Occurrence and Clinical Predictors of Osteoporosis in patients with Ankylosing Spondylitis in a tertiaty care center in South India

A Dissertation submitted in partial fulfillment of

M.D (General Medicine) Examination of the Tamil Nadu

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To be held in 2008.

Occurrence and Clinical Predictors of Osteoporosis in patients with Ankylosing Spondylitis in a tertiary care center in South India

CERTIFICATE

This is to certify that the dissertation entitled "*Occurrence and Clinical Predictors of Osteoporosis in patients with Ankylosing Spondylitis in a tertiary care center in South India"* is the bonafide original work of Dr. Pavan Bhargava towards the M.D. Branch-1 (General Medicine) Degree Examination of the Tamil Nadu Dr. M.G.R University, Chennai to be conducted in 2008.

Signature:

Dr. Dilip Mathai
Professor and Head
Department of Medicine
CHRISTIAN MEDICAL COLLEGE
Vellore - 632004.

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Signature:

Guide**:**

Dr. Debashish Danda
Professor of Medicine
Department of Rheumatology
CHRISTIAN MEDICAL COLLEGE
Vellore - 632004.

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C O N T E N T S

INTRODUCTION

Ankylosing spondylitis (AS) is an inflammatory disorder of unknown cause that primarily involves the axial skeleton, though peripheral joints and exta-articular structures are also involved. It usually manifests in the second to third decade and has a male to female ratio varying in literature from 4-10:1, however most recent studies show a ratio between 5:1 to 3:1(1-3). Enthesitis is a classical feature of this disease. Subchondral bone marrow edema, infiltration of lymphocytes and macrophages, and synovitis have been seen in early stages of this disease in the sacroiliac as well as peripheral joints. These processes lead to pannus formation similar to rheumatoid arthritis, joint erosion and ultimately new bone formation. Even though new bone formation is one of the cardinal features of the disease, osteoporosis has been found to occur in patients with AS(4).

The prevalence of osteoporosis in AS among Caucasians has been found in various studies to range from 4.3 to 31%(5-10). These studies utilized various means of assessing bone mineral density (BMD). It has been found that the ideal measure for osteoporosis in AS is the Dual energy X ray absorptiometry (DEXA) of femoral neck and a lateral projection of L3 vertebra(11, 12). In recent times however Quantitative CT (QCT) has been proposed as an alternative and has been shown to correlate well with BMD(10). QCT may in fact be able to pick up osteoporosis at an earlier stage than DEXA, however it is more expensive and less well standardized than DEXA(13).

The pathogenesis of osteoporosis in AS, has not been completely elucidated. In later stages of the disease immobilization plays an important role, however

osteoporosis begins early in AS and has been thought to be related to effects of inflammatory cytokines on osteoclasts and bone turnover(14). Studies have implicated Tumor Necrosis Factor α (TNFα) in the pathogenesis of AS and clinical trials have shown benefit with TNFα blockers. The exact role of TNFα has not been described but studies show that TNFα causes increased osteoclast activation and may hence lead to osteoporosis. The RANK/RANKL/OPG system which plays a pivotal role in osteoclast differentiation and activation may explain the pathogenesis of osteoporosis in AS(15). Studies are however conflicting on the relationship between markers of bone turnover and changes in BMD with some studies showing increased turnover, while others showed no change in the same(5, 12, 14). Thus, the precise mechanisms underlying osteoporosis in AS, remain to be elucidated.

Despite the fact that osteoporosis is a recognized complication of AS and can lead to increased fracture risk – up to five times more than expected, there are no guidelines concerning the diagnosis and treatment of osteoporosis in AS. An audit of diagnosis and treatment of this disorder by rheumatologists in England, revealed grossly inadequate awareness about the need to screen for osteoporosis and also about appropriate treatment(16).

There is therefore, a need to evolve common guidelines for screening and treatment of osteoporosis in patients with AS. Studies are also required to look at relationship between duration of disease and occurrence of osteoporosis. Some studies have shown a positive correlation between duration and osteoporosis, however these studies have been done in Western countries and on patients who were for the most part not on second line therapy. It has been observed that among Indians, there is more

appendicular skeleton involvement, which may represent more severe disease. With more data, the ideal time to screen for osteoporosis can be determined. Establishing various clinical correlates of osteoporosis in AS, including indices such as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) may be helpful as clinical predictors. As a corollary, the effect of treatment on the occurrence of osteoporosis may suggest a causal relationship between osteoporosis and inflammatory activity.

This study is the first ever attempt to determine the prevalence of osteoporosis in Indian patients of AS and to assess whether demographic factors, duration of disease, disease activity or treatment correlate with the occurrence of osteoporosis.

OBJECTIVES OF THE STUDY

1. To determine the occurrence of osteoporosis among a cohort of patients with Ankylosing Spondylitis(AS).

2. To assess whether the following disease indices - the BASDAI(Bath Ankylosing Spondylitis Disease Activity Index), BASFI (Bath Ankylosing Spondylitis Functional Index), or BAS-G (Bath Ankylosing Spondylitis Global Index) have a correlation with osteoporosis in AS.

3. To assess if demographic factors, disease duration, treatment with steroids, DMARDS or laboratory parameters of inflammation have an association with occurrence of osteoporosis in AS.

REVIEW OF LITERATURE

Ankylosing Spondylits

Ankylosing spondylitis (AS) is a chronic inflammatory disease that predominantly affects young men and is associated with the HLA B27 antigen in over 90% of cases(1). Patients generally present in young adulthood. Men are definitely more affected than women (1-3). There is also a rough correlation between the prevalence of HLA B27 and the incidence and prevalence of this disease in a specific population. Presence of HLA B27 in an individual makes one 40 times more susceptible to develop AS in one's life time, as compared to HLA B27 negative people (1). However, there are certain sub-types of B27 such as B27 06, which may in fact be protective against AS. These have been found to be more common in certain races such as blacks, but are uncommon in Indians(17).

The most important symptom of AS is inflammatory back pain, caused by sacroiliitis. Bilateral sacroiliitis is the main diagnostic criterion in the modified NewYork criteria set(18). Other sites of involvement include the spine, peripheral joints, and entheses (capsules, ligaments, and tendons). Extra-articular manifestations vary widely in terms of both frequency and severity. Inflammatory enthesopathy progressing to ossification and ankylosis is the pathologic basis for the disease. Despite advances in technology, the etiology and pathogenesis of this disorder remain elusive. Environmental factors may also play a key role, especially bacteria which could serve as a trigger in susceptible hosts. This is supported by the observation that B 27 transgenic mice do not develop spondyloarthritis if raised in a bacteria free environment (1).

Osteoporosis

Osteoporosis is a disorder of increased bone fragility and low bone mass with a consequent increase in fracture risk(19). It is most commonly seen in the setting of postmenopausal women. However, there are several secondary causes, which include the inflammatory arthritides. Several factors have been implicated in its pathogenesis including – declining estrogen levels, genetic background, nutritional status, alterations in Parathyroid hormone (PTH) levels and growth hormone – Insulin like growth factor (IGF) axis, mechanical strain and factors related to risk of falling. Clinicians must rely on measurements of BMD to diagnose this disorder. A 10% decrease in BMD (1 SD below the mean) at any site confers a 1.6 to 2.6 Relative risk (RR) of hip fracture and a 1.7 to 2.3 RR of vertebral fracture. BMD is reported as two scores namely, Z score and T score. The Z score compares the patients BMD with that of age-matched controls. The T score compares the patients BMD to the mean of a healthy reference population thought to represent the peak bone mass. A T score of –2.5 and below meets WHO criteria for osteoporosis and a score between –2.5 and –1 represents osteopenia(20).

The Magnitude of the Problem

Diffuse osteoporosis responsible for loss of bone strength is a recently reported feature of AS. The bone loss predominates at the spine. Late in the disease, vertebral fractures constitute a rare but non-negligible source of morbidity and mortality related mainly to neurological compromise(4).

The prevalence of osteoporosis in AS has been assessed in several studies and varies from 4.3% to 31%. The prevalence has been found to depend on several factors – disease duration, age, sex, disease activity, presence of syndesmophytes and also depends on the method used to assess osteoporosis. A summary of all studies undertaken to assess BMD in AS patients is shown in Table 1. Most of these studies were done in Caucasian populations. The studies encompass the entire gamut of the disease – in terms of duration, sex, activity and treatment. However no data is available from India. The various factors affecting osteoporosis are discussed below.

Table 1. Summary of studies to assess osteoporosis in patients with AS

Authors [reference]	Number of Patients	Mean age, sex ratio, mean disease duration	Measurement technique	BMD, lumbar spine	BMD, femoral neck	BMD, radius
Devogelaer et al (21)	70 10	39 years, 60 M, 10 F, 15 years 8 M, 2 F	DXA QCT	M: decreased F: not decreased Decreased	ND -	No Difference
Bronson et al (12)	15	23-74 years, 15 M , not specified	DXA	Normal	Decreased	ND
Donnelly et al. (22)	87	44 years, 62 M, 25 F, 16 years	DXA	M: decreased F: not decreased	Decreased	ND
Mullaji and Ho (23)	33	37,8 years, 27 M, 6 F, M1: 8.7 years; M2: 11.7 years; F: 6.8 years	DXA	M1:decreased M2:normal F:Decreased	Decreased in all groups	ND
El Maghraoui et al. (5)	80	36.7 years, 52 M, 28 F, 8.7 years	DXA	Osteopenia: 31%, Osteoporosis: 18.7%	Osteopenia : 41.2%, osteoporosis: 13.7%	ND
Toussirot et al (7)	71	39.1 years, 49 M, 22 F, 10.6 years	DXA	Osteopenia: 32.4%, Osteoporosis: 14.1%	Osteopenia : 22.5%, osteoporosis: 4.3%	ND
El Maghraoui et al. (24)	37	36.4 years, 37 M, 6.8 years	QCT	Osteopenia: 29.7%, Osteoporosis: 27%	_	_
Juanola et al (6)	18	36.7 years, 18 F, 15.1 years	DXA	Osteopenia 11% Osteoporosis None	No difference	ND
Karberg et al (10)	103	66 M, 37 F,	DXA DEQCT	Osteopenia 31% Osteoporosis 14% Osteopenia 44% Osteoporosis 11%	Osteopeni\ a 52% Osteoporosis 24%	ND

M, males; F, females; BMD, bone mineral density; DPA, dual-photon absorptiometry; DXA, dual-energy X-ray absorptiometry; QCT, quantitative computed tomography; ND, not done.

Factors affecting occurrence of the problem

Sex

Studies have shown that osteoporosis in AS is more common among male patients (21). One study also reported a higher prevalence of vertebral fractures in males with AS (25). A higher prevalence of osteoporosis in men with AS as compared to females, may be related to more severe disease, and the presence of an androgen deficiency (28).

