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Radiographic vertebral fractures develop in patients with ankylosing spondylitis during 4 years of TNF-α blocking therapy

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Abstract

Objective

To determine the prevalence and incidence of radiographic vertebral fractures in ankylosing spondylitis (AS) patients treated with TNF-α blocking therapy for 4 years and to explore the relationship with patient characteristics, clinical assessments, radiographic damage, and bone mineral density (BMD).

Methods

This study included consecutive AS patients with active disease from the Groningen Leeuwarden AS (GLAS) cohort treated with TNF-α blocking therapy for 4 years and with available thoracic and lumbar radiographs at baseline and at 4 years. Vertebral fractures were assessed by two readers (mild: ≥20-<25%, moderate: ≥25-<40%, severe: ≥40% reduction in vertebral height).

Results

In 27 of 105 (26%) AS patients, radiographic vertebral fractures were observed at baseline. These patients were significantly older, had larger occiput-to-wall distance, and more spinal radiographic damage. During 4 years of TNF-α blocking therapy, 21 (20%) patients developed at least one new fracture. Older age, smoking, higher BASFI, low lumbar spine BMD (Z-score ≤-2), presence of moderate vertebral fractures, and use of anti-osteoporotic treatment at baseline were associated with the development of new fractures. Most fractures were mild and occurred in the thoracic spine. The improvement in lateral spinal mobility and lumbar spine BMD during treatment was significantly less in patients with new fractures (median change of 0.8 vs. 2.8 cm and 0.3 vs. 0.8 Z-score, respectively).

Conclusion

The prevalence of radiographic vertebral fractures was high in AS patients with active disease. Although clinical assessments and BMD improved significantly, new vertebral fractures still developed during 4 years of TNF-α blocking therapy.

Key words

ankylosing spondylitis, tumour necrosis factor-alpha blocking therapy, spinal fracture, incidence, bone density

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Introduction

Ankylosing spondylitis (AS) is a chronic rheumatic inflammatory disorder which is characterised by the combination of inflammation, excessive bone formation, and bone loss in the axial skeleton. Bone loss reflected by low bone mineral density (BMD) is a common feature of AS and can already be observed at early stages of the disease (1, 2). Severe bone loss may lead to vertebral fractures. These fractures can cause increased back pain and may result in progressive kyphosis, neurological symptoms, and instability (3-6). Pain and complications may have large impact on daily activities and health-related quality of life.

Previous population-based studies have shown that AS patients are at increased risk of developing vertebral fractures, as reported in medical records (7-10). The prevalence of vertebral fractures assessed on radiographs varies from 10 to 43% (11-19). Vertebral fractures are found to be associated with several risk factors, including male gender, older age, longer disease duration, low body weight, smoking status, the presence of spinal radiographic damage according to mSASSS, poor spinal mobility, peripheral joint involvement, and low BMD (12, 13, 15, 17-23). In a recent observational cohort study of 298 AS patients, the development of new radiographic vertebral fractures in the lumbar spine during 4 years of follow-up was associated with previous vertebral fractures and elevated C-reactive protein (CRP) levels (24). This finding may suggest that anti-inflammatory therapy could have an effect on the development of vertebral fractures.

Two studies reported about the influence of conventional treatment on the risk of vertebral fractures in AS. In a UK population-based case-control study including 758 AS patients, patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) showed a decreased risk of having any clinical fracture, including vertebral fractures, after adjustment for several confounding variables (8). In a large Spanish population-based cohort study, an increased clinical fracture risk was found in AS patients compared to patients without rheumatic diseases. However, this increased risk was not found in AS patients who used NSAIDs on a regular basis (10).

Until now, little is known about the influence of tumour necrosis factor-alpha (TNF-α) blocking therapy on radiographic vertebral fractures. An observational cohort study showed that 6 of 118 (5%) AS patients receiving TNF-α blocking therapy developed new vertebral fractures in the lumbar spine during 2 to 4 years follow-up (24). Furthermore, one retrospective study reported 5 new radiographic vertebral fractures in the lumbar spine of 59 AS patients who were treated with TNF-α blocking therapy for at least 4 years (25). Data on the actual prevalence and incidence of vertebral fractures in both the thoracic and lumbar spine during TNF-α blocking therapy are scarce in AS.

The objectives of the present prospective observational cohort study were to determine the prevalence of radiographic vertebral fractures in AS patients with active disease before the start of TNF-α blocking therapy and to investigate the incidence of vertebral fractures in these patients during 4 years of TNF-α blocking therapy. Furthermore, to explore the relationship of vertebral fractures with patient characteristics, clinical assessments, radiographic damage, and BMD.

