Cardiovasc Intervent Radiol (2010) 33:1243–1252
DOI 10.1007/s00270-010-9821-2

WORK IN PROGRESS

Is 3T-MR Spectroscopy a Predictable Selection Tool in Prophylactic Vertebroplasty?

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Received: 11 November 2009 / Accepted: 20 January 2010 / Published online: 13 February 2010

Abstract This study was designed to confirm relationships between decrease of bone mineral density and increase of marrow fat and to delineate, through MR spectroscopy, vertebral body at high risk for compression fracture onset to justify prophylactic vertebroplasty. We enrolled 127 women: 48 osteoporotic, 36 osteopenic, and 43 normal subjects, who underwent DXA and MR examination of spine. Then, we selected 48 patients with at least two acute osteoporotic vertebral fractures with interposed normal "sandwich" vertebrae; all patients underwent MR examination of spine. Significant statistical differences were found among "Fat Fraction" (FF) values in normal, osteopenic, and osteoporotic subjects: 59.8 ± 5.1%; 64.8 ± 4.4%; and 67.1 ± 3.3%. A mild, significant, negative correlation was observed between T-score and vertebral fat content ($r = -0.585$; $P = 0.0000$). In the second part of the study, 9 new vertebral fractures were observed in 48 patients (19%): 6 were "sandwich" vertebrae (12.5%), and 3 were located in distant vertebral body. The mean FF in sandwich fractured vertebrae was 72.75 ± 1.95 compared with the FF of the nonfractured sandwich, and distant control vertebrae were 61.83 ± 3.42 and 61.42 ± 3.64. We found a significant statistical difference between fractured and nonfractured vertebrae ($P < 0.001$). The results of this study suggest that MR spectroscopy could be a reliable index to predict the risk of new compression vertebral fracture and could be used for vertebroplasty planning contributing to clarify the possibility to add prophylactic PVP to standard treatment.

Keywords Osteoporosis · MR 3T spectroscopy · Vertebroplasty · MRI · Vertebral fractures

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Introduction

Osteoporosis is a disease characterized by low bone mass and structural deterioration of bone tissue that leads to bone fragility and increased fracture susceptibility [1]. This pathology affects approximately 40% of women and 20% of men older than aged 50 years [2, 3].

To date in Europe, approximately 438,750 vertebral compressive fractures (VFCs) are diagnosed every year with an incidence of 117 fractures for 100,000 people each year. Pathological nature fractures are caused in 85% of cases by primary osteoporosis and in the remaining 15% by neoplastic pathology and secondary osteoporosis. Vertebral fractures usually become evident due to pain, which can have variable intensity, generating reduction in patient's quality of life, functional limitations, depression, disability, height loss, spinal instability, and, in many cases, kyphotic deformity that could compromise lung capacity.

Percutaneous vertebroplasty (PVP) was introduced into literature in 1987 [4]. Since then, PVP has been performed to treat back pain associated with vertebral body compression fractures caused by various factors, and it is now widely performed due to its drastic pain-relieving effects. The goal of this technique is to obtain structural stabilization of fractured vertebral body by injecting a self-curing cement substance that uses polymethylmethacrylate (PMMA) as the main component. However, few patients

return to the hospital due to recurrent back pain after PVP. The main discussion is lacking regarding the cause of new compression fracture after PVP; new collapse occur more often in the adjacent vertebral bodies to those treated by PVP [5–7] and in the "sandwich" bodies levels localized between two somatic collapses [8].

In the case of the "sandwich" body fracture, there is no consensus in vertebral body preventive treatment. In this sense if a high-risk or initial vertebral fracture could be reliably determined and predicted, in particular in "sandwich" bodies, use of the prophylactic PVP in the vertebral body may be justified [9–13].

Bone mineral density (BMD) is perhaps the best index available to assess the risk of osteoporotic fracture. Lindsay et al. reported that each reduction of one standard deviation of BMD corresponds to a 60% increase in the risk of vertebral fracture [14].

^{1}H-MRS is a useful new metabolic technique to study water and triglyceride chemical composition of bone marrow into somatic cancellous bone in vivo. Adipocytes and osteoblasts share a common progenitor (mesenchymal stem cells) in bone marrow; in this sense, increased adipogenesis may be associated with decreased osteoblastogenesis [15–17].

This preliminary study has two goals: (1) to confirm relationships between BMD decrease and marrow fat increase, and (2) to delineate and determine through MR spectroscopy performed before any PVP in "sandwich" vertebral body whether a high-risk condition or new compression fracture onset is present to justify prophylactic vertebroplasty treatment.

Materials and Methods

This study was approved by our institutional review board, and all patients provided written, informed consent.

