

Bone fragility in sarcoidosis

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ABSTRACT

Purpose: Few studies have suggested that sarcoidosis may be associated with low bone mineral density (BMD) and fragility fractures. However, studies on bone mineral loss or fractures in sarcoidosis are conflicting. This study aimed to evaluate: 1) the history of fragility fractures in patients with sarcoidosis; 2) the correlation of bone fragility with severity of sarcoidosis disease.

Methods: We selected 252 sarcoidosis patients (54.7 ± 12.1 years) and age- and sex-matched healthy controls. We evaluated BMD at the lumbar spine (BMD-LS), femoral neck, and total hip (BMD-TH), and also the occurrence of any fracture. Forced expiratory volume in one second, forced vital capacity, and diffusion capacity for carbon monoxide (DLCO) were also assessed.

Results: BMD T-scores were lower in sarcoidosis patients than in healthy controls, but the difference was statistically significant only for BMD-LS ($p < 0.01$) and BMD-TH ($p < 0.05$). Moreover, BMD-LS and BMD-TH values were significantly associated with DLCO (%) ($p < 0.05$). The prevalence of fragility fracture was higher in patients with sarcoidosis than in controls (30.6% vs. 12.3%). The sarcoidosis patients with a higher number of vertebral fractures (>3) also showed reduced values on pulmonary function test parameters, particularly DLCO (%).

Conclusions: This study shows that fragility fractures are significantly more frequent in patients with sarcoidosis than in control subjects. Furthermore, a greater number of vertebral fractures was linked to worse pulmonary function tests.

KEYWORDS

Sarcoidosis, osteoporosis, bone fragility, vertebral fractures.

Introduction

Sarcoidosis is a multi-system inflammatory disease of unknown etiology characterized by the formation of granulomas in various organs. It can involve almost any organ of the body, but most commonly affects the lungs. Sarcoidosis is considered to be the consequence of a chronic immunological response triggered by an association of genetic susceptibility with specific infectious or environmental factors. The prevalence of the disease is 4.7-64.0 per 100,000, and its annual incidence is 1.0-35.5 per 100,000 [1].

The symptoms of sarcoidosis are not specific and can differ markedly according to organ involvement and disease course. Respiratory symptoms and fatigue are the most common symptoms at any stage of the disease. In chronic inflammatory diseases such as asthma, chronic obstructive pulmonary disease [2], and rheumatoid arthritis [3], bone mineral density (BMD) is decreased and the risk of clinical and radiological vertebral fractures is increased. Sarcoidosis, too, can affect bone tissue both directly and indirectly, although direct bone involvement is rare (3-12%). Moreover, bone health can be indirectly compromised through several mechanisms. The link between bone involvement and sarcoidosis has not yet been fully clarified. Changes in calcium metabolism, particularly hypercalciuria and hypercalcemia, are quite common in sarcoidosis [4,5].

Data on BMD values in sarcoidosis patients are few and

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heterogeneous. Some studies have shown increased bone turnover [6], and several studies have suggested that sarcoidosis may be associated with low BMD [7,8]. On the contrary, some more recent studies have shown normal BMD [9,10]. Moreover, studies on fractures in sarcoidosis are scarce and conflicting. A few have reported a high prevalence of fragility fractures and vertebral deformities in patients with sarcoidosis. The finding that sarcoidosis patients have a high risk of fracture even with normal levels of BMD suggests that other independent factors are involved [11-13].

Conversely, other authors have concluded that sarcoidosis per se does not cause fragility fractures and that osteoporotic fractures in sarcoidosis were driven mainly by the use of glucocorticoids (GCs). In fact, after cessation of GCs, the risk of fragility fracture in sarcoidosis diminished [14].

This single-center, cross-sectional study aimed to evaluate: 1) whether patients with sarcoidosis have an increased risk of

clinical fractures compared with healthy controls; 2) the association of bone fragility with severity of sarcoidosis disease.

Materials and methods

A single-center, cross-sectional study was conducted in 252 patients (age range 31–83 years; mean age 54.7 ± 12.0 years) affected by sarcoidosis, monitored at the Siena Regional ILD Referral Center from January 2018 to December 2021. The disease was diagnosed according to international guidelines^[15,16].

