Bone mass in ankylosing spondylitis

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ABSTRACT

Specific spine ossifications or syndesmophytes are considered to be a hallmark of ankylosing spondylitis (AS) and to reflect a process of bone formation. Conversely, AS patients may develop osteoporosis (OP), as suggested by radiographic studies, an increased frequency of the vertebral fracture rate and reduced bone mass. Dual energy X-ray absorptiometry measurements have clearly demonstrated decreased bone mineral density (BMD) at both the lumbar spine and femoral neck. However, for patients with advanced spinal changes, ossifications may yield normal or increased values for the lumbar spine BMD. Assessment of biochemical markers of bone metabolism have shown that both bone formation and resorption are involved, with enhanced urinary excretion of markers of collagen breakdown in patients with active disease and raised inflammatory parameters, and changes in the levels of some bone growth factors. The pathophysiology of this osteoporosis in AS mainly involves disease activity and, very likely, inflammatory cytokines. Finally, vertebral fractures complicating this bone loss contribute to spine deformity in patients with AS.

Introduction

Ankylosing spondylitis (AS) is an inflammatory rheumatic disease characterized by inflammation of the entheses in the axial and peripheral skeleton and affects mainly young male patients. Typical clinical features include sacroiliac joint pain and backache and progressively, the patients could develop a dorsal kyphosis. Specific spine ossifications or syndesmophytes are considered to be a hallmark of the disease, reflecting a process of bone formation. In contrast, AS patients may developed osteoporosis (OP), leading in some cases to fractures. Classically, OP is considered to be a late and negligible feature of AS. However, a growing number of studies have reported an increased frequency of fractures and the presence of low bone mass in AS.

In 1877, Fagge described for the first time bone fragility during an autopsy of a patient with AS (1). Osteoporosis was then described as a clinical feature of longstanding AS or conversely, as a primary event of the disease (2). Further reports claimed that this bone involvement could have clinical consequences such as fractures and contributes to spinal deformity of AS patients.

This review focuses on bone mass and results of biochemical markers of bone turnover in AS.

Radiological data and frequency of vertebral fractures in ankylosing spondylitis

In 1971, a radiographic study performed by Hanson *et al.* found moderate to severe OP in 29/50 patients (3). Only two vertebral crush fractures were observed and the patients had no fractures in the peripheral bones. Spencer *et al.* then reported similar findings with the presence of radiological OP in 30.5% patients (4). In these studies, OP strongly correlated with disease duration, patient age and older age at onset. In the same way, a relationship between axial skeleton OP and the presence of syndesmophytes and/or discitis or Romanus lesions was observed in most patients (4). These studies concluded that OP is a late complicating feature of AS with mild fracture prevalence.

Morphometric methods for assessing vertebral fractures were then used and the prevalence of such fractures was evaluated to be 18% (5): in this controlled study, patients with fractures had increased formation of syndesmophytes and a greater degree of spinal deformity and spine rigidity as evaluated by the Schöber test, chest expansion, and distance from wall to tragus (5). Additional recent studies have evaluated the prevalence of vertebral fractures in AS to be in the range of 10.3-16.7% (6,7). Surprisingly, a higher frequency for vertebral

fracture (40.9%) was found in a Turkish study (8). In these studies, the commonest fracture site was the thoracic spine. Ankylosing spondilitis patients with fractures were significantly older, had longer disease duration and more advanced spinal limitation with less mobility (6). The recent study by Mitra *et al.* found that vertebral fractures were also a feature of AS with a mild disease duration (mean duration: 9.8 years) and without advanced spinal changes (7). Finally, an epidemiological survey by the Mayo Clinic found that AS patients had higher risk for vertebral fracture (OR: 7.6; CI: 4.3 - 12.6) while there was no increase in the risk for fracture in the limbs (9). Table I lists the different studies evaluating the vertebral fracture rate in AS.

Apart from vertebral crush fractures, spinal fractures which may pass through the vertebra (transvertebral) or through the disk (transdiscal) may occur in AS (10). They mainly affect the cervical region after minor trauma and are difficult to diagnose and manage (11). It is believed that these fractures result in part from the ankylosing process inducing spine rigidity and also from mechanical factors. In this respect, they could be compared to stress fractures.