Patients and methods

Study population

This study included consecutive AS patients with active disease enrolled in the Groningen Leeuwarden AS (GLAS) cohort who started TNF-α blocking therapy between November 2004 and December 2008 and continued this treatment for 4 years. Switching between different TNF-α blocking agents was allowed. Patients with available radiographs at baseline and after 4 years of follow-up were selected (Fig. 1).

GLAS is an ongoing prospective, longitudinal, observational cohort study of AS patients with follow-up visits according to a fixed protocol in daily clinical practice in the North of the Netherlands (26). Included patients were 18 years of age or older, fulfilled the modified New York criteria for AS

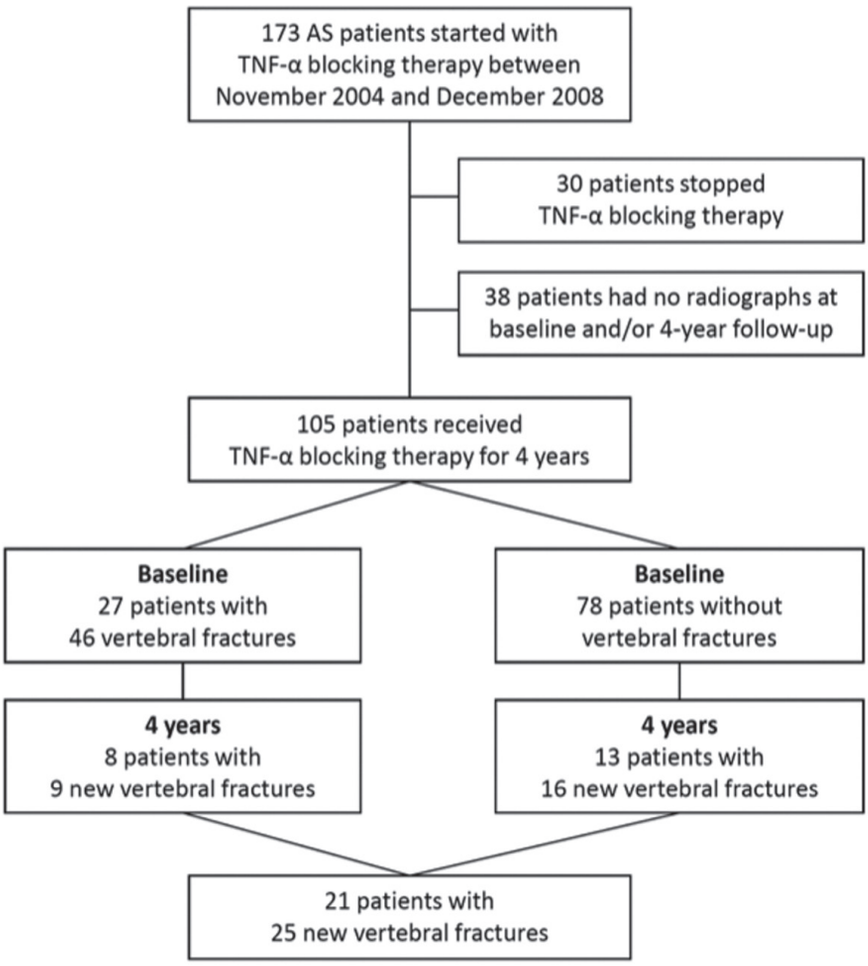

Fig. 1. Flowchart of analysed AS patients from the GLAS cohort.

(27), and fulfilled the criteria to start TNF-α blocking therapy according to the ASAS consensus statement (active disease defined as Bath AS Disease Activity Index (BASDAI) ≥4 and/or based on expert opinion) (28). Patients started using infliximab, etanercept, or adalimumab based on the judgment of the treating rheumatologist and/or the specific preference of the patient. In the GLAS cohort, the standard regimen for infliximab was 5 mg/kg intravenously at 0, 2, 6 weeks and then every 8 weeks, for etanercept 50 mg (once) or 25 mg (twice) subcutaneous injection every week, and for adalimumab 40 mg subcutaneous injection every two weeks. Patients were clinically evaluated at baseline, after 3 and 6 months, and then every 6 months. Continuation of treatment was based on BASDAI improvement (≥50% or two units compared with baseline) and/or expert opinion at each follow-up visit. Patients received concomitant medication as usual in daily clinical practice (29).

The GLAS cohort was approved by the local ethics committees of the Medical Center Leeuwarden (MCL) and the University Medical Center Groningen (UMCG). All patients gave written informed consent according to the Declaration of Helsinki.

Data collection

At baseline, the following patient characteristics were recorded: gender, age, body mass index, duration of symptoms, time since diagnosis, HLA-B27 status, years of smoking, history of extra-articular manifestations, presence of peripheral arthritis (defined as ≥1 swollen joint), and use of NSAIDs, disease-modifying anti-rheumatic drugs (DMARDs), systemic corticosteroids, or anti-osteoporotic treatment (bisphosphonates and/or calcium/vitamin D supplements).