All patients underwent regular clinical evaluations at the Siena Referral Center for Osteoporosis, Department of Internal Medicine, University Hospital of Siena (Italy).

Patients taking drugs that interfere with bone metabolism, such as anabolic steroids, teriparatide, vitamin D analogs, denosumab or bisphosphonates, were excluded from the study. Other exclusion criteria were all secondary forms of osteoporosis such as chronic renal failure (with a glomerular filtration rate of less than 30 ml/min), hyperparathyroidism, hypothyroidism, and known malignancy. At the time of data collection, 160 patients (63%) were on pharmacological therapies including prednisone ($n = 136$; 85%) and disease-modifying anti-rheumatic drugs ($n = 72$, 45%). Age- and sex-matched healthy controls were recruited from a sub-group of individuals living in the area of Siena (Italy), who had been participating in a larger epidemiological study^[17]. Serum concentrations of calcium (corrected for albumin), phosphate, total alkaline phosphatase, creatinine, intact parathyroid hormone (PTH), and 25-hydroxyvitamin D (25OHD) were gathered. Serum 25OH and serum PTH were both determined by immunoradiometric assay. In each patient BMD was measured at the lumbar spine [BMD-LS] and at femoral subregions, i.e., the femoral neck and the total hip [BMD-TH] using a dual-energy X-ray absorptiometry device (Lunar Prodigy; GE Healthcare, Waukesah, WI, USA). Osteopenia and osteoporosis were defined by a T-score of between -1 SD and -2.5 SD, and a T-score ≤ -2.5 SD, respectively.

Data on previous fracture history, in particular details of fracture sites, were collected during an osteoporosis examination. All radiological images since diagnosis of sarcoidosis were independently evaluated for the presence of vertebral fractures according to the semi-quantitative method of Genant^[18]. Vertebral fracture was defined as an at least 20% loss of anterior or posterior vertebral body height.

The following lung function parameters were measured according to American Thoracic Society/European Respiratory Society (ATS/ERS) standards^[15,16], using a Jaeger body plethysmograph with corrections for temperature and barometric pressure: forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), FEV1/FVC, total lung capacity, residual volume, lung diffusion capacity for carbon monoxide (DLCO) and DLCO/alveolar volume.

Statistical analysis

Data were expressed as mean values \pm standard deviations. Study variables were tested for normal distribution. The sig-

nificance between the means was tested using Student's *t*-test. Categorical variables were compared using Chi-square test or Fisher's exact test, as appropriate. The correlations between the groups were analyzed using Pearson's correlation test. Analysis of variance (ANOVA) was used to analyze the association of lung function tests with number of vertebral fragility fractures. All tests were two-sided, and $p < 0.05$ was considered statistically significant. All statistical tests were performed using SPSS 10.1 statistical software (SPSS 10.1).

Results

Table I shows the clinical, biochemical and densitometric parameters of the sarcoidosis patients and healthy controls. There were no significant differences between the two groups for age, BMI, or serum levels of calcium, phosphate, or vitamin D. Serum creatinine and PTH levels were slightly higher in the patients affected by sarcoidosis with respect to the healthy controls ($p < 0.05$). Moreover, BMD values, expressed as T-score and Z-score, were lower in the patients affected by sarcoidosis than in the healthy controls, but the difference was statistically significant only for BMD-LS ($p < 0.01$) and BMD-TH ($p < 0.05$).

The age- and BMI-adjusted partial correlations of BMD values with lung function tests are reported in Figure 1. In particular, BMD-LS and BMD-TH were significantly associated with DLCO (%) ($r = 0.20$, $p < 0.05$ and $r = 0.17$, $p < 0.05$ respectively).

Table I Clinical, biochemical and densitometric parameters of the study population.