Duration of Disease

It has been shown that femoral BMD correlates inversely with disease duration(10). The lumbar spine BMD however increases with advancing disease(26). This is due to extraspinal ossification causing an artefactual increase. A lateral projection of L3 vertebra may enable us to get a true BMD of the spine in advanced disease(12). A new method, which has shown promise is the QCT and, using this it was found that spine BMD also correlates inversely with disease duration(10). Using femoral BMD, the prevalence of osteoporosis in patients with AS for less than 5 years duration was found to be 11%, as compared to 29% in those with disease duration of more than 10 years(10). Another study in Brazil demonstrated a positive correlation between BMD at lumbar spine, and hip with disease duration (26). Thus prolonged duration of disease is a definite predictor for osteoporosis.

Disease activity

In a study on 80 patients with AS, Maghroui et al showed that increased disease activity correlated with elevated markers of bone resorption (5). Similar relationships have been demonstrated in several other studies(9). However none of these studies demonstrated a relationship between clinical disease activity and BMD. In one study it was shown that, BMD did not differ between patients with active and inactive disease (26). It has also been shown that inflammatory markers such as ESR and CRP do not correlate with BMD(26). Thus the relationship of disease activity with osteoporosis remains unclear. Further data may help in clarifying this relationship. If such a relationship exists, disease activity may serve as one of the predictors for osteoporosis in AS.

Awareness of the Problem

In a study conducted among rheumatologists in the UK, out of 310 respondents only 31.6% assessed bone mass as part of routine management of AS. DEXA was the method of choice for assessing osteoporosis, however, most of them did not wish to assess hip BMD. When given case scenarios of patients with AS and osteoporosis, only 75% said that they would use a bisphosphonate for treatment(16). This illustrates the lack of awareness regarding this common complication of AS.

Ideal tool to assess BMD in AS

DEXA is a precise, reproducible and standardized tool to measure BMD. However, as mentioned above, lumbar spine BMD in advanced AS shows a misleading increase due to presence of bridging syndesmophytes (10, 26). Thus in mild and moderate AS, spine BMD shows reduction, but in severe disease it progressively increases. Femoral neck BMD however has been shown to have an inverse relationship with disease duration and severity and is reduced in all patient groups(11). The lateral decubitus projection of L3 is more sensitive than posteroanterior projection in detecting osteoporosis in moderate and severe AS(12). Thus this may be an alternative to femoral neck BMD.

Another method that has been tried is the Quantitative Computerized Tomography (QCT). This has been found to be of use in patients with severe disease and extraspinal ossification in whom DEXA shows falsely high values in spine BMD. In a study on 103 patients of AS with disease duration more than 10 years, spinal DEQCT showed osteoporosis in 18% of them, while only 4% were osteoporotic by DEXA. However, in the same cohort, femoral DEXA showed osteoporosis in 29%(10). QCT measurements have still not been standardized and are not available as widely as DEXA. Also there is a higher radiation dose in the case of QCT. QCT may be of use in patients with advanced disease, or in patients with hip arthroplasty.

In view of this data, the ideal tool would be a femoral neck BMD. Where available, a Lateral projection of L3 may also be of use, since it has been shown that this vertebra is the first site of bone loss in AS(14).

Validity of DEXA in Indian setting

BMD as measured by DEXA is considered the gold standard for diagnosing osteoporosis. A drawback using this method in our setup maybe that the machine used for these measurements utilizes Caucasian controls to calculate and report T scores. The issue of whether there is a difference between the BMD of Indian and Caucasian populations has been addressed to some extent. Two studies have shown that normal Indian women had lower BMD as compared to Caucasian controls. Another necropsy based study however showed no difference between Indians and Caucasian controls(27). In a recent study from AIIMS – men and women with optimal sunlight exposure, diet and physical activity were evaluated to assess biochemical parameters of bone metabolism and BMD. This study revealed that all the subjects had normal calcium, phosphorus, alkaline phosphatase, 25 OH vitamin D levels and PTH. However measurement of BMD revealed that 35-50% of men and 14-32% of women were osteopenic at different sites. In addition 10% of men had osteoporosis at the lumbar spine using western controls (28). Since these men and women had normal biochemical parameters, optimum diet, sunlight and physical activity, the difference in BMD may be related to ethnicity. Thus there is a need to establish normative data for Indians. Thus determination of T scores in relation to the Indian subjects may provide a more accurate picture of the prevalence of osteoporosis and osteopenia in our population, than comparison with Caucasian controls.

Mechanism of Osteoporosis in AS

The mechanism underlying osteoporosis in AS has not been conclusively elucidated, however several factors may play a role in this process. Earlier it was thought that immobilization and lack of physical activity were the main factors responsible for osteoporosis in AS. It has however been shown that the development of osteoporosis is a multi-factorial process. The following mechanisms have been proposed

1. Immobility related to pain and stiffness early in the disease and to spinal ankylosis later on, may cause osteoporosis. In late AS, the mechanical support provided by extraspinal ossification may divert gravitational, motional and compressive stresses away from vertebral trabeculae, resulting in diminished trabecular density, as predicted by Wolf's Law. However, established osteoporosis has been found in patients who had early disease without noticeable functional impairment(14). Thus in such cases systemic factors are likely to be of more importance.

2. Glucocorticoids, which are widely used to treat inflammatory joint disease, are known to promote bone loss. However, glucocorticoids are rarely used to treat AS, and osteoporosis has been found in series of glucocorticoid-naïve patients with AS, rheumatoid arthritis, or systemic lupus erythematosus. Nonsteroidal anti-inflammatory drugs, also used in inflammatory joint disease, have not been shown to adversely affect bone in humans, although a few studies in animals suggested an ability to promote bone loss.

3.Although androgen deficiency has been suggested in AS patients, several studies have found similar incidences of hormone level abnormalities in patients and controls(29).

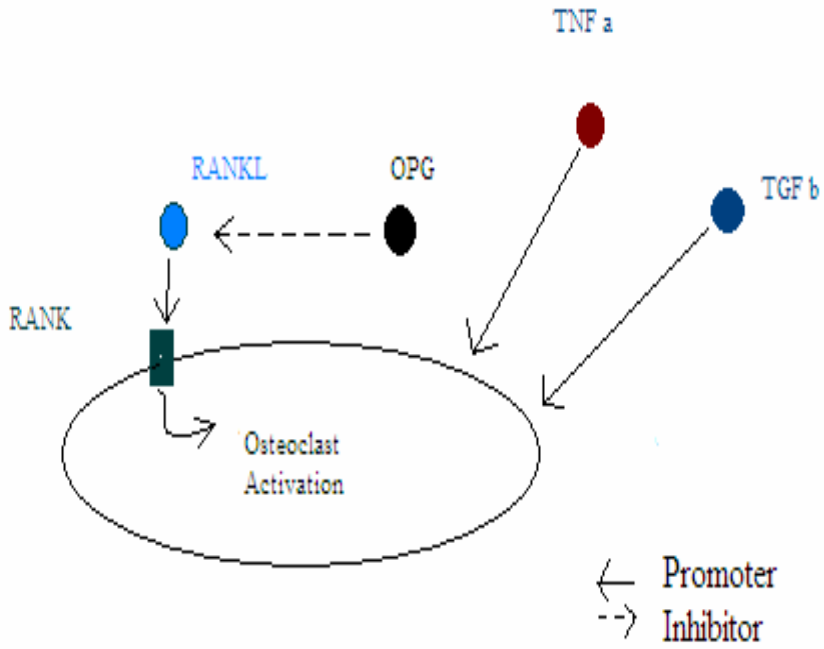
4.Decreased BMD at the femoral neck in early disease suggests that systemic mediators may be involved in the pathogenesis of osteoporosis in AS. Several cytokines including TNF α and Tumor necrosis factor β (TNF β) as well as both murine and porcine interleukin 1(IL1) have been found to be potent osteoclast activating factors (OAF) in vitro. Serum levels of interleukin-6 (IL-6) and TNF α have been found to be higher in patients with AS than in patients with non-inflammatory back pain.

In AS, positive correlation was found between levels of IL-6 and TNF α and measures of disease activity and severity(30). However, measurements of bone turnover markers have yielded highly conflicting results. Inflammation of the entheses and synovium may result in increased release of pro-inflammatory cytokines, whose deleterious effects on bone metabolism have been established(31). TNF α, IL-1, and IL-6 induce bone metabolism imbalances in animals and humans(31, 32). Thus, in several studies, significant correlations were found between bone turnover markers (pyridinoline, deoxypyridinoline, C- and N-telopeptide crosslinks, and osteocalcin) and the levels of pro-inflammatory cytokines or their markers (erythrocyte sedimentation rate and C-reactive protein) used in clinical practice(8, 9, 14). Individual studies have found reduced markers of bone formation (osteocalcin) in patients with AS(8). This suggests that there is an uncoupling of the processes of bone formation and resorption leading to a resultant decrease in bone mass.

5.Another important factor seems to be the RANKL/RANK/OPG system. Studies have shown that Osteoprotegerin(OPG),(a molecule which neutralizes Receptor Activator of Nuclear Factor kB Ligand (RANKL)) are lower in patients with AS who have osteoporosis(9). RANKL is a molecule that binds to and activates RANK present on osteoclasts. This subsequently leads to osteoclast activation and may subsequently produce osteoporosis. Recent studies have shown that higher RANKL levels and higher RANKL/OPG ratio are seen in AS patients with lower BMD(15). In other inflammatory conditions associated with osteoporosis, it has been shown that RANKL may cause an autocrine production of TNF α leading to further osteoclast activation(33). This mechanism may be of importance in AS as well. This data suggests an important role for this mechanism in producing osteoporosis in AS.

6. Clinically silent bowel disease may contribute to the development of bone loss, according to a small number of studies showing bowel lesions in nearly two-thirds of patients with AS investigated routinely (34, 35). These lesions may lead to decreased calcium and vitamin D absorption leading to osteoporosis.

Figure 1.



Schematic Representation of factors involved in osteoclast activation.

Biochemical Markers of Bone Metabolism

Markers of Bone formation

Serum Osteocalcin

Serum osteocalcin is a very sensitive and specific marker for bone formation. Oseteocalcin synthesis is stimulated by Parathyriod Hormone and 1,25-dihydroxy vitamin D3. Serum osteocalcin levels are decreased in hypoparathyroidism, in clinical situations leading to low turnover osteoporosis, and in patients receiving glucocorticoids(36, 37). Circulating levels of serum osteocalcin have been shown to be reduced in patients with AS, suggesting reduced bone formation(14). In one study there was a negative correlation between osteocalcin levels and femoral neck BMD(8). However some authors have reported unaltered serum osteocalcin levels in AS.