Clinical disease status was assessed using the BASDAI (30), C-reactive protein (CRP), AS Disease Activity Score ($ASDAS_{CRP}$) (31, 32), and Bath AS Functional Index (BASFI) (33). Spinal mobility was measured by occiput-to-wall distance, chest expansion, lateral spinal flexion, and the modified Schober test.

Serum levels of 25-hydroxyvitamin D (25OHvitD) were measured by radioimmunoassay (RIA; DiaSorin, Stillwater, MN, USA; IE-CV 15%; UMCG and MCL until July 2008) or electrochemiluminescence immunoassay (ECLIA; Modular Analytics E170, Roche Mannheim, Germany; IE-CV 7.1%; MCL since July 2008). Vitamin D deficiency was defined as 25OHvitD levels <50 nmol/L (34).

Spinal radiographic damage of the cervical and lumbar spine was assessed by two independent trained readers (FM and RC) blinded to patient characteristics using the modified Stoke AS Spine Score (mSASSS) on a scale of 0-72 (intraclass correlation coefficient : 0.98) (35, 36).

Assessment of vertebral fractures

Lateral radiographs of the thoracic and lumbar spine were assessed at baseline and after 4 years of follow-up (mean 4.0±0.4 years) by two independent trained readers (FM and RC). Readers were blinded to patient characteristics and time sequence of radiographs. Vertebral fractures were scored using the method of Genant *et al*., a semiquantitative technique evaluating the anterior, middle, and posterior heights of the 4th thoracic vertebra (Th4) to the 4th lumbar vertebra (L4) (37). A prevalent vertebral fracture was defined as ≥20% reduction in any vertebral height. Vertebral fractures were divided in grades 0 to 3: grade 0 (normal), <20% height reduction; grade 1 (mild), ≥20-<25% reduction; grade 2 (moderate), ≥25-≤40% reduction; and grade 3 (severe), >40% reduction. If the measurement was complicated because of new bone formation or erosions at the corners of the vertebral bodies, a lengthened imaginary line that represents the original edge of the vertebral body was used. If this was not possible due to, for ex-

ample, complete ankylosis or large erosions, the vertebral body was scored as missing. In addition, vertebral bodies were excluded when vertebral heights could not be measured in case of abnormalities matching with spondylodiscitis or degenerative changes. In case of discrepancy between the two readers, vertebrae were reassessed by the same readers. When discrepancy persisted after reassessment, a third independent reader (SA) measured vertebral heights. The score of the primary reader closest to the third reader was used.

After 4 years of follow-up, a new vertebral fracture was recorded if a patient developed a vertebral fracture in a vertebral body that was normal at baseline. Worsening of previous fractures was also recorded and analysed separately.

Inter-observer reliability between the two readers regarding the grades of vertebral fractures was good with a linear weighted kappa of 0.78 for baseline and 0.86 for 4 years radiographs, and absolute agreement of 93% for both time points.

BMD measurement

BMD of the lumbar spine (anterior-posterior projection at L1-L4) and hip (total proximal femur) were assessed at baseline and after 4 years of follow-up. BMD was measured by dual-energy X-ray absorptiometry (DXA; Hologic QDR Delphi (MCL) or Hologic DQR Discovery (UMCG)). The NHANES reference database was used to calculate Z-scores (the number of standard deviations above or below the mean of age- and gender-matched adults) (38). The use of BMD Z-scores instead of BMD T-scores is preferred in premenopausal women and in men younger than 50 years of age according to the International Society for Clinical Densitometry since age is not taken into account in T-scores (39).

Statistical analysis

Results were expressed as mean ± SD or median (range) for normally distributed and non-normally distributed data, respectively. Independent samples *t*-test, Mann-Whitney U-test, and Chi-Square or Fisher's Exact test were used as appropriate to compare differences between patients with and without vertebral fractures. *P*-values ≤0.05 were considered as statistically significant. Statistical analysis was performed with IBM SPSS Statistics 20 (SPSS, Chicago, IL, USA).

Table I. Baseline characteristics of the AS study population, stratified for patients with and without vertebral fractures at baseline.

