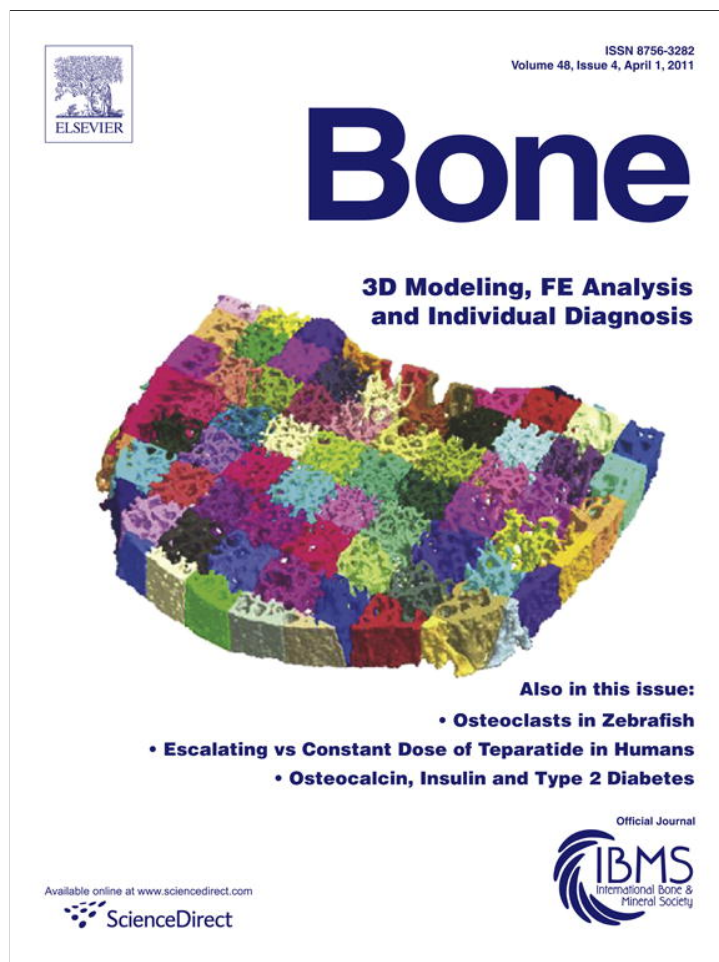


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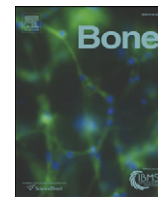
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## Vulnerability of healthy vertebrae in patients with and without previous vertebral fracture

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### ARTICLE INFO

#### Article history:

Received 5 July 2010

Revised 12 October 2010

Accepted 14 December 2010

Available online 23 December 2010

Edited by: Felicia Cosman

#### Keywords:

Vertebral fractures

Wedge angle

Healthy vertebrae

Kyphosis

### ABSTRACT

Vertebral deformities are associated with a marked increase in morbidity, mortality, and burden in terms of sanitary expenditures. Patients with vertebral fractures have a negative impact in their health, less quality of life, and loss of functional capacity and independence.

The purpose of this study was to explore the vulnerability of healthy vertebrae in patients who have sustained already a compression fracture and in patients who do not have prevalent fractures in the thoracic spine; and to explore the association of the deformity in healthy vertebrae with different variables, such as bone mineral density (BMD), body mass index, age, loss of height, presence of clinical kyphosis, history of other osteoporotic fractures, and falls occurring during the last year.

Clinical data and complementary studies from 175 postmenopausal outpatients were analyzed. These women (age:  $69.7 \pm 11.1$  years) had not received any treatment for osteoporosis. Anteroposterior and lateral radiographs of the thoracic spine and bone densitometry of the hip were obtained; morphometry was performed in 1575 thoracic vertebrae from T4 to T12.

The angle of wedging of each vertebral body was calculated using a trigonometric formula. Then, the sum of wedge angles of vertebral bodies (SWA) was determined, and Cobb angle was measured.

In patients with vertebral fractures, after excluding the angles of fractured vertebral bodies, the mean wedge angle of the remaining vertebrae (MWAhealthy) was calculated. The same procedure was followed in patients without vertebral fractures. MWAhealthy was considered as an indicator of the structural vulnerability of non-fractured vertebrae.

Patients with prevalent fractures had lower BMD, wider Cobb angle, and higher sum of wedge angles than patients without vertebral fractures. The proportion of patients with accentuation of clinical kyphosis was higher in the group with prevalent vertebral fractures. A highly significant difference was found in the MWAhealthy, which was higher in patients with prevalent fractures ( $4.1 \pm 1.3^\circ$  vs.  $3.0 \pm 1.1^\circ$ ;  $p < 0.001$ ). Patients showing vertebral fractures had  $7.1 \pm 4.2$  cm height loss in average, significantly superior than that found among non-fractured women ( $3.6 \pm 3.2$  cm;  $p < 0.01$ ).

In multivariate analysis, the increase of MWAhealthy was associated with advancing age ( $p < 0.02$ ), lower femoral neck BMD ( $p < 0.005$ ), presence of clinical kyphosis ( $p < 0.01$ ) and vertebral fractures ( $p < 0.02$ ).

This study presents evidence that a series of factors independently influence the increase in wedging deformity of vertebral bodies that are not fractured yet. These factors could contribute to an increased vulnerability of the vertebrae, making them more susceptible to fracture.

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### Introduction

Osteoporotic vertebral compression fractures (VFX) constitute a serious public health problem. Its importance grows as life expectancy increases [1]. Population studies carried out in different countries

have demonstrated that VFX are frequent and their prevalence and incidence rates increase with age both in men and in women [2–5].

The prevalence rate of vertebral fractures in women aged 50 years is approximately 10% and reaches 25–50% at age of 80 [6,7]. Among different types of vertebral deformities described by morphometric studies, compression fractures are the most frequent [7,8]. Two thirds of vertebral fractures are localized in the thoracic spine between the fourth (T4) and the twelfth (T12) vertebrae [9]. Epidemiological

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studies show that individuals with previous VFX have a higher probability of sustaining appendicular fractures [10–12]. Besides, the presence of a VFX increases the risk of a new VFX fivefold [13,14]. The probability of sustaining a new VFX in the year after a VFX increases significantly [15].

