Prevalence and risk factors of osteoporosis in patients with ankylosing spondylitis: a 5-year follow-up study of 504 cases

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Abstract

Objective

The objective of this study was to assess the prevalence and risk factors of osteoporosis (OP) in patients with ankylosing spondylitis (AS).

Methods

Demographic and clinical data of 504 AS patients were collected. Bone mineral density (BMD) measurements of the lumbar spine, proximal femur and forearm were performed by dual-energy x-ray absorptiometry at baseline and follow-up. 106 cases of sex- and age-matched healthy volunteers were enrolled as normal controls.

Results

In contrast to normal controls, AS patients displayed a higher prevalence of both OP (9.7% vs. 0%) and osteopenia (57.5% vs. 34.9%). The prevalence of OP was significantly higher and the BMD were significantly lower in patients with elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) than patients with normal ESR and CRP. Juvenile onset, morning stiffness lasting over 0.5 hours and elevated ESR levels were risk factors for bone loss at the lumbar spine; Male gender, older age, hip involvement and lack of regular treatment were risk factors for bone loss at the femur. 173 cases were followed up for 1 to 5 years, BMD changes per year at the lumbar spine, femur and forearm were 4.8%, 2.7%, and 2.6% respectively. There was no significant difference in annual BMD change between patients treated with or without low dose glucocorticoids (GCs). Hip involvement and persistent elevated ESR levels, but not GCs treatment, were associated with decreased BMD at both the lumbar spine and the femur during follow-up in longitudinal regression analysis.

Conclusion

High disease activity and hip involvement are risk factors of bone loss in patients with AS. Low-dose GCs treatment in AS does not increase the risk of OP.

Key words

ankylosing spondylitis, bone mineral density, osteoporosis, glucocorticoids

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Introduction

Ankylosing spondylitis (AS) is a chronic systemic inflammatory disease mainly characterised by inflammation of the axial joints. Osteoporosis (OP) is commonly seen in AS even in the early stage of the disease (1-4), and is associated with increased risk of fracture and decreased quality of life, worsens the prognosis of AS. The exact mechanism and causes of bone loss in AS are not fully identified yet. In early disease, inflammation may play a dominant role (1, 2, 4, 5). In late AS, "bamboo-like" spine and ankylosis of hip joint result in decreased mobility, which may induce disuse OP (6).

Aggressive intervention at the inflammatory stage is effective for preventing bone loss in patients with AS (7-9). TNF inhibitors are effective in decreasing disease activity in AS, but cannot be widely used in our country for the high price. Low-dose glucocorticoids (GCs) are widely accepted for the treatment of rheumatoid arthritis (10, 11). However, systemic GCs use for the treatment of AS is still controversial (12-16). To assess the prevalence and risk factors of OP and identify the effect of low-dose GCs treatment in AS and bone mineral density (BMD), we monitored 504 patients with AS in this 5-year follow-up study.

Subjects and methods

Patients

A total of 504 consecutive AS patients in the Department of Rheumatology at the First Affiliated Hospital of Shantou University Medical College from 2005 to 2010 were enrolled. The diagnosis of AS was made according to the Modified New York criteria (17). Patients with comorbidities that affected bone metabolism were excluded. A total of 106 cases of sex- and age-matched healthy volunteers were enrolled as the control group.

At baseline, 385 patients had not been treated with any anti-rheumatic drugs. The remaining 119 patients had been treated with conventional anti-rheumatic drug regularly for more than three months. During follow-up, all patients accepted treatments with non-steroidal anti-inflammatory drugs, one to two conventional disease-modifying anti-rheumatic drugs (sulfasalazine/methotrexate), as well as calcium and vitamin D supplement daily. A total of 173 cases were followed up for 1~5 years and took at least twice BMD measurements, among them, 93 cases added low-dose GCs (5–10 mg prednisone daily, or equivalent) in their treatments (GC group), the other 80 cases continued treatments without GCs (N-GC group).

This study was approved by the Ethics Committee of Shantou University Medical College. Informed consent forms were signed.

Clinical data collection

Patients' medical history, physical examination, body mass index (BMI), Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI), laboratory tests, BMD, radiographs, CT, MRI at baseline and follow-up were obtained from medical records and analysed. An elevated erythrocyte sedimentation rate (ESR) was defined as an ESR >20 mm/1h. Elevated C-reactive protein (CRP) was defined as a CRP >8 mg/L.