	All patients n=105	Vertebral fractures† Present n=27	Vertebral fractures† Absent n=78	*p*-value
Male	76 (72)	23 (85)	53 (68)	0.133
Age (yrs)	41.8 ± 10.9	46.2 ± 9.5	40.3 ± 11.0	**0.013**
BMI (kg/m^2)	26.3 ± 4.1	26.4 ± 3.5	26.3 ± 4.3	0.869
Duration of symptoms (yrs)	16 (1-47)	20 (3-47)	14 (1-41)	0.141
Time since diagnosis (yrs)	7 (0-34)	7 (0-28)	6 (0-34)	0.950
HLA-B27+	86 (83)	21 (78)	65 (84)	0.433
Smoking (yrs)	11 (0-54)	17 (0-54)	7 (0-45)	0.051
Peripheral arthritis	22 (21)	5 (19)	17 (22)	0.697
NSAID use	89 (85)	22 (82)	67 (86)	0.582
DMARD use	24 (23)	6 (22)	18 (23)	0.927
Systemic corticosteroid use¥	5 (5)	1 (4)	4 (5)	1.000
Anti-osteoporotic treatment	18 (17)	5 (19)	13 (17)	0.826
Calcium/vitD	10 (9)	3 (11)	7 (9)	0.715
Bisphosphonates & calcium/vitD	8 (8)	2 (7)	6 (8)	1.000
BASDAI (range 0-10)	6.0 ± 1.7	6.1 ± 1.4	5.9 ± 1.8	0.770
$ASDAS_{CRP}$	3.8 ± 0.8	4.0 ± 0.6	3.8 ± 0.8	0.298
CRP (mg/L)	15 (2-99)	17 (2-99)	14 (2-82)	0.217
BASFI (range 0-10)	6.0 (0.3-9.7)	5.5 (1.3-8.4)	6.2 (0.3-9.7)	0.553
Occiput-to-wall distance (cm)	4.8 (0.0-34.5)	8.0 (0.0-18.5)	4.0 (0.0-34.5)	**0.039**
Chest expansion (cm)	3.0 (0.5-10.0)	3.0 (0.5-10.0)	3.0 (0.5-7.0)	0.964
Lateral spinal flexion (cm)	7.8 (0.0-29.5)	6.5 (1.8-18.0)	8.0 (0.0-29.5)	0.427
Modified Schober test (cm)	2.5 (0.1-6.3)	2.2 (0.3-6.3)	2.5 (0.1-5.8)	0.900
25OHvitD (nmol/L)	62 (12-186)	61 (12-104)	64 (13-186)	0.370
25OHvitD <50 nmol/L	24 (24)	8 (30)	16 (22)	0.444
mSASSS (range 0-72)	12 (0-72)	21 (1-72)	10 (0-72)	**0.030**
BMD LS Z-score	-0.5 ± 1.5	-0.9 ± 1.1	-0.4 ± 1.6	0.204
LS Z-score ≤-1	43 (43)	13 (54)	30 (40)	0.223
LS Z-score ≤-2	15 (15)	4 (17)	11 (15)	0.754
BMD hip Z-score	-0.4 ± 1.0	-0.4 ± 0.9	-0.4 ± 1.1	0.784
Hip Z-score ≤-1	30 (30)	7 (28)	23 (31)	0.801
Hip Z-score ≤-2	5 (5)	0 (0)	5 (7)	0.327

Values are presented as number of patients (%), mean ± SD or median (range).
AS: Ankylosing spondylitis; BMI: Body mass index; HLA: Human leukocyte antigen; NSAID: Non-steroidal anti-inflammatory drug; DMARD: Disease-modifying anti-rheumatic drugs; BASDAI: Bath AS disease activity index; ASDAS: AS disease activity score; CRP: C-reactive protein; BASFI: Bath AS functional index; 250HvitD: 25-hydroxy vitamin D; mSASSS: Modified stoke AS spine score; BMD: Bone mineral density; LS: Lumbar spine.
†Defined as ≥20% vertebral height reduction. ¥Three patients used prednisone (5-7.5 mg/day) and two budesonide (3mg/week, 6 mg/day).

Results

In total, 105 of 173 AS patients received TNF-α blocking therapy for 4 years and had radiographs available at baseline and after 4 years of follow-up (Fig. 1). Patient characteristics were comparable between included and excluded patients, except for the use of calcium/vitamin D supplements (17% versus 4%, $p<0.05$) and lumbar spine BMD Z-score (mean -0.52±1.49 *vs*. -0.04±1.44, $p<0.05$).

