

How Should Clinicians Manage Osteoporosis in Ankylosing Spondylitis?

Ankylosing spondylitis (AS)¹ is characterized by chronic inflammation leading to ankylosis of the axial skeleton and the sacroiliac joints. This may ultimately progress to complete rigidity of the spine. AS has a prevalence of between 1 and 18 per 1000 in the white European population²⁻⁶, but varies in other population groups, correlating with the frequency of the genetic marker HLA-B27⁷⁻¹⁰.

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration. In 1994 the World Health Organization (WHO) classified bone mineral density (BMD) as normal, osteopenic, or osteoporotic in terms of the T score derived from BMD measurements¹¹. The incidence of fractures doubles with each standard deviation (SD) decrease in T score¹² and continues to increase exponentially with decreasing T scores¹³, being inversely related to BMD values¹⁴⁻¹⁸.

Current definitions of osteoporosis and osteopenia have been validated for postmenopausal women, and therefore may not be strictly applicable to patients with systemic diseases such as AS. Osteoporosis fracture risk is, however, associated with BMD measurements (T score) of less than -2.5 SD in both sexes¹⁹ and therefore, in the absence of validated figures in this population, it is reasonable to accept the WHO classification as a basis for management decisions.

AS is usually diagnosed in the third and fourth decades of life, with males predominating in most population surveys, at a ratio of 5:1³. It is likely that the sex ratio is closer to unity in reality, with males being prone both to more severe disease^{20,21} and to the development of osteoporosis²². In contrast, involutional osteoporosis tends to occur from the fifth decade onwards and is more common in women than men^{12,23}, but osteoporotic vertebral fractures have been shown to occur equally in men and women over 50 years of age²⁴.

Bone loss leading to osteoporosis is a well recognized feature of inflammatory arthritides, including AS²⁵. It seems paradoxical, however, that AS, a disease characterized by unusual and excessive calcification and bone formation in extraosseous tissues, should be a secondary cause of osteoporosis. In patients with coexisting AS and osteoporosis it is usually the AS that is diagnosed first, although occasionally osteoporosis may be the presenting feature²⁶.

HOW BIG IS THE PROBLEM OF OSTEOPOROSIS IN AS?

The reported prevalence of osteoporosis varies from

18.7%²⁷ to 62%²⁸. This may reflect different methods used in the quantification of osteoporosis and variation in patient selection.

Reid, *et al*²⁹ showed that men with AS lost bone at a rate of 2.2% annually with a 2.9% annual loss of total body calcium, compared with an annual loss of total body calcium of only 0.7% in men without AS and over the age of 50 years³⁰.

Studies of bone histology from iliac crest³¹ and rib²⁸ have revealed a higher prevalence of osteopenia in patients with AS, with both trabecular bone mass and cortical wall thickness being lower than control values, while the relative osteoid volume and thickness of osteoid were greater.

An increased prevalence of axial osteoporosis occurs even in early, mild forms of AS³²⁻³⁴, and the demineralization process continues for many years into the advanced stages of the disease. Thus due to the continual bone resorption as well as the reduced capacity of shock absorption, the already rigid spine is at risk of developing fractures and becoming increasingly deformed and kyphotic.

RISK OF OSTEOPOROTIC FRACTURES IN AS

Osteoporotic vertebral compression fractures affect up to 21% of patients with AS, at a rate more than 5 times that expected^{33,35-37}, and may occur silently^{35,37}. Vertebral compression fractures can occur as early as the third decade of life²⁴. In contrast to the generalized bone loss that occurs in rheumatoid arthritis, in AS, osteoporosis and its associated fractures appear to affect the spine exclusively^{24,28,29,32-36,38,39}. Cooper, *et al*³⁶, in a retrospective population based study, described a significantly increased incidence of fractures of the axial skeleton in patients with AS [standardized morbidity ratio (SMR) = 7.6]. In contrast, the risk of sustaining a fracture of the appendicular skeleton was identical to that expected (SMR 1.0). The cumulative incidence of spinal fracture in the AS cohort was higher than expected within 5 years of diagnosis of AS, with observed rates peaking 2 to 3 decades after diagnosis (Figure 1).

