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# Radiographical Texture Analysis Improves the Prediction of Vertebral Fracture

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**Study Design.** Compression biomechanical tests using fresh cadaveric thoracolumbar motion segments.

**Objective.** The purpose of this study was to determine if the combination of bone texture parameters using bone microarchitecture, and bone mineral density (BMD) measurement by dual-energy x-ray absorptiometry provided a better prediction of vertebral fracture than BMD evaluation alone.

**Summary of Background Data.** Bone strength is routinely evaluated using BMD, as measured by dual-energy x-ray absorptiometry. Currently, there is an ongoing debate about the strengths and limitations of bone densitometry in clinical practice. To assess the fracture risk properly, other factors are important to be taken into account such as the macro- and microarchitecture of the bone. Recently, a new high-resolution x-ray device with direct digitization, named bone microarchitecture (BMA, D3A Medical Systems), has been developed to provide a better precision of texture parameters than those previously obtained on digitized films. **Methods.** Twenty-seven 3-level thoracolumbar motion segments (T11, T12, L1, and L2, L3, L4) of excised spines, obtained at the Anatomy Department of Marseille, were studied using bone microarchitecture to estimate 3 textural parameters: fractal parameter Hmean, co-occurrence matrix, and run-length matrix, dual-energy x-ray absorptiometry to measure BMD, and mechanical compression tests to failure. All specimens were examined by computed tomography before and after compression. The prediction of the vertebral failure load was evaluated using multiple regression analyses.

**Results.** Twenty-seven vertebral fractures were observed with a mean failure load of 2636.3 N (standard deviation, 996 N). Fractal parameter Hmean, co-occurrence matrix, and run-length matrix were each significantly correlated with BMD ( $P < 0.01$ ) and bone strength ( $P < 0.01$ ). Combining bone texture parameters and BMD significantly improved the fracture load prediction from adjusted  $r^2 = 0.701$  to adjusted  $r^2 = 0.806$  ( $P < 0.01$ ).

**Conclusion.** In these excised vertebrae, the combination of bone texture parameters with BMD demonstrated a better performance in the failure load prediction than that of BMD alone.

**Key words:** spine , vertebral , fracture risk , microarchitecture , biomechanics , texture analysis , osteoporosis .

**Level of Evidence:** N/A

Osteoporosis is an age-related progressive skeletal disease characterized by low bone mass and microarchitectural deterioration, with a consequent increase in bone fragility and susceptibility to fracture. The most frequent osteoporotic fracture is the vertebral compression fracture,<sup>1</sup> which decreases the patient's quality of life.<sup>2</sup>

Bone strength is routinely assessed using bone mineral density (BMD), as measured by dual-energy x-ray absorptiometry (DXA). The current definition of osteoporosis is a BMD T-score that is more than 2.5 standard deviations (SD) below the peak bone mass.<sup>3</sup> Each SD decrease in BMD is associated with a -1.5- to -3.0-fold increase in osteoporotic fracture risk.<sup>3</sup> Similarly, osteopenia is defined as a T-score between -1.0 and -2.5, whereas a T-score above -1.0 is considered normal.<sup>4</sup> However, many individuals without densitometric osteoporosis have greater risk of fracture, and a significant percentage of fractures occurs in females with BMD values above -2.5 SD.<sup>5</sup> These cutoff values were originally intended to assess the prevalence of osteoporosis, and not, as it is common practice nowadays, to be used as a treatment threshold. There is an ongoing debate about the strengths and limitations of bone densitometry in clinical practice. To assess *P* fracture risk accurately, it is important to take other factors into account, such as clinical risk factors as well as the macro- and micro-

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currently included in the definition of osteoporosis.<sup>6</sup> It is now possible to assess trabecular thickness, trabecular separation, star volume, and bone volume/trabecular volume by different techniques. The bone microarchitecture (BMA) can be measured 3-dimensionally (3D) using high-resolution quantitative computed tomography. In postmenopausal females, vertebral and nonvertebral fractures are associated with low volumetric BMD and architectural alterations of the cortical and trabecular bone, measured by high-resolution quantitative computed tomography, partially independently of the BMD.<sup>7</sup> However, this technique cannot be applicable to large sample groups in routine clinical settings for cost and availability.<sup>8</sup> There is a growing interest in the use of techniques with broad availability, such as x-ray devices or bone densitometry.<sup>9,10</sup> However, these projectional methods transform a 3D structure into a 2-dimensional image, and thus must be validated for bone strength analysis. Recently, a new high-resolution x-ray device with direct digitization, named BMA, has been developed to provide a greater accuracy in texture parameters than were previously obtained on digitized films.<sup>11,12</sup> Furthermore, the combination of BMD and bone texture analysis on the calcaneus has been shown to improve the fracture risk evaluation by adding information related to microarchitecture.<sup>12</sup> However, because the calcaneus is not prone to osteoporotic fracture, a direct assessment of the spine would seem to be clinically more pertinent. Because BMA has not yet been assessed on vertebrae, we have designed a preliminary study on anatomical specimens.

