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Prevalence and risk factors of osteoporosis and vertebral fractures in patients with ankylosing spondylitis

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ABSTRACT

Ankylosing spondylitis (AS) is characterized by inflammation of the entheses and paravertebral structures, leading in time to bone formation at those sites. As well, vertebral bone loss is also a recognized feature of AS

Objective: To calculate the prevalence and risk factors of osteoporosis and vertebral fractures in patients with AS.

Methods: Eighty patients with AS were enrolled in the study. Clinical, biological and radiological status was assessed by the Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI), ESR and C-reactive protein (CRP), Bath AS Radiology Index (BASRI) and modified stoke AS spine score (mSASSS). BMD of the hip and spine was measured and vertebral fractures were defined using a combination of Genant semiquantitative (SQ) approach and morphometry by VFA (fracture vertebral assessment).

Results: The years ± 11.8. The mean BMI was 22.8 kg/m^2 ± 4.1 and the mean disease duration was 10.8 years ± 6.6. Prevalence of osteoporosis was 25%. 18.8% of patients had a vertebral fracture (grades 2 and 3). Factors associated with osteoporosis were low weight and BMI and longer disease duration, higher ESR, CRP, BASFI and BASDAI. Vertebral fractures were associated with advanced age, longer disease duration, higher BASFI, BASRI and mSASSS and reduced BMD and *T*-score at the hip site, presence of osteoporosis at any site. Multiple logistic regression analysis (Table 4) revealed that parameters significantly associated with osteoporosis were BASDAI (OR = 1.05, 95% confidence interval [CI]: 1.03–1.09); disease duration (OR = 1.13, 95%CI: 1.03–1.25); and BMI (OR = 0.82, 95%CI: 0.69–0.93). The presence of VFs (grades 2 and 3) were independently associated with disease duration (OR = 1.50, 95%CI: 1.07–2.10); and mSASSS (OR = 1.17, 95%CI: 1.05–1.30).

Conclusion: Osteoporosis is common in patients with AS and seems to be related to disease activity while vertebral fractures appear to be related to the duration and structural severity of the disease rather than BMD.

Introduction

Bone is a target in many inflammatory rheumatic diseases [1,2]. The interaction between inflammation and bone is characterized by a wide range of changes in bone remodeling and is associated with an increased risk of fractures [3]. However, in ankylosing spondylitis (AS) the disease itself has a characteristic of not only reduced but also increased bone formation which contributes to syndesmophyte formation and joint ankylosis particularly in advanced disease [4]. Osteoporosis is considered now as a common feature of AS even in early stages of the disease. However, studies of vertebral fractures are conflicting.

Dual energy X-ray absorptiometry (DXA) is a practical and safe method to measure bone mineral density (BMD) [5]. However, this method had some limitations particularly related to projection; spinal measurements in AS patients may be artificially increased as a consequence of ligamentous calcifications or sclerosis of the vertebral margins or end plates [6,7].

The standard method to assess vertebral fracture is radiography of the thoraco-lumbar spine. However, there is no gold standard for the definition of osteoporotic vertebral fracture (VF). A number of methods have been developed for interpretation of spinal X-rays, including the Genant semi-quantitative method, which has been used as a surrogate gold standard in a number of key osteoporosis studies [8]. This approach is more objective and reproducible than other qualitative methods. Vertebral morphometry using DXA also known as vertebral fracture assessment (VFA) is a fast, low-radiation technique which produces images that are of sufficient quality to be used to diagnose the presence of vertebral deformity consistent with fracture [9]. VFA has demonstrated utility for vertebral visualization and thus is an important tool for fracture detection in women and men. VFA offers "point of service" convenience for the patient when it is done at the same visit as for BMD measurement by DXA, with far less radiation than standard radiography. A recent study compared conventional radiography to VFA and showed good agreement

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Table 1
Study population characteristics ($n=80$)

	Mean±DS	Range
Age (years)	38.9±11.8	21–72
Disease duration (years)	10.8±6.6	1–35
Weight (cm)	66.3±12.4	41–95
Height (m)	1.70±7.9	1.52–1.83
BMI (kg/m^2)	22.8±4.1	14.6–33.6
ESR (mm/h)	29.5±17.5	2–85
CRP (mg/l)	37.6±46.5	1–262
BASDAI	52.6±20.9	0–90
BASFI	54.6±23.7	0–93
BASRI spine	3.8±3.6	0–12
BASRI hip	1.6±1.5	0–4
mSASSS	28.6±22.3	0–70
Coxitis: n(%)	52 (65)	
BMD lumbar spine (g/cm^2)	1.041±0.1	0.698–1.685
BMD total hip (g/cm^2)	0.940±0.1	0.565–1.328
Lumbar spine T-score	−1.2±1.4	−4.0–4.1
Total hip T-score	−0.7±1.2	−3.6–2.3

between the two techniques in measuring global vertebral wedging, expressed as (mean) AP-ratio [2].