Vertebral deformities are associated with higher morbidity, mortality, and financial burden for health services [16,17].

Patients with VFX suffer a negative impact, with deterioration of their quality of life, and loss of both functional capacity and independence [18–21].

Although some cross-sectional studies reveal a tendency towards the deformation of vertebral bodies with age in both sexes, the evidence of an association between increasing anterior deformity, age and VFX is still controversial [22–24].

Until now there is no clear evidence about an association between slight deformities in vertebral bodies and low bone mineral density (BMD) [25,26]. The pattern of changes in the shape of vertebral bodies in the thoracic spine in association with age is not completely clear.

The purpose of this study was to explore the vulnerability of healthy vertebrae in patients that have sustained already a vertebral compression fracture, and in patients that do not present prevalent fractures in the thoracic spine; and to explore the association of the deformity in vertebrae without structural involvement with different variables such as BMD, body mass index (BMI), age, loss of height, presence of clinical kyphosis, past history of other osteoporotic fractures and of falls during the previous year.

## Patients and methods

We studied 189 consecutive postmenopausal ambulatory patients, without previous treatment for osteoporosis, aged between 50 and 90 years, visiting the Center for the Study of the Climacteric (CEC) in the Hospital Provincial del Centenario of Rosario city between March and December 2008. Clinical data (medical history, physical examination) and laboratory tests were analyzed; AP and lateral X-ray films of the thoracic spine, and hip bone densitometry (DXA) were obtained.

### Exclusion criteria

Exclusion criteria were: radiologic evidence of vertebral deformities due to conditions other than osteoporosis, such as congenital malformations, Scheuermann's disease, Paget's disease of bone, scoliosis, ankylosing spondylitis, severe osteoarthritis; clinical or biochemical evidence compatible with primary hyperparathyroidism, chronic renal disease, collagen diseases, and current or past intake of osteoactive medication.

Three patients with Scheuermann's disease, three with significant scoliosis, one with primary hyperparathyroidism, three with poor quality X-ray studies, and four with severe osteoarthritis were excluded.

### Anthropometric data

Historical height was obtained interrogating about height at age 25. Present height was measured with a stadiometer with a 0.1 cm precision. Weight was measured in a clinical scale with a 0.1 kg precision. BMI was calculated by dividing weight in kg by height in m<sup>2</sup>.

### Densitometric studies

Bone densitometry was made with a Lunar DPX equipment.

### Radiological studies

Radiographs of the thoracic spine were performed according to a standard protocol. Antero-posterior and lateral films of the spine were

taken with the patients in a standing position. The X-ray beam was centered in T7. The focus-to-film distance was 120 cm.

### Morphometric evaluation—Cobb angle

First, a qualitative evaluation was made to exclude vertebral deformity causes other than osteoporotic fractures and poor quality X-ray films.

Radiologic morphometry was performed in 1575 vertebrae of the thoracic spine from T4 to T12, belonging to the 175 patients that were included in the study. Measurements were made by one examiner (MM), who stayed blind to all other patients' data.

Six points were marked in each vertebral body, corresponding to the four corners and the midpoints of the endplates. A Vernier caliper was used, with a precision of tenths of a millimeter. In each vertebral body measurements were made of the anterior, middle and posterior heights, in order to define the presence of compression fractures with Genant's semiquantitative method, and of the superior endplate in order to calculate the angle of vertebral wedging [27]. The SQ (semiquantitative) Genant's approach is frequently used to identify prevalent (and/or incident) vertebral fractures, and consists of a visual qualitative assessment of the radiological characteristics of the vertebrae (end plate-cortical margin) as well as the reduction in the vertebral body height. Vertebrae are graded as normal (grade 0), with mild fracture (grade 1) when there is a 20–25% reduction in the anterior, middle or posterior height), moderate fracture (grade 2), 25–40% reduction in any height, and severe fracture (grade 3), which corresponds to a reduction of more than 40% in any height.

For the purpose of this study, a vertebral compression fracture was defined (according to Genant's method) when the anterior or middle height was decreased by at least 20% (or 4 mm) compared to the posterior height, and when qualitative changes were recognized. This criterion was exclusively used to discriminate between patients with and without fractured vertebrae, independently from the grade or severity of vertebral deformity.

In every radiographic film the wedge angle of each vertebral body was determined using a trigonometric formula [28]. Then, the sum of the wedge angles of T4–T12 vertebral bodies (SWA) was calculated. Finally, Cobb angle was measured.

In patients with vertebral fractures, after excluding the angles belonging to fractured vertebral bodies, the sum of the angles corresponding to the uncompromised vertebrae was made, and the average of this sum was calculated (MWAhealthy). The same procedure was undertaken in patients without vertebral fractures. MWAhealthy was considered as an indicator of the structural vulnerability of non-fractured vertebrae.

### Measurement precision

In order to evaluate intra-operator reliability, a trained observer with very good level of skill, measured dimensions of thoracic vertebrae twice in a subsample of 20 radiographs, totaling 1,080 measurements. Time elapsed between both measurements was at least a week.

### Statistical analysis

Variables studied were age, BMI, hip BMD, Cobb angle, MWAhealthy, presence of VFX and clinical kyphosis, loss of height (since age 25 to present day), history of falls in the last year, and past history of fractures.

Analysis of results: The values of the measurements are presented as mean ± standard deviation (SD). Categorical variables were expressed as percentage.

Chi square ( $\chi^2$ ), Student *t*-test, and multivariate regression analyses were performed.

The approach suggested by D. G. Altman and J. M. Bland for the evaluation of the agreement between two repeated measurements was applied. It is based on graphical techniques and uses simple calculations [29]. This graphic method represents the difference of paired values observed with respect to their mean value. Besides, “concordance limits” are defined combining the mean and the SD of the differences (Mean ± 2 SD). This type of graphic allows the identification of extreme differences, and the evaluation of the tendency using a lineal regression analysis. When no systematic error exists, the points are distributed at random at both sides of the straight line corresponding to 0 difference between measurements. The SD of repeated measurements on the same object is known as the within-subject SD (WSSD). This may be used to evaluate the measurement error size. The assumption that the WSSD is the same for all measured objects was tested applying the Pitman’s variance ratio test.