In this project we studied thoracolumbar motion segments of excised spines using this high-resolution x-ray device, to assess 3 textural parameters: fractal parameter Hmean, co-occurrence matrix, and run-length matrix. Our primary objectives were to correlate the bone texture features in the vertebrae with bone strength to determine if the combination of the texture parameters and BMD provided a better prediction of vertebrae fracture than BMD evaluation alone.

## MATERIALS AND METHODS

### Vertebral Motion Segments

Twenty-seven fresh 3-level thoracolumbar motion segments (T11, T12, L1 = 14; and L2, L3, L4 = 13) from 15 human spines were obtained at the Anatomy Department of Marseille within 10 days after death, in accordance with institutional safety and ethics regulations. Donor consent for research purposes was obtained prior to death. All specimens were carefully cleaned off muscle tissue. Intervertebral disc and ligaments were kept intact. The vertebrae were labeled as VB1, VB2, and VB3 from the top to the bottom.

The specimens were stored at  $-20^{\circ}\text{C}$ . All specimens were thawed at room temperature for 24 hours before testing. Thus, only one cycle of defrosting was required.

After defrosting, all spines were first examined with computer tomography screened by a musculoskeletal radiologist for signs of previous fracture and metastatic bone disease (Figure 1). Vertebral body (VB) height was measured using numeric calipers accurate to 0.1 mm. The age range of the

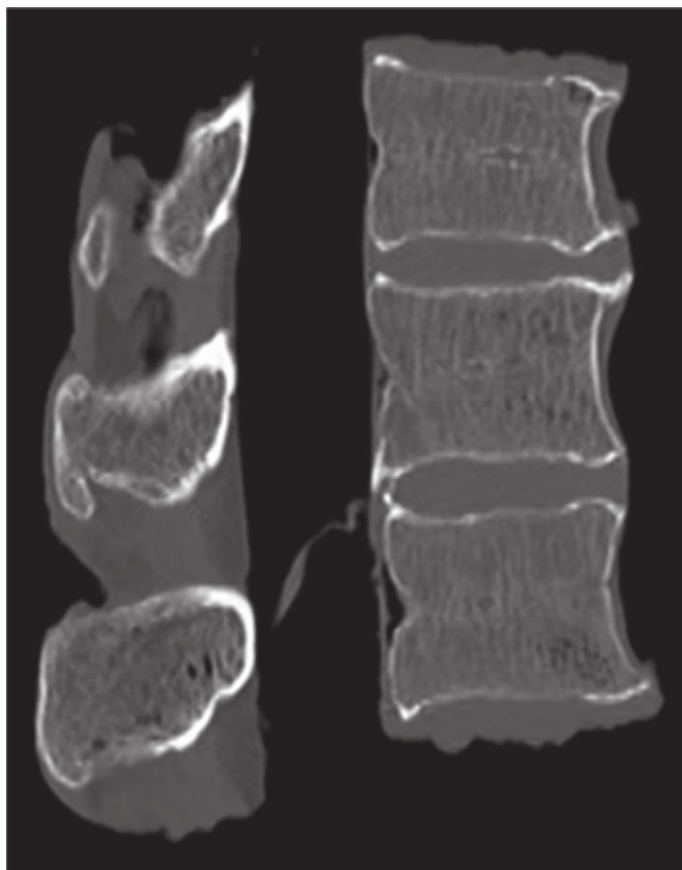
27 specimens from 15 donors (7 females, 8 males) was from 48 to 97 (mean = 81.6; SD = 12.9). No information was available on the cause of death or previous illnesses.