Patients

The study was performed between June 2007 and July 2009. In the first part of the study, we enrolled in this prospective study 127 women patients as a part of another ongoing study; the subjects were divided as: 48 osteoporotic (age 70.2 ± 2.2 years), 36 osteopenic (age 70.6 ± 2.1 years), and 43 normal subjects (age 66.3 ± 4.7 years).

The exclusion criteria for patient selection were: (1) clinical or imaging evidence of metabolic bone disease or metastases; (2) history of spine surgery or radiation therapy; (3) osteoporosis drug therapy; (4) presence of implants contraindicated for MR examination; and (5) incomplete MR examination.

All subjects underwent dual x-ray absorptiometry (DXA) and MR examination, which involved ^{1}H-MR spectroscopy and morphologic imaging of lumbar spine. The MR examination was performed within a mean of 7 (range, 5–9) days after DXA.

For the second part of the study, we enrolled 48 patients with acute osteoporotic vertebral fractures. In this group, all patients underwent MR examination, which involved ^{1}H-MR spectroscopy and morphologic MR imaging of thoracolumbar spine.

Inclusion criteria were: (1) clinical evidence of acute dorsal and/or lumbar pain without radicular involvement, elicited by percussion over the vertebral spinous process; and (2) imaging evidence of at least two acute vertebral collapses with morphologically normal sandwich vertebra interposed.

We excluded from this study patients with back pain attributed to myelopathy or radiculopathy resulting from spinal stenosis, disc herniation, and facets pathology.

DXA Examinations

The bone density average of four lumbar vertebrae (from L1 to L4) on the anteroposterior projection (Lunar, iDEXA, General Electric Healthcare, USA) was used to obtain a value expressed in grams per squared centimeters (g/cm^2). Based on the World Health Organization [17], subjects were grouped into three categories: normal bone density defined as T-scores = −1; osteopenia as T-score between −1.0 and −2.5; and osteoporosis as T-score = −2.5.

MR Examination

The morphologic and spectroscopic imaging were conducted utilizing a high-field (3T) whole-body imaging system (Philips Intera Achieva, Best, Netherlands), 2.5 commercial release, with a maximum gradient strength, and a slew rate of 80 mT/m and 200 mT/m/ms, respectively, using a body coil for signal transmission and six channel synergy spine phase-array Sense-Torso coil for signal reception.

Standard protocol included sagittal plane T1-weighted Turbo Spin Echo (TSE) (TR shortest, TE 7.2 ms, slice thickness 3 mm, gap 0.4 mm, FOV 300 mm, and 512 × 512 matrix); sagittal plane T2-weighted TSE (TR shortest, TE 120 ms, slice thickness 3 mm, gap 0.4 mm, FOV 300, and 512 × 512 matrix), and selective fat suppression (STIR) sagittal plane T2-weighted TSE to detect the presence of intraspongious bone marrow edema, as specific index of recent vertebral body fracture.

^{1}H-MRS was performed with PRESS sequence (double spin-echo Point REsolved Spatially localized Spectroscopic

sequence) with the two-dimensional (2D) technique optimized for quantitative assessment of water and lipids, with a single voxel analysis. Field homogeneity was adjusted through an automatic procedure of localized three-dimensional (3D) shimming. We utilized the following parameters: TR 2000 ms, TE 35 ms, spectral width 4 Hz, and matrix 512 × 512. The acquisition time average of the spectroscopy sequence was 2.17 min for each vertebral body examined.

The standard volume of interest (VOI) was 1.5 × 1.5 × 1.5-cm^3 located centrally in the vertebral body; special care was taken to avoid cortical profile or endplate of vertebral body, cerebrospinal fluid, vertebral vein, or disk. Data were subsequently evaluated by two radiologists (SM and EF) with 12 years of MR imaging working experience. Data were analyzed utilizing Spectro View scanner.

In all patients (normal, osteopenic, and osteoporotic subjects) included in the first part of the study, we performed three acquisitions with voxels positioned at the level of L2, L3, and L4, with a total of 381 vertebral bodies. In patients included in the second part of the study, with normal somatic body interposed between vertebral collapses, we performed at least two acquisitions with voxel placed within normal "sandwich" vertebra and in a control vertebral body, taken in a distant underlying or overlying vertebral collapses cluster.

According to the study by Trout et al. we divided the thoraco-lumbar spine in different clusters: cluster 1, T2-T6; cluster 2, T7-T10; cluster 3, T11-L2; cluster 4, L3-L5 [7].