Bone mineral density assessment

BMD of lumbar spine (anterior-posterior at L1–L4), left proximal femur (femoral neck, trochanter, and Ward's triangle), and forearm were measured using dual energy x-ray absorptiometry (DEXA, DMS Lessos, France) at baseline and every 1 to 2 years thereafter. All of the coefficients of variation of short-term precision in all the three sites were less than 1.0%. BMD level was expressed as a T-Score or Z-Score. T-Score (for postmenopausal women, and men over 50) = (measured value - peak value)/standard deviations of BMD for normal adults. Z-Score (for premenopausal women, children and men under 50) = (measured value -mean value of the same age group)/standard deviations for BMD of the same age group. The World Health Organization classification system (18, 19) was applied to define normal BMD (T/Z-Score > -1 SD), osteopenia (-2.5<T/Z-Score ≤ -1 SD), and osteoporosis (T/Z-Score ≤ -2.5 SD).

Statistical analysis

Statistics Package for Social Sciences 19.0 (SPSS 19.0) was used for the statistical analysis. Student's *t*-test or one-way analysis of variance (ANOVA) was performed to compare the differences among the groups. The chi square test was used for frequency comparisons. Logistic regression analysis was used to evaluate the impact factors of BMD at baseline. Longitudinal regression analysis (mixed models) was performed to assess the influence of disease activity and severity on the course of BMD during follow-up. *p*-values <0.05 were considered statistically significant.

Results

Bone mineral density in ankylosing spondylitis and normal control groups

Among the 504 patients, 417 were male and 87 were female (male: female ratio at 4.8:1), the mean age was 29.1±10.7 years; the mean disease duration was 7.7±6.4 years. Among the 106 normal controls, 87 were male and 19 were female (male: female ratio at 4.6:1), the mean age was 29.7±11.2 years. There was no significant difference in age and percentage of male gender between AS and the normal controls. The rate of normal BMD in AS patients was 32.7%, significantly lower than that of 65.1% in the normal controls; the prevalence of osteopenia and OP in AS were 57.5% and 9.7% respectively, significantly higher than those of 34.9% and 0% in the normal controls ($p<0.01$). In the AS group, OP had the highest frequency at the proximal femur (9.2%), followed by lumbar spine (3.2%), and lowest at the forearm (1.3%).

Factors impacting bone mineral density in ankylosing spondylitis

The characteristics of the patient groups at baseline are showed in Table I. Patients with OP (n=49) were older and had longer disease duration, higher percentage of males, lower BMI, higher disease activity (higher frequency of night pain, longer duration of morning stiffness, higher levels of ESR and CRP), higher grades of sacroiliitis, and higher prevalence of hip involvement than patients without OP ($p<0.05$).