### DXA Measurements

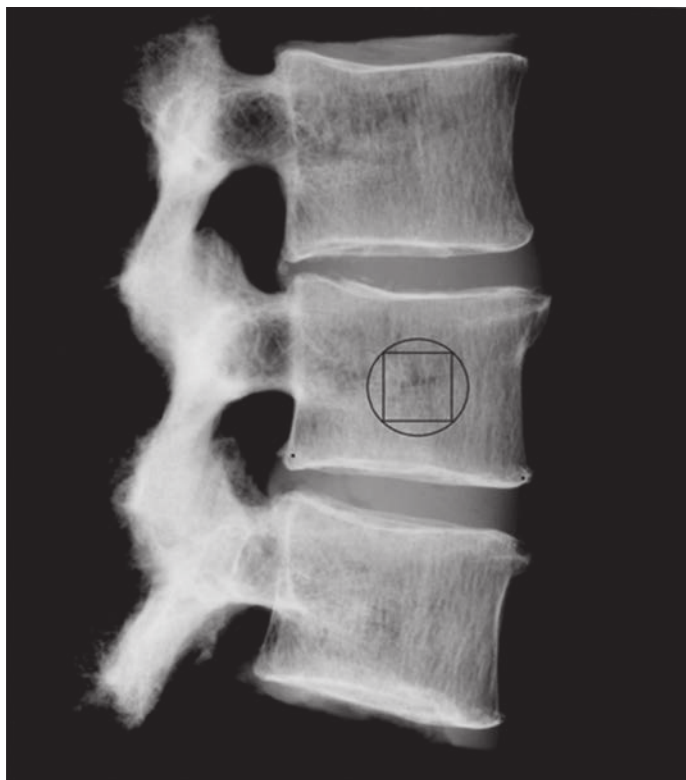
The specimens were positioned similar to *in vivo* examination conditions in a vessel filled with tap water up to 15 cm in height to simulate soft tissue. DXA measurements were taken with a Prodigy Scanner (GE/Lunar; GE Medical Systems, Milwaukee, WI). BMD was measured in each VB in each specimen. The measurements were assessed using the Lunar Prodigy Advance software (GE Medical Systems). The BMD value of VB2 of each specimen was noted.

### Bone Texture Analysis

A high-resolution x-ray device (BMA, D3A Medical Systems, Orleans, France) with a new  $15 \times 23$ -cm detector with a  $50\text{-}\mu\text{m}$  pixel was used to get the digitized profile radiograph of these vertebral segments. The following parameters were used: 50 kV, 8 mA, and 0.8 m focal distance. During the study, a calibration test was carried out each day of examination using an external phantom to detect any potential drift of the instrumentation.<sup>11</sup> The specimens were positioned similar to *in vivo* examination conditions, vertically, on a stool. A region of interest (ROI) of  $150 \times 150$  pixels was selected in the center of the VB on a lateral view, in a standardized manner (Figure 2).



**Figure 1.** Initial CT scan of vertebral motion segment. Sagittal reconstruction. CT indicates computed tomography.



**Figure 2.** BMA image demonstrating the position of the ROI used for the measurement of textural parameters. BMA indicates bone microarchitecture; ROI, region of interest.

The texture parameters obtained for each ROI were the fractal dimension Hmean, the co-occurrence matrix, and the run-length matrix.<sup>12</sup> The gray levels of the ROIs were fitted to the most used fractal model for texture images: the fractional Brownian motion. Fractal shapes were then described by a single parameter, H (Hurst exponent), related to the fractal dimension, D, by  $H = 2 - D$ .<sup>12</sup> For gray-level run-length analysis, adjacent pixel runs ( $n, n + 1$ ) were defined in a given direction, and parameters were computed on the basis of on the run-length distribution histogram.<sup>8</sup> Co-occurrence matrices characterized the joint probability of having a pair of gray levels separated by a given distance in any given direction.<sup>8</sup>

### Mechanical Testing

An imprint of the endplates of each segment was made using a common epoxy resin.<sup>13</sup> The resin enabled thoracolumbar motion segments to be set in the vertical axis of the compression device.

The thoracolumbar motion segments were then placed between platens on a materials testing machine (Figure 3). Each specimen was loaded to failure in a universal testing machine (Instron 5566, Instron, Canton, MA) at the velocity of 15 mm/min.<sup>14</sup> The orientation of the vertebral motion segments in the loading apparatus was designed to simulate an osteoporotic compression fracture.<sup>13</sup> Compression was applied to the superior platen along the central axis of the VB until failure occurred. Failure was defined as a precipitous



**Figure 3.** Loading apparatus for mechanical testing of the vertebral motion segment in compression.

decrease in load with increasing compression of the VB. Force and deformation data were recorded.<sup>15</sup>

All specimens were then examined by computed tomography, and VB height was measured again after compression and compared with the first CT.

