in which VFA was performed prospectively on all patients referred for DXA for bone mass assessment, the prevalence of moderate or severe vertebral fractures in patients with osteoporosis was 22% (18), very similar to the results observed by us.

Vertebral fracture assessment conducted by quantitative morphometry performed by X-ray absorptiometry (DXA) allows us to detect prevalent vertebral fractures, which are often not clinically recognized at the time they occur. Many studies had already validated the reliability of VFA interpretation against radiographs, mainly in detecting moderate to severe vertebral fractures (19-21). As shown by others, using VFA, clinicians correctly identified 94% of radiographically defined grade 2 and grade 3 vertebral fractures and 96% of non-fractures vertebrae were correctly identified as normal on VFA (19).

The fact that VFA can be performed at the same time BMD is measured constitutes a valuable oppor-

tunity. The relative risk of new fractures is increased 4.4 times in the presence of a vertebral fracture. Additionally, it also increases the risk of fragility fractures at other sites as well (5). A vertebral fracture is associated with a 19% chance of new vertebral fractures within the next 12 months (22).

An additional advantage is the simultaneous visualization of both thoracic and lumbar spine on a single image, thus using low exposure. The radiation dose for VFA is 3 micro-Sieverts ( $\mu\text{Sv}$ ), whereas that for a simple radiograph of the lumbar spine is 600  $\mu\text{Sv}$  (23). A 3  $\mu\text{Sv}$  radiation dose is considered extremely low and comparable to the exposure dose received during a normal day (23). Since it is a digital technique, VFA allows for image manipulation and, thus, visualization enhancement, which leads to more accurate measurements. Besides, the parallel distortion caused by the X-rays' obliquity in relation to the vertebra is minimized, for the VFA performed by DXA emits rays that are perpendicular to the vertebra, especially when conducted at the supine position. VFA acquisition increases scan time in 10-15 seconds in addition to the time required for placing the patient in lateral decubitus position. The quantitative analysis is laborious, as measurements are performed individually on each vertebra. Nevertheless, it is possible to proceed in a so-called semi-quantitative manner, in which the vertebrae are graded solely by visual inspection without performing direct measurements on each vertebra, which facilitates the work and, consequently, reduces the cost of test. Several studies have already shown an excellent correlation between quantitative and semi-quantitative analyses (15,24-26) specially when referring to moderate and severe fractures.

One disadvantage of VFA is that the visualization of vertebrae above T7 is hindered by the juxtaposition of thoracic structures. On the other hand, osteoporotic vertebral fractures are uncommon in this region. As shown by others, severe and moderate fractures above T7 are less than 5% of prevalent vertebral fractures (18). There are difficulties for assessing the vertebrae in this region even with the use of radiography, which is considered as the standard imaging method for assessing fractures (18).

The detection of mild fractures, however, presents difficulties both for VFA as by conventional radiographs (27). Such fact reflects the inherent difficulty that exists in determining minimal deformities in the vertebrae (grade 1 fractures), regardless of the method.

Furthermore, mild fractures (grade 1) have been shown to have lesser clinical importance given their weaker association with new fractures, causing lesser loss of stature and less back pain (28). The severity of vertebral fractures has proven better at predicting a non-vertebral fracture than has BMD itself (8). For this reason, only moderate and severe fractures between T7 and L4 were included in our analysis.

The exact cost of this diagnostic method has not been well established in several countries yet. In 2006, the amount paid by Medicare in Los Angeles for a VFA was \$40.48 (US Dollars) versus \$84.94 (US Dollars) for a radiograph of the thoracic and lumbar spine (29).

This investigation corroborates previous studies that showed that predisposition to fracture is not dependent solely on BMD. In our population, there was no difference in BMD between the groups. Considering that all patients were receiving treatment, some of them showed densitometry scan results compatible with osteopenia at the test conducted for this study. Other risk factors played an important role in predicting the risk of vertebral fracture, such as age, total body mass and body fat mass.

Adipocytes and osteoblasts are derived from the same progenitor cells in the mesenchymal tissue, therefore there can potentially exist autocrine and paracrine effects of adiponectin on bone metabolism. Adiponectin is a hormone that is exclusively secreted by adipose tissue into the blood stream. Its blood plasma levels are inversely related to the percentage of body fat in adults. Some studies have already shown there exists a relation between serum adiponectin and risk of fractures in men, irrespectively of other factors like BMI and BMD. This relation, however, has not been established in women (30).

The difference in renal function was probably due to older age and lower weight observed in the group with FV, since there was no difference in the serum creatinine levels in both groups. Nonetheless, that may have contributed to greater fragility, as renal dysfunction progresses with abnormalities of bone turnover and mineralization, leading to a loss of bone strength (31).

Most patients were receiving treatment with bisphosphonates and cholecalciferol and, therefore, the correlation with bone remodeling markers, PTH and 25OHD was hindered.

In summary, vertebral fractures were diagnosed by VFA realized during DXA examination in 17% of patients followed in an outpatient clinic for osteoporosis,

and in more than 80% of them this diagnosis was hitherto unknown. Despite the fact that all patients in this study already had a diagnosis of osteoporosis, knowing whether or not a vertebral fracture exists is of utmost importance, since such knowledge can change their therapeutic approaches. Various studies have already shown that treatment reduces not only the risk of new fractures but also the number of hospitalizations (32-35). Therefore, routine VFAs in addition to densitometry scans might modify the evaluation of the risk of new fractures of such a patient, changing the diagnosis from osteopenia or osteoporosis to "severe osteoporosis" in cases where a VF is detected. To take the opportunity of the presence of the patient in the diagnostic center and to use the full resources that modern DXA devices offer, increasing the accuracy of assessing the risk of fractures, seems a quite appropriate strategy.

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