Vertebral compression fractures are more frequent in male (13.7%) than female (8.3%) patients, and increase with increasing age, disease duration, and spinal restriction^{33,36,37}, and in the presence of peripheral joint involvement and more extensive syndesmophyte formation^{35,40}.

SPINAL FRACTURES FOLLOWING MINIMAL INJURY

Minor trauma can lead to transpinal fracture and dislocation

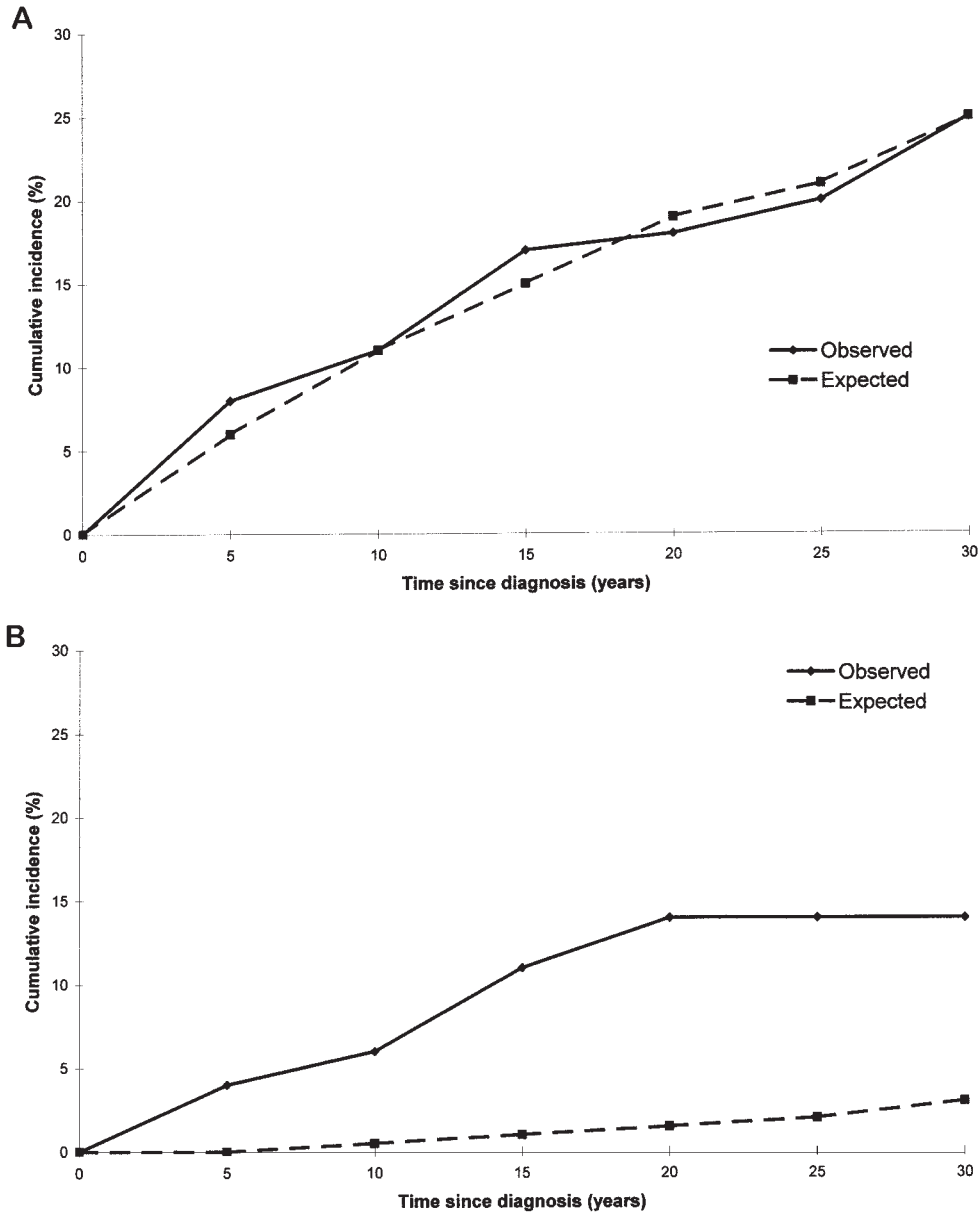


Figure 1. A. Observed and expected cumulative increase of any limb fracture among residents of Rochester, Minnesota, USA, diagnosed with AS, 1935–89. B. Observed and expected cumulative increase of thoracolumbar spinal compression fracture among Rochester residents diagnosed with AS, 1935–89. Adapted with permission³⁶.

