Spinal fractures in ankylosing spondylitis: prevalence, prevention and management

In patients with ankylosing spondylitis (AS), the risk of vertebral fractures (VFs) is increased. Case finding and fractures in patients with AS is a clinical challenge for several reasons. First, back pain and hyperkyphosis are mostly attributed to disease-related inflammation and structural damage in terms of erosions and syndesmophytes, and not to an eventual VF. Second, the most frequent VFs are classical wedging, biconcave or crush VFs as seen in postmenopausal women and the elderly, but once multilevel ankylosis of the spine is manifested, fractures can also occur in other parts and directions of the vertebrae (transvertebral, in the dorsal arch structures and through the ankylosed extravertebral calcifications of ligaments and intervertebral discs) and in the cervical spine. Diagnosis of these atypical fractures is much more difficult. Besides the pathology of fractures in general in patients with AS, VFs are associated with hyperkyphosis of the spine and can result in irreversible neurological complications. In this review, the authors propose a five-step approach for fracture prevention, starting with case finding and the subsequent difficulties in imaging, followed by risk evaluation, differential diagnosis and therapeutic strategies and follow-up, in order to translate current knowledge on fracture risk and fracture prevention, in general, towards patients with AS.

KEYWORD: ankylosing spondylitis ■ approach for fracture prevention ■ follow-up of spinal fracture (risk) ■ spinal fracture risk ■ therapeutic strategies

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Patients with chronic inflammatory diseases, such as rheumatoid arthritis, systemic lupus erythematosis, inflammatory bowel disease (IBD) and chronic obstructive pulmonary diseases, have an increased risk for bone fragility resulting in an increased risk of vertebral and nonvertebral fractures. These diseases are characterized by inflammation-induced bone loss and erosive bone destruction. Therefore, guidelines advocate fracture prevention in such high-risk patients. By contrast, in patients with ankylosing spondylitis (AS), inflammation also induces bone loss and bone erosions, but typically new bone formation is found, both intra-osseous (such as in the sacroiliac joints) and extra-osseous (such as in syndesmophytes). In the early 1970s, Cawley *et al.* showed, on a postmortem transversally sliced spine specimen of a patient with long-standing AS, the multiple bone changes in vertebrae and their annexes, including intravertebral bone loss, intra- and extra-osseous bone sclerosis, syndesmophytes, disc destruction, disc calcifications and vertebral wedging resulting in hyperkyphosis (Figure 1) [1]. In patients with AS, the risk of vertebral fractures (VFs) is increased, but case finding and prevention of VFs in patients with AS is a clinical challenge (Table 1). First, back pain and hyperkyphosis are mostly attributed to disease-related inflammation and structural damage, and an eventual VF could be overlooked if no imaging of the spine is performed. Second, besides classical VFs in the ankylosed spine, fractures can also occur in the vertebral annexes. Third, the complex combination of bone changes in the vertebrae interferes with the interpretation of the spine bone density.

AS belongs to the group of spondyloarthritides, which comprises a wide spectrum of clinical entities with shared features, including AS, as inflammatory back pain and arthritis associated with IBD, Crohn's disease and ulcerative colitis and psoriatic arthritis [2]. In the concept of spondyloarthritides, AS is the most known type with chronic inflammation mainly of the axial skeleton. Prevalence of AS within the entire group of spondylarthropathies varies between 15 and 50%, according to several authors [3,4]. AS is characterized by enthesitis, sacroiliitis and spinal inflammation. These features may lead to ossification of the spinal ligaments, joints and discs, and to progressive rigidity of the spine. Besides articular and spinal manifestations, patients with AS may suffer from extra-articulair manifestations, such as IBD (5–10% of patients), psoriasis (10–25% of patients) and uveitis (1–53% of patients), where prevalence rates vary depending on clinical and methodological characteristics of the studies [5–7].

Ankylosis of the spine (ultimately resulting in a bamboo spine) and thoracic hyperkyphosis are typical clinical features of long-standing AS, but

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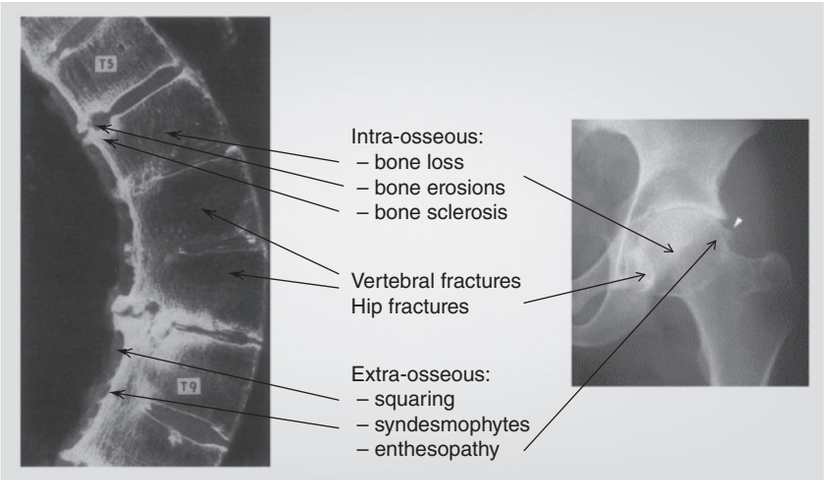

Figure 1. Bone changes in the spine in ankylosing spondylitis: bone loss and bone formation.
Adapted with permission from [1].

not all patients with AS develop ankylosis and/or hyperkyphosis. The available imaging techniques have contributed to the authors' understanding of these pathological changes, and include conventional radiography, MRI, bone scintigraphy, computer tomography and dual-energy x-ray absorptiometry (DXA) [8,9].