A reliability analysis was also applied to evaluate measurement precision. Intra-class correlation coefficient (ICC) was used to compute intra-observer reliability. ICC is defined as the proportion of total variability that is due to patients’ variability. Like every proportion, the ICC values can oscillate between 0 and 1, so that the maximal possible concordance corresponds to a value of ICC = 1. On the other side, the value ICC = 0 is obtained when the observed concordance equals that expected to occur randomly. Values below 0.30 indicate bad or null concordance; those between 0.31 and 0.50 low reliability; those between 0.51 and 0.70 a moderate concordance; those between 0.71 and 0.90 good concordance; and those above 0.90 an excellent reliability [30].

All analyses were conducted using the statistical software package, STATA version 10.1. Significant level was set at  $p < 0.05$ .

**Results**

The sample included 175 patients (age: 69.7 ± 11.1 years) that were divided in two groups: Patients without VFx (n = 130) and patients with VFx (n = 45). The prevalence rate of vertebral compression fractures of the thoracic spine was 25.7%. Of all observed fractures, 86.7% were wedge deformities; 8.3% were biconcave fractures and 5.0% were total collapses (crush fractures).

Table 1 resumes the characteristics of the sample. Patients had a mean age above 65 years and those that presented any vertebral fracture, were older than the patients without VFx. Since age constitutes an important risk factor, the values of different continuous variables were adjusted for age.

As can be seen in Table 1, patients with prevalent fractures have lower BMD, higher Cobb angle, and higher SWA than patients without fractures. The proportion of patients with notorious clinical kyphosis was higher in the group with prevalent vertebral fractures. Regarding the proportion of patients with past history of falls and fractures of the appendicular skeleton, it was higher among patients with vertebral fractures, although p values were in the limit of statistical significance. There were no significant differences between both groups regarding BMI. A highly significant difference in the mean wedge angle of

**Table 1**  
General characteristics of the series.

Variables	Patients without VFx (n: 130)	Patients with VFx (n: 45)	p	p (age-adjusted)
Age (years)	67.7 ± 11.12	75.3 ± 9.0	<0.001	–
BMI (kg/m <sup>2</sup> )	27.0 ± 4.8	26.4 ± 3.8	0.6160	0.793
BMD (g/cm <sup>2</sup> )	0.774 ± 0.13	0.699 ± 0.11	<0.001	0.132
Cobb angle (°)	44.3 ± 13.3	64.5 ± 12.8	<0.0001	<0.001
SWA (°)	27.3 ± 10.2	48.3 ± 13.6	<0.0001	<0.0001
MWAhealthy (°)	3.0 ± 1.1	4.1 ± 1.3	<0.0001	<0.001
Loss of height (cm)	3.6 ± 3.2	7.1 ± 4.2	<0.001	0.01
Clinical kyphosis (%)	36.2	84.4	<0.0001	–
History of falls (%)	35	51	0.063	–
History of other Fx (%)	23	37	0.055	–

**Table 2**  
Bivariate studies in the whole sample.

Variables, dependent/independent	All patients (n: 175)
Cobb angle/age	r: 0.49; p<0.0001
MWAhealthy/Cobb angle	r: 0.67; p<0.0001
MWAhealthy/BMD	r: -0.41; p<0.0001
SWA/age	r: 0.48; p<0.0001

healthy vertebrae (MWAhealthy) was found, which was higher in patients with prevalent fractures. Patients with prevalent vertebral fractures showed a mean loss of height of 7 cm, significantly higher to that found among non-fractured women (3.7 cm). When adjusted for age, only BMD loses statistical significance.

*Bivariate analyses*

Table 2 shows the increase in radiologic kyphosis (expressed by the mean Cobb angle) with increasing age in all patients in the sample. This association is maintained both in patients with and without prevalent vertebral fractures (Fig. 1).

Fig. 2 shows the association between radiologic kyphosis measured with Cobb angle and wedging of healthy vertebrae in patients with and without vertebral fractures.

*Wedging of healthy vertebrae*

Table 2 shows that patients with higher BMD have lower mean wedge angle in their healthy vertebrae; the inverse association is highly significant.

This inverse relation found in the total sample is maintained in the group of patients with vertebral fractures, in which the degree of wedging in healthy vertebrae increases with lower BMD (Fig. 3). Although with lesser adjustment, the association is maintained in patients without prevalent fractures.

Finally, there was a positive association between the sum of wedge angles and age of the patients in the total sample (Table 2), and in patients with and without fractures (Fig. 4).

*Morphometry precision*

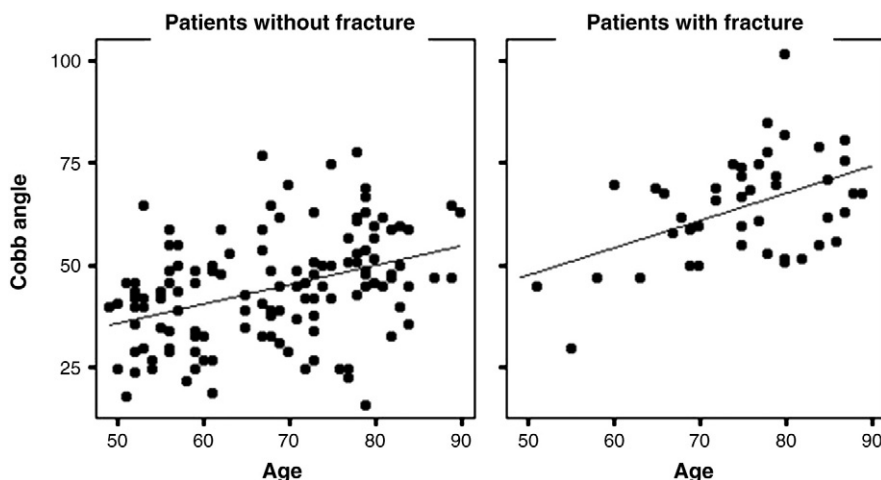
Fig. 5 shows the Bland–Altman graph of intra-observer measurements. The concordance limits obtained according to this method were -0.757 and 0.741 mm, corresponding to the upper and lower lines in the graph. The central line corresponds to a zero difference between measurements. The points were randomly distributed at both sides of the line corresponding to zero difference between measurements, and so a systematic error in measurements can be ruled out. It should also be noted that there were no significant differences between WSSD (p = 0.753), indicating a low measurement error.