traumatizing the spinal cord^{41,42}. The diagnosis of spinal fracture is frequently delayed in patients with preexisting back pain. The resulting neurological deficit ranges from mild sensory loss to complete paraplegia, with a higher incidence of spinal cord injury among patients with AS^{43,44}. Post-injury immobilization is of utmost importance following fracture–dislocation^{41,43}.

RISK ASSESSMENT OF OSTEOPOROSIS IN AS

While the evaluation of osteoporosis in patients with AS is essentially the same as for any other patient group, the

skeletal changes that occur in this condition may raise important issues of interpretation. The severity and activity of disease, as well as low body mass index and low fat mass percentage are high risk associations of osteoporosis and AS²⁷.

A combination of imaging techniques (Table 1) and analysis of appropriate biochemical markers of bone turnover (Table 2) is used in the evaluation of osteoporosis. In addition, underlying secondary causes (Table 3), found among 17% of AS patients with osteoporotic vertebral compression fractures, should be identified and treated³⁵.

Table 1. Imaging techniques used in the evaluation of osteoporosis.

Technique	Sites	Reproducibility, %	Radiation Dose, mSv	Notes
Radiology (plain radiograph)	Lumbar spine, femoral neck, radius, calcaneum		0.9	Up to 50% bone lost before demineralization becomes apparent. Difficult to quantify. Plain radiographs have been used to assess osteoporosis in AS in several studies ^{22, 28, 40}
Single energy x-ray absorptiometry (SXA)	Radius, calcaneum	5–8	0.02	Sites at which BMD can be measured are of limited clinical value in patients with AS
Dual energy x-ray absorptiometry (DEXA)	Lumbar spine, femoral neck	4–6	0.02–0.04	A precise method with a low radiation dose ⁹²
Quantitative computerized tomography (QCT)	Lumbar spine	5–15	2–10	Measures lumbar spine trabecular bone BMD; more expensive and a higher radiation dose than DEXA ⁹²
Quantitative ultrasound	Calcaneum			Correlation with other techniques and sites not evaluated

Adapted from: Plaut S. Radiation protection in the x-ray department. Oxford: Butterworth-Heinemann; 1993.

Table 2. Biochemical markers of bone turnover and their changes in AS.

Bone resorption			
Urinary	Pyridinium crosslinks of collagen: pyridinoline, deoxypyridinoline ^{27,70,93–98}		↑ in AS. ↑↑ in the presence of active inflammation ^{27, 55, 70} Levels unaffected by NSAID treatment
	Crosslinking telopeptides of type 1 collagen: C-terminal and N-terminal telopeptides ²⁷		
	Hydroxylysine glycosides ⁹⁹		
	Hydroxyproline (fasting) ⁹³		
	Calcium (fasting) ⁹³		
Serum	Tartrate resistant acid phosphatase ⁹³		
Bone formation			
Serum	Osteocalcin		↓ in AS ^{66,67, 76} . Sensitive and specific marker of bone formation. Synthesis stimulated by PTH and 1,25 (OH) ₂ D ₃ Unchanged in AS ^{55,70, 100}
	Bone-specific alkaline phosphatase		
	Procollagen type 1: C-terminal and N-terminal propeptides		Inverse relationship with APR in seronegative spondyloarthritis ⁶⁸
	IGF-1 and IGFBP3		Levels reflect osteoblast function

PTH: parathyroid hormone; 1,25 (OH)₂D₃: 1,25-dihydroxyvitaminD₃; APR: acute phase response; IGF-1, insulin-like growth factor-1; IGFBP3: insulin-like growth factor binding protein-3.

ETIOLOGY OF OSTEOPOROSIS IN AS

The etiology of osteoporosis in AS is complex and may involve both mechanical and biochemical factors, as follows.