Spectral assignments were based on previous studies [16, 18–20], and only peaks that were clearly identifiable were measured. All spectral have shown a water peak located at 4.65 ppm and a lipid peak, bulk methylene protons (–$(CH_2)_n$–) approximately 1.33 ppm, distant to 3.1 ppm (220 Hz). Both peak amplitudes were measured to determine vertebral marrow fat content: Fat Fraction (FF), which was defined as the relative fat signal in terms of a percentage of total signal amplitude (water and lipid) and calculated according to the following equation:

$$\mathrm{FF}\% = [I_{\mathrm{fat}}/(I_{\mathrm{fat}} + I_{\mathrm{wat}})]\,\%,$$

where I_{fat} and I_{wat} are the peak amplitudes of fat and water, respectively.

Follow-Up Protocol and Outcome Evaluation

In patients enrolled in the second part of the study, we performed a standard morphologic MR of the thoraco-lumbar spine (T1-TSE, T2-TSE, and T2-STIR in the sagittal plane) and double orthogonal projection radiographs of the thoracic and lumbar vertebrae within an interval of 3 and 6 months. Subjects on this group were instructed to return to the hospital in case of new back pain onset; in these cases plain radiographs and MRI were taken at this point of time.

We considered new compression fracture: as evidence of bone marrow edema on the T2-STIR images confirmed by corresponding localized pain elicited by percussion over spinal level or reduced vertebral height on morphologic MRI and/or plain radiography. Two radiologists (EF and SM) reviewed imaging findings.

Statistical Analysis

Mean values for vertebral fat content, lipid, and water line widths were calculated in all subjects. Data were grouped according to bone density (normal bone density, osteopenia, and osteoporosis), and the mean values for marrow fat content for each bone density group were calculated and compared using Student's t test. To analyze the correlation between bone density (T-score) and the marrow fat content, Spearman's correlation test was employed.

We used two-sample t tests to compare marrow fat fraction of vertebral body with new compression fractures and those without new vertebral compression fractures. Statistical analyses were performed with software SPSS 15.0 (SPSS Inc., Chicago, IL). A P value <0.05 was considered statistically significant.

Results

No significant age difference was present among osteopenic and osteoporotic subjects, whereas a significant statistical difference was founded between normal and both osteopenic and osteoporotic patients in the first part of the study (Table 1). In this part of the study, we excluded 7 of 127 subjects (1 osteopenic, 3 osteoporotic, and 3 normal subjects) initially recruited because of motion artefacts depicted in images.

This resulted in a final cohort of 120 subjects (Table 1). We analyzed L2, L3, and L4 vertebral levels, calculated the mean FF, and compared with T-score. Morphologic imaging proved to be highly diagnostic, especially with T2-STIR sequence, which, in recent fractures detection (occurred within a period of less than 6 months) distinguishing from stabilized fractures.

The mean FF value obtained from three measurements was 59.8 ± 5.1% in the normal subjects, 64.8 ± 4.4% in the osteopenic subjects, and 67.1 ± 3.3% in the osteoporotic subjects with significant statistical differences founded among FF values on three groups (Table 1; Figs. 1, 2, 3).

For paired data, a mild, significant, negative correlation was observed between T-score and vertebral fat content ($r = -0.585$; $P = 0.0000$; Fig. 4).

Table 1 MR spectroscopy results and T-score in all subjects of first study group

	Normal	Osteopenic	Osteoporotic	Normal vs. osteopenic	Normal vs. osteoporotic	Osteopenic vs. osteoporotic
No. patients	40	35	45			
Age (year)	66.3 ± 4.7	70.6 ± 2.1	70.2 ± 2.2	<0.001	<0.001	0.44
T-score	0.04 ± 0.1	−1.6 ± 0.2	−3.3 ± 0.4	<0.001	<0.001	<0.001
FF* (%)	59.8 ± 5.1	64.8 ± 4.4	67.1 ± 3.3	<0.001	<0.001	0.03