The aim of this study was to calculate the prevalence and risk factors of osteoporosis and densitometric VFs in patients with AS.

Methods

Patients

The study group consisted in 80 patients (67 men, 13 women) with AS who fulfilled the modified New York criteria for the classification of AS [10] and who presented consecutively between January 2007 and March 2008. Patients with other forms of spondyloarthropathy (including AS secondary to inflammatory bowel disease or psoriasis), or with a history of neuroendocrine disorders (thyroid, parathyroid disorders, anticonvulsant usage etc.), chronic renal or liver diseases, systemic high dose corticosteroid usage, excessive alcohol intake were excluded. Clinical assessment included demographic data (age, gender, height, weight, body mass index; BMI, kg/m^2). Disease duration was defined as the time elapsed between the onset of first disease related symptoms and enrollment. Clinical, biological and radiological status was assessed by the Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI), ESR and C-reactive protein (CRP). All of the women included in the study were premenopausal.

Bone mineral density measurements

The DXA scans were obtained by standard procedures supplied by the manufacturer for scanning and analysis. All BMD measurements were carried out by 2 experienced technicians. Daily quality control was carried out by measurement of a Lunar phantom. At the time of the study, phantom measurements showed stable results. The phantom precision expressed as the coefficient of variation percentage was 0.08. Moreover, reproducibility has been assessed recently in clinical practice and showed a smallest detectable difference of 0.04 g/cm^2 (spine) and 0.02 (hips) [11,12]. Patient BMD was measured at the lumbar spine (anteroposterior projection at L1–L4) and at the femurs (i.e., femoral neck, trochanter, and total hip). Using the Moroccan female normative data [13] for lumbar spine and hip, the World Health Organization (WHO)classification system [14] was applied, defining osteoporosis as T-score≤ -2.5 and osteopenia as $-2.5<T$-score<-1. Study participants were categorized by the lowest T-score of the L1–4 lumbar spine, femur neck, or total femur. Male patients were also categorized using the same criteria since there is still no internationally accepted consensus for osteoporosis in men. The Moroccan male normative database was used for T-score calculation: the mean (SD) values for young normal adults in the Moroccan male normative database were 1.205 g/cm^2 (0.15) for lumbar spine, 1.147 g/cm^2 (0.16) for femoral neck, and 1.161 g/cm^2 (0.16) for total hip.

Vertebral assessment

Imaging performance could be obtained by lateral spine imaging when performing bone mineral density (BMD) measurement using DXA, with specific software, the so-called vertebral fracture assessment (VFA). Vertebral fracture (VF) evaluation was performed (T4 to L4) qualitatively then semi quantitatively using the Genant classification. VFA was classified using a combination of Genant semiquantitative (SQ) approach and morphometry in the following manner: each VFA image was inspected visually by a reader (IG) who had a previous training session in VFA, to decide whether it contained a fracture in any of the visualized vertebrae. Each vertebra that was judged as fractured by visual inspection was measured using built-in morphometry and assigned a grade based on Genant SQ scale, where grade 1 (mild) fracture is a reduction in vertebral height of 25%, grade 2 (moderate) a reduction of 26–40%, and grade 3 (severe) a reduction of over 40%. Subjects with no fractures were included in the non-fracture group, whereas those with grade 2 or higher fracture were included in the fracture group. These were also scored using scoring method assessing the corners of the vertebrae: Bath AS Radiology Index (BASRI) [15] and modified stoke AS spine score (mSASSS) [16]. Each corner is scored for the presence of squaring, sclerosis, erosions, syndesmophytes and bridging syndesmophytes. The maximal score is 72.

Statistical analysis

Statistics Package for Social Sciences (SPSS Inc., Chicago, IL) was used for statistical analyses. Results are expressed in mean± SD. Osteoporosis and VF prevalence was calculated. Risk factors of osteoporosis (any sites) and VFs (grades 1, 2 and 3 using the Genant classification) were tested for significance using the analysis of variance ANOVA. Multivariate regression analysis was used to estimate the independent effects of some clinical and laboratory variables on osteoporosis and VFs.