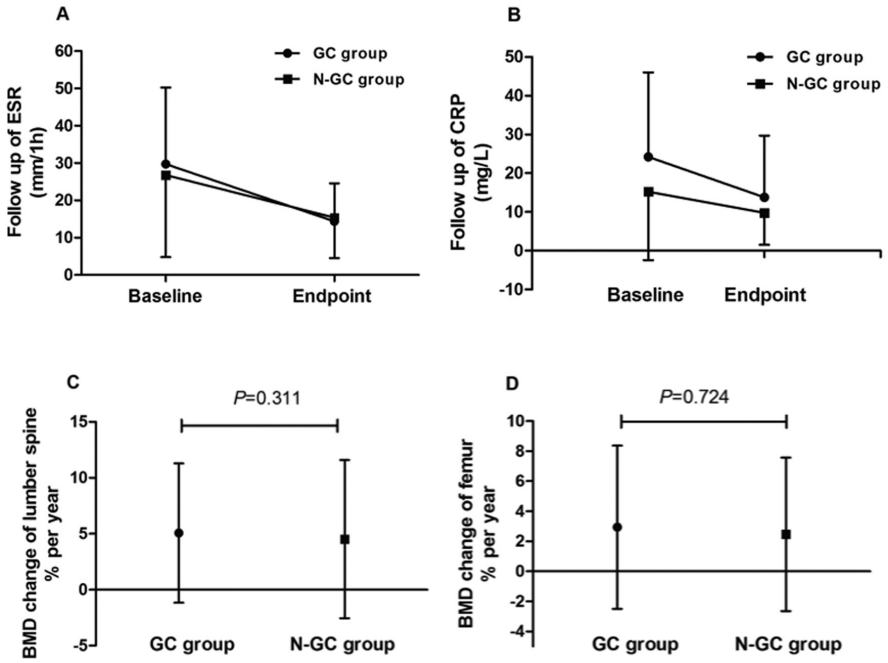

Fig. 1. Follow up of erythrocyte sedimentation rate (ESR, Fig. 1-A), C-reactive protein (CRP, Fig. 1-B) and annual bone mineral density change at the lumbar spine (Fig. 1-C) and the femur (Fig. 1-D) between glucocorticoid (GC) group and N-GC group. The mean levels of ESR and CRP were higher at baseline and decreased more obviously in GC group. There was no significant difference in annual BMD change at the lumbar spine (5.0% *vs*. 4.5%) and the femur (2.9% *vs*. 2.5%) between GC group and N-GC group.

The prevalence of OP tended to be higher in the untreated group than that in the regularly treated group (10.9% *vs*. 5.9%), although no statistical significant difference was found (Not showed in the table).

To identify the impact of inflammation on bone mass, we compared BMD and other characteristics between patients with elevated ESR or CRP (n=326) and patients with normal ESR and CRP (n=178). As showed in Table II, the mean age, disease duration and BMI, and the percentage of male gender, hip involvement and syndesmophyte formation were comparable between the two groups. Patients with elevated ESR or CRP had higher percentage of sacroiliitis (grade) ≥3 than patients with normal ESR and CRP, and lower percentage of the former under regular anti-rheumatic treatment. The prevalence of OP was significantly higher (12.3% *vs*. 5.1%), and the BMD at the spine (0.832 g/cm^2 *vs*. 0.887 g/cm^2) and femur (0.762 g/cm^2 *vs*. 0.789 g/cm^2) were significantly lower in patients with elevated ESR or CRP than patients with normal ESR and CRP.

Among the 504 patients, 109 cases accompanied with hip involvement, 127 cases had syndesmophyte formation. The prevalence of OP and osteopenia were higher, and the BMD in all sites tended to be lower in the hip involvement group than those in patients without hip involvement. The prevalence of OP and osteopenia also tended to be higher in patients with syndesmophyte formation than those with normal spine, but there was no significant difference in BMD between the two groups (Table III).

Logistic regression analysis showed that juvenile onset, morning stiffness lasting over 0.5 hours and elevated ESR levels were risk factors and higher BMI was protective factor for bone loss at the lumbar spine. Male gender, older age, hip involvement and lack of regular treatment were risk factors, and a longer course of treatment and higher BMI were protective factors for bone loss at the femur (Table IV).

Follow up results

In follow-up studies performed in 173 patients for 1~5 years (mean follow-up duration: 27.0±15.7 months), the rate of normal BMD tended to be increased, and the prevalence of OP and osteopenia tended to be decreased over time,

Table I. Characteristics of the patient groups with different BMD level at baseline.

	Normal BMD (n=165)	Osteopenia (n=290)	Osteoporosis (n=49)	*p*-value	*p'*
Age (years)	28.6 ± 11.4	28.8 ± 10.2	32.4 ± 11.1	0.052	**0.017**
Disease duration (years)	7.1 ± 6.3	7.7 ± 6.2	9.7 ± 7.1	**0.024**	
Male gender n (%)	125 (75.8)	249 (85.9)	43 (87.8)	**0.014**	
BMI (kg/m^2)	21.9 ± 3.7	20.4 ± 3.6	19.0 ± 3.0	**0.000**	
Night pain (+) n (%)	71 (43.0)	151 (52.1)	30 (61.2)	**0.046**	
Morning stiffness > 0.5 hour n (%)	25 (15.2)	68 (23.4)	17 (34.7)	**0.009**	
ESR (mm/1h)	23.2 ± 20.2	25.0 ± 20.8	33.5 ± 24.1	**0.002**	
Elevated ESR n (%)	70 (42.4)	136 (46.9)	32 (65.3)	**0.019**	
CRP (mg/L)	16.8 ± 12.3	18.0 ± 13.4	26.7 ± 22.1	**0.000**	
Elevated CRP n (%)	86 (52.1)	166 (57.2)	37 (75.5)	**0.015**	
Sacroiliitis (grade) ≥ 3 n (%)	76 (46.1)	174 (60.0)	46 (93.9)	**0.000**	
Hip involvement n (%)	29 (17.6)	64 (22.1)	16 (32.7)	0.076	**0.023**
Syndesmophyte formation n (%)	34 (20.6)	80 (27.6)	13 (26.5)	0.250	0.379
Under regular treatment n (%)	42 (25.5)	70 (24.1)	7 (14.3)	0.257	0.102