### Statistical Analysis

Statistical analyses were performed with SPSS version 17 (SPSS, Chicago, IL) and supervised by a statistician. Descriptive statistics (mean and SD) were computed for all quantitative study parameters. To assess correlations between measured variables (texture parameters BMD, fractal parameter Hmean, and co-occurrence matrix and run-length matrix) and failure load respectively, we used Spearman correlation coefficients. To identify the best predictors of failure load, linear multiple regression models were computed. First, univariate linear regressions were completed with failure load as the dependent parameter and the measured variables as independent parameters. Then, a backward linear regression was carried out. The variables that entered into the model were those with a *P* value less than 0.20 in the univariate model

and remained in the final model variables with a  $P$  value less than 0.05.

## RESULTS

We observed 27 vertebral fractures. Three specimens were excluded from the mechanical tests for technical reasons. The mean failure load was 2636.3 N (SD = 996). The mean BMD in our cohort was 0.88 g/cm<sup>2</sup> (SD = 0.23). BMD is correlated with all the values of BMA (Table 1).

Load to failure is significantly correlated to BMD ( $P < 0.01$ ) and to Hmean ( $P < 0.01$ ), co-occurrence matrix ( $P < 0.01$ ), and run-length matrix ( $P < 0.01$ ) (Table 2; Figures 4, 5).

Stepwise regression with backward elimination demonstrated that combining bone texture parameters and BMD significantly improved the fracture load prediction from adjusted  $r^2 = 0.70$  for DXA alone to adjusted  $r^2 = 0.81$  ( $P < 0.01$ ) (Table 3).

## DISCUSSION

Osteoporotic vertebral fractures are associated with increased morbidity and mortality.<sup>16</sup> The standard diagnostic technique for assessing osteoporosis and monitoring therapy is DXA measuring BMD.<sup>3</sup> Jager *et al*<sup>17</sup> demonstrated that the prevalence of vertebral fracture was 14% in patients with normal BMD in a consecutive sample of 2500 patients referred for BMD. Indeed, a biomechanical study demonstrated that during strenuous compressive loading of the vertebra, the tissue near and including the endplates is at its highest risk of initial failure.<sup>18</sup>

However, although BMD can predict vertebral bone strength to some extent, other factors of the so-called bone quality contribute to bone strength, such as macroarchitecture, microarchitecture, mineralization, and size and quality of the crystal, as well as rate of bone turnover.<sup>19</sup> Microarchitecture is, in particular, one of the most relevant contributors of bone strength and is part of the definition of osteoporosis.<sup>20</sup> Because osteoporosis decreases bone density as well as the number of trabeculae and increases the trabecular separation, it also alters x-ray attenuation in bone, and thereby changes the density and texture of the image.

A study on *ex vivo* vertebrae analyzed by a finite element model has shown that microstructural variability has a significant effect on the mechanical properties and tissue stress of the human vertebral cancellous bone. Considering

**TABLE 1. Correlation Coefficients Between BMD and Textural Parameters**

	BMD
Hmean	0.737*
Co-occurrence	0.492*
Run-length	0.539*

$P < 0.01$ .

BMD indicates bone mineral density.

**TABLE 2. Correlation Coefficients Between Load to Failure, BMD, and Textural Parameters**

	Load
BMD	0.844*
Hmean	0.606*
Co-occurrence	0.725*
Run-length	0.727*

$P < 0.01$ .