In late AS, the mechanical support provided by extraspinal bone may divert gravitational, motional, and compressive stresses away from the vertebral trabeculae, resulting in diminished trabecular density, as predicted by Wolf's law⁴⁵. In early disease, in the absence of extraspinal bone, systemic factors are likely to be of more importance⁴⁶.

Genetic factors⁴⁷ and corticosteroid treatment³⁷ probably make only a small contribution to the lowered BMD in AS.

Decreased BMD at the femoral neck in early disease^{32,34,37,39,48} suggests that systemic mediators may be involved in the pathogenesis of osteoporosis in patients with AS. Several cytokines including human tumor necrosis factor- α (TNF- α) and lymphotoxin (TNF- β)⁴⁹ as well as

both murine and porcine interleukin 1 (IL-1) have been found to be potent osteoclast activating factors (OAF) *in vitro*^{50,51}. Serum concentrations of IL-6 and TNF- α have been found to be higher in patients with AS than in subjects with noninflammatory back pain⁵². In AS, positive correlations were found between IL-6 levels and TNF- α and measures of disease activity and severity. IL-6 levels are also known to correlate with inflammatory activity in other rheumatic diseases^{53,54}.

Agents such as calcitonin and interferon- γ can inhibit cytokine stimulated bone resorption^{49,50}. As more detailed understanding of the complex interactions between different cytokines and their influence on bone turnover is obtained, it may become possible to inhibit osteoclast activating factor activity therapeutically during periods of disease activity to prevent the development of osteoporosis.

Table 3. Secondary causes of osteoporosis

Endocrine	Thyrotoxicosis Primary hyperparathyroidism Cushing's syndrome Hypogonadism
Gastrointestinal	Malabsorption syndrome (e.g., celiac disease) Partial gastrectomy Liver disease (e.g., primary biliary cirrhosis)
Rheumatological	Rheumatoid arthritis Ankylosing spondylitis
Malignancy	Multiple myeloma Metastatic carcinoma
Drugs	Corticosteroids Heparin
Other factors	Low body mass index (< 19 kg/m ²) ¹² Nutritional factors, e.g., alcohol ^{101, 102} , caffeine ¹⁰²⁻¹⁰⁴ Inactivity Cigarette smoking ^{101, 105} Racial origin (Caucasians) Positive family history ¹⁰⁶

ASSESSMENT OF OSTEOPOROSIS IN AS

There is an increasing range of options for measuring bone state in people with AS and others, although many have not been formally validated in this population. Measurements of BMD and biochemical markers of bone turnover may all contribute to a full assessment.

Determining BMD in AS

Plain radiographs have been used in the assessment of osteoporosis in subjects with AS^{24,28,40}, but are unreliable, are difficult to quantify, and may not detect demineralization until up to 50% bone loss has occurred. Much more precise imaging techniques are available for the determination of BMD (Table 1), of which dual energy x-ray absorptiometry (DEXA) scanning is the most frequently used. As in other forms of osteoporosis, measurement of BMD by DEXA scanning is an attractive and increasingly available option.

However, several studies have shown that vertebral BMD measured by DEXA may not truly reflect the osteoporotic fragility of the lumbar spine through all the stages of AS^{24,29,37-39,48,55-59}. While DEXA scanning reliably detects vertebral osteoporosis in early AS and involutional osteoporosis, a misleading *increase* in lumbar BMD values may be observed in patients with advanced AS, due to the presence of bridging syndesmophytes that mask the osteopenia of the L1-L5 vertebrae^{24,37-39,58}. In a group of patients with AS, Reid, *et al*²⁹ found a significant correlation between a syndesmophyte count of L1-L5 vertebrae and the difference between the expected bone mass in the lumbar vertebrae and the total body. Their data strongly suggested that an unexpectedly high vertebral bone mineral content reflects new bone formation in the spondylitic spine. A similar false elevation in BMD has also been shown to occur in elderly patients with osteoporosis in the presence of osteophytes⁵⁹.