In this review, the authors use the five-step approach for fracture prevention as formulated for primary osteoporosis and translated it towards patients with AS (Figure 2).

The need for case finding: increased fracture risk in AS

Risk of fracture

VFs in AS have already been described in the 1950s, mainly as case reports in patients with advanced disease and spinal ankylosis. These initial case reports presented AS patients with VFs after relatively minor trauma, most often described in the cervical spine with neurological complications (Table 1). Other VFs were considered, for a long time, to be rare in AS [10]. However, several authors identified AS patients with chronic back pain and sometimes a history of trauma who were hospitalized for reasons other than AS in whom they found previously unrecognized VFs in the thoracolumbar spine [10]. The prevalence of VFs has been documented in one population-based and two case–controlled studies. However, these studies varied in the definition and size of VFs, referral bias and patient selection [11–13]. In a retrospective population-based study with a mean age of 33 years in the USA, Cooper *et al.* demonstrated that the relative risk of radiographic VFs (defined as a radiologist's report of compression, wedging or collapse of one or more thoracic or lumbar vertebral bodies) in 158 patients with AS was 7.6-times higher than in healthy controls, especially in men (relative risk: 10.7 compared with 4.2 in women). The cumulative incidence

Table 1. Risk of clinical vertebral fracture.

Study (year)	Patients (n)	Age (mean or range), years	VF (%)	Recruitment	Ref.
Cooper *et al.* (1994)	158	34	9.5	Population	[11]
Toussirot *et al.* (1999)	71	39	1.4	Consecutive	[43]
Baek *et al.* (2005)	76	28	4	Consecutive	[68]
Donnelly *et al.* (1994)	87	44	10.3	Consecutive	[19]
Jun *et al.* (2006)	68	31	16	Consecutive	[69]
Ralston *et al.* (1990)	111	41	18	Consecutive	[44]
Mitra *et al.* (2000)	66	38	17	Mild AS	[23]
Lange *et al.* (2005)	84	32–46	17	Disease activity	[41]
Sambrook and Geusens (2012)	50	50	58	Hyperkyphosis	[67]
Vosse *et al.* (2009)	135	46–54	31	OASIS	[12]
Devogelaer *et al.* (1992)	70	35–39	4	ND	[27]
Ghozlani *et al.* (2009)	80	39	19	Consecutive	[36]
vdWeijden *et al.* (2012)	113	38	15	Recent SpA	[70]
Arends *et al.* (2011)	128	41	39	Consecutive	[47]
Klingberg *et al.* (2012)	204	50	1.5	ND	[37]

AS: Ankylosing spondylitis; ND: No data; SpA: Spondyloarthritides; VF: Vertebral fracture.

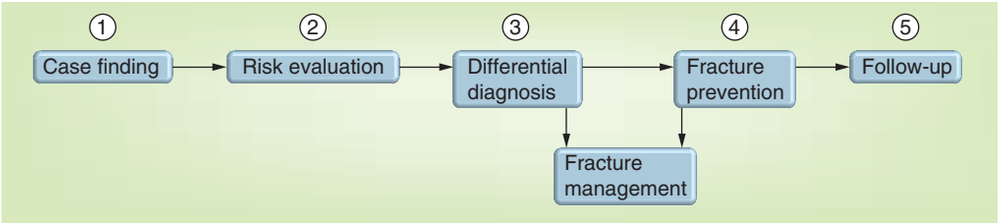

Figure 2. Five-step fracture prevention.
Data taken from [67].

was already 5% higher within 10 years of diagnosis of AS and peaked at 15% after 20 years. However, by contrast, the risk of nonvertebral fractures was not increased in these studies (only one hip fracture was mentioned). In a retrospective primary care-based nested case–control study using the data from the General Practice Research Database in the UK, 758 patients with AS were included, of whom more than half were younger than 60 years. A total of 54.9% had a history of any fracture, and 4.5% had a clinical VF. The risk of clinical VFs (defined as wedge, diabolo or crush VFs in their medical records) was increased (odds ratio [OR]: 3.3) compared with subjects without AS, even after adjustment for confounders [12]. The risk of nonvertebral, wrist or hip fractures was not increased, except in AS patients with IBD in whom the risk of any clinical fracture was increased (OR: 2.8). The Cooper *et al.* and Vosse *et al.* studies included only classical VFs in the thoracic and lumbar vertebral bodies (wedging, biconcave and crush) as seen in osteoporotic VF in postmenopausal women and the elderly [11,12].