Of the 105 included AS patients, 72% were male, mean age was 42±11 years, median symptom duration was 16 years (range: 1–47), and 83% were HLA-B27 positive (Table I). All women were 50 years or younger and premenopausal. Patients had active disease at baseline, mean BASDAI was 6.0±1.7 and mean ASDAS was 3.8±0.8. Median mSASSS was 12 (range: 0–72) and mean BMD Z-scores were -0.5±1.5 in the lumbar spine and -0.4±1.0 in the hip. History of inflammatory bowel disease, uveitis, and psoriasis were present in 10%, 28%, and 11% of the patients, respectively. Twenty-one (20%) patients started with infliximab, 67 (64%) with etanercept, and 17 (16%)

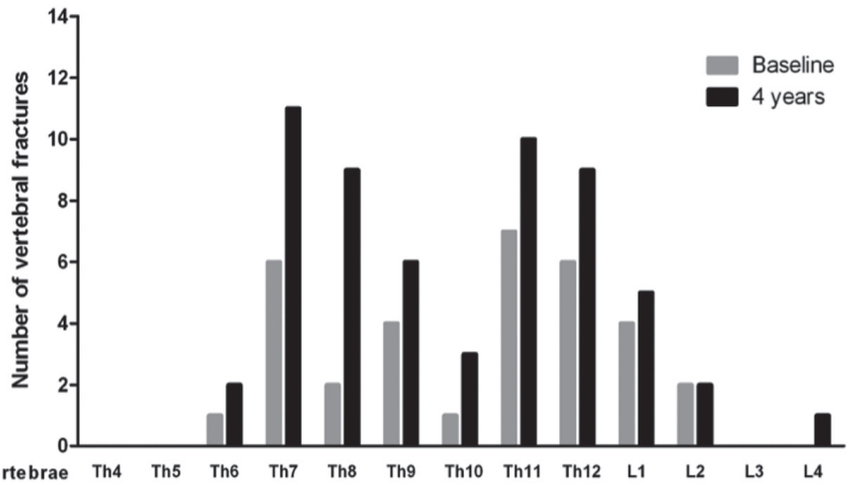

Fig. 2. Locations and number of vertebral fractures visible at baseline and after 4 years.

Table II. Baseline characteristics of AS patients with and without new vertebral fractures after 4 years follow-up.

	New vertebral fractures		*p*-value
	Present n=21	Absent n=84	
Male	17 (81)	59 (70)	0.419
Age (yrs)	46.8 ± 12.2	40.5 ± 10.2	**0.017**
BMI (kg/m^2)	26.7 ± 5.2	26.2 ± 3.7	0.590
Duration of symptoms (yrs)	18 (3-47)	16 (1-36)	0.743
Time since diagnosis (yrs)	9 (0-34)	5 (0-31)	0.129
HLA-B27+	15 (71)	71 (86)	0.127
Smoking (yrs)	24 (0-54)	10 (0-40)	**0.036**
Peripheral arthritis	4 (19)	18 (22)	1.000
NSAID use	16 (76)	73 (87)	0.222
DMARD use	6 (29)	18 (21)	0.486
Systemic corticosteroid use	2 (9)	3 (4)	0.261
Anti-osteoporotic treatment	8 (38)	10 (12)	**0.004**
Calcium/vitD	2 (9)	8 (10)	1.000
Bisphosphonates & calcium/vitD	6 (29)	2 (2)	**0.001**
BASDAI (range 0-10)	6.0 ± 1.3	6.0 ± 1.8	0.814
$ASDAS_{CRP}$	3.9 ± 0.6	3.8 ± 0.8	0.711
CRP (mg/L)	17 (2-70)	15 (2-99)	0.601
BASFI (range 0-10)	6.9 (1.7-9.7)	5.5 (0.3-9.7)	**0.038**
Occiput-to-wall distance (cm)	7.5 (0.0-34.5)	4.5 (0.0-28.0)	0.122
Chest expansion (cm)	3.2 (0.5-9.0)	3.0 (0.5-10.0)	0.723
Lateral spinal flexion (cm)	6.5 (1.8-17.3)	8.0 (0.0-29.5)	0.618
Modified Schober test (cm)	3.0 (0.3-6.3)	2.2 (0.1-5.8)	0.670
25OHvitD (nmol/L)	60 (12-104)	65 (18-186)	0.097
25OHvitD <50 nmol/L	6 (30)	18 (23)	0.501
mSASSS (range 0-72)	14 (0-72)	11 (1-72)	0.752
BMD LS Z-score	-0.7 ± 1.6	-0.5 ± 1.5	0.563
LS Z-score ≤-1	10 (50)	33 (42)	0.507
LS Z-score ≤-2	6 (30)	9 (11)	**0.038**
BMD hip Z-score	-0.4 ± 1.3	-0.4 ± 1.0	0.977
Hip Z-score ≤-1	7 (35)	23 (29)	0.585
Hip Z-score ≤-2	1 (5)	4 (5)	1.000
Vertebral fractures (≥grade 1)	8 (38)	19 (23)	0.147
Vertebral fractures (≥grade 2)	5 (24)	7 (8)	**0.046**

Values are presented as number of patients (%), mean ± SD or median (range).
See Table I for abbreviations.

with adalimumab. Twenty-four (23%) patients switched to another TNF-α blocking agent during follow-up. Patients were exposed to TNF-α blocking agents for 98% of the follow-up time (IQR: 93–100%).