Results

The basic characteristics and BMD measurements of AS patients are shown in Table 1. The mean age of the study population was 38.9 years±11.8. The mean BMI was 22.8 kg/m^2±4.1 and the mean disease duration was 10.8 years±6.6. Fifty two patients (65%) had coxitis. According to the WHO classification, prevalence of osteoporosis was 25%.

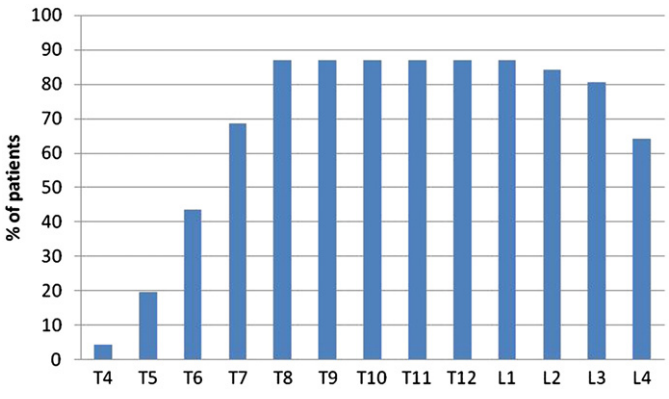

Fig. 1. Vertebral visualization using VFA.

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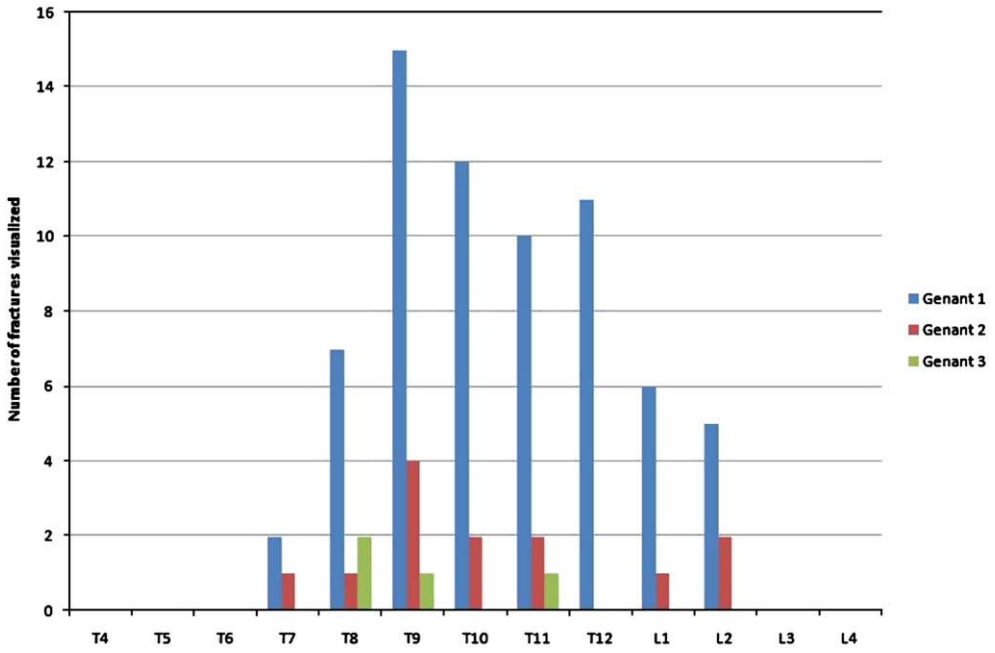

Fig. 2. VFA-identified fracture distribution.

Vertebral visualization and fracture identification on VFA

In these 80 patients, 68.1% of vertebrae from T4–L4 and 83.3% from T8–L4 were adequately visualized on VFA (Fig. 1). The percentage of vertebrae not visualized at T4, T5, and T6 levels was 95.7%, 80.4, and 56.5%, respectively. VFs grade 1 were detected in 23.8% (19/80) and VFs grades 2 and 3 were detected in 18.8% (15/80) of these patients: 11 (73.3%) had grades 2 and 4 (26.7%) had grade 3. Among patients with VFA-identified fracture grades 2 and 3, 12 (80%) had only a single vertebral fracture, while the other 20% had two or more. These fractures were most common in the mid-thoracic spine and at the thoraco-lumbar junction (Fig. 2).