In a retrospective case–control hospital discharge study in Sweden, which included 265 AS patients, the risk of clinical VFs (in the cervical, thoracic or lumbar spine) was increased (n = 131, median age of 41 years, OR: 7.1). In addition, the risk of all fractures (n = 181, median age 71 years, OR: 4.0) and of hip fractures was increased (n = 64, median age 72 years, OR: 2.5) [13].

In one prospective 22-year cohort study, 17,764 hospital admissions of AS patients in Sweden were recorded, of which 700 were owing to a spine fracture; 398 at the cervical spine (2.2% of all AS admissions) and 302 at the thoracolumbar spine (1.7% of all AS admissions) [14]. From these studies, it can be concluded that the risk of radiographic and clinical VFs is increased in AS, already at young age, and most prominently in men. The risk of all clinical fractures is also increased in AS patients with IBD and presumably also in elderly AS patients. The risk of hip fractures is not increased in those studies mainly studying younger patients, but in the Swedish study at a median age of 71 years, the risk of hip fractures was also increased.

Classical VFs can be diagnosed by radiography and by DXA using VF assessment (VFA). The advantage of VFA is low irradiation and its high negative predictive value for the presence of VFs [15]. Classical VFs are most commonly graded semiquantitatively, using the Genant score, and divided into mild, moderate and severe wedged, biconcave or crush fractures, according to deformities of >20, >25 and >40% [16]. MRI and bone scintigraphy can be helpful to determine whether a VF is recent or old, according to the presence of bone edema [17]. The diagnosis of VFs other than classical VFs is often a challenge on classical radiography. MRI, computer tomography and bone scintigraphy are then helpful to identify the exact location and extent of these VFs.

Several types of clinical and radiographic VFs have been documented in AS. First, classical VFs can occur in the thoracic and lumbar vertebral bodies (wedging, biconcave or crush) as seen in osteoporotic VFs in postmenopausal women and the elderly. Second, once multilevel ankylosis of the spine has occurred, long lever arms develop in the spine on which forces can act, even during minor trauma. Fractures can then occur not only as a classical VF, but also in other parts and directions of the vertebrae (transvertebral, in the dorsal arch structures and through the ankylosed extravertebral calcifications of ligaments and intervertebral discs) and in the cervical spine (FIGURE 3). It should be noted that spondylodiscitis (erosive discal Anderson's lesions) is characterized by destruction of the vertebral endplates, resulting in destruction of the vertebrae and should be discerned from a classical VF [18].

Clinical consequences

VFs can result in typical localized back pain with signs and symptoms of an acute fracture. However, acute and chronic back pains are also typical features of a flare or persisting inflammation in the spine. Only when imaging of the spine is available, and when these images are

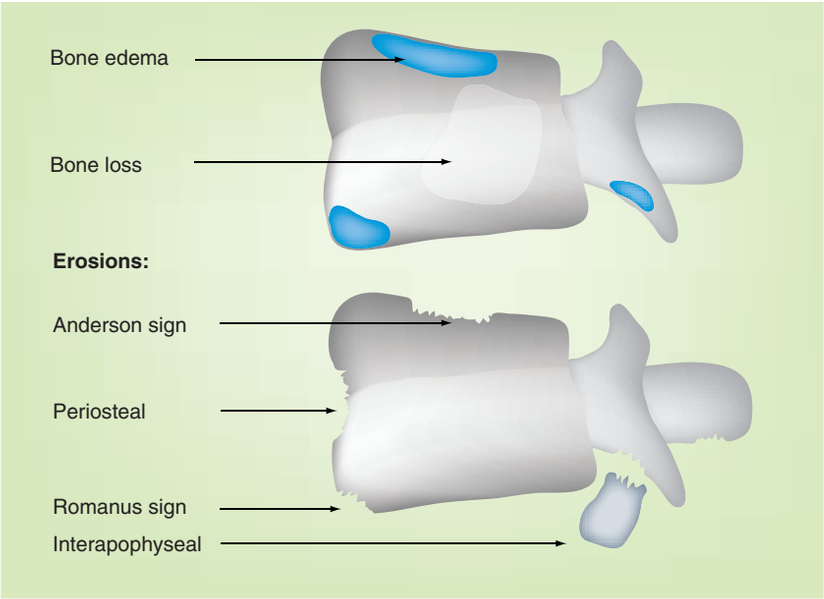

Figure 3. Spondylodiscitis with Anderson's lesion. Erosive destruction of the endplates surrounded by bone edema, resulting in vertebral deformations.

adequately screened, can VFs be identified or excluded as the source of back pain in AS. However, many classical VFs are overlooked and/or not reported, even when imaging of the spine is available [16]. In addition, radiographic VFs can occur silently [17,18]. Wedged VFs contribute to hyperkyphosis [19–25] independently from Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) [26]. Once a spinal segment becomes ankylosed by syndesmophytes, the hyperkyphosis resulting from wedged VFs becomes irreversible [20,26].