These data are expressed as mean ± standard deviation. BMD: bone mineral density; BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein. *p*: comparison of characteristics in patients with different levels of BMD. *p':* Comparison of characteristics between patients with normal BMD or osteoporosis.

Table II. Characteristics of the patient groups with different disease activity at baseline.

	Patients with elevated ESR or CRP (n=326)	Patients with normal ESR and CRP (n=178)	*p*-value
Age (years)	29.1 ± 10.6	29.0 ± 10.9	0.903
Disease duration (years)	7.6 ± 6.4	7.9 ± 6.4	0.668
Male gender n (%)	276 (84.7)	141 (79.2)	0.122
BMI (kg/m^2)	20.8 ± 3.8	20.7 ± 3.4	0.939
Sacroiliitis (grade) ≥ 3 n (%)	209 (64.1)	87 (48.9)	**0.001**
Hip involvement n (%)	75 (23.0)	34 (19.1)	0.309
Syndesmophyte formation n (%)	81 (24.8)	46 (25.8)	0.806
Under regular treatment n (%)	55 (16.9)	64 (36.0)	**0.000**
Osteopenia n (%)	189 (58.0)	101 (56.7)	0.789
OP n (%)	40 (12.3)	9 (5.1)	**0.009**
BMD of spine (g/cm^2)	0.832 ± 0.148	0.887 ± 0.162	**0.001**
BMD of femur (g/cm^2)	0.762 ± 0.137	0.789 ± 0.123	**0.041**
BMD of forearm (g/cm^2)	0.644 ± 0.065	0.646 ± 0.070	0.716

These data are expressed as mean ± standard deviation. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BMI: body mass index; OP: Osteoporosis; BMD: bone mineral density.

although no statistical significant difference was found. BMD at all the sites increased significantly during follow-up, with a mean increase per year of 4.8% at the lumbar spine, 2.7% at the femur and 2.6% at the forearm (Table V).

To identify the effect of low-dose GCs treatment in AS and BMD, we compared the baseline and follow-up data between GC group (n=93) and N-GC group (n=80). There was no significant difference in age, disease duration, and percentage of male gender, hip or spine involvement, and duration of follow-up between the two groups. The mean levels of ESR, CRP, and the percentage of elevated ESR and elevated CRP were higher in the GC group, indicating that GC group had higher disease activity than N-GC group at baseline. There was no significant difference in the prevalence of osteopenia and OP between the two groups at baseline (GC group *vs*. N-GC group: 73.1% *vs*. 60.0%, and 8.6% *vs*. 10.0%). At the endpoint, all disease activity indexes (ESR, CEP, and BASDAI) and functional index (BASFI) decreased significantly, and BMD increased significantly in both groups. BMD changes per year at all the sites were comparable between the two groups (GC group *vs*. N-GC group: 5.0% *vs*. 4.5% at the lumbar spine, 2.9% *vs*. 2.5% at the femur, and 2.0% *vs*. 3.4% at the forearm).

During follow-up, all patients in the GC group added low-dose GCs in their treatments; the mean accumulated dose was 5.7 g (1.1g–14.9g). To further identify the impact of accumulated dose of GCs on BMD, we divided the GC group into two subgroups: one group with accumulated dose of GCs less than 5 g (n=48); the other group with accumulated dose of GCs more than or equal to 5 g (n=45). At the endpoint, there was no significant difference in BMD change at both the spine (5.5% *vs*. 4.6%) and the femur (3.0% *vs*. 2.8%) between the two subgroups.

Longitudinal regression analysis (mixed models) showed that hip involvement at baseline and high level of ESR during follow-up, but not GCs treatment, were associated with decreased BMD at both the lumbar spine and the femur. High level of BASFI during follow-up was also associated with decreased BMD at the femur.