DEXA scanning at the lumbar spine has indicated that the degree of osteopenia is greatest in AS patients with milder disease, determined both clinically (by modified Schober's testing)³⁷ and radiologically²⁴. Osteopenia is also more marked in those with a shorter duration of disease²⁴. Single-energy quantitative computerized tomography (QCT) has revealed more marked bone loss at this site, the discrepancy between the 2 measurements being most marked in patients with more severe AS, the majority of whom had normal DEXA values. While QCT values may appear low in postmenopausal women⁶⁰ and immobilization⁶¹, it is unlikely that this would account for the degree of osteopenia found. The decrease in BMD measured by QCT in the presence of relatively normal DEXA values reflects 2 opposite trends: central trabecular osteopenia and peripheral new bone formation, which effectively transforms vertebral bodies into long bones.

While lumbar spine BMD is reduced in those with mild or moderate AS, but progressively increases with advancing disease, femoral neck BMD is reduced in all patient groups and follows the opposite trend, being inversely related to disease severity and duration. Femoral neck measurements have revealed osteopenia in between 72% and 93% of patients with AS, but in addition femoral neck measurements have indicated greater severity of osteopenia than lumbar spine measurements^{48,55}. The lateral decubitus projection at the L3 vertebra (LAT-L3) is more sensitive than the conventional posteroanterior (PA) projection in detecting osteoporosis in moderate to severe AS⁵⁵, as well as in advanced degenerative joint disease⁶² and in glucocorticoid induced osteoporosis⁶³. Bone loss observed on LAT-L3 scans correlates with bone loss at the hip. This view isolates the vertebral body from the ankylosed posterior elements of the spine, without interference from overlying ribs or the ilium (as occurs at L1, L2, and L4).

Therefore, while conventional PA DEXA remains a precise and reproducible way to identify and to monitor the response to treatment of osteoporosis in patients with early AS, in the later stages of the disease calcification in paraspinal tissues may result in paradoxically high lumbar BMD measurements, and alternative imaging techniques must be considered. The choice of technique, DEXA at the femoral neck, LAT-L3 DEXA, or QCT, will usually be determined by the availability of these facilities. A cutoff point, in terms either of the clinical stage of AS or of a radiological grading of disease, beyond which PA DEXA measurements lose their value remains to be determined.

Will, *et al*⁵⁶ showed a 5% decrease in BMD at the carpus as well as reduced BMD at the femoral neck of patients with advanced AS compared to controls, suggesting that with progressive disease, bone loss begins to involve cortical as well as trabecular bone.

These studies^{24,33,37,48,55,56} show that in AS, there is a continual demineralization predominantly affecting the

axial skeleton, with BMD progressively falling with disease duration and increased spinal restriction, associated with a significantly increased rate of vertebral fracture. In conventional DEXA examinations this is most accurately assessed by measurements of femoral neck BMD.

Measurement of appendicular skeletal BMD

Current data indicate that the increased risk of fractures in patients with AS relates exclusively to the axial skeleton rather than the limbs. Therefore the use of imaging techniques that focus on appendicular BMD, such as calcaneal ultrasound, would appear illogical in this group, at least until such methods have been carefully validated.

Should we be measuring bone turnover in the clinic?

Biochemical markers differ in sensitivity and specificity, and are not disease-specific. These markers can help to identify subjects who are likely to respond to some forms of treatment for osteoporosis⁶⁴, and to monitor response to treatment⁶⁵.

Both decreased bone formation⁶⁶⁻⁶⁹ and increased bone catabolism^{27,68,70} have been reported in patients with AS, although there is not a clear consensus of findings between different groups. These studies emphasize the importance of simultaneous measurement of many indicators of bone formation and destruction.

While measurements of markers of bone formation and bone degradation may provide insight into the pathogenesis of osteoporosis in AS, there are currently insufficient data to determine what role they should play in routine clinical management. Due to the chronic nature of AS, accurate information regarding the most appropriate methods of monitoring osteoporosis will be slow to accumulate. For this reason it is difficult to justify use of such markers currently in clinical practice.