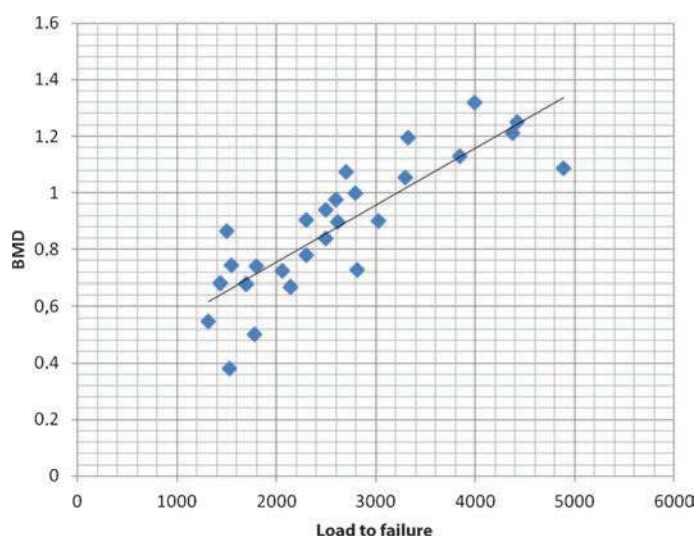
BMD indicates bone mineral density.

microstructural variability may improve the understanding of bone fragility and the assessment of vertebral fracture risk.<sup>21</sup>

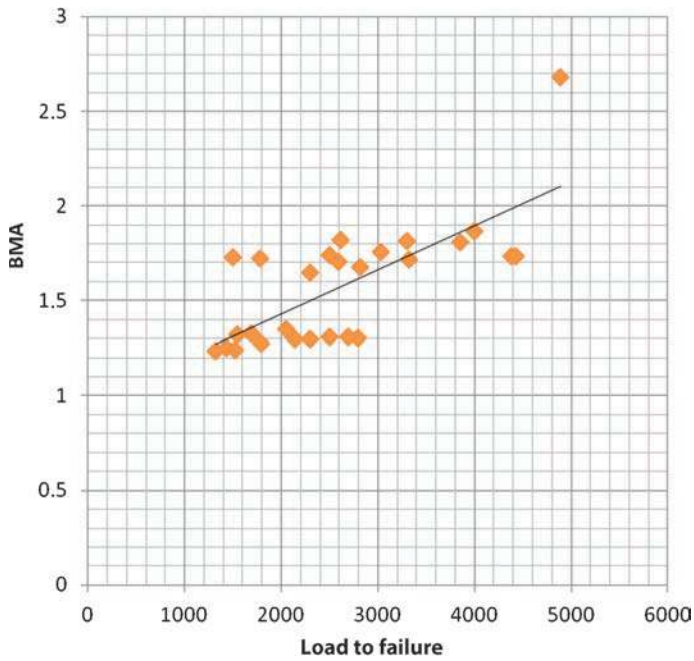
Another biomechanical study on *ex vivo* lumbar vertebrae analyzed for BMD by DXA and microarchitecture by high-resolution peripheral quantitative computed tomography, by virtual biopsies and then tested in axial compression, indicates that the regional variation of microarchitecture assessment expressed by heterogeneity parameters may enhance a prediction of vertebral fracture risk.<sup>22</sup>

Therefore, the issue of whether the bone texture analysis has the potential to assess the quality of certain bones complementary to and independent of BMD measurements has become a crucial research topic.

The trabecular bone score (TBS) is a new gray-level texture measurement that uses an experimental variogram of 2-dimensional projection images. TBS is not an estimator of fractal dimension. A recent review study has shown that although microarchitecture may influence the TBS, today there is insufficient evidence that a TBS measurement provides reliable information on the status of the BMA for a given patient.<sup>23</sup>



**Figure 4.** Graph displaying the relation observed between the vertebral failure load (in Newton, abscissa) and BMD (in grams per square centimeter, ordinate) in 27 specimens. BMD indicates bone mineral density.



**Figure 5.** Graph displaying the relation observed between the vertebral failure load (in Newton, abscissa) and textural parameters in 27 specimens. BMA indicates bone microarchitecture.

The texture of projectional images obtained by radiography reflects the trabecular bone 3D microarchitecture and exhibits the properties of fractals.<sup>24</sup> Consequently, the alterations of trabecular bone provide an increase of fractal dimension, which means a decrease of Hmean parameter.<sup>25</sup> Generally, the decrease of fractal parameter Hmean is considered as an index of higher image irregularity or complexity. Therefore, the less isotropic the bone texture is, the lower the mechanical properties are.