FF fat fraction

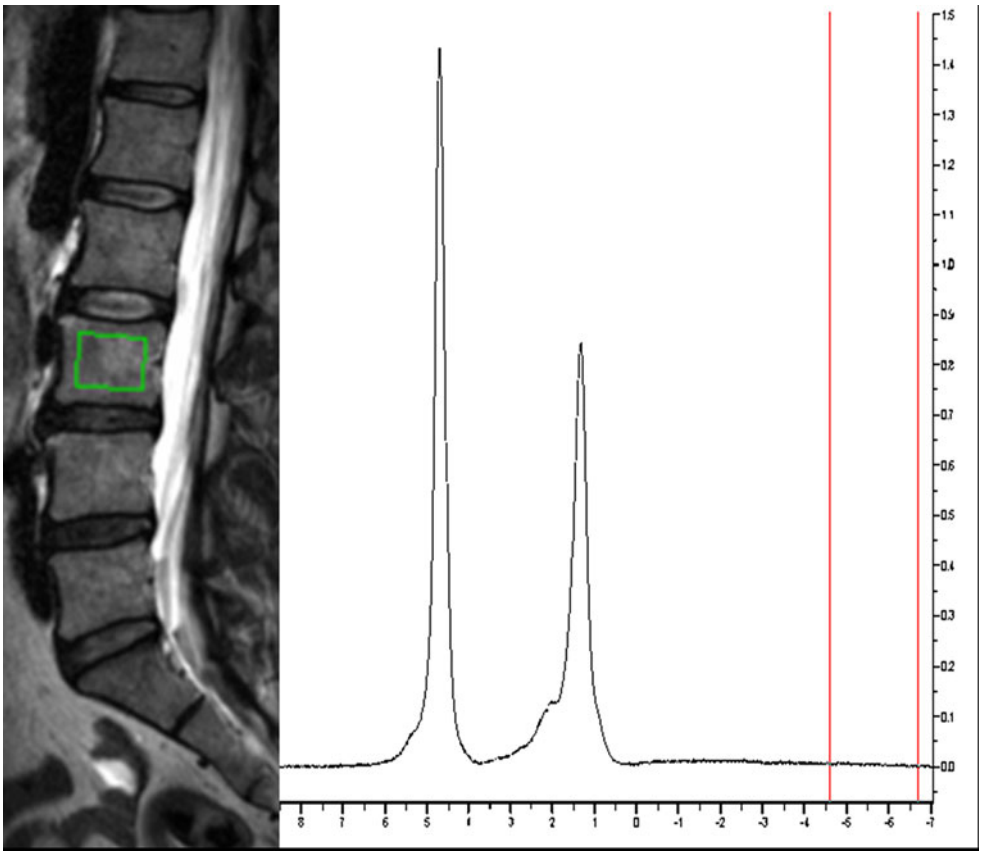

Fig. 1 Spectroscopic analysis in a 65-year-old healthy woman volunteer (T-score 0.53) with a FF of 40.5%

In the second part of the study, we analyzed 48 subjects affected by at least two vertebral collapses with a normal vertebral body interposed ("sandwich" vertebra), resulting in a total of 96 vertebral bodies (60 thoracic and 36 lumbar vertebrae). Nine new vertebral fractures were observed in 48 patients (19%; Table 2). Six of nine vertebral fractures were "sandwich" vertebrae, and three were distant, not analyzed vertebral body.

Mean FF value in fractured sandwich vertebra was 72.75 ± 1.95 compared with 61.83 ± 3.42 in nonfractured sandwich vertebrae. Moreover, FF of the distant control vertebral body was 61.42 ± 3.64. We obtained a significant statistical difference between the fractured and nonfractured sandwich vertebral bodies ($P < 0.001$; Table 2; Fig. 5) and between the fractured sandwich vertebrae and the distant noncollapse control vertebral body ($P < 0.001$; Table 2; Figs. 5, 6).

Discussion

Vertebral fractures are the most common of all osteoporotic fractures and are considered a serious and irreversible local complication of a systematic disease. The major disease that causes vertebral compression fracture is primary osteoporosis in 85% and secondary osteoporosis in 15%, with a European incidence of 117 vertebral compressive fractures per 100,000 people each year. Wasnich et al. reported that fracture prevalence is a strong and independent predictor of future fractures in untreated as well as in treated patients with osteoporosis [21].

Increased knowledge of the natural history of the osteoporotic disease is needed, and one of the goals should be to find a technique that could predict the presence of a new vertebral fracture. One of the major limitations of bone risk fracture determination is the inadequate evaluation of bone