The prevalence of VFs was increased in older patients with low total hip BMD (Figs. 3 and 4). Factors associated with osteoporosis were low weight and BMI and longer disease duration, higher ESR, CRP, BASFI and BASDAI. VFs were associated with advanced age, longer disease duration, higher BASFI, BASRI and mSASSS, reduced BMD and *T*-score at the hip site and presence osteoporosis at any site (Tables 2 and 3).

Multiple logistic regression analysis (Table 4) revealed that parameters significantly associated with osteoporosis were BASDAI (OR = 1.05, 95% confidence interval [CI]: 1.03–1.09); disease duration (OR = 1.13, 95%CI: 1.03–1.25); and BMI (OR = 0.82, 95%CI: 0.69–0.93). The presence of VFs (grades 2 and 3) were independently associated with disease duration (OR = 1.50, 95%CI: 1.07–2.10); and mSASSS (OR = 1.17, 95%CI: 1.05–1.30).

The VFs prevalence increased with disease duration. Indeed, none of our patient with less than a 10-year-disease duration AS had VFs, and in the other hand, after an evolution of 13 years, near to 60% of patients with AS had VFs (Fig. 5).

Discussion

Spine is a key fracture site in patients with AS [17–20]. The risk of VFs in AS varies from 0.4% to 58% in the literature. In our study, using VFA, the prevalence of VFs was estimated to 18.8%. Although spine radiographs are considered the gold standard for vertebral fracture detection, VFA offers advantages including patient convenience, lower radiation exposure, cost effectiveness and ease of directly integrating knowledge of bone density and fracture status into prediction of future fracture probability, and thus in the therapeutic decision. Thus, the technique has been validated as useful in evaluating postmenopausal women and men [21]. The main limiting factor in utilizing VFA is the legibility of the

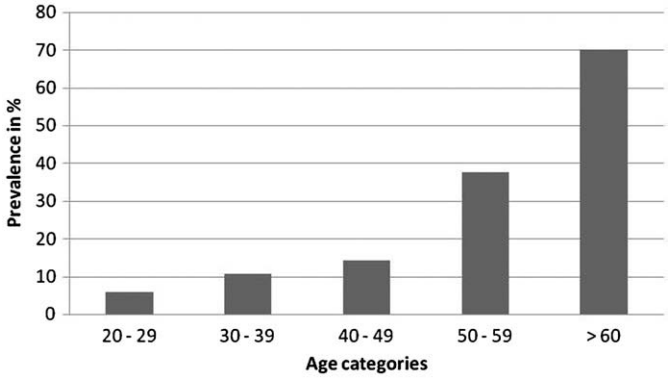

Fig. 3. Vertebral fractures (grades 2 and 3) prevalence (%) based on age groups.

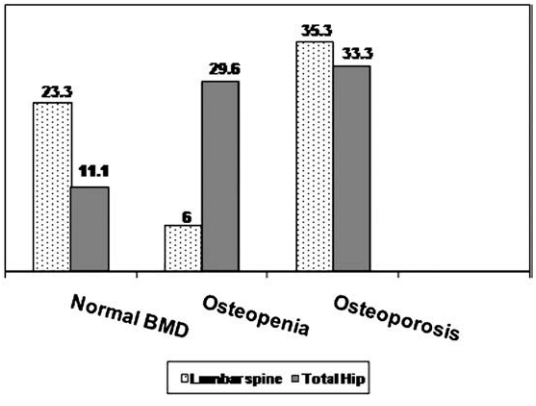

Fig. 4. Vertebral fractures (grades 2 and 3) prevalence (%) based on BMD (WHO classification).

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Table 2
Comparison between patients with and without osteoporosis

	Patients with osteoporosis	Patients without osteoporosis	*p*
	N= 20	N=60	
Age (years)	40.8±12.3	38.5±11.3	NS
Disease duration (years)	14.4±6.5	9.7±6.2	0.006
Weight (cm)	59.5±13.6	69.5±11.4	0.005
Height (m)	1.69±0.7	1.70±0.7	NS
BMI(kg/m^2)	20.7±3.6	23.6±4.1	0.006
ESR (mm/h)	38.4±18.3	25.7±15.3	0.003
CRP (mg/l)	62.8±61	28.2±37	0.003
BASDAI	65.6±15.7	47.9±20.7	<0.001
BASFI	70.5±11.2	49±24.5	<0.001
BASRI spine	5±3.6	3.3±3.6	NS
mSASSS	36.1±21.8	26.2±22.2	NS
BASRI hip	2±1.5	1.5±1.5	NS
Coxitis: *n*(%)	14 (70)	37 (62)	NS

vertebrae. The difficulty is mostly seen in the upper thoracic vertebrae. However, so few osteoporotic fractures occur at this level.