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 binding protein IGFBP3, can increase the anabolic action of IGF-1 in bone, and together their levels reflect osteoblast function(38).

IGF-1 levels are decreased in postmenopausal women and idiopathic male osteoporosis and are directly related to axial bone density in postmenopausal women. Enhanced bone formation occurs post treatment with IGF-1 in idiopathic male osteoporosis(39).

IGFBP3 levels have been found to be reduced in AS, and a positive correlation between the concentration of osteocalcin and IGF-1 has also been reported. The levels of IGFBP3 vary inversely with ESR, suggesting that inflammation may impair production of IGFBP3 in response to GH. The reduced levels may then diminish the activity of IGF-1 in AS(40).

Markers of Bone Resorption

Positive correlations between the concentrations of urinary markers of bone resorption pyridinoline (Pyr), deoxypyridinoline (D-Pyr) and C-telopeptide with morning stiffness, radiological hip score and inflammatory markers like ESR and CRP have been found(14). The latter was most marked among the patients with most active inflammation. Schober index and fat mass percentage have been shown to correlate negatively with these resorption markers(12).

Osteoprotegerin

Osteoprotegerin(OPG) is produced in a variety of tissues, cell types and cell lines. OPG binds and neutralizes RANKL, and thus prevents RANKL activation of RANK. In vivo over-expression of OPG in transgenic mice or administration of OPG to normal rodents inhibited osteoclastogenesis, osteoclast activation and bone resorption, resulting in osteoporosis. Since activated T cells produce RANKL, the RANKL/RANK/OPG system may play an important role in pathogenesis of osteoporosis in inflammatory arthritides.

In a study on 264 AS patients it was shown that OPG levels were significantly lower in patients with AS than in controls. The patients were also found to have lower BMD as compared to the controls(9). A more recent study also showed that the levels of RANKL were higher in patients with AS. The RANKL/OPG ratio was higher in patients who had a lower BMD (15). Thus a decrease in OPG production or an increase in RANKL may be responsible for increased osteoclast activity and subsequent osteoporosis in AS.

Fracture Rates in patients with AS

Vertebral fractures

Vertebral fracture rates in AS from several studies have ranged from 0% to 20% (22, 25, 41, 42). In 1971, Hansen et al, reported findings from routine radiological studies in 50 patients with AS, 10 females and 40 males, aged 24–79 years (41). Disease duration ranged from 3 months to 50 years. Additional risk factors for osteoporosis such as long-term glucocorticoid therapy were present only in a few older patients. Two (4%) patients had vertebral fractures in this series. A study reported by Raltson et al. in 1990 evaluated the vertebral fracture rate in 111 AS patients (98 males and 13 females) with a mean age of 41 years and a mean disease duration of 17 years(41). Vertebral fractures and vertebral biconcave deformities were detected using a standardized vertebral height index determined on lateral radiographs of the spine. Abnormalities were found in 20 (18%) patients (vertebral fractures in 15 and biconcave deformities in five). Similarly, Donnelly et al. found vertebral fractures in nine of 87 (10.3%) patients with spondyloarthropathy (AS, $n = 2$; psoriatic arthritis, $n = 7$; Reiter's syndrome, $n = 1$; enteropathic arthropathy, $n = 7$)(43). The population was composed of 62 males and 25 females with a mean age of 44 years and a mean disease duration of 16 years. The thoracic segment was the main site of vertebral fractures. In a more recent study by Mitra et al, out of 56 patients with mild AS 19.6% had a vertebral fracture as compared to only 2% in controls(14). In this study vertebral fractures did not correlate with biochemical markers of bone metabolism. A recent study also showed that femoral inter-trochanteric BMD correlated with vertebral fractures(44).

Peripheral fractures

Patients with AS had similar peripheral fracture rates as did the population at large in a study by Cooper et al (45).

Treatment of Osteoporosis in AS

Despite the large body of research on osteoporosis in patients with AS, few studies have investigated treatment options. Management of osteoporosis can be divided into preventive and therapeutic approaches. The different treatment options are listed below

1. Bisphosphonates

There is currently no data specifically addressing the issue of treatment of osteoporosis in AS. The bisphosponates are compounds that inhibit bone resorption in a dose dependent manner in patients with involutional osteoporosis. Intermittent cyclical etidronate therapy increases BMD by 6% over a period of 2 years, with a resultant decrease in the rate of new vcrtebral compression fractures. Alendronate increases BMD in both the axial and appendicular skeleton. The annual rate of increase of BMD is 3% at lumbar spine and 2% at femoral neck. The risk of developing fractures at the hip, spine and wrist is decreased by about 50%. Zoledronate is an injectible bisphosphonate, which has been shown to be as effective as alendronate in treating post-menopausal osteoporosis (46). It requires dosing only once a year and may be a convenient treatment option in patients with poor drug compliance. Monthly pamidronate infusions provided symptom relief in two studies of patients with AS. The first was an open label study and the other was a randomized control trial (47, 48). However the effects of BMD were not assessed in either of these studies. Randomized controlled trials to assess the efficacy of bisphosphonates in maintaining BMD and reducing the development of osteoporotic vertebral compression fractures and femoral neck fractures in patients with AS are required.

2. Testosterone

Both male patients with AS and 16% of men with vertebral compression fractures exhibit hypogonadism. Although testosterone treatment increases BMD in hypogonadal men, trials are required to determine the efficacy of this treatment in patients with AS.

3.TNF α inhibitors

Since it is apparent that the inflammation, which is the cause of the disease is also the main factor responsible for osteoporosis, treatment targeting control of inflammation would also help to stop bone loss(49). In the future these may become the treatment of choice given their dramatic efficacy in controlling disease symptoms.

Monitoring of Treatment

As in osteoporosis without AS, assessments of whether treatment is effective or condition is worsening are necessary. However trials have not established the appropriate investigation or interval for monitoring.

PATIENTS AND METHODS

Study Setting

The study was conducted in **Christian Medical College Hospital, Vellore,** a 1800 bedded tertiary care teaching hospital in South India. Patients for the study were drawn from the out patient clinics of the Department of Medicine II and Rheumatology of the Christian Medical College Hospital. The regular rheumatology clinics function twice a week and have an average attendance of 200 patients with rheumatological diseases each day. In addition to this patients were also drawn from the Spondyloarthritis and crystal arthritis clinic. The Department provides both out-patient and in-patient care for these patients. Patients are drawn from all parts of the country and represent a wide area stretching far beyond Tamil Nadu.

Study Design

The study was a cross-sectional study. The study design and methods were approved by the Institutional Research Committee of the Christian Medical College, Vellore.

Subjects

All patients with Ankylosing Spondylitis attending the out-patient clinic who fulfilled the inclusion criteria and consented to participate in the study were recruited.

Inclusion Criteria

1. Age > 18 years

2. Satisfying the Modified New York Criteria for Ankylosing Spondylitis

Modified New York Criteria

1. Low back pain of at least 3 months duration, improved by exercise and not relieved by rest
2. Limitation of lumbar spine in sagittal and frontal planes
3. Chest expansion decreased relative to normal values for age and sex
4. Bilateral sacroiliitis grade 2-4
5. Unilateral sacroiliitis grade 3-4

Patients require one radiological criterion and one clinical criterion for diagnosis.

Exclusion Criteria

1. Patients on bisphosphonates or on other medications which influence bone metabolism
2. Severe infections or co-morbidities
3. Patients with other diseases, which may influence bone density

Subject Enrolment and Conduct of Study

Participants were recruited in this study from the out patient clinics of the Department of Medicine II and Clinical Immunology and Rheumatology in Christian Medical College, Vellore. Patients over 18 years of age with AS who satisfied the inclusion criteria were approached for enrollment. Informed consent was obtained from these patients for inclusion in the study, following which base line parameters were assessed. This included anthropometric measurements, Finger floor distance, Schober's test, Occiput wall distance and a detailed history of previous therapy. BASDAI, BASFI, BAS-G scores were determined utilizing standard forms for the same. These indices have been

standardized and evaluated as published previously(50-52). The forms used are included in Annexure 2. These are self-administered questionnaires and were filled by the patients at time of inclusion in the study. Blood was collected for Complete blood counts, Liver function tests, ESR and CRP. Radiographs of the Sacroiliac joints were taken in all cases. In addition lumbar spine radiographs were also obtained when possible. Patients then underwent Dual Energy X-ray Absorptiometry (DEXA) to assess bone mineral density at femoral neck and/or lumbar spine. Patients remained on NSAID therapy and other second line therapy as started prior to the commencement of the study. During the study, patients were given education regarding the nature of disease, prognosis, treatment and importance of compliance with drugs and physiotherapy.

Definition of Outcomes

Osteoporosis – Defined as T score < -2.5.

Osteopenia – Defined as T score between –1 and –2.5

Normal – T score above –1.

Description of Metrological measurements

Modified Schober test - Using a pen to the midpoint between the posterior superior iliac spines (PSIS) is marked. Then two points are identified and marked: (1) one that is 10 cm superior to the PSIS level on the spine, and (2) one that is 5 cm inferior to the PSIS level on the spine. As the patient flexes the spine as far as possible without bending the knees, the distance between the original and moved superior marks is measured and recorded.

Normal values are more than 7.5 cm. The test is interpreted as positive if the movement of the mark is less than 5 cm (53).

Finger floor distance (FFD) – This was the distance measured between finger tips and floor while patient flexed his spine maximally anteriorly. This can be used as a measure of overall spine flexion and is useful in following up a patient.

Occiput Wall Distance (OWD) – With the patient standing back to a wall, with feet, buttocks and shoulders touching the wall, the distance between the occiput and wall was measured.

Chest Expansion – With the patient standing the circumference of the chest was measured after complete expiration and then following a maximal inspiration at the level of the nipples. The difference in these values was taken as the chest expansion. This is restricted due to the calcification of costovertebral, intercostals and sternocostal enthesopathic sites.

Description of Disease Indices

BASFI (Annexure II) - The BASFI(50) is a set of 10 questions designed to determine the degree of functional limitation in those with AS. The ten questions were chosen with a major input from patients with AS. The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the patients' ability to cope with everyday life.

A 10cm visual analog scale is used to answer the questions. This improves both the sensitivity of the index to change and its capacity to elicit a range of responses across the entire scale. The mean of the ten scales gives the BASFI score – a value between 0 and 10.

BASDAI (Annexure III) - Like the BASFI, the BASDAI(51) consists of 10cm visual analog scales used to answer 6 questions pertaining to the 5 major symptoms of AS:

- Fatigue
- Spinal pain
- Joint pain / swelling
- Areas of localized tenderness
- Morning stiffness.