Furthermore, reliability analysis shows that the resulting ICC was 0.9975 with a 95% confidence interval between 0.9970 and 0.9979. This value was significantly different from zero (p < 0.00001). The degree of agreement was almost perfect, and the confidence interval was narrow, indicating that the point estimate was reliable.

*Multivariate study*

A multivariate analysis was performed taking MWAhealthy as a dependent variable. Age, BMI, BMD, clinical kyphosis, past history of fractures and previous falls were included as independent variables.

MWAhealthy was positively associated with age (p < 0.02), presence of clinical kyphosis (p < 0.01), presence of vertebral fracture (p < 0.02); and negatively with BMD (p < 0.005). There were no interactions between independent variables.



**Fig. 1.** Association between radiological kyphosis measured by Cobb angle and age, in patients with and without vertebral fractures ( $r=0.39$ ,  $p<0.0001$ ;  $r=0.47$ ,  $p<0.0011$ , respectively).

The regression equation obtained in the multivariate analysis was:

$$\text{MWA}_{\text{healthy}} = 3.068 + 0.476 (\text{VFx}) + 0.02 (\text{Age}) + 0.473 (\text{Kyphosis}) - 2.099 (\text{BMD})$$

where: VFx and kyphosis take value = 0 when absent and value = 1 when present, while age and BMD take the corresponding measured values.

In fractured patients, the variable VFx = 1; thus the equation is:

$$\text{MWA}_{\text{healthy}} = 3.544 - 2.099 (\text{BMD}) + 0.02 (\text{Age}) + 0.473 (\text{Kyphosis})$$

In non-fractured patients, the variable VFx = 0; thus the equation is:

$$\text{MWA}_{\text{healthy}} = 3.068 - 2.099 (\text{BMD}) + 0.02 (\text{Age}) + 0.473 (\text{Kyphosis})$$

The ordinate at origin in the equation for fractured patients is different from and higher than the one for non-fractured patients.

The difference between these ordinates is 0.476 (15%).

Healthy vertebrae of patients presenting at least one fracture have 15% more wedging than those from patients who have not sustained any fracture (provided they are in similar situation regarding kyphosis, have the same age, and the same BMD).

Mean wedge angle of healthy vertebrae is 3° in patients without VFx and 4° in patients with VFx, which represents a 25% increase in mean wedging. When this is adjusted for the other intervening variables the increase is 15%.

Women of older age, lower BMD, presence of clinical kyphosis, and prevalent vertebral fractures will have a higher wedging in their healthy vertebrae.

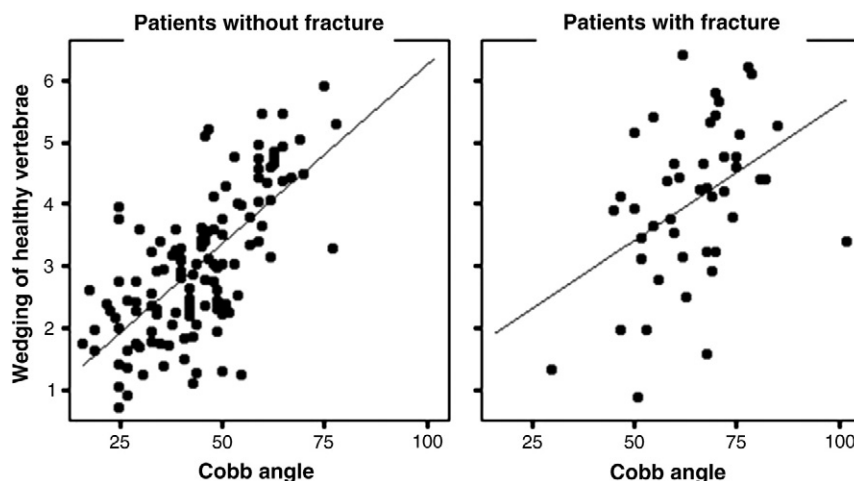
### Discussion

Two thirds of vertebral fractures occur in the thoracic spine [31]. Among them wedge fractures are more frequent than biconcave fractures, and both are more prevalent than crush fractures. Thoracic kyphosis in patients is due to deformities localized in this segment of the spine.

The main goal of our study was to morphometrically explore the vulnerability (wedge deformity) of healthy vertebrae (i.e., not considered as fractured), among patients with and without prevalent vertebral fractures. We also sought to explore the relation of wedging with kyphosis, and to evaluate factors possibly involved in this deformity.

### Precision

Intra-operator reliability obtained in our study was similar to that reported in a clinical study investigating 50 osteoporotic patients [32],



**Fig. 2.** Degrees of vertebral wedging as a function of radiologic kyphosis measured by Cobb angle in patients with and without vertebral fractures ( $r=0.68$ ,  $p<0.0001$ ;  $r=0.43$ ,  $p<0.002$ , respectively).

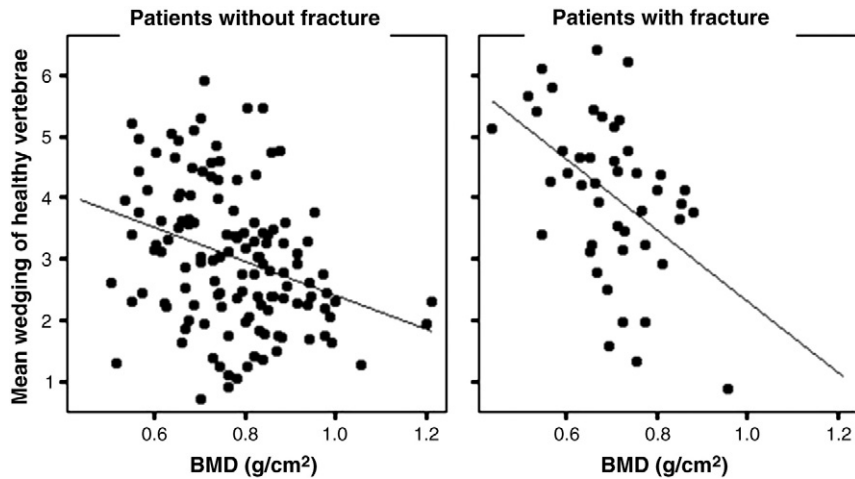


Fig. 3. Association between degree of wedging of healthy vertebrae and BMD in patients with and without vertebral fractures ( $r = -0.32$ ,  $p < 0.0001$ ;  $r = -0.47$ ,  $p < 0.001$ , respectively).

and to that reported in another study of normal and osteoporotic subjects [33].