A high prevalence (between 29 and 91%) of major neurological complications has been reported after clinical VFs in the ankylosed spine [27–30], mostly followed by incomplete neurological recovery. Using a self-reporting questionnaire, the authors identified 66 VFs in 59 AS patients [31]. This represents a minimal prevalence of clinical VF of 0.4%, mainly in younger patients (mean age of 50 years), early in the disease and mainly without trauma or after minimal trauma. In a review of the literature on AS and trauma, Westerveld *et al.* identified 76 articles, describing 345 AS patients with VFs, 81% of which occurred in the cervical spine, but 19% of occurred in the thoraco-lumbar spine, in 66% of cases after low-energy trauma, mostly a fall. In total, 50% of these VFs were transvertebral. In 17% there was a delay of diagnosis, half of the cases were not recognized by the physician in a timely fashion, and in the other half of the cases patients delayed their decision to seek medical attention [32]. Two-thirds of cases had neurological complications. This is in contrast to postmenopausal osteoporosis, senile osteoporosis and secondary osteoporosis owing to other inflammatory diseases. One explanation is that the fully or partially ankylosed spine behaves biomechanically as a long bone that contributes to fractures in the horizontal plane or the dorsal arch [21,33,34], while osteoporotic fractures in postmenopausal women are (only) characterized by height loss, but not by sagital dislocations. These types of VFs tend to be more instable and prone to dislocation with subsequent compression of the spinal cord. This may explain the large percentage of neurological complications seen in this group of patients. In conclusion, VFs occur early in the disease and may result in permanent neurological complaints. Besides, present literature suggests that all fractures, including hip fractures, are increased in the elderly AS population [13].

Fracture risk evaluation in AS

There is, thus, clear evidence that fracture risk is increased in AS. However, 10 years ago, a majority of British rheumatologists did not routinely assess patients with AS for osteoporosis [35]. The clinical question is, therefore, how to identify AS patients at highest fracture risk, in order to select them for considering fracture prevention.

Clinical risk factors

Many risk factors have been documented to be associated with low bone mineral density (BMD) and fracture risk in AS [26], including classical risk factors like gender (male), age, body weight, BMI, fat mass and familial history of fractures. Disease-specific risk factors are: disease activity, back pain (included in BASDAI), stiffness of the spine (included in Bath Ankylosing Spondylitis Functional Index [BASFI] and Bath Ankylosing Spondylitis Metrology Index [BASMI]), tragus–wall distance (included in BASMI), Bath Ankylosing Spondylitis Radiology Index, erythrocyte sedimentation rate, C-reactive protein, duration of disease (although bone loss and VFs have been found already early in the disease), the mSASSS, peripheral joint involvement, coxitis, prednisone use, psoriasis, IBD, persisting back pain even after low-energy trauma, the presence of neurological symptoms and not being on continuous or high-dose NSAIDs. In studies using multivariate analysis, BMD was related to age, gender (male) BASFI, BASMI, BMI, disease duration and menopause in women and VF risk to mSASSS and disease duration [36,37].

BMD in AS

The interpretation of BMD by DXA requires special attention in AS, as results of BMD in the spine are influenced by new bone formation around the vertebrae (periosteal, interapophyseal and ligamental), in the vertebrae (sclerosis) and between the vertebrae (syndesmophytes and discal calcifications) (FIGURE 4) [38]. There is clear evidence that a decrease of BMD occurs early in the disease [30] and persists during follow-up [36,37,39–43], but also that changes in BMD are heterogeneous throughout the skeleton [31,37,40,41,44,45]. It is essential for the interpretation of DXA measurements that patients are categorized in an early or late disease state. Early in the disease, BMD is lowered in the spine of AS patients, but is normal or even increased in late stages (TABLE 2). BMD in the spine was increased by 28% ($p < 0.05$) in eight male patients [45]. These changes of BMD in the spine are heterogeneous and are influenced by the combination of intravertebral bone loss and the presence of new bone formation around the vertebrae.

The heterogeneity of bone changes in the spine has been studied using DXA of the spine in combination with quantitative computer tomography (QCT) of the vertebrae, with lateral DXA of the lumbar spine and with BMD in the hip. Comparing BMD bone measured by QCT with BMD by DXA in the spine and hip clearly showed that trabecular intravertebral BMD by QCT was significantly decreased in both early and late stage, but significantly lower in late in the disease compared with early in the disease (Z score: -1.8 and -3.9, respectively; $p < 0.01$), whereas BMD in the spine was only decreased in early stage (Z score: -1.1), but not in late stage (Z score: 0.8) [42]. BMD in the hip was decreased, but only significantly in late stage.

Others compared anteroposterior DXA of the spine with lateral measurements and showed that laterally measured BMD was lower than in anteroposterior anteroposterior [46]. Unfortunately, lateral scanning has limitations in accuracy and interference with other bony structures (ribs and iliac crest). In a study comparing BMD in the spine and the hip, the difference between BMD in the hip and spine increased with disease duration [47].

The prevalence of osteopenia measured by QCT and DXA of the spine was similar in patients without syndesmophytes, but significantly higher in patients with syndesmophytes when measured with QCT (63 vs 48%; $p < 0.05$) or DXA in the hip (80% vs 48%; $p < 0.05$).