Prevalence of radiographic vertebral fractures at baseline

At baseline, 27 (26%) patients had at least one vertebral fracture with an average of 1.7 vertebral fractures per patient. Of the 46 vertebral fractures at baseline, 33 (72%) were defined as mild (grade 1) and 13 as moderate (grade 2). No severe (grade 3) fractures were observed. Patients with vertebral fractures at baseline were significantly older, had larger occiput-to-wall distance, and higher mSASSS scores than patients without vertebral fractures (Table I). These differences were most pronounced for the 12 (11%) patients with moderate vertebral fractures. These patients were also less frequently HLA-B27 positive, had longer smoking duration, and more often vitamin D deficiency than patients without vertebral fractures (data not shown).

Development of new radiographic vertebral fractures during TNF-α blocking therapy

Over 4 years of TNF-α blocking therapy, 21 (20%) patients developed at least one new vertebral fracture. Of the 25 new fractures, 20 (80%) were mild, 4 (16%) moderate, and 1 (4%) was severe. The majority of vertebral fractures occurred in the middle and lower thoracic spine (Fig. 2).

Patients with new vertebral fractures were significantly older, had longer duration of smoking, scored worse on BASFI, had lower lumbar spine BMD (Z-score ≤-2), more frequent moderate vertebral fractures, and used anti-osteoporotic treatment more often at baseline (Table II).

Of the 46 fractures scored at baseline, 4 (9%) increased in severity from mild to moderate and 29 (63%) did not change in severity. The remaining 13 (28%) fractures were mild but could not be scored after 4 years due to limited quality of radiographs (n=2), new ankylosis of vertebrae (n=3), missing vertebrae

(n=2), or vertebral height reduction just below 20% (n=6).

Relationship with clinical assessments, mSASSS, and BMD during TNF-α blocking therapy

Disease activity (BASDAI, ASDAS, CRP), physical functioning (BASFI), and all spinal mobility measures improved significantly during 4 years of TNF-α blocking therapy (all $p<0.001$, Table III). Patients who developed new vertebral fractures showed significantly less improvement in lateral spinal flexion than patients without new fractures (0.3 *vs*. 0.8 cm, $p<0.05$). The radiographic score (mSASSS) increased during follow-up, but was not significantly different between patients with or without new vertebral fractures (Table III).

BMD improved significantly during 4 years of TNF-α blocking therapy. Patients with new vertebral fractures showed significantly less improvement in lumbar spine BMD than patients without new vertebral fractures (median change in Z-score: 0.3 *vs*. 0.8, $p<0.01$; Table III and Fig. 3). This difference remained statistically significant after excluding patients who received bisphosphonates at baseline (n=8). No significant difference in hip BMD was found between patients with and without new vertebral fractures (Table III).

Table III. Change in clinical assessments, mSASSS, and BMD in AS patients, stratified for patients with and without new vertebral fractures after 4 years of TNF-α blocking therapy.

		New vertebral fractures	
	All patients n=105	Present n=21	Absent n=84
BASDAI (range 0-10)	-2.9 ± 2.2	-2.7 ± 2.1	-2.9 ± 2.2
$ASDAS_{CRP}$	-1.7 ± 1.0	-1.6 ± 1.1	-1.8 ± 1.0
CRP (mg/L)	-10 (-93–21)	-10 (-67–21)	-10 (-93–2)
BASFI (range 0-10)	-2.0 ± 2.1	-1.3 ± 2.0	-2.2 ± 2.2
Occiput-to-wall distance (cm)	-1.3 (-8.5–10)	-0.5 (-5.2–10)	-2.0 (-8.5–7.0)
Chest expansion (cm)	2.0 (-3.0–7.0)	1.8 (-1.2–5.5)	2.0 (-3.0–7.0)
Lateral spinal flexion (cm)	2.3 (-6.2–12.5)	0.8 (-6.2–12.0)	2.8 (4.9–12.5)*
Modified Schober test (cm)	0.7 (-2.0–5.0)	0.2 (-2.0–2.5)	0.7 (-1.0–5.0)
mSASSS (range 0-72)	3 (-4–21)	1 (-3–18)	3 (-4–21)
BMD LS Z-score	0.7 (-1.0–2.8)	0.3 (-0.3–2.5)	0.8 (-1.0–2.8)*
BMD hip Z-score	0.1 (-1.1–2.3)	0.1 (-0.5–1.3)	0.1 (-1.1–2.3)

Values are presented as mean ± SD or median (range).
*$p \leq 0.05$ compared to patients with new vertebral fractures.
See Table 1 for abbreviations.