Discussion

Our study demonstrates that the prevalence of OP and osteopenia in AS are significantly higher than those in the healthy controls, indicating that bone loss is common in AS. The most frequently affected site with OP is the proximal femur (9.2%). The low prevalence of OP (3.2%) at the lumbar spine in our study might be explained by an artefactual increase of BMD resulting from the syndesmophytes formation. Previous studies in long-standing AS also showed that reduced BMD is reflected by low hip BMD; high lumbar spine BMD is related to an artefactual increase related to either the presence of syndesmophytes or the periosteal bone formation (6, 20). Therefore, proximal femur is the preferred site of BMD determinations in late AS using DEXA.

Our study demonstrates an influence of inflammation on BMD. At baseline, patients with OP had higher disease activity than patients without OP; the prevalence of OP was significantly higher and the BMD were significantly lower in patients with elevated ESR or CRP than patients with normal ESR and CRP; logistic regression analysis showed that morning stiffness lasting over 0.5 hours, elevated ESR levels, and lack of regular treatment were risk

Table III. Comparison of characteristics and BMD between patients with or without hip involvement and syndesmophyte formation.

	Hip involvement (n=109)	Non hip involvement (n=395)	*p1*	Syndesmophyte formation (n=127)	Non syndesmophyte formation (n=377)	*p2*
Age (years)	31.2 ± 11.4	28.5 ± 10.5	**0.023**	30.7 ± 11.5	28.5 ± 10.4	0.061
Disease duration (years)	8.9 ± 6.5	7.4 ± 6.3	**0.013**	9.8 ± 7.7	7.0 ± 5.7	**0.000**
Male gender n (%)	89 (81.7)	328 (83.0)	0.735	113 (89.0)	304 (80.6)	**0.031**
BMI (kg/m^2)	20.7 ± 3.7	20.8 ± 3.6	0.700	21.3 ± 3.7	20.6 ± 3.6	0.117
Osteopenia n (%)	64 (58.7)	226 (57.2)	0.779	80 (63.0)	210 (55.7)	0.410
OP n (%)	16 (14.7)	33 (8.4)	**0.048**	13 (10.2)	36 (9.5)	0.821
BMD of spine (g/cm^2)	0.866 ± 0.149	0.878 ± 0.154	0.647	0.877 ± 0.161	0.874 ± 0.150	0.828
BMD of femur (g/cm^2)	0.753 ± 0.147	0.778 ± 0.127	0.080	0.761 ± 0.769	0.775 ± 0.134	0.268
BMD of forearm (g/cm^2)	0.638 ± 0.068	0.647 ± 0.066	0.487	0.651 ± 0.063	0.642 ± 0.067	0.290

These data are expressed as mean ± standard deviation. BMD: bone mineral density; BMI: body mass index; OP: osteoporosis. *p1*: Comparison of characteristics and BMD between patients with or without hip involvement. *p2*: Comparison of characteristics and BMD between patients with or without syndesmophyte formation.

Table IV. Impact factors of bone loss at the lumbar spine and femur in 504 patients of AS at baseline.

	Spinal BMD		Femoral BMD	
	OR	*p*-value	OR	*p*-value
Male gender	1.327	0.325	2.487	**0.005**
Age	1.018	0.247	1.035	**0.049**
Disease duration	0.956	0.065	1.024	0.382
BMI	0.865	**0.000**	0.790	**0.000**
Juvenile onset	1.826	**0.028**	0.911	0.798
Night pain	1.062	0.795	1.133	0.648
Morning stiffness	1.802	**0.022**	1.447	0.246
Sacroiliitis (grade) ≥ 3	1.435	0.284	1.738	0.194
Hip involvement	0.728	0.201	1.313	**0.028**
Syndesmophyte formation	0.829	0.492	1.303	0.348
Lack of regular treatment	0.943	0.542	1.216	**0.043**
Course of treatment	0.931	0.289	0.867	**0.014**
Elevated ESR	1.735	**0.026**	1.064	0.827
Elevated CRP	0.643	0.085	1.092	0.760

AS: ankylosing spondylitis; BMD: bone mineral density; OR: odd ratio; BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table V. Baseline and follow-up BMD variables.