In vertebrae, the bone texture parameters are highly correlated with bone strength. In particular, the fractal parameter Hmean demonstrates significant correlations with bone failure load.<sup>26</sup> Besides, the potential interest of texture analysis has been highlighted in clinical studies, suggesting that DXA and BMA assess different bone parameters.<sup>12,27</sup> In addition, when compared with histomorphometric indices measured

on calcaneus biopsies, Hmean is correlated with a trabecular separation and reflects more BMA than bone mass.<sup>28</sup> All these data suggest that the texture information contained in the trabecular bone structure may determine local bone quality independently of BMD.<sup>25</sup> Therefore, to refine the bone strength prediction, we assessed a combination of conventional BMD measurement on excised vertebral motion segments using DXA and bone texture parameters. We used a high-resolution digital x-ray device to obtain greater accuracy of the textural parameters than that of the secondary digitization of radiographical images.<sup>11</sup>

The ROIs were chosen out of the cortical bone and had to match with the BMD measurement site. To explain the correlation between texture parameters and BMD observed in our cohort, we assumed that some microarchitectural alterations evolving in the same way as BMD may have been captured by density measurements.<sup>12</sup>

Besides, because the bone texture parameters reflect mechanical properties, the fractal parameter Hmean, co-occurrence matrix, and run-length matrix each significantly correlate with bone strength in our study ( $P < 0.01$ ). Finally, in our cohort, multiple regression analyses demonstrated that adding the texture parameters of the trabecular bone of the vertebrae to BMD values led to a better performance in fracture load prediction than that of BMD alone, which is consistent with the previous results obtained in a clinical study on the calcaneus<sup>12</sup> and on the femoral neck.<sup>29</sup>

Although the bone texture analysis is not a technique to assess 3D architecture, this tool for characterizing BMA could be applied clinically to radiographs to detect bone changes related to age and osteoporosis leading to a bone strength decrease. Therefore, patients who have a risk of vertebral fracture with a normal BMD could be identified with BMA and receive preventative treatment.

The digital x-ray detector allows examination at a very low dose (*i.e.*, effective dose  $< 2 \mu\text{SV}$  for a calcaneum examination). In our study, the average dose of the BMA is 0.320 mGy. Therefore, the radiation dose related to BMA is very low in comparison with standard spine radiograph examinations.

Some limitations may be considered inherent to the materials and methods used in our study. Although the use of frozen human cadaveric specimens allowed us to draw conclusions about the actual bone strength, we recognize that the nature of using these types of specimens limits the application *in vivo*.

First, our group of specimens was relatively small, with no data available on the cause of death or previous illnesses and, therefore, cannot be considered as a normal sample regarding the bone status. Nevertheless, the ranges of BMD and failure load in our cohort were similar to previously published *ex vivo* studies.<sup>14</sup>

Second, the small amount of gas related to the degradation contained in the specimens may have altered the BMD measurement and the texture analysis. In the same way, soft-tissue removal may have changed the associations of failure load with densitometric and textural features.

**TABLE 3. Multiple Regression Analysis of Combinations of BMD and Textural Variables (TP: Hmean; Co-occurrence; Run-Length) Used to Explain the Vertebral Failure Load**

	$r^2$	Adjusted $r^2$
BMD	0.71	0.70
BMD and TP	0.82	0.80

The significant level required to enter the equation is  $P < 0.05$ .

BMD indicates bone mineral density; TP, textural parameters.

Third, every specimen was scanned once for BMA measurement but it is known that there is a good reproducibility of textural parameters.<sup>29</sup>

Finally, because we assessed vertebral failure load using a protocol that simulated one type of compression and displacement rate only, our results do not include many additional factors encountered *in vivo*, such as overlying soft tissue, muscular strength, or the nature of a fall.

## CONCLUSION

We have shown that the texture analysis of radiographs obtained from excised vertebral motion segments correlates with the biomechanical strength of the specimens and provides an assessment of the bone quality complementary to the BMD data. To the best of our knowledge, this study is the first to demonstrate that the combination of BMD and the texture analysis using a high-resolution digital x-ray device allows a significantly better prediction of the vertebral bone strength than DXA alone. The data obtained *ex vivo* should now be confirmed by further clinical studies with a better selection of patients at high risk of fracture, who were not detected by the DXA alone. These patients could subsequently be considered as candidates for antiosteoporotic treatment.

## KeyPoints

- ❑ This study shows that fractal parameter Hmean, co-occurrence matrix, and run-length matrix each is significantly correlated with BMD and bone strength.
- ❑ This study demonstrates that adding the texture parameters at the trabecular bone of the vertebrae to BMD values led to a better performance in fracture load prediction than that of BMD alone.
- ❑ The data obtained *ex vivo* should now be confirmed by further clinical studies.

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