*Radiologic kyphosis and age*

Cobb angle is positively associated with age both in fractured and non-fractured patients. The association between this classic indicator of radiologic kyphosis and age is well known; it demonstrates the changes that occur with aging in vertebral bodies and in intervertebral discs [34,35]. It is also well known that although vertebral fractures are associated to a more severe kyphosis, they do not completely explain its presence [35]. The association found here between Cobb angle and age in patients without fractures confirms that radiologic kyphosis is only partly due to the presence of vertebral fractures.

On the contrary, the sum of wedge angles, which also is positively associated with age in patients with Vfx, patients without Vfx and in the total sample, expresses only the contribution of morphometric alterations of vertebral bodies. This observation is in agreement with the finding of a lower anterior height of thoracic vertebrae with age in MRI studies [34].

As expected, we found a positive association between Cobb angle and the sum of wedge angles.

Besides, as mean wedging of healthy vertebrae increases in both groups of patients, Cobb angle also increases. This suggests a contribution of the deformity of healthy vertebrae to the patients' kyphosis.

*Deformity of healthy vertebrae and BMD*

In previous studies, the analysis of the association between the presence of mild vertebral fractures and a decrease in BMD has yielded conflicting results [25,26]. On the other hand, another study found that wedging deformities were associated to a decrease in cortical BMD while biconcave deformities were more strongly associated with trabecular BMD [36].

In the present series a negative association was found between femoral neck BMD and the deformity of healthy vertebral bodies (MWAhealthy) in patients with and without vertebral fractures. It is interesting to remind that the proportion of cortical and trabecular bone at the hip is 7:1.

In a recent study Genant et al. showed that the microarchitectural deterioration of bone determined by microCT and histomorphometry was progressively associated to the severity of vertebral fractures [37]. In another observation by a French group, the number and severity of vertebral fractures were associated to the microarchitectural deterioration of trabecular and cortical bone evaluated with pQCT in tibia and radius, after adjusting for age and BMD [38].

Melton et al. have found that grade 1 vertebral deformities among postmenopausal women are significantly associated with four of the five main variable categories assessed: volumetric lumbar spine bone density (QCT), bone geometry (vertebral apparent cortical thickness),

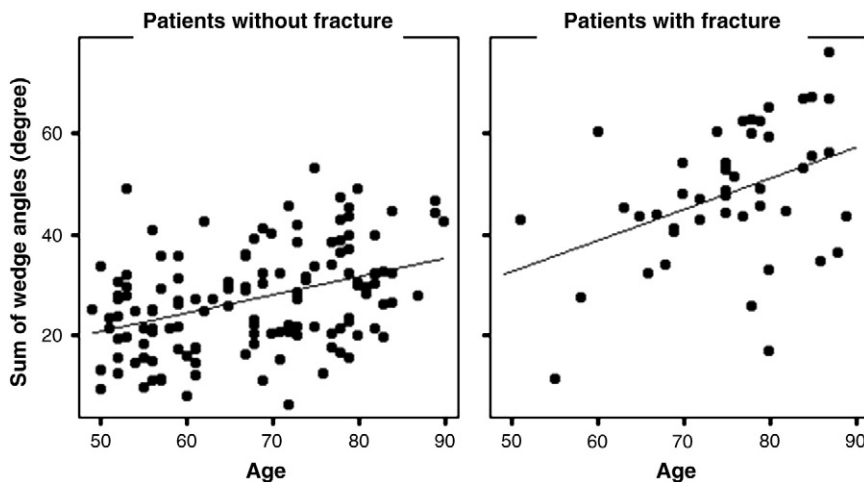


Fig. 4. Relation between the sum of wedge angles and age, in patients with and without vertebral fractures.

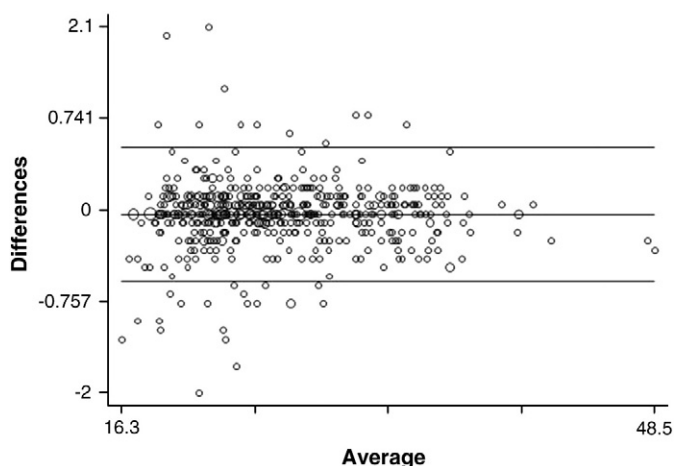


Fig. 5. Bland–Altman graph of intra-observer concordance.

bone strength (overall vertebral compressive strength by finite element analysis), and load-to-strength ratio [39].

Thus, it is fair to conclude that apparently loss of both cortical and trabecular bone, along with microarchitectural deterioration, contributes to vertebral vulnerability.

#### Multivariate analysis

The results of the multiple regression analysis indicate that in this sample of postmenopausal women living in Rosario, a group of variables have significant, simultaneous and independent impact upon mild wedge deformation of healthy vertebral bodies. The increase in mean wedging is associated to the increase in age, the decrease in femoral neck BMD, and the presence of clinical thoracic kyphosis and vertebral fractures.

#### Decrease in BMD

Prior studies have shown that the strength of vertebral bodies is influenced by cortical BMD determined by QCT, which declines significantly with age [40,41]. Besides, *ex vivo* studies of dorsal vertebral bodies found a strong positive correlation between bone mineral content (BMC) and ultimate compressive load for fracture [42].