	SARCOIDOSIS (<i>n</i> = 252)	CONTROLS (<i>n</i> = 250)
Sex (F/M)	148/104	147/103
Age (yrs)	54.7 ± 12.1	56.6 ± 11.9
BMI (kg/m ²)	26.1 ± 4.5	26.0 ± 4.1
Creatinine (mg/dl) (n.v. 0.50–1.10)	1.12 ± 0.32	$0.99 \pm 0.12^*$
Calcium (mg/dl) (n.v. 8.0–11.0)	9.46 ± 0.86	9.26 ± 0.56
Phosphate (mg/dl) (n.v. 2.7–4.5)	3.53 ± 0.58	3.39 ± 0.63
Alkaline phosphatase (U/L) (n.v. 35–105)	71.25 ± 28.73	68.74 ± 21.33
25OHD (ng/ml) (n.v. > 30)	23.44 ± 13.69	23.64 ± 12.9
PTH (pg/ml) (n.v. > 65)	33.09 ± 11.9	$26.40 \pm 112.14^*$
BMD-LS T-score	-1.01 ± 1.30	$-0.70 \pm 1.30^{**}$
BMD-LS Z-score	-0.41 ± 1.28	$0.25 \pm 1.20^{**}$
BMD-FN T-score	-1.03 ± 1.05	-0.99 ± 1.03
BMD-FN Z-score	-0.25 ± 1.10	$0.01 \pm 0.87^*$
BMD-TH T-score	-0.80 ± 1.10	$-0.59 \pm 1.00^*$
BMD-TH Z-score	-0.28 ± 1.00	$0.11 \pm 0.98^*$

Abbreviations: 25OHD=25-hydroxyvitamin D; PTH=parathyroid hormone; BMD-LS=bone mineral density at the lumbar spine; BMD-FN= bone mineral density at the femoral neck; BMD-TH=bone mineral density at the total hip. * $p < 0.05$; ** $p < 0.01$ sarcoidosis vs controls

The prevalence of fragility fractures was higher in the patients with sarcoidosis than in the healthy controls (30.6 vs. 12.3% respectively, $p < 0.001$), as shown in Figure 2. The most frequent fracture sites in the sarcoidosis patients were the vertebrae ($n = 66$), femur ($n = 3$), wrist ($n = 1$), ribs ($n = 3$), humerus ($n = 1$), and lower limbs ($n = 3$). In the healthy controls the previous fragility fracture sites were the vertebrae ($n = 9$), wrist ($n = 8$), ribs ($n = 2$), pelvis ($n = 1$), and lower limbs ($n = 23$) (Figure 3).

Moreover, we evaluated the link between sarcoidosis and bone fragility by studying average lung function measurements in the sarcoidosis population divided by number vertebral fractures. As reported in figure 4, the patients with ≥ 3 vertebral fractures had lower FVC (%), FEV1 (%), and DLCO (%) values (ANOVA = 0.05).

Discussion

This study shows that fragility fractures, predominantly vertebral fractures, are significantly more frequent in patients with sarcoidosis than in control subjects. The risk of clinical

vertebral fractures was found to be increased in sarcoidosis, which is in line with findings in other inflammatory diseases [2,3]. These fractures, reducing lung volume and contributing to a restrictive ventilatory defect, have deleterious effects on pulmonary function tests [19]. In our study, the sarcoidosis patients with a higher number of vertebral fractures also showed lower pulmonary test values.

At present, the possible pathophysiological mechanisms underlying increased bone fragility in sarcoidosis have not yet been clarified. Decreased trabecular BMD within the vertebrae might be one possible explanation for the increased vertebral fracture risk. In our study, the small but significant reduction in lumbar and femoral BMD values in patients with sarcoidosis compared with healthy controls appears to be in agreement with some previous studies [8], but in contrast with most of the others [9,10]. This finding can be explained by the fact that our center, being a referral center for sarcoidosis, manages patients in more advanced stages of the disease, who therefore more frequently show significantly impaired lung volume or lung diffusion capacity. This hypothesis appears to be supported by the correlation we observed between BMD values and pulmo-

Figure 1 Age- and BMI-adjusted partial correlations of BMD-LS (A) and BMD-TH (B) values with DLCO (%) in patients with sarcoidosis.