Bone mass measurements in ankylosing spondylitis

All of the different methods which are currently available for evaluating bone mass have been used in AS: single and dual photon absorptiometry (SPA and DPA, respectively), dual energy X-ray absorptiometry (DEXA), quantitative computed tomography (QCT) and more recently, quantitative ultrasound techniques (QUS).

Dual photon absorptiometry and dual energy X-ray absorptiometry

There are 13 studies in the current literature that examined bone mass in AS by DPA and/or DEXA (5-8, 12-20). Taken together, the results were similar and decreased values for bone mineral density (BMD) at the femoral neck were found. The lumbar spine BMD has also been found to be reduced in patients with early or mild disease without advanced spinal changes. Conversely, when the patients had advanced disease with spinal ossifications, lumbar spine BMD was found to be normal or increased. In one study, DEXA measurements in both the lateral and postero-anterior projections of the lumbar spine were performed and the lateral projection of L3 was found to be a more sensitive indicator of the vertebral BMD compared to the postero-anterior projection (16). Most of these studies included a controlled population and the WHO criteria for osteoporosis were used in some cases, revealing that AS patients had osteopenia more frequently (T score: -1 SD to -2.5 SD) and osteoporosis more rarely (T score <-2.5 SD) (17, 18). However, some of these results should be regarded with caution since the patients included had psoriasis, inflammatory bowel disease or reactive arthritis and not primary AS (6, 17). Table II shows the results of different studies of bone mass measurements using DPA or DEXA.

Recently, total body measurements were performed in AS using DEXA and it was found that patients with OP had a lower body mass index and fat mass percentage (17). We also performed total body measurements in a series of 57AS patients and found a decreased total BMD. However, no lean and/or fat mass involvement was evident in our series (20).

Single photon absorptiometry

Two studies have evaluated the BMD at the radius. No difference between AS and controls was found (5, 14)

Quantitative computed tomography

There was only one study evaluating lumbar spine BMD using QCT. Quantitative computed tomography values were found to be lower compared to controls. Moreover, the QCT measurements were compared to those with DPA and the QCT values were in general lower than the DPA values. Additionally, atrophy of the posterior spinal muscles was also observed (14).

Quantitative ultrasound measurements

Only one study, performed by our group, has evaluated bone mass in a series of 57 AS patients and 60 healthy controls using this new technique. However, QUS measurements (broadband ultrasound attenuation, speed of sound and stiffness)

Table I. Prevalence of vertebral fractures in ankylosing spondylitis.

Author (ref.)	Number of patients and controls	Mean age (years) Sex ratio (M/ F) Mean disease dur. (yrs.)	Frequency of vertebral fractures (%)
Hanson (3)	50 no controls	range: 29-75 40/10 ND	2/50 (4%)
Ralston (5)	111 30 controls	41 98 /13 17	20/111 (18%)
Donnelly (6)	87 Controls: population of 1035 women	44 62/25 16	9/87 (10.3%) (Controls: 1.9%)
Mitra (7)	66 39 controls	37.8 66/0 9.8	11/66 (16.7%) (Controls: 2.6%) OR: 5.92; CI: 1.4-23.8
Sivri (8)	22 no controls	36.8 20/2 9.8	9/22 (40.9%)
Cooper (9)	158 Controls: local population corresponding to 2398 person-years of observation	33.8 121/37 ND	15/158 (9.5%) (Controls 3.4%) OR: 7.6; CI: 4.3-12.6

M: male; F: female; OR: odds ratio; CI: confidence interval; ND: not done.

Table II. Bone mass measurements in ankylosing spondylitis: the current literature.