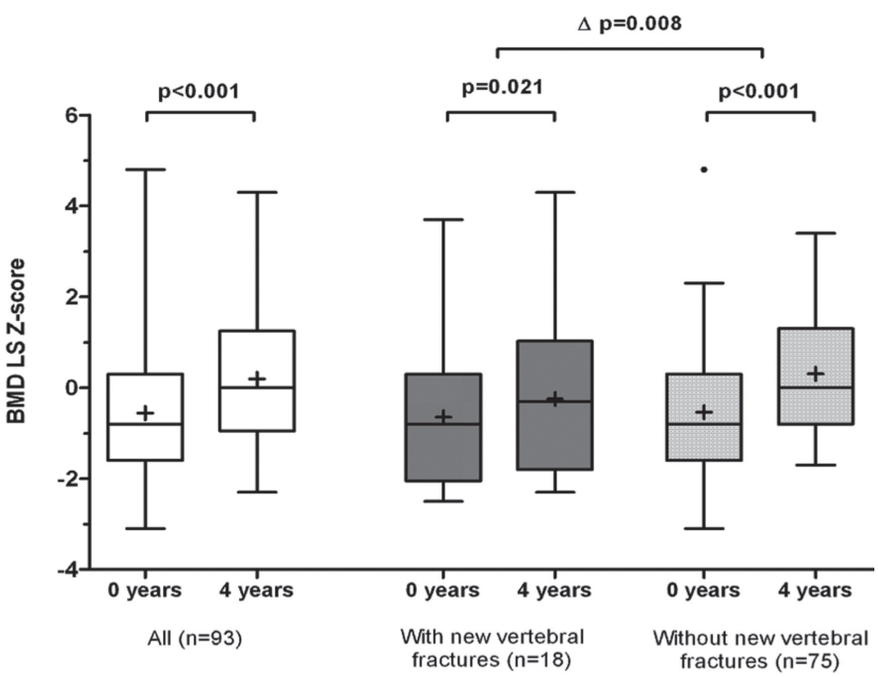

Fig. 3. Bone mineral density of the lumbar spine of patients with DXA at baseline and after 4 years of TNF-α blocking therapy, stratified for AS patients with and without new vertebral fractures.

Discussion

This prospective observational cohort study investigated the prevalence and incidence of radiographic vertebral fractures, defined as at least 20% reduction in vertebral height, in the thoracic and lumbar spine of 105 AS patients treated with TNF-α blocking therapy in daily clinical practice for 4 years. In a large proportion of patients (26%), radiographic vertebral fractures were found before start of TNF-α blocking therapy and 20% developed ≥1 new vertebral fracture during 4 years of follow-up. Most vertebral fractures were mild and were located in the middle and lower part of the spine (Th7-Th9 and Th11-L1). The prevalence rate and location of vertebral fractures are comparable with findings of previous studies in AS and early spondyloarthritis (16, 17, 20). Cross-sectional studies in which the same scoring method was used, reported prevalence rates of 12–43% in AS patients with variable disease duration, disease activity, and treatment regimens (16-19). A general population-based study reported a prevalence rate of approximately 5% of radiographic vertebral fractures in persons younger than 50 years (40). In comparison to the general population, the prevalence rates found in AS are very high.

Limited data are available on the incidence of radiographic vertebral fractures during TNF-α blocking therapy. A previous observational cohort study of 298 AS patients with different treatment regimens, including TNF-α blocking therapy, reported an incidence rate of 14% of radiographic vertebral fractures in the lumbar spine after 4 years of follow-up (24). In our study, a higher incidence rate (20%) was found because we also included the thoracic spine where most vertebral fractures were found.

The presence of vertebral fractures be-

fore start of TNF-α blocking therapy was associated with older age, higher occiput-to-wall distance, and a higher mSASSS representing more spinal radiographic damage. The associations were most pronounced in patients with moderate (grade 2) vertebral fractures. These results are in line with findings of previous cross-sectional studies in AS and early spondyloarthritis and suggests an association between vertebral fractures and worse clinical outcome (12, 17-20).

The presence of vertebral fractures was not significantly associated with low BMD. This lack of association may be explained by the fact that the measurement of lumbar spine BMD (anterior-posterior projection by DXA) is affected by new bone formation in AS such as syndesmophytes, ligament calcifications, and fusion of facet joints. Therefore, lumbar spine BMD is not a valid and sensitive method to diagnose osteoporosis in AS patients with excessive bone formation reflected by advanced radiographic damage (41). However, a significant association between new vertebral fractures and low lumbar spine BMD at baseline was found in our study. The most plausible explanation for this is that chronologically vertebral fractures are the result or outcome of excessive bone loss reflected by low BMD (42). Therefore, low lumbar spine BMD can be valuable in recognising AS patients who are at risk of developing vertebral fractures in the future.