More patients have osteopenia and osteoporosis in the hip than in the spine in late-stage disease [40,41], but still less than when compared with intravertebral BMD measured by QCT [41,42] or to lateral DXA of the spine [37]. A T score below -1.0 was more frequently found in the femoral neck than in the spine in patients with and without syndesmophytes (FIGURE 5) [38]. Quantitative ultrasound parameters were found to be similar between patients with AS and controls, suggesting that the quantitative ultrasound method did not provide additive information to DXA [43].

No guidelines on indications for DXA for BMD and VFA in AS are available. The more risk factors that are present, the more there is indication for evaluating BMD and VFA. In view of the early development of bone loss and VF, this could be an argument to consider these examinations in all patients at an early stage when they present with active disease, in order to have baseline values that can be useful during follow-up.

It is unclear whether the fracture risk prediction algorithms and the Garvan fracture risk calculator can be used for fracture prediction, as gender (male) and younger age in AS are opposite to classical fracture risks that are used in the calculations of fracture risk prediction algorithms and the Garvan fracture risk calculator [37].

Finally, bone markers have been studied in AS patients and many differences are found [39,47,23,48–53]. To date, the use of bone markers is controversial and has yet to be defined [35].

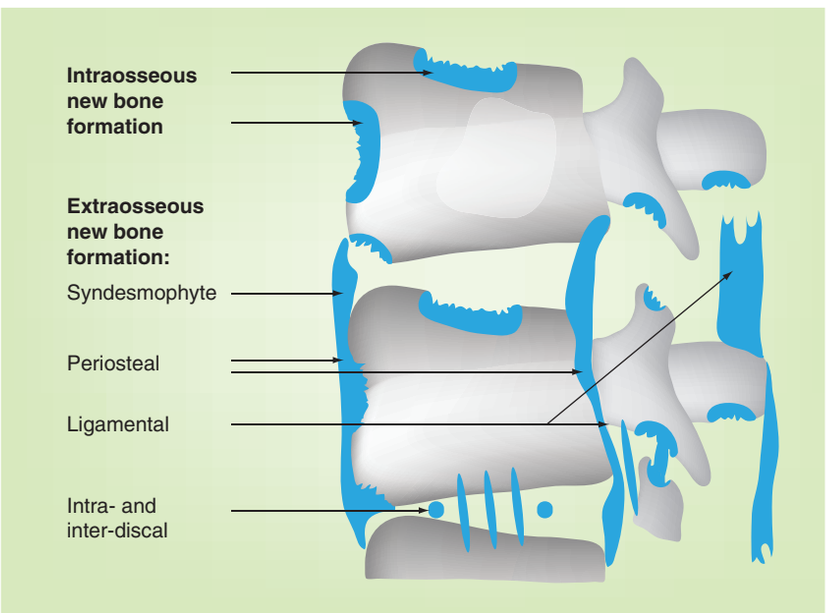

Figure 4. Intra- and extra-osseous new bone formation in ankylosing spondylitis.

Table 2. Prevalence of osteoporosis and ostepenia in ankylosing spondylitis.

Study (year)	Patients (n)	Age (years)	Disease duration (years)	Location	Ope (%)	Opo (%)	Recruitment	Ref.
Karberg *et al.* (2005)	103	34–49		Spine	31	14	Consecutive	[40]
				Femoral neck	52	24		
	27		<5	Spine	41	15		
				Femoral neck	26	11		
	48		<5–10	Spine	31	15		
				Femoral neck	50	25		
	28		>10	Spine	36	4		
				Femoral neck	57	29		
Klingberg *et al.* (2012)	204						Invitation	[37]
	144	>50		Any	44	21		
	44	Women >50		Spine (AP)	34	27		
				Spine (Lat)	34	45		
				Total hip	46	0		
				Femoral neck	56	9		
				Radius	39	16		
	100	Men >50		Spine (AP)	14	7		
				Total hip	33	0		
				Femoral neck	44	9		
				Radius	33	16		
Lange *et al.* (2005)	84			Spine	19	13		[41]
				Total hip	25	18		
				QCT spine	17	43		
	27			Spine	11	0		
				Total hip	15	1		
				QCT spine	15	19		
	20			Spine	25	10		
				Total hip	30	25		
				QCT spine	20	65		
Ghozlani *et al.* (2009)	80	40 ± 12		Any		25		[36]
Toussirot *et al.* (1999)	71			Spine	32	14		[43]
				Femoral neck	23	4		
El Maghraoui (2011)	80			Spine	31	19		[5]
				Femoral neck	41	14		

AP: Anteroposterior; Lat: Lateral; Ope: Osteopenia; Opo: Osteoporosis; QCT: Quantitative computer tomography.

In summary, BMD measurement is valuable at the spine and hip in early stages. In late stages of the disease, BMD in the spine should be interpreted with caution, and therapeutic decisions should be based merely on BMD in the hip. In addition, the presence of an ankylosed spine should be considered as a risk for VF of the vertebral bodies and their annexes despite any result of BMD.