It has been reported that only patients with the most severe VFs come to clinical attention (which means that the majority of patients with VFs remain undetected). Even in the presence of symptomatic clinical VFs, they can be clinically overlooked in AS patients as acute and chronic back pain is common. Thus, diagnosing VFs is not an easy task in general, but their clinical consequences in aggravating spine deformation (hyperkyphosis) and complications are increasingly recognized. Moreover, VFs in AS are often overlooked even when radiographs are available [2]. Importantly, our study showed that about 30% of patients with osteopenia and 20% with normal BMD who otherwise may not have been identified as being at greater fracture risk were found to have unappreciated evident vertebral fracture (grades 2 and 3). It is well known in postmenopausal women that about half of fractures occur in patients without densitometric osteoporosis and that other factors than BMD may play a role. In this case, recognition of VFs by imaging of the spine change the patient's diagnostic classification, estimation of fracture risk, and threshold for pharmacological intervention as treatment of patients with prevalent VFs reduces the risk of future fractures even when the baseline *T*-score is above the osteoporosis diagnostic cutpoint of −2.5. Thus, these data suggest that VFs should be evaluated in patients with AS even when BMD is normal or in the “osteopenic” range.

Table 3
Prevalence and risk factors of vertebral fractures

	Patients without vertebral fractures	Patients with vertebral fractures (grade 1)	Patients with vertebral fractures (grade 2 and 3)	*p*
	n=46	*n*=19	*n*=15	
Age (ans)	37.2±9.1	34.9±10.1	49.3±14.4	<0.001
Disease duration (years)	8.3±3.9	10.0±7.4	19.3±5.5	<0.001
Weight (kg)	68.2±12.0	61.4±10.4	66.6±14.5	NS
Height (m)	1.71±0.7	1.69±0.8	1.66±0.8	NS
BMI (kg/m^2)	23.1±3.9	21.3±3.7	23.9±4.9	NS
ESR (mm/1st H)	29.2±18.9	28.9±14.8	30.8±17.3	NS
CRP (mg/l)	26.4±24.6	48.9±60.7	57.7±67.1	0.035
BASDAI	49.0±20.8	58.5±21.5	56.3±21.5	NS
BASFI	50.2±23.5	55.3±24.7	67.1±19.8	0.055
BASRI spine	2.5±2.3	2.5±2.5	9.4±2.7	<0.0001
mSASSS	21.0±18.3	23.2±20.3	58.8±8.7	<0.0001
BASRI hip	1.5±1.5	1.4±1.6	2.5±1.3	NS
Lumbar spine BMD (g/cm^2)	1.052±0.1	0.933±0.13	1.059±0.2	NS
Total hip BMD (g/cm^2)	0.987±0.1	0.909±0.1	0.841±0.1	0.005
Lumbar spine *T*-score (DS)	−1.15±1.0	−1.55±1.1	−1.19±2.4	NS
Total hip *T*-score (DS)	−0.40±1.1	−0.97±1.3	−1.3±1.1	0.027
Coxitis *n*(%)	29 (63.0)	9 (47.4)	14 (93.3)	0.125
Osteoporosis *n*(%)	8 (17.4)	5 (26.3)	7 (46.7)	0.027

Comparison between the 3 groups used analysis of variance (ANOVA) for quantitative variables and chi-square test for qualitative variables.

Table 4
Results of multivariate logistic regression analysis for osteoporosis and vertebral fracture

	T-score ≤ −2.5	Vertebral fracture (grade 2 or 3)
Age	0.92 (0.80–1.07)	0.97 (0.84–1.12)
Disease duration	1.13 (1.03–1.25)*	1.50 (1.07–2.10)*
BMI	0.82 (0.69–0.93)*	1.20 (0.87–1.66)
BASDAI	1.05 (1.03–1.09)*	1.01 (0.95–1.07)
Lumbar spine BMD	–	12.15 (0.41–359.7)
mSASSS	1.01 (0.97–1.04)	1.17 (1.05–1.30)*

* Indicates significant odds ratio. Numbers are presented as odds ratio (95% confidence intervals in parentheses).