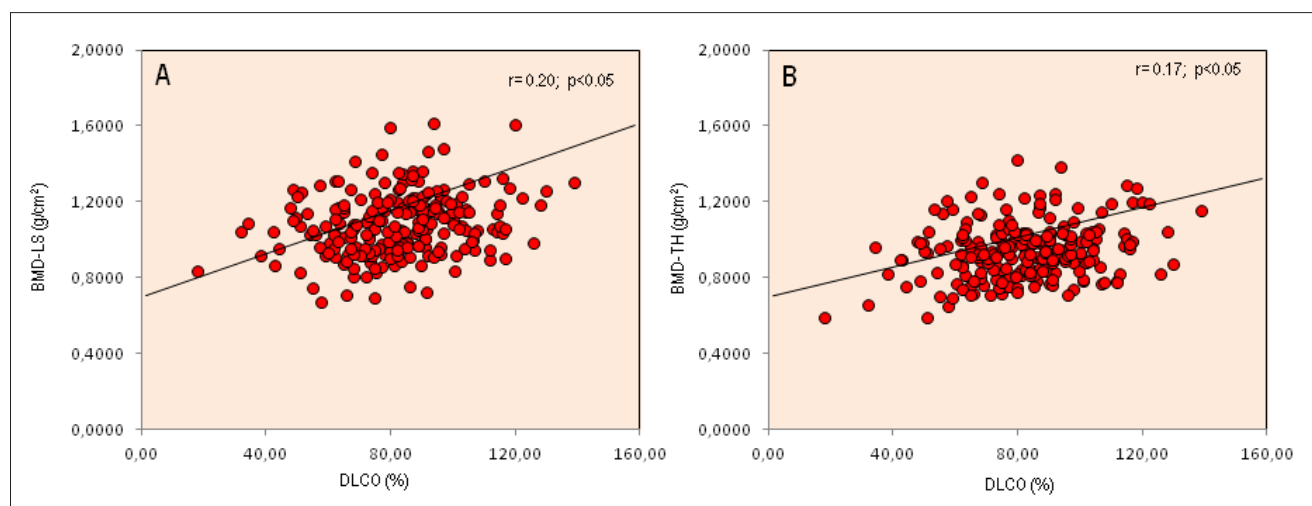
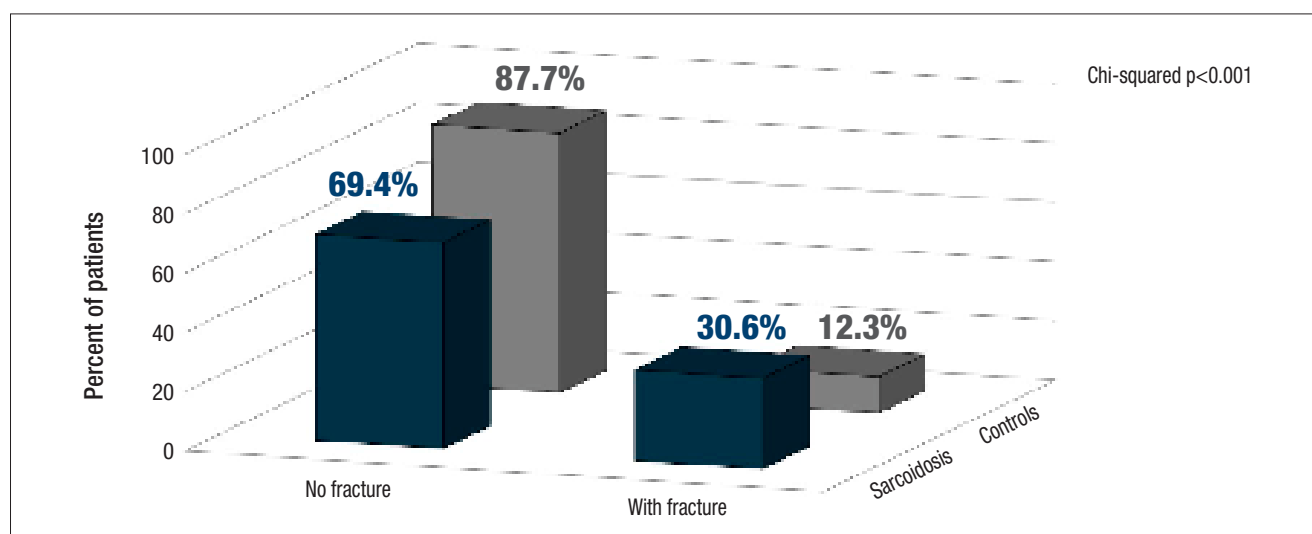


Figure 2 Percentages of sarcoidosis patients and healthy controls with fragility fractures.



nary tests, particularly DLCO. A similar link between vertebral fracture burden and pulmonary tests was observed in a previous study in patients with severe pulmonary fibrosis [15].