The results of our study suggest that as the BMC decreases the structure of the vertebral body deteriorates, even if it has not yet sustained a clear biomechanical failure.

#### Clinical kyphosis

An association between the presence of clinical kyphosis and the mean wedging deformity of healthy vertebral bodies was found, independent of age and BMD. This observation has several possible explanations. Thoracic bending *per se* could produce a higher compressive force on the anterior portion of vertebral bodies. As the body's gravity axis is translated forward, the moments of flexion would increase.

In concordance with our results, there is recent biomechanical evidence that the increase in thoracic curvature is associated to the increment in the mean moments of flexion in the spine. The latter have their peak in the mid-thoracic spine (T8). Thoracic kyphosis affects the spine's loading profiles generated by gravity and muscular contraction [43].

A significant negative association has been found between the weakness of para-vertebral muscles and a marked thoracic kyphosis [44,45]. This could contribute to the mechanical compressive effect on the anterior segments of the vertebrae.

A study of mathematical modeling found that the increment in the degree of kyphosis produces a 19% increment in compressive force and a 40% increment in the required strength of spinal extensor muscles at the level of T7/T8 [46].

#### Age

The independent effect of age on the deformity of healthy vertebrae could correspond in part to a prolonged exposure to repeated trauma. In a study of fatigue properties of osteoporotic cadaveric thoracic vertebral bodies, an inverse relationship was found between the number of loading cycles and the percentage of ultimate compressive load for fracture [42]. In daily life activities vertebrae receive a mechanical load equivalent to two or three times the body weight [47]. Mechanical load on the vertebrae increases if the mass of the vertebral body situated above moves ahead of its rotation axis [47]. Using a CT-based nonlinear finite element model, it was determined that the mean load needed to generate a fracture is significantly less upon bending forward. Besides, in that load configuration, the anterior–superior portion of the vertebral body was the most frequent site of fracture [48]. Most patients in the present sample are housewives and domestic workers. They carry out multiple activities in daily life related to cleaning tasks that imply flexion movements of the trunk and object lifting.

During senescence there is a qualitative deterioration of bone tissue. A study of microstructural parameters in trabecular bone of cadaveric lumbar vertebrae from Chinese men identified –among other alterations related to age– regional decreases in bone volume and in the number of trabeculae that were comparatively more marked in the region anterior of vertebral bodies [49]. Similar observations with microCT in cadaveric specimens found regional deterioration in parameters of bone architecture involving the anterior portion of vertebral bodies, associated to a decrease in vertebral strength [50].

The contribution of microtraumas and microdamage to the development of microfractures and diffuse damage increasing with age has been reported [51]. In trabecular bone of lumbar vertebral bodies the density of microfractures increases exponentially with age, and is associated to deterioration of the microarchitecture [52]. Furthermore, accumulation of microdamage in cortical bone has been observed [53]. Besides, the insufficiency of microfracture repair mechanisms and the increase of bone turnover rate must be taken in consideration [53,54].

#### Prevalent fractures

Healthy vertebrae from patients with prevalent fractures have a mean wedge deformity that is 15% higher than that corresponding to patients without fractures. This could indicate a higher structural vulnerability of the former under mechanical stress. This could be related to modifications in the load vectors incident upon the non-fractured vertebral bodies, to already mentioned qualitative factors of bone material, perhaps linked to a certain genetic predisposition independent from BMD [55]. In a case-control study performed in Rochester (MN), the uncompromised lumbar vertebrae from fractured patients presented a significant decrease of volumetric BMD (QCT), of macro-structural parameters (cortical area, apparent cortical thickness) and of estimates of compressive strength (finite element analysis) [56].

#### Final considerations

In a recent prospective study, the sum of anterior heights of vertebral bodies, measured in basal conditions, had an excellent capacity to predict new vertebral fractures. This morphometric index,

coincident with our indicator of vulnerability (the mean of the sum healthy vertebrae), would express –according to the authors– the accumulation of multiple and repeated trabecular microfractures even when no macroscopic fractures have yet occurred. These minimal reductions of vertebral bodies' height could result in bigger deformities and, with time, in definite fractures [57].

Increasing vertebral deformities could be the expression of a time-dependent “creep process” (continuing deformation under constant load) due to the inability of mechanical recovery from deformities produced by a prolonged static or cyclical load [58].

In an *ex vivo* study the process of deformity (creep process) was significantly higher in the anterior region of vertebral bodies. Besides, a significant residual deformation was observed, that in the anterior segment of vertebral bodies reached 71% of the initial deformity. The main anterior “creep deformation” was associated to an increment in the anterior wedging of the vertebral bodies. The latter showed a tendency to increase with low BMD [59].

The anterior segments of the vertebrae have lower BMD and more microstructural alterations, that make them less resistant to applied loads, especially with small angles of flexion [60].

The continued accumulation of microcracks in cortical bone is associated to the aforementioned residual deformity (residual strains) [61].

The present study offers evidence that a series of factors independently influence the increasing wedging deformity of vertebral bodies not yet considered as fractured: prevalent vertebral fractures, the presence of marked kyphosis (hyperkyphosis), low BMD and advancing age. These factors could contribute to a higher vulnerability of the vertebrae, making them more susceptible to fractures.

The limitations of this study arise from its cross sectional design; however, they suggest that non-fractured, mildly deformed vertebrae present a structural morphometric deterioration that increases with age. This observation could be expressing creep deformity accumulated over time [61].

In the thoracic spine, wedge deformity of vertebral bodies would be a continuous and progressive process. In addition to it, sudden events of structural failure would occur, depending on the balance between the capacity to resist biomechanical solicitations and the loads that vertebrae have to bear during daily activities.