Another problem is that there is no universally accepted golden standard for diagnosing VFs. The prevalence and incidence of VFs is therefore influenced by the definition of the degree of deformation of the vertebral body and there are therefore continuing discussions on which deformity of a vertebral body should be called a fracture. The presence (from a height loss of >25% at the anterior, mid or posterior part of the vertebral body), number and severity of VFs (silent or clinical) are associated with an increased risk of new fractures, even in the short term. So, we choose in our study to call as a fracture a vertebral deformity >stage 2 of the Genant semi-quantitative method. However, including or excluding stage 1 fractures from analysis did not have any effect on the results.

The precise etiology or mechanism of VFs in AS has not been clearly determined. Previous studies have suggested that the majority of VFs were caused by mechanical injuries such as minor falls and motor vehicle accidents [22]. However, reduced bone mass (osteopenia or osteoporosis) was also identified as one of the clinical features of AS [23]. Based on this finding, it has been proposed that osteoporosis is a major determinant in the development of VFs in AS, although some studies have shown no association between BMD measurements and VFs [19,20].

There was an ongoing conflict of opinions about an association between BMD levels and disease activity variables such as ESR, CRP, and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Some studies failed to identify relationships between disease activity measurements (ESR, CRP, and BASDAI) and BMD levels [24]. In contrast, as observed in our study, other studies showed that a reduced lumbar spine BMD was detected in AS patients with higher levels of parameters of symptomatic severity [25,26].

Previous studies proposed the limitations of using only lumbar spine BMD measurement to predict the risk of VFs in AS patients. In our study, we also failed to identify a correlation between VFs and lumbar BMD levels. Others risk factors have been reported associated with fractures of the vertebral body including age, low body weight, low BMD, disease duration, disease activity and low hip BMD. In our study, more extensive syndesmophytes and mSASSS score even if they falsely increased BMD, they did not protect against VFs, which joined several previous studies [25–27].

Our study has strengths and limitations. The assessment of fracture was carefully conducted using standard procedures of acquisition, and standard reading of all VFA. All the morphometric assessments were made by an experienced investigator after training sessions and after a previous global visualization. Before diagnosis of fracture, a non-osteoporotic origin was considered for each deformity. However, even history of trauma was inquired, we cannot exclude that some subjects did not report remote traumas. The main limitation lies in the fact that the study is cross-sectional and it did not assess other factors such as biochemical factors of bone remodeling and 25 OH vitamin D status. Further studies with long follow-up designs are needed to evaluate the vertebral fracture risk of patients with AS.

In summary, osteoporosis is common in patients with AS and seems to be related to disease activity while VFs appear to be related more to the duration and structural severity of the disease than BMD.

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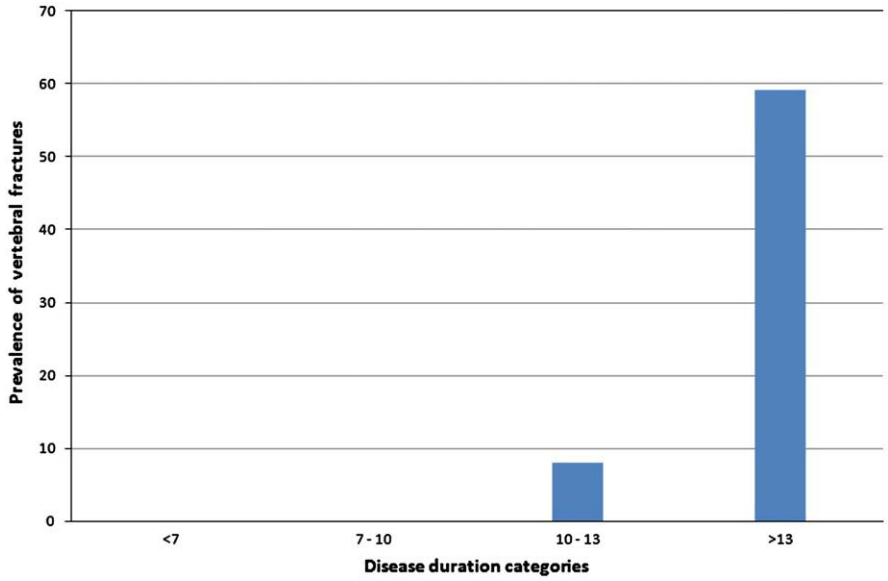

Fig. 5. Prevalence of vertebral fractures according to disease duration (divided in quartiles).

Measuring BMD in early disease should include DXA in the spine and hip. In advanced disease, BMD evaluation should rely on hip DXA and VFA can be used to look for the presence of fracture.

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