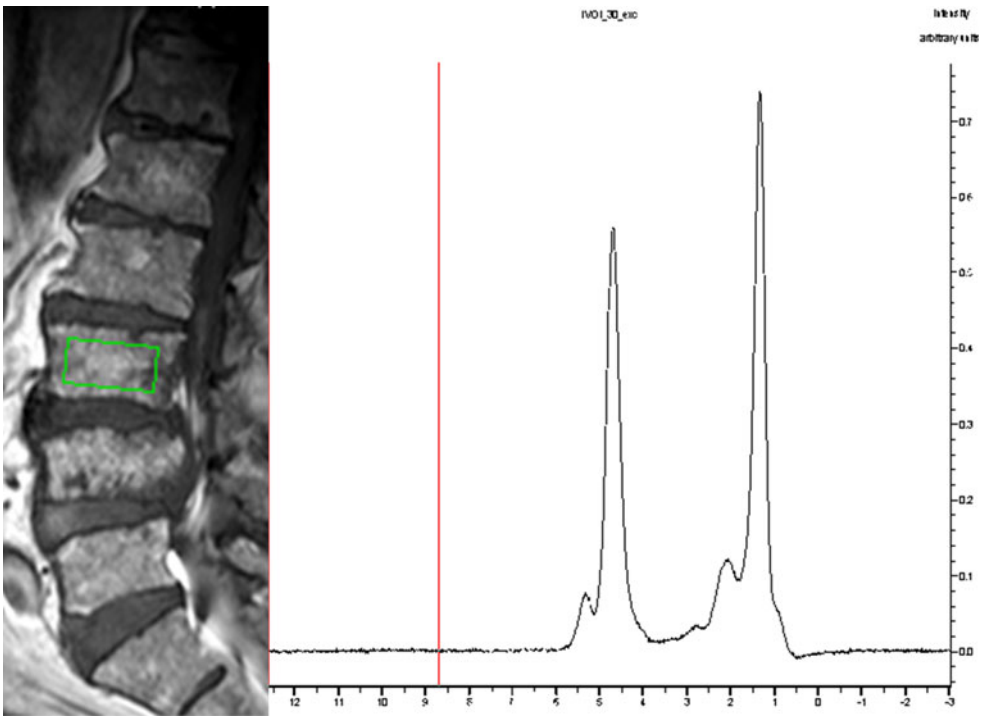

Fig. 2 Spectroscopic analysis in a 75-year-old osteopenic woman (T-score −1.75) with a FF of 57%

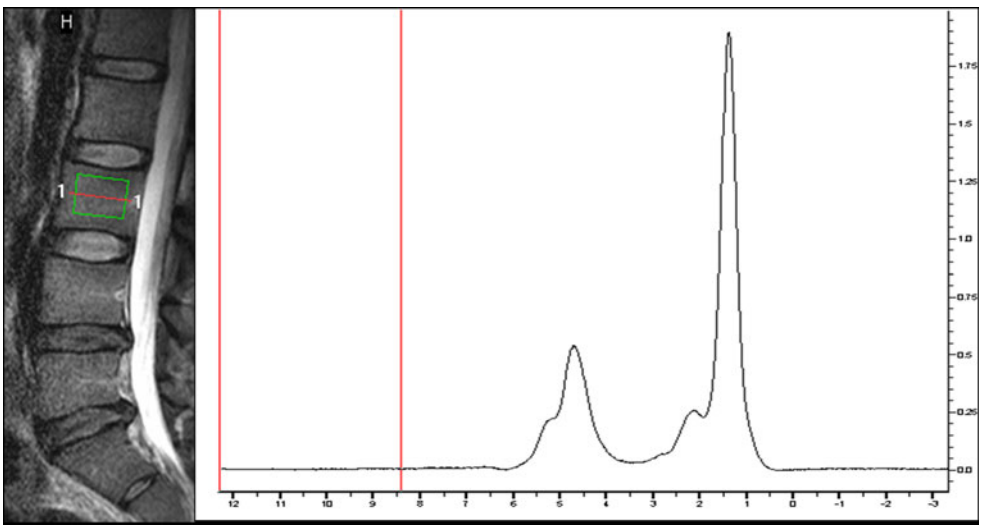

Fig. 3 Spectroscopic analysis in a 79-year-old osteoporotic woman (T-score −3.45) without vertebral fracture with a FF of 73%

status, currently based on bone mineral density (BMD). BMD provides exclusively a quantification of bone mineral component. Other components, such as bone marrow (which is constituted by different quantities of lipids and water), are present in spongy bone tissue, and their relative presence may contribute to the determination of vertebral resistance to fracture.

Actually no studies have assessed the degree of bone weakening beyond which normally occurring forces may cause vertebral collapse or have delineated the specific threshold at which the risk is highly significant. BMD and T-score are the main parameters linked to bone weakening [22]. The imaging examination that offers the possibility of calculating those two parameters and therefore the degree of bone strength is DXA, but this assesses only bone mineral quantity within somatic body. To date in the literature, no studies have evaluated the possibility of MR spectroscopy to predict new vertebral fracture risk.