Differential diagnosis

In patients with multilevel ankylosis and persisting pain, neurological symptoms and (even minor) trauma, MRI, QCT and bone scintigraphy can be helpful to exclude fracture of the dorsal arch structures. Once a patient at high risk of fractures is identified, the next step is differential diagnosis. In patients with high fracture risk, with or without a prevalent VF, in whom medical treatment is considered to prevent fractures, medical history, clinical examination and laboratory examination allows diagnosis of previously unknown contributors to secondary osteoporosis and metabolic bone disease, which should be corrected [54]. Malabsorption (in case of IBD), calcium intake and vitamin D status should be checked and corrected [55].

Therapeutic strategies of VF in AS

It is clear that many factors influence fracture risk, including low BMD and ankylosis of the spine (Figure 6). If VF is diagnosed it should be treated *lege artis*. (Neuro)surgical advice is indicated in case of VF in an ankylosed spine, especially in the presence of neurological symptoms. Pain owing to VF is treated with analgesics.

However, most patients with AS and back pain are treated with NSAIDs, and NSAIDs deserve special attention in the context of AS. First, for adequate fracture healing, a certain degree of inflammation with COX-2 expression seems to be required [56]. NSAIDs inhibit COX-2 activity, and in that way markedly impairs fracture healing in animal models. However, to date, there are no data to show that fracture healing is impaired by COX-2 inhibition in humans. In view of the findings in animals, it is probably wise to temporarily stop NSAIDs after a recent fracture in AS and replace them with analgesics. On the other hand, there is increasing evidence that continuous use or high-dose use of NSAIDs in AS slows the development of syndesmophytes, and ultimately ankylosis in the spine. This could be an explanation as to why the risk of VF was decreased in NSAID users [12]. Thus, the effect of NSAIDs in AS is twofold: they prevent the development of syndesmophytes, but at the time of a fracture, they could show fracture healing.

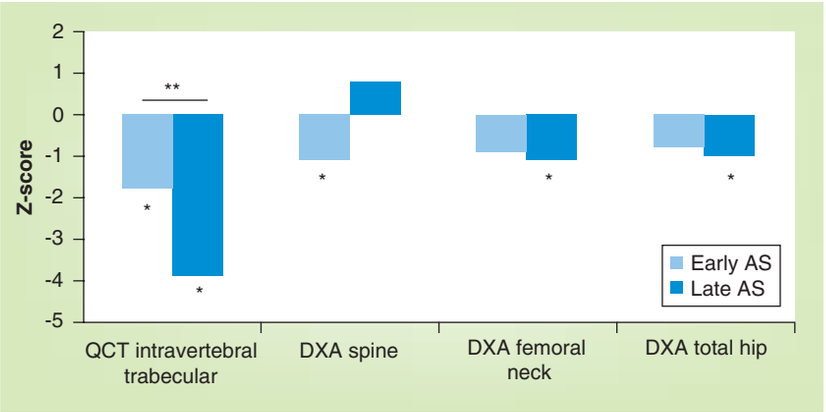

Figure 5. Dual-energy x-ray absorptiometry versus quantitative computer tomography of the spine as ankylosing spondylitis according to disease duration. Early ankylosing spondylitis: only sacroiliitis; late ankylosing spondylitis: plus extensive syndesmophytes.
*p < 0.05 versus zero; **p < 0.05 between groups.
AS: Ankylosing spondylitis; DXA: Dual-energy x-ray absorptiometry; QCT: Quantitative computed tomography.
Adapted with permission from [42].

Effects of anti-osteoporotic drugs on fractures in patients with AS

Prevention of fractures in patients with AS is relatively simple in those patients with clinical risk factors for osteoporosis and a low T score (less than -2.5), in other words, when there is an indication for anti-osteoporotic treatment irrespective of the presence of AS.

Another starting point for treatment is the presence of vertebral fractures, since the risk for future fractures is elevated in patients with vertebral fractures, irrespective of BMD. General lifestyle measures are important for all patients with rheumatic diseases: an adequate calcium intake, prevention of falls, adequate vitamin D levels and prevention of immobilization when possible. In addition, the prescription of adequate immunosuppressive medication to reduce inflammation-induced bone loss is important, which has particularly been documented for the use of (some of the) TNF-blocking agents in AS.

It is important to realize that the relative risk of fractures is increased in AS patients and, thus, the absolute fracture risk is particularly high in those patients with a high background fracture risk, for instance elderly patients with an active AS. Therefore, in patients with AS with a BMD in the lower osteopenic range and with one or more prevalent vertebral deformities, the start of anti-osteoporotic treatment is a serious option. However, in the very large group of AS patients with a BMD in the osteopenic range, treatment decisions are more complicated. In fact, these statements are based on data from patients with primary osteoporosis, thus, in patients without a secondary cause of osteoporosis.