## References

- Christensen K, Doblhammer G, Rau R, Vaupel JW. Aging populations: the challenges ahead. *Lancet* 2009;374:1196–208.
- Van der Klift M, De Laet C, McCloskey EV, Hofman A, Pols HAP. The incidence of vertebral fractures in men and women: the Rotterdam Study. *J Bone Miner Res* 2002;17:1051–6.
- Ling X, Cummings SR, Mingwei Q, Xihe Z, Xiaoashu C, Nevitt M, Stone K. Vertebral fractures in Beijing, China: The Beijing Osteoporosis Project. *J Bone Miner Res* 2000;5:2019–25.
- Clark P, Cons-Molina F, Delezé M, Ragi S, Haddock L, Zanchetta JR, et al. The prevalence of radiographic vertebral fractures in Latin American countries: the Latin American Vertebral Osteoporosis Study (LAVOS). *Osteoporos Int* 2007;20:275–82.
- Felsenberg D, Silman AJ, Lunt M, Armbrecht G, Ismail AA, Finn JD, The European Prospective Osteoporosis Study (EPOS) Group. Incidence of vertebral fracture in Europe: Results from the European Prospective Osteoporosis Study (EPOS). *J Bone Miner Res* 2002;17:716–24.
- Link TM, Guglielmi G, Van Kuijk C, Adams JE. Radiologic assessment of osteoporotic vertebral fractures: diagnostic and prognostic implications. *Eur Radiol* 2005;15:1521–32.
- Jackson SA, Tenenhouse A, Robertson L, the CaMos Study Group. Vertebral fracture definition from population based-data: preliminary results from the Canadian Multicenter Osteoporosis Study (CaMos). *Osteoporos Int* 2000;11:680–7.
- Ismail AA, Cooper C, Felsenberg D, Varlow J, Kanis JA, Silman AJ, O'Neill TW, The European Vertebral Osteoporosis Study Group. Number and type of vertebral deformities: epidemiological characteristics and relation to back pain and height loss. *Osteoporos Int* 1999;9:206–13.
- Genant HK, Jergas M, Palermo L, Nevitt M, Valentin RS, Black D, Cummings SR. Comparison of semiquantitative visual and quantitative morphometric assessment of prevalent and incident vertebral fractures in osteoporosis. *J Bone Miner Res* 1996;11:984–96.
- Ross PD. Clinical consequences of vertebral fractures. *Am J Med* 1997;103:305–435.
- Lauritzen JB, Lund B. Risk of hip fracture after osteoporosis fractures: 451 women with fracture of lumbar spine, olecranon, knee or ankle. *Acta Orthop Scand* 1993;64:297–300.
- Klotzbuecher CM, Ross PD, Landsman PD, Abbott III TA, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *J Bone Miner Res* 2000;15:721–39.
- Melton L, Atkinson E, Cooper C, O'Fallon W, Riggs B. Vertebral fractures predict subsequent fractures. *Osteoporos Int* 1999;10:214–21.
- Ross PD, Davis JW, Epstein RS, Wasnich RD. Pre-existing fractures and bone mass predict vertebral fracture incidence in women. *Ann Intern Med* 1991;114:919–23.
- Lindsay R, Silverman S, Cooper C, Hanley D, Barton I, Broy S, et al. Risk of new vertebral fracture in the year following a fracture. *JAMA* 2001;285:320–3.
- Matthis C, Weber U, O'Neill TW, Raspe H, The European Vertebral Osteoporosis Study Group. Health impact associated with vertebral deformities: results from the European Vertebral Osteoporosis Study Group (EVOS). *Osteoporos Int* 1998;8:364–72.
- Kado DM, Duong T, Stone KL, Ensrud KE, Nevitt MC, Greendale GA, Cummings SR. Incident vertebral fractures and mortality in older women: a prospective study. *Osteoporos Int* 2003;14:589–94.
- Cockerill W, Lunt M, Silman AJ, Cooper C, Lips P, Bhalla AK, et al. Health related quality of life and radiographic vertebral fracture. *Osteoporos Int* 2004;15:113–9.
- O'Neill TW, Cockerill W, Matthis C, Raspe HH, Lunt M, Cooper C, et al. Back pain, disability and radiographic vertebral fracture in European women: a prospective study. *Osteoporos Int* 2004;15:760–5.
- Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 2006;17:1726–33.
- Pasco JA, Henry MJ, Korn S, Nicholson GC, Kotowicz MA. Morphometric vertebral fractures of the lower thoracic and lumbar spine, physical function and quality of life in men. *Osteoporos Int* 2009;20:787–92.
- Puche RC, Morosano M, Masoni A, Pérez Jimeno N, Bertoluzzo SM, Podadera JC, et al. The natural history of kyphosis in postmenopausal women. *Bone* 1995;17:239–46.
- Ferrar L, Jiang G, Eastell R. Vertebral wedge angle measured by morphometric X-ray absorptiometry. *Osteoporos Int* 2001;12:914–21.
- Ferrar L, Jiang G, Adams J, Eastell R. Identification of vertebral fractures: an update. *Osteoporos Int* 2005;16:717–28.
- Leidig-Bruckner G, Limberg B, Felsenberg D, Bruckner T, Holder S, Kather A, et al. Sex difference in the validity of vertebral deformities as an index of prevalent vertebral osteoporotic fractures: a population survey of older men and women. *Osteoporos Int* 2000;11:102–19.
- Szulc P, Munoz F, Marchand F, Delmas PD. Semiquantitative evaluation of prevalent vertebral deformities in men and their relationship with osteoporosis: the MINOS study. *Osteoporos Int* 2001;12:302–10.
- Genant HK, Wu CY, Van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res* 1993;8:1137–48.
- Horsman A. Morphometric measurement of the vertebral wedge angles. In: Nordin BEC, editor. *Calcium, Phosphate and Magnesium*. Churchill Livingstone: Edinburgh; 1976. p. 577–8.
- Bland JM, Altman DC. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307–10.
- McGraw KO, Wong SP. Forming inferences about some intraclass correlation coefficients. *Psychol Methods* 1996;1:30–46.
- Gehlbach SH, Bigelow C, May S, Walker M, Kirkwood JR. Recognition of vertebral fractures on a clinical setting. *Osteoporos Int* 2000;11:577–82.
- Wu C, van Kuijk C, Li J, Jiang Y, Chan M, Countryman P, Genant HK. Comparison of digitized images with original radiography for semiquantitative assessment of osteoporotic fractures. *Osteoporos Int* 2000;11:25–30.
- Rea JA, Chen MB, Li J, Marsh E, Fan B, Blake GM, et al. Vertebral morphometry: a comparison of long-term precision of morphometric X-ray absorptiometry and morphometric radiography in normal and osteoporotic subjects. *Osteoporos Int* 2001;12:158–66.
- Goh S, Tan C, Price RI, Edmondston SJ, Song S, Davis S, Singer KP. Influence of age and gender on thoracic vertebral body shape and disc degeneration: an MR investigation of 169 cases. *J Anat* 2000;197:647–57.
- Kado DM, Prenovost K, Crandall C. Narrative review: hyperkyphosis in older persons. *Ann Intern Med* 2007;147:330–8.
- Ito M, Hayashi K, Yamada M, Nakamura T. Vertebral measurement for assessment of osteoporosis. *Br J Radiol* 1994;67:759–63.
- Genant HK, Delmas PD, Chen P, Jiang Y, Eriksen EF, Dalsky GP, Marcus R, San Martín J. Severity of vertebral fracture reflects deterioration of bone micro-architecture. *Osteoporos Int* 2007;18:69–76.
- Sornay-Rendu E, Cabrera-Bravo JL, Boutroy S, Munoz F, Delmas P. Severity of vertebral fractures is associated with alterations of cortical architecture in postmenopausal women. *J Bone Miner Res* 2009;24:737–43.
- Melton III LJ, Riggs BL, Keaveny TM, Achenbach SJ, Kopperdahl D, Camp JJ, Rouleau PA, Amin S, Atkinson EJ, Robb RA, Therneau TM, Khosla S. Relation of vertebral deformity to bone density, structure, and strength. *J Bone Miner Res* 2010;25:1922–30.
- Andresen R, Werner HJ, Schober HC. Contribution of the cortical shell of vertebrae to mechanical behaviour of lumbar vertebrae with implications for predicting fracture risk. *Br J Radiol* 1998;71:759–65.
- Haidekker MA, Andresen R, Werner HJ. Relationship between structural parameters, bone mineral density and fracture load in lumbar vertebrae, based