In the first part of this study, we performed MR spectroscopy analysis of three groups of patients, characterized by normal and weak bone, and observed a significant difference in FF values between these, in particular comparing normal, osteopenic, and osteoporotic groups. Our results

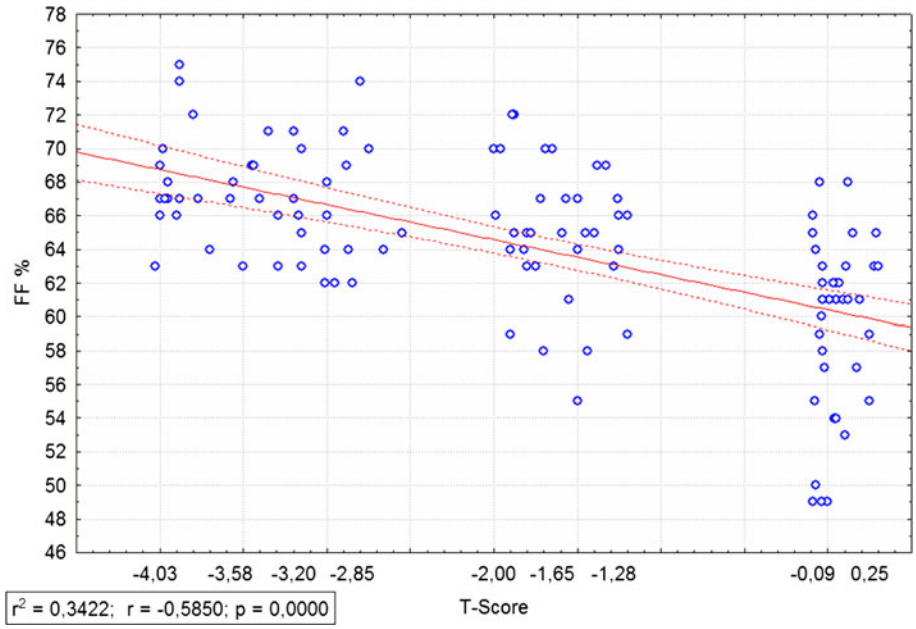

Fig. 4 Scatterplot illustrates the correlation between the FF values and the T-score

Table 2 Fat fraction values between collapsed and noncollapsed vertebral bodies

	No. of vertebral bodies fractured	No. of vertebral bodies nonfractured	FF% vertebral body fractured	FF% vertebral body nonfractured	*P* value
Sandwich vertebral body	6	42	72.75 ± 1.95	61.83 ± 3.42	<0.001
Distant vertebral body	3	45	NC	61.42 ± 3.64	
Total vertebral body	9	87	72.75 ± 1.95	61.63 ± 3.51	<0.001

NC not calculated

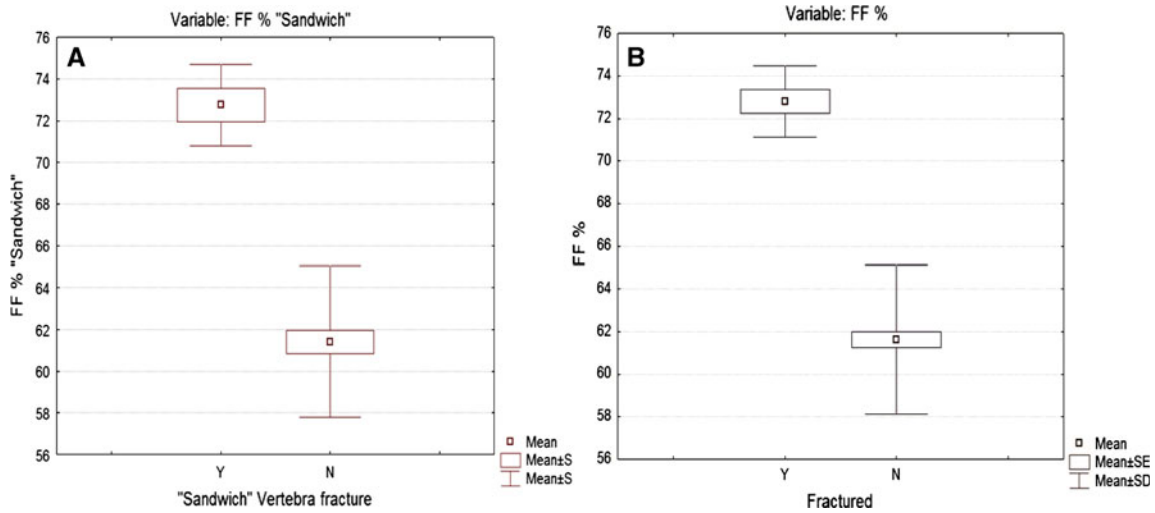

Fig. 5 Difference in FF values between fractured "sandwich" vertebrae and nonfractured sandwich vertebrae (**A**) and between the total number of vertebrae fractured and not fractured (**B**). The numeric values are indicated in the Table 2

were in agreement with those obtained in recent studies performed in the lumbar spine with a 1.5T scanner [16, 23, 24], 3T scanner [25], and the proximal femur [26]. These studies add information on demonstrating that vertebral marrow fat content increased as bone density decreased. The close relationship between T-score and marrow fat content evaluated by MR spectroscopy confirms that the technique could be used to assess osteoporotic patients.