Unfortunately, intervention studies demonstrating the effectiveness of one of the available anti-osteoporotic drugs (e.g., bisphosphonates) demonstrating fracture reduction in patients with secondary osteoporosis owing to rheumatoid arthritis, or systemic lupus erythematosis or AS, have not yet been performed yet. No randomized trials have been conducted in AS patients using bisphosphonates or other anti-osteoporotic drugs, with bone parameters, such as change in BMD end points. Obviously, the most critical end point is reduction in fractures, but studies with fracture reduction are usually much larger and much more costly than studies with BMD change as an end point. However, the effectiveness of several anti-osteoporotic drugs (bisphosphonates, strontium ranelate, selective estrogen receptor modulators, denosumab and teripartide/parathyroid hormone) has been clearly demonstrated in postmenopausal women with primary osteoporosis, which is a strong argument to prescribe these drugs in patients with inflammatory rheumatic disorders, particularly in those with high background fracture risk and moderate or high disease activity. Bisphosphonates (alendronate, risedronate and zoledronate) are usually first choice, because they are widely prescribed, generally safe and effective, even in the prevention of hip fractures, although there are some concerns about the long-term safety [57]. Whether treatment with bisphosphonates can also prevent transdiscal fractures

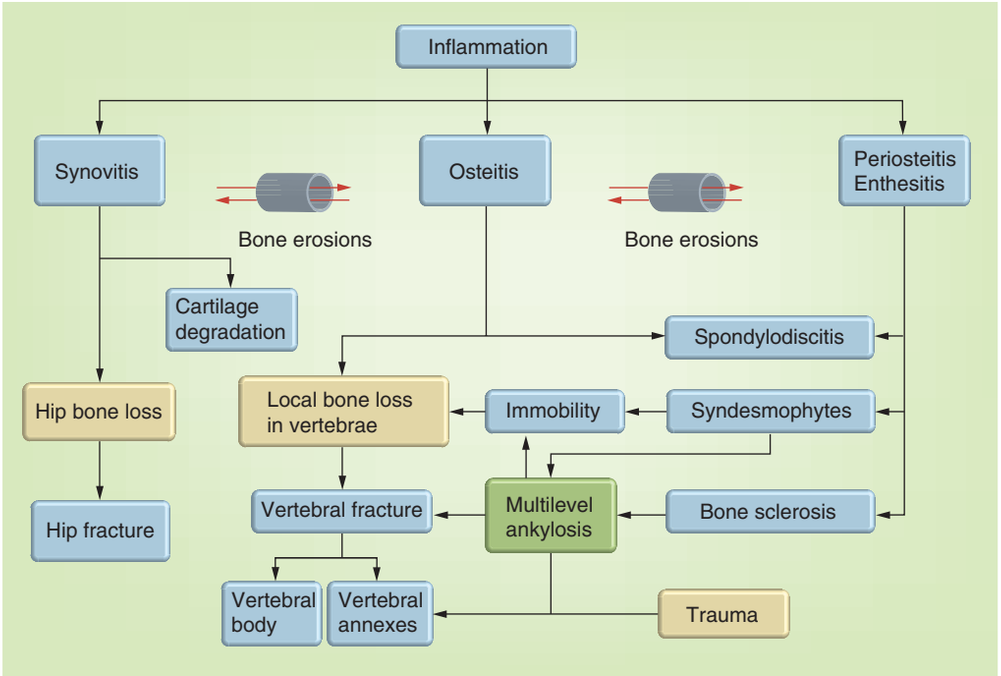

Figure 6. Pathophysiology of vertebral fractures in ankylosing spondylitis: implications for fracture prevention.
Data taken from [71].

or fractures of the dorsal structures in the ankylosed spine is unknown. Thus, the main point is the discrepancy between the overwhelming data showing reduction of vertebral, and to a lesser extent nonvertebral, fracture reduction in postmenopausal women with osteoporosis (but without AS), and the absence of data in patients with AS and a BMD in the range of osteoporosis or osteopenia with a prevalent vertebral fracture.

Another point is the formation of syndesmophytes in patients with AS. Although the pathophysiology of the formation of syndesmophytes has not been fully elucidated, it is characterized by new bone formation. Since bisphosphonates and denosumab lower the bone turnover, it can be hypothesized that if they have an effect on syndesmophytes, it would be a favorable, inhibiting effect. In an open study in 21 AS patients, treatment with pamidronate, two-times a year 60-mg intravenously, had no effect on disease activity in patients with moderately active AS, nor was there any effect on syndesmophyte formation [58]. It could be suggested that the negative effect of that study is related to the relative low dosage of pamidronate. Maksymowych *et al.* gave 60-mg pamidronate intravenously five-times over a 7-week period in nine patients with active AS with a remarkable result: the mean and tender joint count decreased by 93.8 and 98.2%, while erythrocyte sedimentation rate and C-reactive protein decreased from 30 to 14.4 and from 44 to 11/8 [59]. The BASDAI decreased by 44%. In addition, the magnitude of enhanced MRI signal after gadolinium injections decreased after pamidonate therapy. Another argument for an anti-inflammatory effect was the acute lymphopenia in eight out of nine patients on day two after the first infusion. In our opinion, these data are remarkable, and probably related to the high dosage of pamidronate. The authors elegantly discuss the limitations of this study, particularly its open design. Nevertheless, their conclusion is that these data reinforce the rationale for a randomized, double-blinded evaluation. In a study from Germany, comparable results were found: in 12 patients with AS, the BASDAI decreased in an open study, from 5.4 to 4.6 [60]. Later, in a randomized study, monthly infusions with pamidronate 60-mg intravenously versus 10-mg pamidronate (no placebo arm) were compared in a randomized design: the BASDAI decreased with 35 versus 15% ($p = 0.002$); statistically significant reductions were also found for BASFI and BASMI [61]. Taken together, these data suggest that high-dose bisphosphonates might have a treatment effect on disease activity in patients with AS.