To give each symptom equal weighting, the mean of the two scores relating to morning stiffness is taken. The resulting 0 to 50 score is divided by 5 to give a final 0 – 10 BASDAI score.

BAS-G (Annexure IV)- The BAS-G is essentially an objective way of asking the question:

"How have you been over the last *x* months?" The BAS-G consists of two questions which ask patients' to indicate, on a 10cm visual analog scale, the effect the disease has had on their well being over the

– last week

– last six months.

The mean of the two scores gives a BAS-G score of 0 –10. The higher the score, the greater the perceived effect of the disease on the patient's well being.

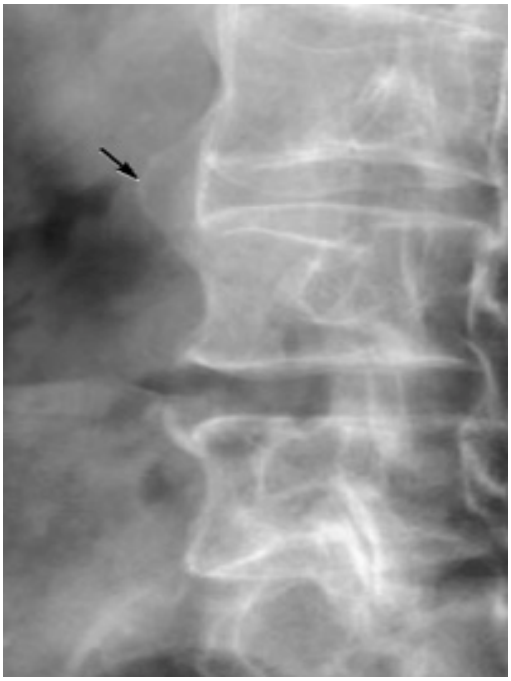


Figure 2. Radiograph showing syndesmophytes and bridging ossification.

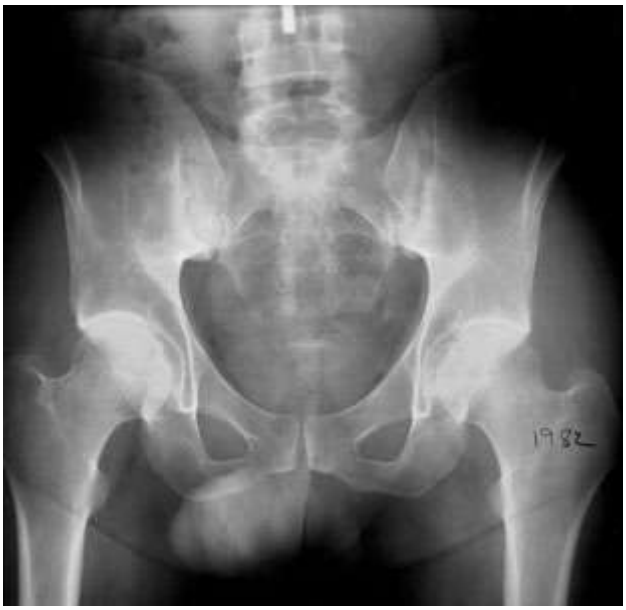


Figure 3. Radiograph showing bilateral sacroiliiits.

Grading of Sacroiliac Radiographs (54)

Grade 0 - Normal

Grade 1 – Fuzzy margins

Grade 2 – Definite irregularity of joint lining, but no narrowing of space: rather sometimes there may be widening due to inflammatory fluid collection

Grade 3 – Definite irregularity of joint lining, with narrowing of joint space, but not completely fused.

Grade 4 - Complete Ankylosis

Dual Energy X Ray Absorptiometry (DEXA)

DEXA utilizes an X ray tube to produce photons with two distinct photoelectric peaks. The basic principle is that when the beam passes through a region of the body containing both bone and soft tissue, attenuation occurs at both energy peaks. Since one of these peaks is preferentially attenuated by bone the contribution by soft tissue can be mathematically calculated and subtracted. This ability to separate bone from soft tissue, allows the quantification of bone density in areas of the skeleton surrounded by large or irregular masses of soft tissue.

Since X ray tubes produce a beam with a wide range of photon energies machines use methods to produce two distinct photoelectric peaks. Certain manufacturers use K-edge filters, while others use alternate pulses of varying voltage to the X ray tube.

DEXA is an improvement on the previous technique of Dual Photon Absorptiometry as it requires shorter time, reduced radiation exposure, is less expensive and has greater precision.

Two types of DEXA scanners are available – "pencil beam or "fan-array". Pencil beam scanners employ a narrowed X ray beam that moves in tandem in a rectilinear pattern with the detector. Fan-array scanners utilize a much broader beam and an array of detectors, leading to shortened scan times with enhanced resolution. The machine used during this study was a Hologic Delphi – W, which is a fan-arrray scanner (55).

Sample Size Calculation

The sample size for the study calculated using an expected prevalence of osteoporosis in AS of 15% with a precision of 7.5% was 100 subjects. The usual precision utilized is between 5-10% and hence for this study a mid-way value of 7.5% was chosen. The assumed prevalence of osteoporosis was based on previous studies showing a range from 4 to 31 % in AS. Most of these studies employed sample sizes ranging from 30-80.

Sample Size Formula – $n = 4\,p\,(1-p) / d^2$

Where n – sample size, p- estimated prevalence and d – precision.

Statistical Analysis

Data entry was done using the Statistical Package for the Social Sciences **(SPSS)** software package (version **15)**. Descriptive statistics were calculated using SPSS software. Prevalence of osteoporosis was calculated for the entire sample utilizing Western controls. Prevalence of osteoporosis was also ascertained in groups divided according to disease duration, severity and treatment and correlation coefficients for the various parameters in relation to osteoporosis were calculated. Logistic regression analysis was also performed to assess which variables independently affected BMD.

Figure 4 Hologic DEXA Machine

RESULTS

Demographic Characteristics

Age

The mean age of the study population was 36 (±11) years. The ages ranged from 18 to 64 with the majority of the people being between the age of 20 and 40.

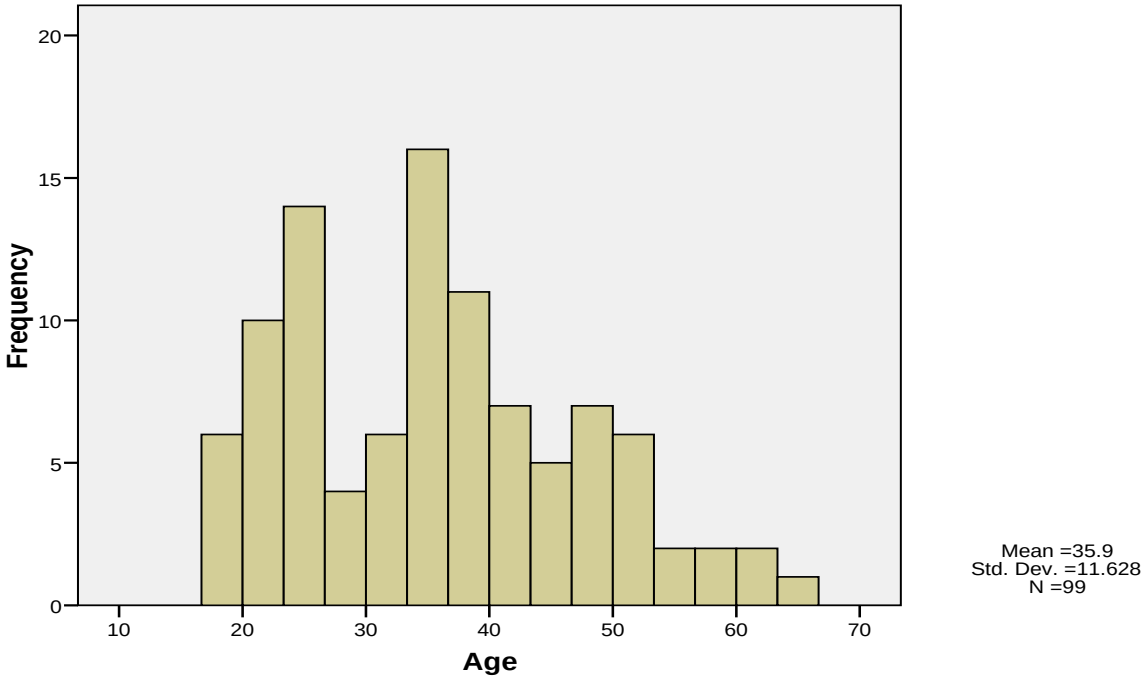


Figure 5 – Histogram showing distribution of age among study population

Sex

The majority of patients in the study population were male (90%). The male : female ratio was 10:1.

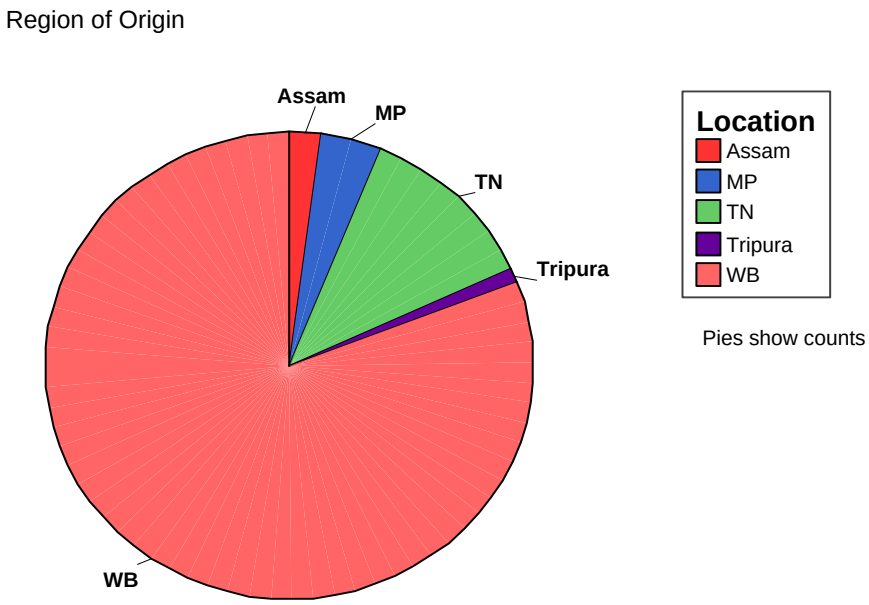
Region of origin

The distribution of patients by state of origin is shown in table 2.