Glucocorticoids are the key therapy of sarcoidosis, and it is well known that chronic use of these drugs can lead to secondary osteoporosis [20]. In fact, high doses and long-term use of GCs exert harmful effects on bone cells, including osteoblasts, osteoclasts, and osteocytes, leading to impaired bone formation and resorption. GC excess inhibits the proliferation and differ-

entiation of osteoblasts and enhances the apoptosis of osteoblasts and osteocytes, eventually contributing to reduced bone formation. Effects of GC excess on osteoclasts mainly include enhanced osteoclastogenesis, increased lifespan and number of mature osteoclasts, and diminished osteoclast apoptosis, which together result in increased bone resorption [21].

Indeed, the role of GC treatment in bone fragility in patients with sarcoidosis has not yet been elucidated. Some studies found an increased risk of any fracture among sarcoidosis

Figure 3 The most common fracture sites in sarcoidosis patients and in healthy controls.

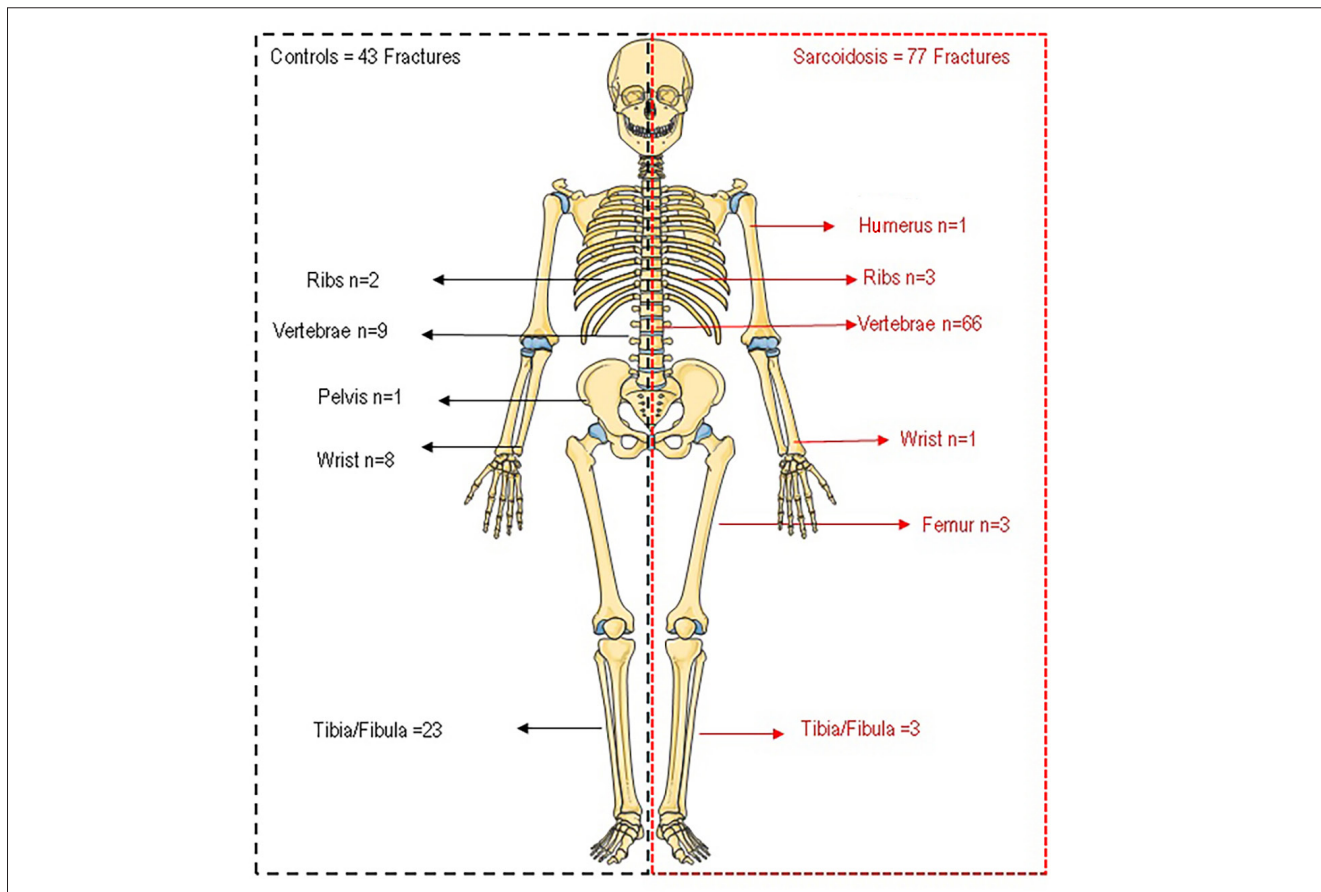
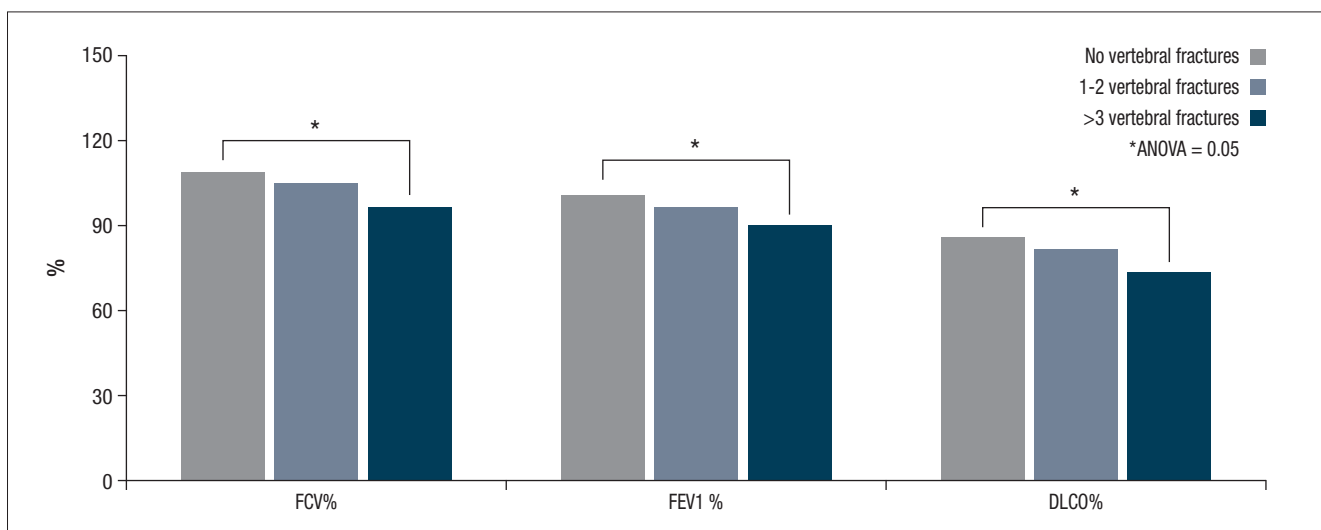