Author (reference)	No. of patients	Mean age (yrs.) Sex ratio M/F	Mean disease duration (years)	Technique for bone mass measurement	Results (compared to controls) Lumbar spine BMD	Femoral neck BMD	Other sites
Reid (12)	10	42 8 / 2	13.2	DPA	Increased in males, reduced in females	ND	
Will (13)	25	33 25 / 0	11.5	DPA (Novo)	Decreased BMD: 0.82 / 0.91 g/cm^2)	Decreased (BMD: 0.83 / 0.92 g/cm^2)	
Ralston (5)	111	41 98 / 13	17	SPA (Norland 287)	ND	ND	Radius: no difference between AS with and without vertebral fractures and controls
Devogelaer (14)	70	39 60/10	15.4	DPA (Novo)	Decreased in men (Z-score -0.73), normal in women	ND	
				SPA (Norland)			Radius: no diference from controls
				QCT	Decreased values		
Mullaji (15)	33	37.8 27 / 6	6.8 - 11.7 (range)	DEXA (Norland XR-28)	Normal for patients with advanced spine disease, decreased for the others	Decreased	Total body: no difference from controls
Donelly (6)	87 (62 AS; 25 SpA)	44 62 / 25	16.4	DEXA (Hologic QDR)	Normal values for pts. with advanced disease, decreased in early disease	Reduced values	
Sivri * (8)	22	36.8 20 / 2	9.8	DPA (Osteotech)	Reduced in moderate AS versus advanced disease	Reduced in moderate AS vs mild & advanced disease	
Bronson (16)	19	50.5 19 / 0	25.2	DEXA (Hologic QDR)	Normal values for postero-anterior projections (T score: 0.22 / -0.4)	Decreased values (T score: -1.45 / -0.81)	Lumbar spine lateral projection: decreased values (0.68 g/cm2 / 0.86 g/cm^2)
El Magrahoui * (17)	80 (64 AS; 16 SpA)	36.7 52 / 28	12.3	DEXA (Hologic QDR)	Decreased values (T score -1. 15)	Decreased values (T score: -1.18)	Total body: reduced fat mass percentage in pts. with osteoporosis
Meirelles (18)	30	37 27 / 3	17	DEXA (Hologic QDR)	WHO definition: osteopenia: 23% osteoporosis: 27%	WHO definition: osteopenia: 31% osteoporosis: 45%	
Gratacos * (19)	34	33 27 / 7	7.5	DEXA (Lunar DPX-L)	Follow-up study (19 mos.): 5 % loss	Follow-up study (19 mos.): 3 % loss	
Toussirot (20)	57	38.0 41 / 16	10.6	DEXA (Lunar DPX-IQ)	Reduced values (T score: -0.91 / -0.06)	Reduced values (T score: -0.31 / 0.23)	Total body: normal values for lean-fat masses. Reduced whole body BMD
Mitra (7)	66	37.7 66 / 0	9.85	DEXA (Hologic QDR)	Reduced values (T score: -1.1)	Reduced values (T score: -1.4)	

AS: ankylosing spondylitis; SpA: spondylarthropathy; DPA: dual photon absorptiometry; SPA: single photon absorptiometry; DEXA: dual energy X-ray absorptiometry; QCT: quantitative computed tomography; BMD: bone mineral density; *: uncontrolled study.

did not differ between patients and controls. Conversely, in this study AS patients had decreased BMD values (including the lumbar spine, femur [neck, Ward's triangle and trochanter] and total body) as evalutated by DEXA (20).

Other methods

Finally, Reid *et al.* evaluated total body calcium by *in vivo* neutron activation in AS. Mean total body calcium was reduced by 5.3% compared with controls (12).

Biochemical markers of bone formation and resorption

The serum markers of bone turnover, including serum calcaemia and phosphorus, calcium regulating hormones (PTH, 25 OH D3) were found to be normal in AS (21). A trend for increased urinary excretion of calcium has been reported, but was not further confirmed (21, 22). The fasting urinary calcium/creatinine ratio was normal in the study by Will *et al.* (13). More recent studies have evaluated the urinary excretion of new markers of bone resorption, i.e. markers of collagen breakdown: pyridinoline, deoxypyridinoline and also fragments of C-telopeptide of the α1 chain of type I collagen or β-CTX (16, 17, 23-26). In general, the urinary levels of these markers of collagen breakdown were found to be normal except in patients with high levels of inflammatory activity (26). In fact, a good or strong correlation was found between these markers of bone resorption and indices of disease activity (the erythrocyte sedimentation rate [ESR] and acute phase reactants). In a 19-month follow-up study, Gratacos *et al.* clearly demonstrated the relationship between the loss of BMD and disease activity as evaluated by acute phase reactants and the serum level of inflammatory cytokines (interleukin-6) (19). Conversely, the biochemical markers of bone resorption did not correlate with the spine and femoral neck BMD, and this could be explained by the fact that BMD is a longitudinal variable while markers of bone resorption or formation are transverse variables (19, 26).