Table 2. State of Origin

State	Number
Tamil Nadu	12
West Bengal	81
Assam	2
Tripura	1
Madhya Pradesh	4

Figure 6. Distribution by region of origin



BMI

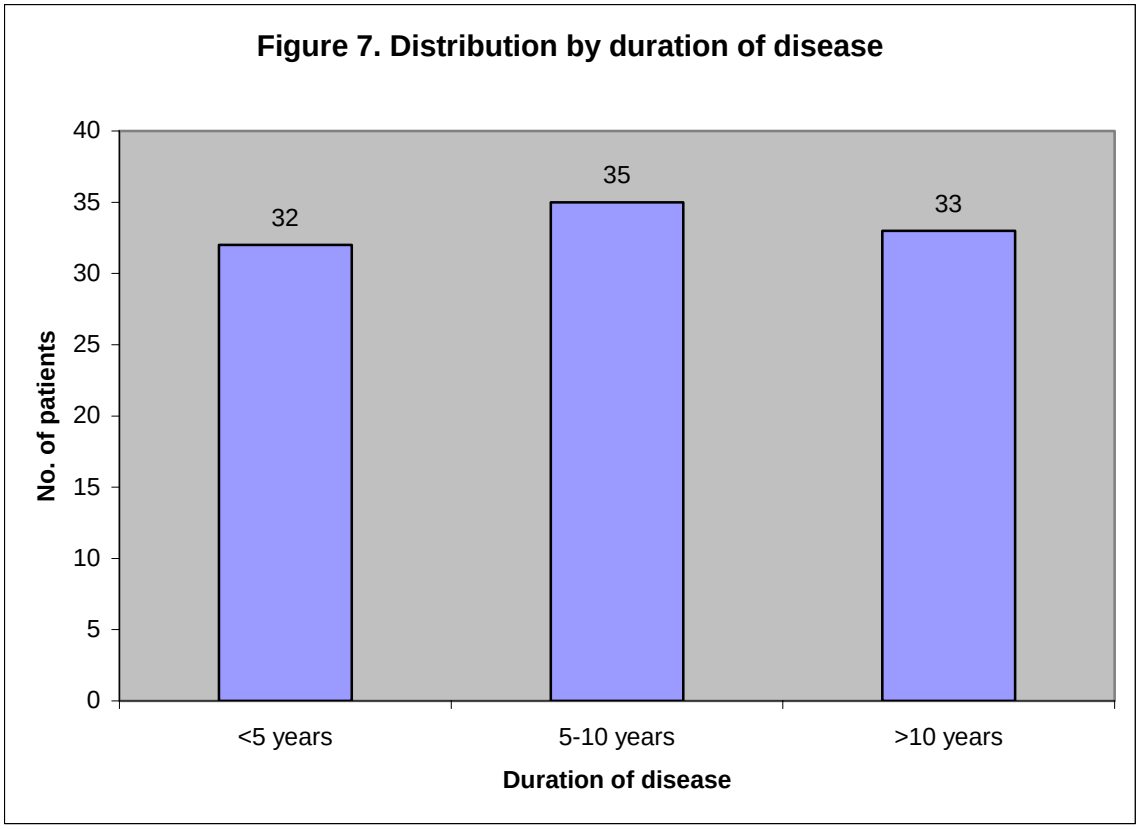
The mean BMI of the population was 21.5(±4.15) kg/m^2 and ranged from 14.6 to 32.4 kg/m^2.

Duration of Disease

The median duration of disease for the study population was 8 years. This ranged from a minimum of 1 year to a maximum of 34 years. In Table 3 we can see that there is an even distribution of the patients among the three groups – those with disease duration less than 5 years, duration 5 to 10 years and more than 10 years.

Table 3 – Distribution of study population by duration of disease

Duration of Disease	Number
Less than 5 years	32
5 – 10 years	35
>10 years	33



Treatment with sulfasalazine ± methotrexate

56 % of people in the study population had received sulfasalazine ± methotrexate at initial presentation. The mean duration of treatment was 1.5 (±2.3) years. Subsequently all patients were initiated on both sulfasalazine and methotrexate.

Steroid Use prior to presentation

The prevalence of steroid usage was fairly low in the study population. Only 10 % of the population had received steroids at any point of time during their illness.

Disease Indices

BASDAI – Mean BASDAI for the population was 1.98(±1.2).The values ranged from 0 to 4.8 The mean BASDAI did not differ significantly between the three groups based on disease duration.

BASFI – Mean BASFI was 5.22(±2.4). The values ranged between 0 and 9,75. The mean BASFI did not differ significantly between the three groups based on disease duration.

BAS – G – Mean BAS G was 1.2(±0.55), with a range from 0 to 2.

Laboratory Studies

ESR - Mean ESR was 46 (±32) with a range of 2-135.

ESR showed no correlation with disease activity as assessed with BASDAI.

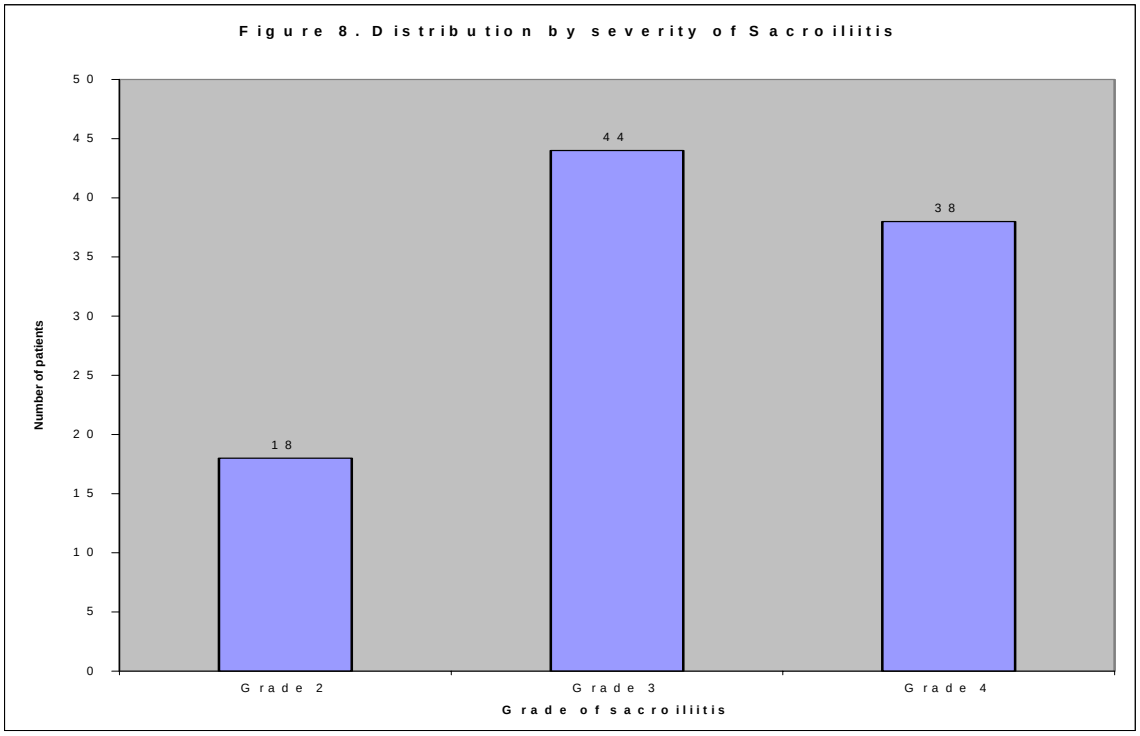
CRP – Mean CRP was 32.8 (**±**38) and a range of 0-164

CRP showed a positive correlation with the BASDAI. (r=0.258,p=0.04)

Radiological Studies

SI joint X ray

All patients had clear evidence of radiological SI joint involvement. Mean grade of sacroiliitis was 3.22 ± 0.728.



Spine X ray

Spinal radiographs were available for 65 of the patients. 10 patients (15%) had evidence of vertebral compression fractures. Syndesmophytes were seen in 30 patients (46%).

Metrological Data

The following is a summary of the metrological data for the cohort.

Table 4 – Summary of metrological data for study population

Parameter	Mean ± Std deviation	Range
Finger floor distance	**22.8 ± 16.9 cm**	**0 – 65 cm**
Schober's	**2.64 ± 1 cm**	**0 – 5 cm**
Occiput wall distance	**2.9 ± 4.6 cm**	**0 – 24 cm**
Chest expansion	**2.65 ± 0.8 cm**	**1 – 5 cm**

BMD

One hundred subjects underwent BMD measurement using DEXA. Utilizing WHO criteria for osteoporosis, overall **37%** were found to have osteoporosis either at the spine or the hip.

BMD at lumbar spine

Ninety two subjects underwent BMD measurement of spine using DEXA.

Mean BMD at lumbar spine for the population was 0.903 (±0.17) gm/ sq cm.

The mean T score was –1.72 (±1.52).

Utilizing Caucasian controls as provided by the manufacturer.

Osteoporosis was seen in 35 subjects out of 92 (38%).

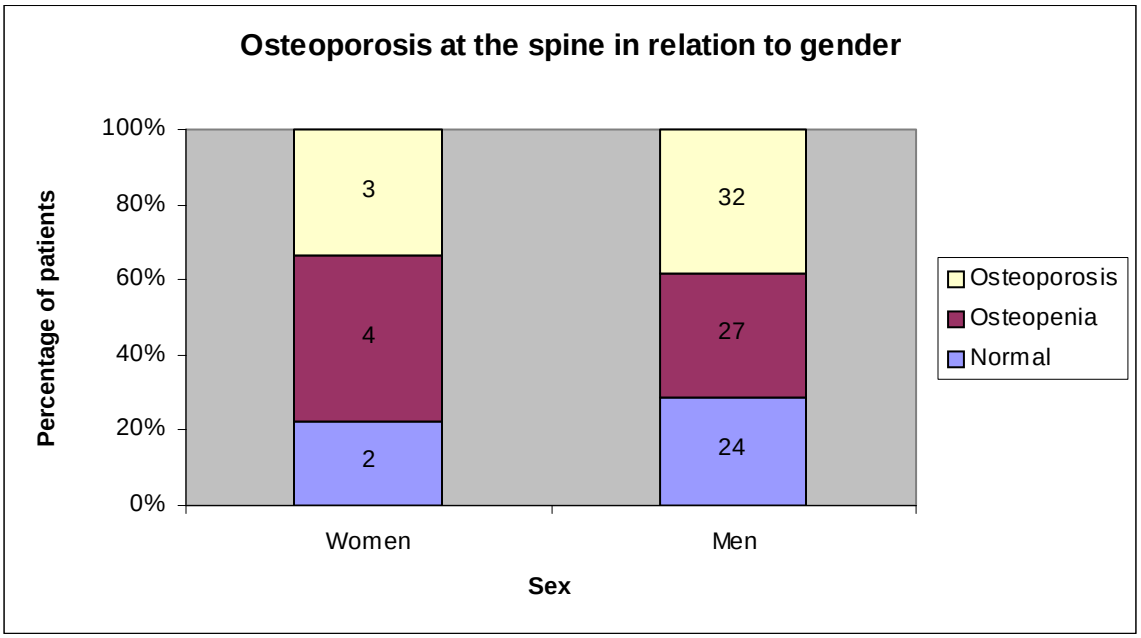
Osteopenia was seen in 31 subjects out of 92 (33%).