Biochemical markers of bone formation

Serum osteocalcin. Serum osteocalcin is a very sensitive and specific marker of bone formation. Osteocalcin synthesis is stimulated by parathyroid hormone and 1,25-dihydroxyvitamin D₃. Serum osteocalcin concentrations are decreased in patients with hypoparathyroidism⁷¹, in clinical situations that lead to low turnover osteoporosis⁷², and in patients receiving glucocorticoids⁷³⁻⁷⁵. Circulating levels of serum osteocalcin have been shown to be reduced in patients with AS and other inflammatory arthritides, suggesting reduced bone formation^{66,67,76}. Other authors have reported unaltered serum osteocalcin levels in AS^{55,70}.

Insulin-like growth factor 1 (IGF-1) and IGF binding protein 3 (IGFBP3). IGF-1 mediates the effect of growth hormone (GH) at the tissue level, including bone. Its main binding protein, IGFBP3, can increase the anabolic action of IGF-1 in bone, and together their levels reflect osteoblast function⁷⁷.

IGF-1 levels are decreased in postmenopausal women⁷⁸ and idiopathic male osteoporosis⁷⁹ and are directly related to axial bone density in postmenopausal women⁸⁰. Enhanced bone formation occurs following treatment with IGF-1 in male idiopathic osteoporosis⁸¹.

IGFBP3 levels have been found to be reduced in patients with AS, and a positive correlation between the concentrations of IGF-1 and osteocalcin has also been reported⁶⁹. IGFBP3 levels correlate negatively with erythrocyte sedimentation rate (ESR), suggesting that inflammation could impair the synthesis of IGFBP3 in response to GH. The reduced IGFBP3 levels could diminish the activity of IGF-1 in AS.

Biochemical markers of bone resorption

Positive correlations between the concentrations of the urinary bone resorption markers pyridinoline (Pyr), deoxypyridinoline (D-Pyr), and C-telopeptide with early morning stiffness, Larsen radiological hip score, and the inflammatory markers ESR and C-reactive protein (CRP) have been found^{27,68,70}. The latter was most marked in the subgroup of patients with more active inflammation (CRP > 20 mg/l)⁶⁸. Schober index and fat mass percentage have been shown to correlate negatively with these urinary bone resorption markers²⁷.

Nonsteroidal antiinflammatory drug (NSAID) treatment does not alter the urinary excretion of Pyr, implying that at therapeutic doses NSAID have no significant influence on bone metabolism⁷⁰.

Inverse relationships between bone formation and acute phase response have also been revealed by negative correlations between ESR and procollagen I C-terminal peptide levels⁶⁸ and IGFBP3 levels⁶⁹.

These studies suggest that during phases of active inflammation, bone formation is uncoupled from bone resorption, leading to overall loss of bone⁶⁸⁻⁷⁰. The resultant osteoporosis may well correlate with overall levels of disease activity during the course of the disease. If a more detailed relationship between acute phase response and rate of bone loss can be established, strategies of intermittent prophylactic antiresorptive therapy could be targeted during these more active phases, even in those who are not found to be osteoporotic on screening. As normal ESR and CRP levels do not exclude active disease, the potential benefit of antiresorptive therapy during symptomatic flares should be investigated.

TREATMENT OF OSTEOPOROSIS IN AS

As it is not currently possible to stratify patients into high and low risk groups, all subjects with AS should be screened for osteoporosis. While they may have normal BMD on initial measurements, osteoporosis may well develop during the course of their disease. Management of osteoporosis can be divided into preventive and therapeutic approaches

which inhibit bone resorption and stimulate bone formation. These are summarized in Table 4.

Bisphosphonates. There are currently no data specifically addressing the value of bisphosphonates in the treatment of osteoporosis in patients with AS. Etidronate and alendronate, the 2 most commonly used bisphosphonates in the UK, inhibit bone resorption in a dose dependent manner in patients with involutional osteoporosis. Intermittent cyclical etidronate therapy increases BMD, in both sexes, by around 6% over a 2 year period⁸²⁻⁸⁶, with a resultant decrease in the rate of new vertebral compression fractures^{12,82}. It is generally thought to have little if any effect at the femoral neck⁸³⁻⁸⁵ or forearm^{84,86}, although Selby, *et al*⁸⁶ described a 10% increase in proximal femoral BMD in men with osteoporosis.

Alendronate increases BMD in the axial and appendicular skeleton. The annual rates of increase of BMD are around 3% at the lumbar spine and 2% at the femoral neck¹². The risk of developing new spinal, hip, and wrist fractures is roughly halved at each site.