Figure 4 Values of pulmonary tests in patients affected by sarcoidosis divided by the presence and severity of vertebral fractures.



patients treated with GCs compared with non-users^[8,22]. Moreover, a recent study by Bours et al. reported that in sarcoidosis patients, neither the higher dose nor the cumulative dose of GCs significantly increased the risk of fracture^[13]. The heterogeneity of the data on GC treatment can be explained by the fact that these drugs, in inflammatory diseases such as sarcoidosis, reduce cytokine release and inflammatory status, which may partially compensate for their direct negative effect on bone^[14,23]. Sarcoidosis activity itself may be a major risk factor for vertebral fractures. The fact that the risk of clinical vertebral fractures was increased, whereas the risk of all fractures was not different compared with what was observed in matched controls, suggests that sarcoidosis probably has a negative impact on the trabecular bone without affecting the cortical bone.

The main limitations of this study are the lack of data on markers of bone turnover and inflammation. In addition, no information was available on muscle strength or mass or on fall risk. Its main strength is the large sample size for this rare disease, and the comparison with healthy controls.

Conclusions

Our data show that patients with sarcoidosis have an increased risk of clinical vertebral fractures. The severity of sarcoidosis disease appears to be a risk factor for bone fragility. Therefore, we conclude that all patients with sarcoidosis require a bone status evaluation so that their fracture risk can be defined and adequate therapy can be initiated in order to prevent vertebral fractures.

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