Serum markers of bone formation include osteocalcin (OC). In one study, serum OC was significantly reduced in AS compared to controls, suggesting a low rate of bone formation (22). This decreased serum OC concentration was not confirmed in other studies (16, 21, 26). Apart from OC, serum markers of bone formation were evaluated in AS, including alkaline phosphatase and its specific isoenzyme, bone alkaline phosphatase (BAP). Higher serum levels of BAP were found in one study (25) while there were normal levels in two others (16, 23). Bone growth factors such as bone promoting factors have also been evaluated in AS patients and decreased serum levels of insulin-like growth factor binding protein-3 (IGFBP-3) were found in our own series of AS patients, suggesting an involvement of the insulin-like growth factor-I (IGF-I)/IGFBP-3 axis (27). Conversely, serum concentrations of TGFβ1, another bone growth factor involved in bone formation, did not differ between AS and controls, suggesting that this growth factor does not play an important role in the bone loss of this disease (28).

Histomorphometric studies

There is little data on the bone histology and histomorphometric changes in the bone of patients with AS. Hanson *et al.* performed histomorphometric analyses on rib biopsies and showed decreased cortical thickness and retarded bone formation (3). No information about cancellous bone was available. In another study, 16 white males with AS underwent bone biopsy to evaluate histomorphometric variables. Osteopenia, mineralization defects and osteomalacia were found, while bone resorption variables were similar to those obtained in controls. Additionally, dynamic variables showed a decreased mineral apposition rate and a relationship between disease duration and osteoid volumes, while surface erosions correlated negatively with the disease duration. These data suggest the presence of mineralization defects and a depression in bone formation, contrasting with normal bone resorption indices (29). However, the status of circulating vitamin D was not given in this study.

Pathophysiology of bone impairment in ankylosing spondylitis

Thus, OP seems to be a common clinical feature in AS and may be observed even in the early stage of the disease (7, 13). Although the consequences of this bone fragility, i.e. fractures, mainly involve the spine, both the axial and peripheral skeleton showed decreased values in DEXA (20). Spine fractures are generally observed after minor trauma and therefore low bone mass is not the only factor contributing to the pathogenesis of these fractures. In addition, the vertebral fractures in AS may go unrecognized and be attributed to exacerbations of the disease. Moreover, compression fractures contribute to spine deformity (5).

Different factors could explain this bone loss in AS:

1. A reduced range of movement secondary to spine ossifications. However, bone loss is observed in patients with a short disease duration and without advanced spine changes (7, 13).
2. Treatments may in part play a role. Corticosteroids are rarely used in AS and it has been proposed that non-steroidal antiinflammatory drugs (NSAIDs) could induce bone loss in animals (30). However, data supporting the contribution of NSAIDs in OP are still lacking.
3. A hormonal disorder has also been suggested and reduced androgen levels have been reported in some studies (31, 32), but were not further confirmed (33). In addition, no significant correlation between sex hormones, BMD, and vertebral fractures were found in male AS patients (33).
4. Finally, the most likely explanation for OP in AS is disease activity. Indeed, bone turnover as evaluated by markers of collagen breakdown correlated negatively with disease activity and inflammation parameters (ESR, CRP) (26). Presumably, inflammatory cytokines such as interleukin-6, but also interleukin-1 and TNFα, play an important role (19). It is also likely that bone growth factor (IGF-I and its binding proteins) is related to the inflammatory process (27). All of this data supports the hypothesis of a relationship between inflammation markers and bone metabolism and therefore, skeletal bone loss.

Treatment

No specific treatment is available for AS osteoporosis. Bisphosphonates could be

used as these drugs have been found to be effective in AS. Etidronate was administered in a controlled (but unpublished) study, and resulted in improvement in pain, morning stiffness, and also BMD (34). Pamidronate was given in an open study and a significant improvement in disease activity (assessed by clinical indexes) and ESR after 6 monthly infusions was observed (35). However, the use of bisphophonates in AS deserves further longitudinal and controlled studies.

Conclusion

OP is a clinical feature of AS and can be observed in the early stages of the disease. This bone involvement should be considered as an extra-articular manifestation of the disease rather than as a complicating feature. Both bone resorption and formation processes are involved, as suggested by studies of biochemical markers of bone turnover and histologic changes. Thus, OP is probably caused by numerous factors, chiefly disease activity and certain inflammatory parameters such as cytokines. Therefore, AS patients with high disease activity, raised ESR and high levels of acute phase reactants should be followed carefully as they are at high risk of developing OP.

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