Denosumab, a monoclonal antibody against RANKL, is an attractive new therapeutic agent for osteoporotic patients. The reason why this has not been investigated further, is probably the exciting and much stronger effects of TNF

blockers in AS. Some studies have been carried out in patients with AS, observing the changes in BMD during treatment with TNF-blocking agents. In a study over 2 years in 54 AS patients, no change in BMD was observed in the lumbar spine, and some decrease was found in the femoral neck. However, a large difference in bone loss at the femoral neck was found in those patients with and without systemic inflammation: -4.1 versus -1.2%; p = 0.007 [62].

Recently, Arends *et al.* published data on 111 consecutive AS patients all treated during 3 years with TNF-blocking agents: they observed an increase in the BMD of the spine and hips, expressed as a Z score [63]. However, for those patients who cannot tolerate TNF blockers, or have contraindications or in which the cost price of the drugs is a limiting factor, high-dose bisphosphonates or denosumab may be an alternative, particularly in patients with an increased fracture risk, for example, with a T score of less than -2.5. The situation is somewhat more complicated in patients with AS: local bone loss and local new bone formation can be found in the same patient. Obviously, this makes it more difficult to decide which drugs to prescribe, in other words, collaborative studies elucidating the pathogenesis and new intervention studies are urgently needed in these patients. Another reason to advocate further investigations on the effects of bisphosphonates and denosumab in AS is the more or less disappointing results of treatment with theoretically disease-modifying drugs, such as sulfasalazine and methotrexate in patients with AS: no effect on any variable was found in a systematic literature review [64].

Follow-up & duration of treatment

As stated earlier, as with every osteoporosis patient, the first concern is to avoid trauma. Serious attention should be given to lifestyle advice, such as stoping smoking, moderate alcohol intake and exercise (fall prevention). Patients should be checked on calcium intake, vitamin D status and if necessary these should be supplied. In the case of active disease, adequate immune suppressive therapy is indicated. Presently, this indicates NSAIDs with their positive effect on symptoms, mobility and probably even on syndesmophyte formation. In very active patients with AS, TNF-blocking agents can be prescribed to suppress disease activity and subsequently prevent bone loss. There are no data on the effect of teriparatide or parathyroid hormone in postmenopausal osteoporosis. Therapy with bisphosphonates or denosumab is continued for 5 years and re-evaluated following the guidelines, including BMD, VFA and risk evaluation. If fracture risk remains high, treatment could be continued.

Conclusion

The proposed five-step approach for fracture prevention is applicable in patients with AS, as well as in primary osteoporotic patients. Case finding, risk evaluation, differential diagnosis, therapy and follow-up are not different. The most obvious problem is the vulnerability of the ankylosed spine and the larger risk of neurological complications. In this view, the management of vertebral fractures in patients with AS needs a multidisciplinary approach with rheumatologists, neurologists, (neuro)surgeons and rehabilitation physicians.

Future perspective

The question is if we need a vertebral fracture prevention study. NSAIDs seem to have a positive effect on pain and syndesmophyte formation, but a negative effect on fracture healing in animal studies. Bisphosphonates influence disease activity; they prevent bone loss, and have positive effects on fracture healing and fracture risk. However, do they suppress syndesmophyte formation? Denosumab prevents bone loss, and has positive effects on fracture healing and fracture risk [65,66], but there is no effect on inflammation and it is unknown if it could affect syndesmophyte formation. TNF-blocking agents seem to have an antiresorptive effect on bone, but no effect on the formation of syndesmophytes is documented, and syndesmophytes are correlated with vertebral fracture risk so their beneficial effect is yet to be established [67]. So yes, there is a clear need for a VF-prevention study in combination with outcome on syndesmophyte formation. This is the only way to provide the clinician with answers to our questions on how and when to treat patients with AS and osteoporosis.

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Executive summary

- The authors propose a five-step approach in the fracture prevention, starting with case finding and the subsequent difficulties in imaging, followed by risk evaluation, differential diagnosis and therapeutic strategies and follow-up.
- Vertebral fractures occur early in the disease; all fractures, including hip fractures, are increased in the elderly population.
- Many clinical risk factors for osteoporosis are defined in patients with ankylosing spondylitis, both generally accepted and disease-specific risk factors.
- Bone mineral density assessment in early disease should be performed by dual-energy x-ray absorptiometry of the hip and spine; in late disease only the hip should be measured.
- Patients with ankylosing spondylitis and a high risk of fractures should be treated with bisphosphonates.

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