	Baseline	Endpoint	*p*-value
Osteopenia n (%)	116 (67.1)	103 (59.5)	0.147
OP n (%)	16 (9.2)	15 (8.7)	0.851
BMD of spine (g/cm^2)	0.830 ± 0.155	0.904 ± 0.163	**0.000**
BMD of femur (g/cm^2)	0.723 ± 0.127	0.749 ± 0.115	**0.000**
BMD of forearm (g/cm^2)	0.618 ± 0.075	0.633 ± 0.067	**0.000**
Change per year (%)			
Lumbar spine		4.8 ± 6.6	
Femur		2.7 ± 5.3	
Forearm		2.6 ± 6.1	

Variables are expressed as mean ± standard deviation. BMD: bone mineral density; OP: osteoporosis.

factors for bone loss in AS. Follow-up data also showed that persistent high levels of ESR were associated with lower BMD at both the lumbar spine and the femur at the endpoint in the mixed-model regression analysis. After 1~5 years of regular anti-rheumatic treatment, most patients acquired lower disease activity and significant increases of BMD at all the sites. These results support the view that persistent inflammation is an etiologic factor of bone loss in AS (1, 2, 4, 5, 21), and the gain of bone mass is associated with reduction of inflammation (7-9). Therefore, aggressive intervention at the progressing stage is important for preventing bone loss in patients with AS.

Our study also shows that hip involvement not only promotes bone loss at the femur, but also affects BMD improvement at the lumbar spine during follow up. The association between hip involvement and bone loss might be explained by systemic and local inflammation at the hip on one hand; on the other hand, both pain at the early stage and hip ankylosis at late AS will decreased the mobility of the patients, which may induce disuse osteoporosis (6). Previous study demonstrated that low femoral BMD is associated with vertebral fracture in patients with AS (22). Therefore, in patients with hip involvement, it is recommended to start anti-inflammation and preventive anti-OP treatment as early as possible.

Short-term low-dose GCs treatment in RA was reported to reduce the disease activity, and long-term treatment delays structural damage progression in RA (10, 11). However, systemic GCs treatment for managing AS is still controversial (12-16). Also as inflammatory disease, why RA reveals good response to systemic low-dose GCs treatment but AS not? There has not yet been a convincing answer to this question. Li *et al*. reported that in the treatment of juvenile AS, no more than 15mg prednisone daily for 1–6 months is good for controlling the disease activity, and shows minimal adverse effects on BMD (12). Another double-blind, randomised and placebo-controlled trial demonstrat-

ed that the efficacy of a short-term (2 weeks) treatment with 50 mg or 20 mg prednisolone daily was better than that with placebo (16). In this present study, 173 patients with AS were followed up for 1~5 years and demonstrated that low-dose systemic GCs treatment in patients with active disease was beneficial in retarding the disease activity. Annual BMD changes at all the sites were comparable between the GC group and N-GC group. These results indicated that in active AS, the benefits of low-dose GCs treatment on decreasing inflammatory bone loss by dampening inflammation may outweigh the risk of developing OP. Therefore low-dose GC treatment is beneficial for the treatment of AS and had few impact on BMD.

Our study has limitations. First, it was not a randomised, tight control strategy trial, and was difficult to control all the confounding factors. Second, not all patients underwent DEXA measurements at each year, and the percentage of missing data was relatively high. But as an original clinical database with consecutive patients, some data might be kind of randomly missed. A well-designed, randomised, tight control strategy trial is needed to confirm our results in the future.

In conclusion, OP is common in AS patients. Persistent inflammation is an important factor of bone loss in AS. Low-dose GC treatment is beneficial in controlling inflammation, and dose not increase the risk of OP.