In addition to low lumbar spine BMD, the development of new vertebral fractures during TNF-α blocking therapy was associated with older age, longer smoking duration, and higher BASFI which represents poor physical functioning. In accordance with earlier longitudinal studies in AS patients and in postmenopausal women, persons with previous (moderate) vertebral fractures had an increased risk of developing new vertebral fractures (24, 43, 44). Finally, we found that patients with new vertebral fractures received anti-osteoporotic treatment more frequently at baseline than patients without new fractures. This association was also found in a population-based study of 2,968 postmenopausal women. In this study, the risk of vertebral fractures was increased in participants who used calcium/vitamin D supplements (odds ratio (OR) 1.98) and bisphosphonates or other anti-osteoporotic treatment (OR 3.34) (45). This relationship can be explained by the fact that these drugs are prescribed in patients with an a priori increased risk for the development of fractures. In our study, bisphosphonates were prescribed in patients who used systemic corticosteroids or had osteoporosis according to the WHO definitions (BMD T-score ≤-2.5).

Other known risk factors such as male gender, low body weight, and peripheral joint involvement were not independently associated with the presence or the development of vertebral fractures. We had no data available about dietary intake and other lifestyle aspects. Unfortunately, the number of patients was too small to perform multivariable analysis.

Disease activity, physical functioning, spinal mobility, and BMD improved significantly during TNF-α blocking therapy. The increase in BMD was especially observed in the lumbar spine but also in the hip, as others have reported previously (25, 46-48). An important novel finding is that AS patients who developed new vertebral fractures showed less improvement in spinal mobility (lateral spinal flexion) and in lumbar spine BMD than patients without new fractures. The difference in BMD remained statistically significant after excluding patients receiving bisphosphonates.

In our study, only one vertebral fracture has come to clinical attention because of extreme pain. We hypothesise that in most AS patients vertebral fractures develop gradually which implicates more chronic pain. Most AS patients are used to chronic and varying back pain as part of their disease and therefore most vertebral fractures do not come to clinical attention (23).

This was the first longitudinal study that investigated the incidence of radiographic vertebral fractures in both the thoracic and lumbar spine during TNF-α blocking therapy in a large cohort of AS patients. However, it remained unclear whether TNF-α blocking therapy can reduce the occurrence of new vertebral fractures since no control group was included. Furthermore, some difficulties were present during the measurement and interpretation of especially mild fractures. Due to technical aspects of the radiographs in combination with the methodological aspects of the Genant scoring method, 13 (28%) mild fractures scored at baseline could not be scored after 4 years of follow-up. In 6 of these 13 mild fractures, the vertebral body 'normalised' after 4 years due to measurement error (just below the cut-off value of 20%). These problems persisted after reassessment of vertebral heights in chronological time order and did not occur with moderate fractures. In addition, assessment and interpretation of mild fractures may be limited by the inability to distinguish between deformities related to fractures, deformities related to congenital or natural variation, and deformities related to vertebral body squaring or ankylosing (49). On the other hand, a large hospital-based retrospective cohort study showed that mild radiographic vertebral fractures were rare among adults <40 of age. The prevalence of fractures increased with age suggesting that mild fractures are more likely related to age than to congenital or natural variation (50). Furthermore, we did not found 'squaring' as assessed with the mSASSS in lumbar vertebral bodies with mild fractures.

Conclusion

This prospective observational cohort study showed a high prevalence of radiographic vertebral fractures in AS patients with active disease before the start of TNF-α blocking therapy. Patients with vertebral fractures were older, had worse spinal mobility, and more spinal radiographic damage. During 4 years of TNF-α blocking therapy, 20% of the patients developed one or more new vertebral fractures. Older age, smoking, poor physical functioning, low lumbar spine BMD, presence of moderate vertebral fractures, and use of anti-osteoporotic treatment at baseline were associated with the development of new vertebral fractures. Most fractures were mild and occurred in the

middle and lower thoracic spine. In all patients, a significant improvement in disease activity, physical functioning, spinal mobility, and BMD was found. However, patients who developed new vertebral fractures showed significantly less improvement in spinal lateral flexion and lumbar spine BMD.

This study underlines that radiographic vertebral fractures are frequently found in AS patients in daily clinical practice and also occur during TNF-α blocking therapy. Vertebral fractures are associated with worse clinical outcome. Therefore, it is of clinical importance that treating physicians are aware of this. More research is required to investigate the underlying mechanisms of bone loss and bone formation in relation to the quality of bone in AS and the influence of different treatment regimens, such as TNF-α blocking therapy and bisphosphonates, on vertebral fractures.

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