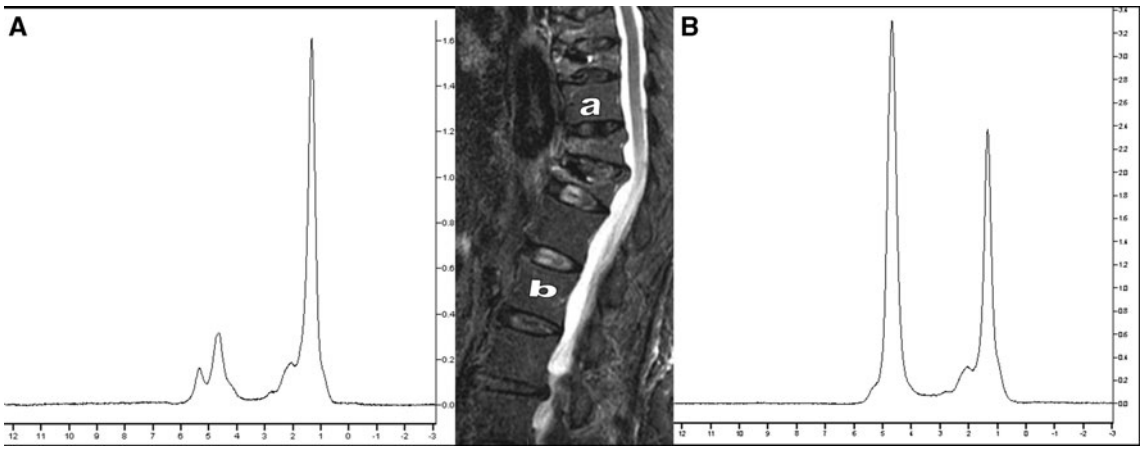

Fig. 6 A 72-year-old woman volunteer with four collapsed vertebral bodies with a normal "sandwich" vertebral body: **A** spectral analysis in the normal interposed vertebral body (FF 72.4%), and **B** spectral analysis in a distant control vertebral body (FF 61%)

In the second part of the study, we selected 48 women with at least two osteoporotic vertebral compression fractures with a normal noncollapse interposed vertebral body, not treated with percutaneous Vertebroplasty procedure. We observed nine new vertebral compression fractures (19%); these results are in agreement with other studies of prevalence performed after PVP [27] and higher than other PVP prevalence studies [7, 28–33].

Data are higher than those obtained by Lindsay et al. for patients with osteoporosis without vertebroplasty [14], because the definition of the vertebral fracture that we used reduced the number of patients and the selection criteria included only patients with at least two vertebral fractures to determine an improved risk of new vertebral compressive fracture.

Correlation Between Marrow Fat Content and Bone Weakness

Adipocytes and osteoblasts share a common progenitor (mesenchymal stem cells) in bone marrow. Accumulating evidence suggests that a reciprocal relationship may exist between these two processes [34]. In particular it has been postulated that increased adipogenesis may be associated with decreased osteoblastogenesis.

Histological studies performed on bone biopsies with regard to the changes in bone with age have shown the progressive, gradual, and constant increase in bone marrow fat content [35]. Particularly Dunnill et al. suggested that with increasing age, there is a switch between hematopoietic red marrow present in youth to yellow marrow. A greater quantity of fat cells is required to replace the loss of cancellous bone and spaces formerly occupied by red marrow. Increased adipogenesis competes with osteogenesis, thus reducing the population of osteoblasts. This theory has found support in animal studies [36]. In this sense, it is thought that the quality of bone marrow plays an important role in vertebral mechanical resistance and that an increase in fats can negatively influence bone strength.

Young bone marrow that fills the intratrabecular spaces functions as a shock absorber and acts as a biomechanical support structure for the cancellous bone. Yellow marrow, due to its high fat content, is a weaker means of biomechanical support than red marrow [37]. Yellow bone marrow is known to consist primarily of saturated and monopoly unsaturated fatty acids [38], but it is unknown if and how this composition varies in osteoporosis.

The relationship between bone marrow fat fraction and bone weakness could be explained by multiple factors. In particular trabecular thinning, often considered the main cause of bone weakening in osteoporosis disease, causes an increase in the intertrabecular spaces filled compensatorily, as many authors suggest, by increased amount of yellow bone marrow [35, 39, 40].

Outcomes evidenced that vertebral marrow fat content increased as bone density decreased (Table 1; Fig. 4).