Difference in osteoporosis between men and women

Women - At the spine, 4 women out of 9 (44%) had osteopenia and 3 women out of 9 (33%) had osteoporosis utilizing Caucasian controls

Men – At the spine, 28 men out of 83 (33%) had osteopenia, while 32 men out of 83 (38%) had osteoporosis utilizing Western controls. Osteoporosis in men and women with AS was not significantly different.

Figure 9.



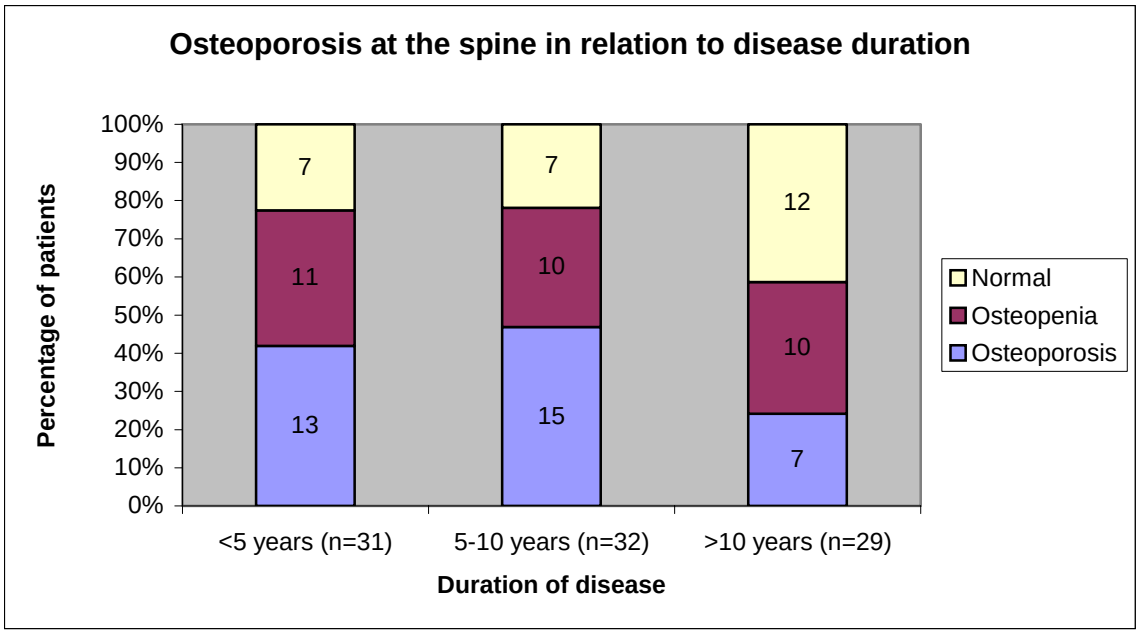
Correlation with disease duration

There was a positive correlation of disease duration with BMD at the spine. The Pearson's correlation coefficient (r) was 0.251 with a 2 tailed **p value of 0.016** which is significant.

Table 5 – Osteoporosis at the spine in relation to disease duration

Duration	Osteopenia (n=31)	Osteoporosis(n=35)
Less than 5 years (n=31)	11(36%)	13(42%)
5 to 10 years (n=32)	10(31%)	15(46%)
> than 10 years (n=29)	10(34%)	7(24%)

Figure 10.



As can be seen from table 5, there is a lower percentage of patients with osteoporosis and osteopenia in the patients with disease duration above 10 years as compared with the other two groups.

Correlation with BMI

There was a moderate positive correlation of BMD with BMI with r=0.405 and **p<0.001.**

Correlation with disease activity (BASDAI)

There was a weak negative correlation of BMD at the spine with disease activity as measured by the BASDAI. r was –0.209 and the two tailed **p value was 0.047**.

Correlation with Functional status (BASFI)

There was no correlation between BMD at the spine and functional status as measured by the BASFI. However in the group of patients with disease duration less than 5 years there was a moderate negative correlation of BMD at the spine with BASFI (r= –0.374, **p=0.04**). A similar relationship was however not seen in patients with disease duration of more than 5 years.

Correlation with ESR, CRP

There was no correlation of BMD with ESR (p=0.64) . However the correlation with CRP **(p=0.05)** attained significance.

Correlation with Radiology

There was no correlation of BMD at the spine with either the grade of sacroiliitis (p=0.272) or the presence of syndesmophytes (p=0.357).

Correlation with prior treatment

There was no correlation of BMD with previous treatment with sulfasalazine/ methotrexate or steroids (p=0.85).

Table 6 . – Associations of Osteoporosis at the spine in AS (Univariate analysis)

Parameter	**Odds Ratio**	**95% CI**	**P value**
BMI > 18	**0.270**	**0.1-0.76**	**0.013**
Duration <15 years	**5.68**	**1.1-25.5**	**0.028**
CRP>20	2.01	0.88-4.77	0.110
BASDAI <3	0.472	0.16-1.3	0.14
BASFI <7	0.88	0.32-2.27	0.751
FFD >15cm	2.25	0.89-5.66	0.08
DMARD>1 yr	1.15	0.45-2.9	0.761

Utilizing a univariate analysis, we find that patients with BMI>18 had significantly lower occurrence of osteoporosis at the spine, while a duration of disease less than and upto 15 years seems to be associated with osteoporosis at the spine. None of the other variables given above are associated with osteoporosis at the spine.

On entering the values with $p<0.15$ in a multivariate regression analysis, **BMI<18 (OR 0.322,p=0.04)** and **duration upto 15 years (OR 5.34, p=0.03)**, still correlate with osteoporosis at the spine, hence suggesting that these are independent associates of osteoporosis.

BMD at Hip

Ninety six of the patients had BMD measured at the hip. Mean BMD at the hip for the population was 0.84 (±0.15) gm/sq cm. The mean T score was –1.2 (± 1.02)

Utilizing Western Controls:

Osteoporosis was seen in 8 subjects out of 96 (8.3%).

Osteopenia was seen in 55 subjects out of 96 (57%).

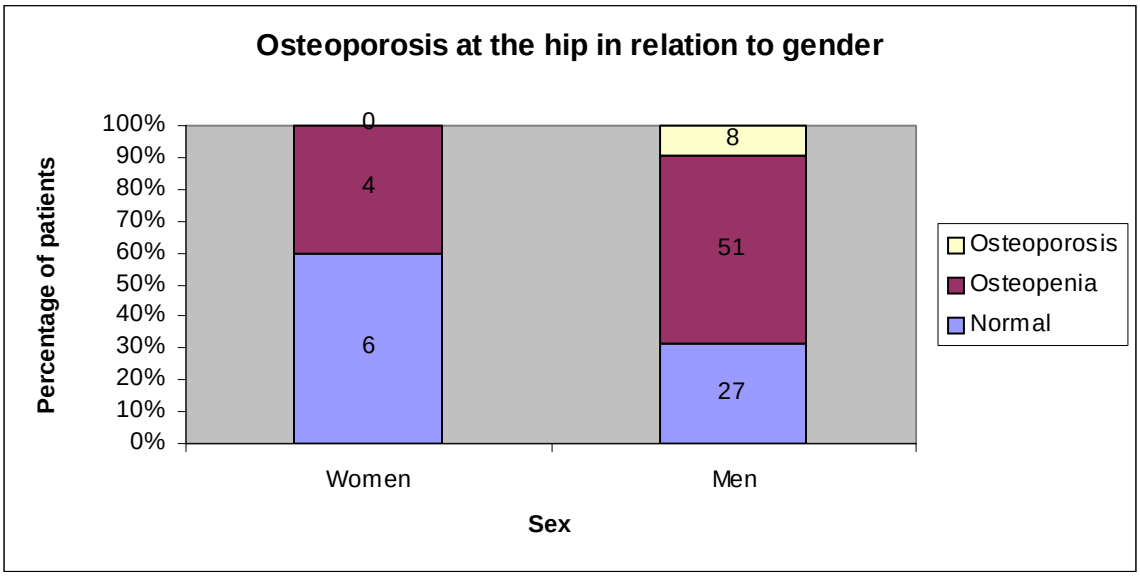
Difference in osteoporosis between men and women

There was no significant correlation between sex and osteopenia (p=0.43) or osteoporosis (p=0.374)

Table 7 – Distribution of osteoporosis and osteopenia at the hip against sex.

Sex	**Osteopenia (n=55)**	**Osteoporosis (n=8)**
Male (n=86)	51(56%)	8(8%)
Female (n=10)	4(40%)	0(0%)

Figure 11.



Correlation with disease duration

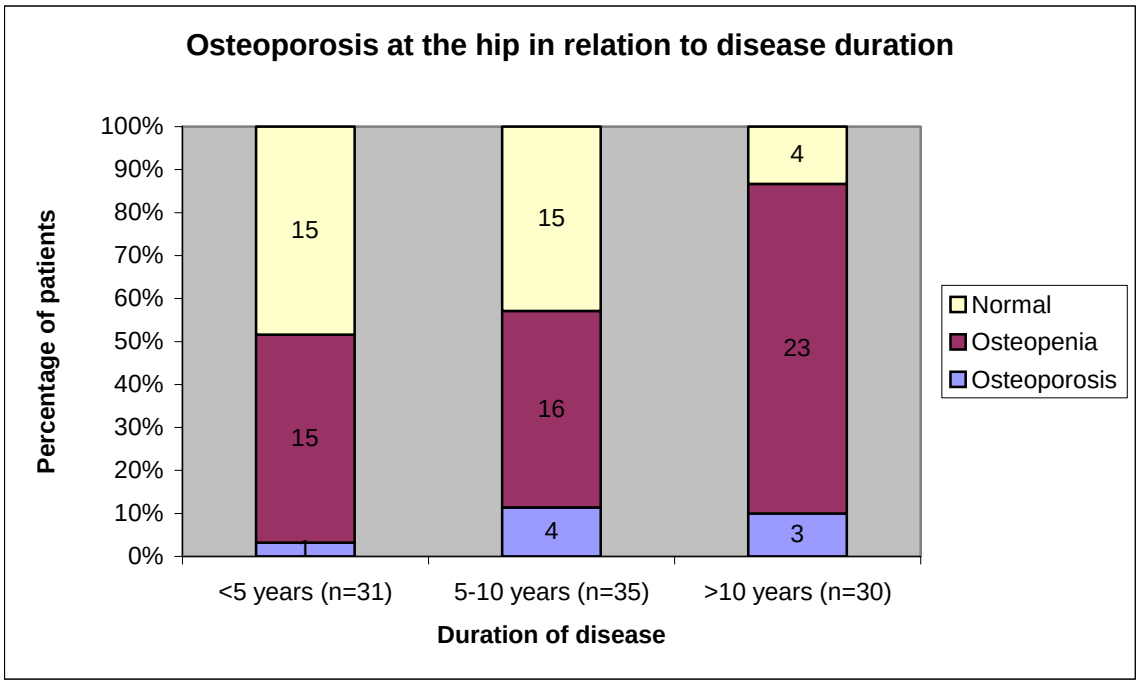
Table 8 – Osteoporosis at the hip utilizing Western controls in relation to disease duration

Duration	Osteopenia (n=54)	Osteoporosis(n=8)
Less than 5 years (n=31)	15(48%)	1(3%)
5 to 10 years (n=35)	16(45.7%)	4(11.4%)
> than 10 years (n=30)	23(75%)	3(10%)

The number of patients with osteoporosis and osteopenia was greatest in the group with duration of disease more than 10 years.