It is possible that bisphosphonates may reduce the tendency for abnormal calcification in AS. However, current evidence of this in humans and laboratory animals is tenuous, although pamidronate may exert a useful anti-inflammatory effect in AS⁸⁷.

Randomized controlled trials to assess the efficacy of current and newer bisphosphonates in maintaining BMD and reducing the development of osteoporotic vertebral compression fractures and femoral neck fractures in subjects with AS are required. Studies are also required to establish whether secondary prevention using bisphosphonates can minimize the development of osteoporosis in AS.

Testosterone. Both male patients with AS⁸⁸ and 16% of men with vertebral compression fractures exhibit hypogonadism⁸⁹. Although testosterone treatment increases BMD in hypogonadal men^{90,91}, trials are needed to determine the efficacy of this treatment in male patients with AS.

Monitoring treatment. As in osteoporosis not associated

with AS, assessments of whether the condition is worsening and whether treatment is effective are necessary. While trials have not established the appropriate investigations and intervals for monitoring, this information is badly needed.

SUMMARY

Osteoporosis is a common complication of AS, with an incidence between 18.7% and 62%. The prevalence of osteoporosis is greater in males, and increases with increasing patient age and disease duration. Osteoporosis is also more common in patients with syndesmophytes, cervical fusion, and peripheral joint involvement. These variables are not all independent, as they may be indicators of disease duration.

Osteoporosis in patients with AS is largely confined to the axial skeleton, in contrast to the pattern of osteoporosis seen in rheumatoid arthritis. BMD at the lumbar spine and femoral neck may be severely reduced, while most studies indicate that carpal and radial BMD remain within normal limits.

The development of syndesmophytes in late AS can lead to difficulties in the use of DEXA scanning to determine lumbar BMD, as the extraspinal bone may obscure osteoporotic vertebrae. Under these circumstances more accurate assessment of lumbar BMD, and one that correlates better with femoral neck BMD, may be obtained by quantitative CT scanning or DEXA scanning of the lateral aspect of the L3 vertebra.

Osteoporosis in AS significantly increases the risk of vertebral compression fractures within 5 years of the diagnosis of AS. The risk of a vertebral compression fracture occurring over a 30 year period following the diagnosis of AS is 14%, compared to 3.4% for population controls. In patients with vertebral osteoporosis relatively minor trauma, such as slipping, can lead to spinal fracture and dislocation with subsequent damage to the spinal cord. There is a higher incidence of spinal cord injury following spinal fracture dislocations in patients with AS, and the resulting neurological deficit can range from mild sensory loss to complete paraplegia.

Cytokines such as TNF- α and IL-6 may play an important part in the pathogenesis of osteoporosis in early AS, and IL-6 levels have been correlated with markers of disease activity and severity. In late AS, mechanical factors such as decreased mobility and the support provided by extraspinal bone may play a role in vertebral osteoporosis.

Screening patients with AS for the presence of osteoporosis is an important, but contentious subject. This and subsequent monitoring needs to be considered in all patients, but longterm studies are needed to determine with confidence which patients should undergo screening, by which methods, and how often. The treatment of osteoporosis in AS is at present similar to that used for primary osteoporosis, except that due to the male predominance and a relatively young age of patients, there is a limited role for

Table 4. Treatment of osteoporosis.

Primary prevention

- Nutrition (vitamin D, dairy products, calcium supplements)
- Lifestyle factors (physical activities, adequate sun exposure)

Secondary prevention and established osteoporosis

- As for primary prevention
- Calcium supplementation — ideally nocté^{107, 108}
- Thiazides¹⁰⁹
- Calcitonin^{64, 110, 111}
- Testosterone⁸⁸⁻⁹¹
- Anabolic steroids^{12, 111}
- Vitamin D metabolites¹¹
- HRT¹¹²
- Bisphosphonates^{12, 82-86}
- Exercise regimens¹¹²⁻¹¹⁴ (weight bearing and site-specific)

hormone replacement therapy. Exercise regimens and bisphosphonates are widely used, but a study of the relative efficacy of different bisphosphonate agents in patients with AS is required.

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