Sandwich Vertebra and Prophylactic PVP

Whether new compression fractures are attributable to PVP or natural course of osteoporosis is unclear at present. According to an interdisciplinary consensus conference guideline on vertebroplasty, only symptomatic fractures unresponsive to conservative treatment must be treated. Actually there is no consensus of the use of prophylactic percutaneous vertebroplasty procedure in particular in "sandwich" vertebral body without compression fracture [41]. Instead in many ongoing studies, for example the study performed by Hierholzer et al. [8], it was observed that in 316 treated patients a total of 65 sandwich levels

were generated in 65 patients and of these 7 patients (11%) suffered from sandwich-body fractures during follow-up. In our study performed with nontreated patients, we found six incidental sandwich vertebral body fractures (12.5%).

The study was designed to find an accurate and reliable imaging examination to detect vertebral bodies at high risk for compression fracture and consequently to perform a Vertebroplasty prophylactic treatment. First, it was important to demonstrate that the presence of new vertebral fracture after PVP treatment is not necessarily a consequence of the interventional radiology treatment. Percutaneous vertebroplasty was first described by Galibert et al. in 1987 and has been performed to treated painful vertebral compression fracture secondary to osteoporosis and neoplasms [4]. Is reported that the complications rate associated with PVP is 1–3% [28], including pulmonary cement embolism, cement extravasation with subsequent cord or roots compression associated to neurologic disorders, and allergic reactions [42]. In addition some authors have indicated that there could be an increased risk of collapse in vertebral bodies contiguous to the level treated with PVP [7, 28, 43].

Experimental data performed by Rohlmann et al. [44] and Baroud and Bohner [45] suggested that altered biomechanical properties of disk-somatic complex is associated with increased intradiscal pressure after PVP, producing increased mechanical stress to the endplates of adjacent vertebral bodies. Other authors have suggested that the presence of new vertebral fracture is not a complication of PVP [27, 46, 47].

Lindsay et al. suggested that up to 25% of patients with vertebral compression fracture develop new compression fractures within 1 year [14]. In that study were analyzed women with osteoporosis without any PVP treatment.

We also selected for our study women with at least two vertebral compression fractures who did not undergo PVP and observed the presence of nine new vertebral fractures (19%). This preliminary data suggest that the presence of new vertebral fracture in osteoporotic patients is a natural ongoing of the disease; then the presence of a fracture could be considered a risk factor for subsequent incidental fracture.

Secondly, we considered that if the risk of a new compression fracture could be evaluated early and reliably, vertebral bodies at higher risk for compression fractures could be treated with prophylactic PVP in the same session with fractured bodies. Recently, studies have been performed in the field of prophylactic PVP [48, 49]. As we explained previously, one of the major limitations in the determination of bone fracture risk is the inadequate evaluation of the bone status, currently based on BMD. In fact BMD provided exclusively a quantification of the bone mineral component, whereas other components, such as bone marrow, which is present in spongy bone tissue, could contribute in determining fracture resistance. MR spectroscopy provides a fine evaluation of vertebral bone marrow changes due to primary or secondary pathologies and highlights differences not easily assessable with conventional imaging, because metabolic abnormalities often precede structural changes. Proton MR spectroscopy, a quantitative method considered in this study, separates the total bulk MR signal into its components of distinct lipid and water signals. The water signal comes mostly from red marrow, whereas lipid signals are mainly related to yellow marrow.

To date, this is the first study to evaluate the capability of MR spectroscopy for determining the risk of vertebral bone fracture. The results obtained are preliminary but relevant in observation that a significant difference in fat content between new vertebral fracture and vertebral levels without fracture used as control ($P < 0.001$).

Because of the reduced number of patients, we are not be able to delineate the FF threshold to indicate high-risk vertebral fracture; many others studies are needed to confirm our data and to determine sensibility and efficacy of the MR spectroscopy for determination of vertebral bone fracture risk.

If we consider MR a reliable and specific image analysis in vertebral fracture detection, we advocate in global spinal assessment, related also to high-risk vertebral body evaluation, the possibility to utilize new, useful, additional, quantitative evaluation of tissue components. In this sense, we postulate that in the upcoming future, MR spectroscopy may be easily applied and attached to routine MR imaging, without substantial time penalty, for the early identification of physiological as well as biochemical changes in vertebral bone.

The results of this study suggest that MR spectroscopy could be a reliable index to predict the risk of new compression vertebral fracture and could be used for PVP planning, contributing to clarify the possibility to add prophylactic PVP to standard treatment. However, because of the small number of subjects examined in this preliminary study, these findings alone cannot justify the introduction of preventive PVP for routine approach to these patients. In our opinion other studies need to be performed, combining MR spectroscopy and the apparent diffusion coefficient (ADC) and fractional anisotropy (FA) derived from the MR-Diffusion Tensor Imaging (DTI) to improve sensitivity and specificity of noninvasive imaging in PVP planning.

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