- on high resolution computed tomography, quantitative computed tomography and compression tests. *Osteoporos Int* 1999;9:433–40.
- [42] Lindsey DP, Kim MJ, Hannibal M, Alamin TF. The monotonic and fatigue properties of osteoporotic thoracic vertebral bodies. *Spine* 2005;30:645–9.
- [43] Briggs AM, van Dieën JH, Wrigley TV, Greig AM, Phillips B, Kai Lo S, Bennell KL. Thoracic kyphosis affects spinal loads and trunk muscle force. *Phys Ther* 2007;87:595–607.
- [44] Sinaki M, Wollan PC, Scott RW, Gelczer RK. Can strong back extensors prevent vertebral fractures in women with osteoporosis? *Mayo Clin Proc* 1996;71:951–6.
- [45] Mika A, Unnithan VB, Mika P. Differences in thoracic kyphosis and in back muscle strength in women with bone loss due to osteoporosis. *Spine* 2005;30:241–6.
- [46] Keller TS, Harrison DE, Colloca CJ, Harrison DD, Janik TJ. Prediction of osteoporotic spinal deformity. *Spine* 2003;28:455–62.
- [47] Duan Y, Seeman E, Turner CH. The biomechanical basis of vertebral body fragility in men and women. *J Bone Miner Res* 2001;16:2276–83.
- [48] Matsumoto T, Ohnishi I, Bessho M, Imai K, Ohashi S, Nakamura K. Prediction of vertebral strength under loading conditions occurring in activities of daily living using a computed tomography-based nonlinear finite element method. *Spine* 2009;34:1464–9.
- [49] Gong H, Zhang M, Yeung HY, Qin L. Regional variations in microstructural properties of vertebral trabeculae with aging. *J Bone Miner Metab* 2005;23:174–80.
- [50] Hulme PA, Boyd SK, Ferguson SJ. Regional variation in vertebral bone morphology and its contribution to vertebral fracture strength. *Bone* 2007;41:946–57.
- [51] Forwood MR, Vashishth D. Translational aspects of bone quality—vertebral fractures, cortical shell, microdamage and glycation: a tribute to Pierre Delmas. *Osteoporos Int* 2009;20(Suppl 3):S247–53.
- [52] Arlot ME, Burt-Pichat B, Roux JP, Vashishth D, Bouxsein M, Delmas PD. Microarchitecture influences microdamage accumulation in human vertebral trabecular bone. *J Bone Miner Res* 2008;23:1613–8.
- [53] Diab T, Vashishth D. Morphology, localization and accumulation of in vivo microdamage in human vertebral cortical bone. *Bone* 2007;40:612–8.
- [54] Vashishth D, Koontz J, Qiu SJ, Lundin-Cannon D, Yeni YN, Schaffler MB, Fyhrie DP. In vivo diffuse damage in human vertebral trabecular bone. *Bone* 2000;26:147–52.
- [55] Michaëlsson K, Melhus H, Ferm H, Ahlborn A, Pedersen N. Genetic liability to fractures in the elderly. *Arch Int Med* 2005;165:1825–30.
- [56] Melton III LJ, Riggs BL, Keaveny TM, Achenbach SJ, Hoffmann PF, Camp JJ, et al. Structural determinants of vertebral fracture risk. *J Bone Miner Res* 2007;22:1885–92.
- [57] Diacinti D, Pisani D, Barone-Adesi F, Del Fiacco R, Minisola S, David V, et al. A new predictive index for vertebral fractures: the sum of the anterior vertebral body heights. *Bone* 2009;46:768–73.
- [58] Yamamoto E, Paul Crawford R, Chan DD, Keaveny TM. Development of residual strains in human vertebral trabecular bone after prolonged static and cyclic loading at low load levels. *J Biomech* 2006;39:1812–8.
- [59] Pollintine P, Luo J, Offa-Jones B, Dolan P, Adams M. Bone creep can cause progressive vertebral deformity. *Bone* 2009;45:466–72.
- [60] Adams M, Pollintine P, Tobias JH, Wakley GK, Dolan P. Intervertebral disk degeneration can predispose to anterior vertebral fractures in the thoracolumbar spine. *J Bone Miner Res* 2006;21:1409–16.
- [61] Zioupos P, Hansen U, Currey JD. Microcracking damage and the fracture process in relation to strain rate in human cortical bone tensile failure. *J Biomech* 2008;41:2932–9.