There was a negative correlation of BMD at hip with disease duration. r was –0.209 and this was significant. **(p value – 0.046).**

Figure12.



Correlation with BMI

There is a positive correlation between BMI and BMD at hip, r=0.322**, p=0.001**.

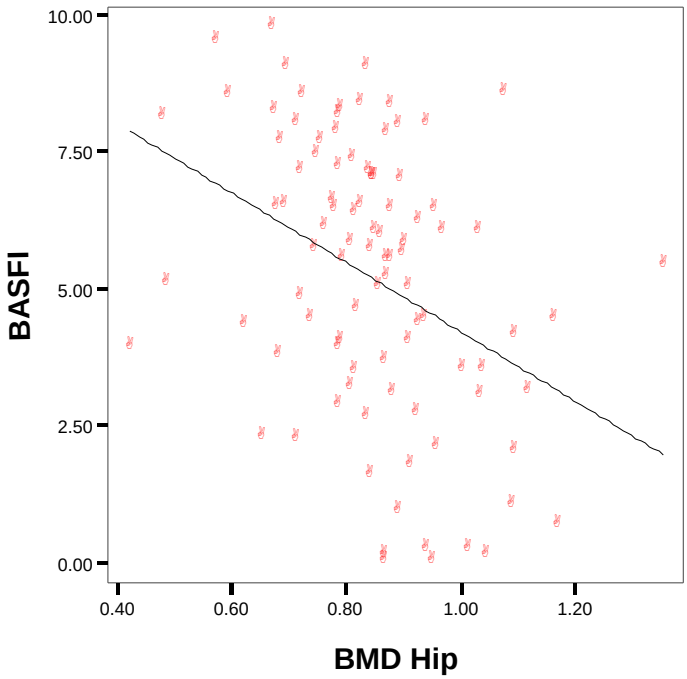
Correlation with disease activity (BASDAI)

There was no correlation between disease activity as assessed by the index BASDAI and BMD at the hip. (p-0.103)

Correlation with Functional status (BASFI)

There was a moderate negative correlation between the score on the BASFI and the BMD at the hip. The Pearson's correlation coefficient was –0.380 with a **p value < 0.001**.

Figure 13. – Scatter plot of BASFI against BMD hip.



Correlation with FFD

There was a strong negative correlation between FFD and BMD at the hip, r=-0.47, **p<0.001.**

Correlation with ESR, CRP

There was no correlation between BMD at hip and ESR **(p-0.076)** and CRP(p-0.611) values for the subjects.

Correlation with Radiology

There was a positive correlation between presence of syndesmophytes and the occurrence of osteoporosis or osteopenia at the hip. 64 patients had imaging of the lumbosacral spine. Of these patients 29 were found to have syndesmophytes while the remaining did not. In the group with syndesmophytes, 86.2% of the patients had either osteoporosis or osteopenia while in the group without syndesmophytes only 51.4% had either osteoporosis or osteopenia at the hip **(p-0.005).**

Table 9 – Crosstabulation between occurrence of Osteoporosis/osteopenia at the hip and syndesmophytes

	Syndesmophytes (n=29)	No Syndesmophytes(n=35)
Osteoporosis or osteopenia present(n=43)	25(86.2%)	18(51.4%)
Osteoporosis or osteopenia absent (n=21)	4(13.8%)	17(48.6%)

Crosstabulation between osteoporosis at the hip and syndesmophytes also revealed a positive correlation, that was significant **(p- 0.012)**.

Effect of Treatment

There was no correlation between osteoporosis at the hip and previous treatment with Sulfasalazine ± methotrexate or steroids. r – 0.15 (p-0.886).

DISCUSSION

This is the first study to assess occurrence of osteoporosis in AS in India. The world over, nine other studies have addressed this issue. The present study is the second largest in this series. Our cohort had a majority of male patients, with a male : female ratio of 10:1. This was fairly high compared to other sources in literature, quoting ratios ranging from 4-10:1(1, 4). The reason for this discrepancy is unclear but may be related to gender differences in health seeking behavior. The mean age of the cohort was 36 years, with a majority of subjects being in the age group of 20-40 years. The majority (90%) of the patients hailed from North India. This cannot be fully explained by the pattern of attendance in our out-patient clinics. Earlier studies have shown that HLA B27 prevalence is higher among North Indians as compared to South Indians(56). In one study the prevalence in North India was found to be 6% while in South Indians it was less than 5%(56, 57). In another study the prevalence among North Indian subjects was 4.6% as against 1.1% in South Indian subjects (58). This discrepancy may help to explain the predominance of North Indian patients in our cohort.

The prevalence of osteoporosis at the spine, calculated utilizing Western controls was 38%, while the prevalence of osteopenia was 33%. This is similar to most other series in literature. The most striking fact was that osteoporosis tended to occur early in the disease. At the spine, 42% of patients with disease duration less than 5 years had osteoporosis. It was also noted that the occurrence of osteoporosis at the spine declined with increasing disease duration. This concurs with observations in other studies that showed a positive correlation of BMD at the spine with disease duration(10). The

probable cause for this has been postulated to be an artefactual increase due to paraspinal ossification late in the disease.

The prevalence of osteoporosis at the hip, utilizing Western controls was 8.3%, while the prevalence of osteopenia was 57%. Thus, it appears that bone loss is more marked at the spine than at the hip in patients with AS. This conflicts with a recent study by Karberg et al (10) where it was found that osteopenia and osteoporosis were higher at the hip than at the spine especially in patients with a disease duration of more than 10 years. The reason for this discrepancy is not apparent, but may suggest racial differences in patterns of bone loss. These findings, however, are consistent with a study by Devoglear et al(20) where the largest reduction in spinal BMD as measured by Dual Photon Absorptiometry was seen in men with early AS. In patients with more advanced disease, however, BMD was found to be no different from that of controls in other studies. However QCT showed low bone mass in some of these patients(21). Similar results were reported by Maghraoui et al(5). In our study BMD at the hip correlated negatively with disease duration, which is in keeping with earlier studies (5,10,20).

These observations suggest that the investigation of choice to detect osteoporosis in patients with AS would depend on disease duration. In early disease (<10 years duration) a BMD of the spine would be ideal, while in later stages both a BMD spine and hip would be required. In later stages of the disease a QCT of the spine may also be useful, although it is not yet a standard means of assessment for osteoporosis.

One drawback of the study was that T scores were calculated against Western controls. There is conflicting data as to whether BMD in Indian subjects is the same as

their Western counterparts. It may have been more informative if T scores could have been calculated using normative Indian data.

The prevalence of osteopenia was 33% at the spine and 57% at the hip. Out of these, 17% at the spine and 12% at the hip had T score below –2.0. Studies are conflicting as to whether patients with osteopenia require pharmacological therapy (59-61). Guidelines by various organizations are also unclear on the same (59-61). While the National Osteoporosis Foundation(59) and the American Association of Clinical Endocrinologists(60) suggest the consideration of pharmacologic therapy for women with T scores that are less than –1.5 with additional risk factors, the North American Menopause Society(61) recommends that this intervention be deferred until the T score is lower (–2.0 to –2.5) even with additional risk factors. Thus, it may be prudent to consider pharmacological therapy in the patients with T score less than –2.0. Utilizing this cutoff, more than 50% of patients with AS would require pharmacological therapy to improve BMD, in addition to lifestyle changes.

BMI was found to correlate positively with BMD at the hip and the spine. Using regression analysis, it was found that BMI >18 kg/m^2 was protective for the development of osteoporosis at the spine (OR-0.322, **p-0.04**). Similar findings have been reported in an earlier study by Maghraoui et al (5). The relationship between BMI and osteoporosis has been well established in postmenopausal osteoporosis(62). A similar positive correlation of BMD and BMI seems to exist in patients with AS.

BMD also correlates with metrological measurements. There is a negative correlation between Finger Floor Distance and BMD at hip. It has been shown in an earlier study that vertebral fractures are associated with restriction of spinal movement

(41). Thus, worse metrological measurements may serve as markers for osteoporosis at the hip, prompting screening in those with poor spinal mobility.

There was a weak correlation of BASDAI and CRP with osteoporosis at the spine. However on regression analysis neither of these were independently associated with osteoporosis at the spine. At the hip there seems to be no significant correlation of disease activity as measured by BASDAI or ESR and CRP with osteoporosis. Similar results were found by Camargo et al (25) in a study done on 30 patients. Maghraoui et al (5) in their study on 80 patients concluded that osteoporosis was more in patients with more severe and active disease. However, this was based on a correlation between bone resorption markers and ESR and CRP. They did not find a correlation between BMD and either clinical activity or ESR and CRP. Thus, disease activity does not appear to correlate with osteoporosis at the hip. At the spine, however, more active disease may be a predictor for osteoporosis. Based on this data we recommend that all patients irrespective of activity of disease should be screened for osteoporosis.

There was a correlation between functional status as measured by BASFI with osteoporosis at the hip. This may be related to chronicity of disease, as well as the fact that immobilization due to worse functional status may lead to worsening of osteoporosis. In turn, the worsening osteoporosis may also lead to worsening of symptoms and thus worsen functional status. There are, however, no reports of such a relationship in previous studies. The BASFI may thus serve as a simple tool to identify patients who may be at increased risk for osteoporosis at the hip. We advocate the routine use of this tool in all patients with AS.

A striking correlation was found between syndesmophytes on the spinal radiograph and osteoporosis or osteopenia at the hip (86% vs 51%). This concurs with the study done by Karberg et al (10), where 55 patients were studied and it was found that among patients with syndesmophytes, occurrence of osteoporosis at the hip was 31% as compared to 14% among those without syndesmophytes. Therefore in patients with syndesmophytes on the spinal radiograph, a BMD of the hip would be strongly advocated.