References

1. GRATACÓS J, COLLADO A, PONS F *et al*.: Significant loss of bone mass in patients with early, active ankylosing spondylitis: A follow-up study. *Arthritis Rheum* 1999; 42: 2319-24.
2. HAUGEBERG G, BENNETT AN, MCGONAGLE D, EMERY P, MARZO-ORTEGA H: Bone loss in very early inflammatory back pain in undifferentiated spondyloarthropathy: a 1-year observational study. *Ann Rheum Dis* 2010; 69: 1364-6.
3. VAN DER WEIJDEN MA, VAN DENDEREN JC, LEMS WF, HEYMANS MW, DIJKMANS BA, VAN DER HORST-BRUINSMA IE: Low bone mineral density is related to male gender and decreased functional capacity in early spondylarthropathies. *Clin Rheumatol* 2011; 30: 497-503.
4. BRIOT K, DURNEZ A, PATERNOTTE S, MICELI-RICHARD C, DOUGADOS M, ROUX C: Bone oedema on MRI is highly associated with low bone mineral density in patients with early inflammatory back pain: results from the DESIR cohort. *Ann Rheum Dis* 2013; 72: 1914-19.
5. JUN BAO, YI CHEN, YI-XIAO BAO: Prevalence and risk factors of low bone mineral density in juvenile onset ankylosing spondylitis. *Calcif Tissue Int* 2014; 95: 108-11.
6. KARBERG K1, ZOCHLING J, SIEPER J, FELSENBERG D, BRAUN J: Bone loss is detected more frequently in patients with ankylosing spondylitis with syndesmophytes. *J Rheumatol* 2005; 32: 1290-8.
7. DEMIS E, ROUX C, BREBAN M, DOUGADOS M: Infliximab in spondylarthropathy--influence on bone density. *Clin Exp Rheumatol* 2002; 20 (Suppl. 28): S185-6.
8. KANG KY, LEE KY, KWOK SK *et al*.: The change of bone mineral density according to treatment agents in patients with ankylosing spondylitis. *J Bone Spine* 2011; 78: 188-93.
9. NIGIL HAROON N, SRIGANTHAN J, AL GHANIM N, INMAN RD, CHEUNG AM: Effect of TNF-alpha inhibitor treatment on bone mineral density in patients with ankylosing spondylitis: A systematic review and meta-analysis. *Semin Arthritis Rheum* 2014; 44: 155-61.
10. GRAUDAL N, JÜRGENS G: Similar effects of disease-modifying antirheumatic drugs, glucocorticoids, and biologic agents on radiographic progression in rheumatoid arthritis. *Arthritis Rheum* 2010; 10: 2852-63.
11. GORTER SL, BIJLSMA JW, CUTOLO M *et al*.: Current evidence for the management of rheumatoid arthritis with glucocorticoids: a systematic literature review information the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2010; 68: 1010-4.
12. CHEN LH: Osteoporosis in patients with juvenile ankylosing spondylitis. *Chin J Osteoporosis* 2004; 10: 213-5. (in Chinese).
13. ZOCHLING J, BRAUN J: Developments and current phamacotherapeutic recommendations for ankylosing spondylitis. *Expert Opin Pharmacother* 2006; 7: 869-83.
14. KILTZ U, VAN DER HEIJDA D, MIELANTS H, FELDTKELLER E, BRAUN J: ASAS/EULAR recommendations for the management of ankylosing spondylitis: the patients version. *Ann Rheum Dis* 2009; 68: 1381-6.
15. BRAUN J, VAN DER BERG R, BARALIAKOS X *et al*.: 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2011; 70: 896-904.
16. HAIBEL H, FENDLER C, LISTING J, CALLHOFF J, BRAUN J, SIEPER J: Efficacy of oral prednisolone in active ankylosing spondylitis: results of a double-blind, randomised, placebo-controlled short-term trial. *Ann Rheum Dis* 2014; 73: 243-6.
17. VAN DER LINDEN S, VALKENBURG HA, CATS A: Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984; 27: 361-8.
18. KANIS JA: Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. *WHO Study Group*. *Osteoporos Int* 1994; 4: 368-81.
19. KANIS JA, MELTON LJ III, CHRISTIANSEN C, JOHNSTON CC, KHALTAEV N: The diagnosis of osteoporosis. *J Bone and Mineral Rerearch* 1994; 9: 1137-41.
20. DONNELLY S, DOYLE DV, DENTON A, ROLFE I, MCCLOSKEY EV, SPECTOR TD: Bone mineral density and vertebral compression fracture rates in ankylosing spondylitis. *Ann Rheum Dis* 1994; 53: 117-21.
21. MAILLEFERT JF, AHO LS, EL MAGHRAOUI A, DOUGADOS M, ROUX C: Changes in bone density in patients with ankylosing spondylitis: a two year follow-up study. *Osteoporos Int* 2001; 12: 605-9.
22. JUN JB, JOO KB, HER MY *et al*.: Femoral bone mineral density is associated with vertebral fractures in patients with ankylosing spondylitis: a cross-sectional study. *J Rheumatol* 2006; 33: 1637-41.