It was found in this study, that treatment with sulfosalazine ± methotrexate did not affect occurrence of osteoporosis. However only half of our patients had been on these drugs and this may hence be inadequate to comment. This probably reflects the fact that unlike rheumatoid arthritis, most DMARDS have not been shown to have much benefit in patients with AS(1). Given the probable mechanism of osteoporosis being mediated by the same inflammatory mediators causing the disease manifestations, medications that target these pathways would be expected to halt bone loss(49). Since our cohort did not comprise any patients who had been on long-term biological therapy, the effect of these medications on osteoporosis could not be assessed.

In conclusion, this study demonstrates that osteoporosis and osteopenia are common in Indian patients with AS. Recognizing and treating these complications will help in improving morbidity associated with the disease. Since they occur early in the disease, all patients should undergo screening at presentation. DEXA is still the investigation of choice due to easy availability, low cost and standardization. It would be advisable to obtain DEXA of spine in early disease and both spine and hip later in the disease.

CONCLUSIONS

- Osteoporosis at the spine was found in 38%, while at the hip, it was found in 8.3% of Indian patients with Ankylosing Spondylitis. Osteopenia at the spine was found in 33%, while at the hip, the corresponding figure was 57%. This data suggests that osteoporosis is a common complication of AS and almost two thirds of AS patients have abnormal BMD.
- Bone loss occurs early at the spine and can be seen within the first 5 years of disease onset (42%). Thus, in early cases, BMD at the spine is required to pick up osteoporosis, but later in the disease, BMD hip will help to detect patients who have an artefactual increase in spinal BMD due to paraspinal ossification.
- BMD at the spine ($r=0.4, p<0.001$) and hip ($r=0.32, p=0.001$) correlates positively with BMI. Thus AS patients with higher BMI are at less risk to develop osteoporosis.
- BMD at the hip correlates inversely with functional status as measured by BASFI ($r=-0.38, p<0.001$) and also with FFD ($r=-0.47, p<0.01$).
- Paradoxically, syndesmophytes are strongly associated with osteoporosis or osteopenia at the hip ($p=0.012$). Thus utilization of simple tools such as the BASFI as well as metrological measurements such as FFD may help identify AS patients requiring BMD measurement.
- Based on this study, we recommend that all AS patients at diagnosis should have spinal BMD measurements, and in patients with disease duration more than 5 years or having syndesmophytes, this should be coupled with BMD measurement at the hip.

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ABSTRACT

Title: Occurrence and Clinical Predictors of Osteoporosis in patients with Ankylosing Spondylitis in a tertiary care center in South India

Department: Department of Medicine Unit 2 and Rheumatology,
Christian Medical College Hospital, Vellore - 632004.

Name of the candidate: Dr. Pavan Bhargava,
Postgraduate Student,
General Medicine.

Degree: MD (General Medicine)

Name of the Guide: Dr. Debashish Danda,
Professor of Rheumatology,
Department of Medicine unit 2 and Rheumatology,
Christian Medical College Hospital, Vellore.

Objectives of the study:

To determine the occurrence of osteoporosis among a cohort of patients with Ankylosing Spondylitis(AS) and to assess whether disease indices, demographic factors, disease duration, prior treatment or parameters of inflammation have an association with osteoporosis in AS.

Methods:

One hundred patients with AS were enrolled in the study. Anthropometric measurements, metrological measurements and a detailed history were obtained. BASDAI, BASFI, BAS-G scores were determined. Blood was collected for Complete blood counts, Liver function tests, ESR and CRP. Sacroiliac radiographs were taken. In addition lumbar spine radiographs were obtained when possible. Patients underwent Dual Energy X-ray Absorptiometry (DEXA) to assess bone mineral density at femoral neck and/or lumbar spine. The prevalence of osteoporosis was then calculated and statistical analysis was done to assess the correlates of osteoporosis.

Results:

One hundred subjects were enrolled during the 24 months from March 1, 2005 to April 1, 2007. The mean age was 36 years with a male:female ratio of 10:1. The median duration of disease was 8 years (1-34 years). At the spine 38% of subjects had osteoporosis while an additional 33% had osteopenia. However, at the hip osteoporosis was found in 8% of subjects with osteopenia in 57%. There was a significant positive correlation of BMD at the spine with disease duration($r=0.252, p=0.016$) while BMD at the hip showed a negative correlation ($r=-0.209, p=0.046$). Multivariate analysis revealed that osteoporosis at the spine was significantly less in patients with BMI>18 (OR-0.32, $p=0.04$) while it was positively associated with a disease duration upto 15 years (OR-5.34, p-0.03). At the hip BMD showed a negative correlation with BASFI ($r=-0.38$, $p<0.001$) as well as FFD ($r=-0.47$, $p<0.001$). Osteoporosis at the hip was significantly more in patients with syndesmophytes ($p=0.012$). There was no correlation between

osteoporosis at the spine or hip with disease activity, laboratory parameters of inflammation or previous treatment.

Conclusion

Osteoporosis of spine (38%), rather than that of hip (8%) is prevalent in Indian patients with AS. Osteoporosis at the spine occurs early in the disease. At the spine, a BMI>18 is protective, while a shorter duration of disease (<15 years) is predictive of osteoporosis. At the hip, worse functional status and metrological measurements along with the presence of syndesmophytes are predictive of osteoporosis.

APPENDIX I

DATA COLLECTION FORM

1. NAME :
2. AGE :
3. SEX:
4. ADDRESS:
5. HOSPITAL NUMBER :
6. DURATION OF ILLNESS :
7. HISTORY OF TREATMENT :
8. BASDAI :
9. BASFI :
10. BAS-G:
11. SIGNIFICANT MEDICAL HISTORY :

NSAID USE -	Dose	Duration	Toxicity
Indomethacin			
Naproxen			
Celecoxib			
Diclofenac			
Aceclofenac			
Others			
Biologicals			
Sulfosalazine			
Methotrexate			
Calcium			
Vitamin D			
Proton pump inhibitors			
Steroids			
ORAL			
PULSE			

PHYSICAL EXAMINATION

HEIGHT :

WEIGHT:

BMI:

SWOLLEN JOINTS :

ENTHESOPATHY:
(SITES)

FINGER TO FLOOR DISTANCE:

CHEST EXPANSION

SCHOBERS MEASUREMENT:

OCCIPUT TO WALL DISTANCE:

Psoriasis - Y N

Inflammatory bowel disease – Y N

Extraarticular manifestations –
UVEITIS
PULMONARY FIBROSIS
CARDIAC
RENAL
CNS
VERTEBRAL FRACTURES
DACTYLITIS

LAB STUDIES :

ESR:

CRP :

HB: TC :

Plt : Creat:

AC:
PC:

LFT :

DEXA :

XRAY SI JOINT : Grade I II III IV Nil

Spine X Ray – Syndesmophytes
Loss of lumbar lordosis
Squaring of vertebrae
Decreased vertebral height

Signature of Researcher:
Date:

APPENDIX II

The Bath Ankylosing Spondylitis Functional Index (BASFI)

Please draw a mark on each line below to indicate your level of ability with each of the following activities during the *past month*

HOW DO YOU FIND: **score out of 10**

1 **Putting on your socks or tights without help or aids (eg sock aid)?**

EASY ——— IMPOSSIBLE

2 **Bending forward from the waist to pick up a pen from the floor without an aid?**

EASY ——— IMPOSSIBLE

3 **Reaching up to a high shelf without help or aids (eg Helping Hand)?**

EASY ——— IMPOSSIBLE

4 **Getting out of an arm-less dining chair without using your hands or any help?**

EASY ——— IMPOSSIBLE

5 **Getting up off the floor - without help - from lying on your back?**

EASY ——— IMPOSSIBLE

6 **Standing unsupported for ten minutes without discomfort?**

EASY ——— IMPOSSIBLE

7 **Climbing 12-15 steps without using a handrail or walking aid (one foot on each step)?**

EASY ——— IMPOSSIBLE

8 **Looking over your shoulder without turning your body?**

EASY ——— IMPOSSIBLE

9 **Doing physically demanding activities (eg physio exercises, gardening, sport)?**

EASY ——— IMPOSSIBLE

10 **Doing a full day's activities at home or at work?**

EASY ——— IMPOSSIBLE

TOTAL OUT OF 100	
TOTAL / 10 (BASFI SCORE)	

APPENDIX III

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

a If you are currently taking medication for your AS, please give the name and dose that is on the bottle/packet.

b Please mark on the line below to indicate the effectiveness of the medication in relieving your symptoms.

NO EFFECT _____ VERY EFFECTIVE

Please draw a mark on each line below to indicate your level of ability with each of the following activities during the *past week*

SCORE/10

1 How would you describe the overall level of fatigue/tiredness you have experienced?

NONE _____ VERY SEVERE

2 How would you describe the overall level of AS neck, back or hip pain you have had?

NONE _____ VERY SEVERE

3 How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?

NONE _____ VERY SEVERE

4 How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?

NONE _____ VERY SEVERE

5 How would you describe the overall level of discomfort you have had from the time you wake up?

NONE _____ VERY SEVERE

6 How long does your morning stiffness last from the time you wake up?

_____

0 ½ 1 1½ 2 or more hours

MEAN OF 5 & 6

TOTAL OF 1 TO 4 ADDED TO MEAN OF 5 & 6 (TOTAL OUT OF 50)

TOTAL / 5 (BASDAI SCORE)

APPENDIX IV

The Bath Ankylosing Spondylitis Global Score (BAS-G)

TOTAL / 10

How have you been over the last week?

VERY GOOD _____ VERY BAD

How have you been over the last six months?

VERY GOOD _____ VERY BAD

TOTAL OUT OF 20

TOTAL / 2 (BAS-G SCORE)

BASFI Score Calculation

Score from all questions are calculated using a ruler and added. This figure is divided by 10 to obtain an average. This is the BASFI score. The higher the BASFI score, the more severe the patient's limitation of function due to their AS.

BASDAI Score Calculation

Score from all questions are calculated using a ruler. The mean measurement (score) of questions 5 and 6 is added to the scores from questions 1 to 4. This total is then divided by 5 to give the average. This is the BASDAI score. The higher the BASDAI score, the more severe the patients disability due to their AS.

BAS-G Score

Scores from the 2 questions are calculated using a ruler and added. This figure is divided by 2 to obtain an average, this is the BAS-G score. The higher the BAS-G score, the more severe the effect of AS on the patient's life.

Please Note:

When using visual analog scales of a set length (10cm in the case of the Bath Indices), great care must be taken in reproducing assessment paperwork as repeated photocopying, for example, may distort the length of the lines and therefore will affect the accuracy of the scoring.