EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 10
26-32
Year: 2016

ESTIMATION OF BONE MINERAL DENSITY IN PATIENTS WITH ANKYLOSING SPONDYLITIS IN SILÊMANI PROVINCE

***Dr. Raouf Rahim Mirza, DMR (London), M. Phil. (Leeds-England), FRCP (U.K.)**

Consultant Rheumatologist and A. Prof. Slemani Medical Faculty- Iraqi Kurdstan.

Corresponding Author: Dr. Raouf Rahim Mirza
Consultant Rheumatologist and A. Prof. Slemani Medical faculty- Iraqi Kurdstan.

Article Received on 25/07/2016 **Article Revised on 15/08/2016** **Article Accepted on 05/09/2016**

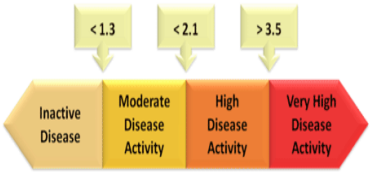
ABSTRACT

Introduction: Ankylosing spondylitis is a chronic inflammatory disease of the axial skeleton manifested by back pain and progressive stiffness of the spine. Patients with Ankylosing spondylitis display a high prevalence of osteoporosis and run a higher risk for fragility fractures. **Aims of the study:** To evaluate bone mineral density in patients with Ankylosing spondylitis and to compare it with matched healthy controls, and determination of the correlation of bone mineral density values with the demographic and clinical characteristics of Ankylosing spondylitis. **Patients and methods**: In this study, 34 patients (19 male and 15 female) with Ankylosing spondylitis from regular attendees of the general hospital/division of Rheumatology at slêmani city from January 2015 to august 2015 were recruited to the study . 34 age and sex matched subjects were included as controls. Iumber spine and femoral necks bone mineral density were measured by dual energy X-ray absorptiometry. Laboratory and clinical disease activity parameters were documented. The results were statistically analyzed. **Results**: Patients with Ankylosing spondylitis had a significantly lower bone mineral density at the right and left femoral neck as compared to age-matched controls (p=0.01, p=0.02 respectively).According to the World Health Organization classification, osteopenia was present in 14.7% of the Ankylosing spondylitis patients at the right femoral neck and in 23.5% at the left femoral neck. No significant lumber bone mineral density reduction were observed as compared to controls. Femoral necks bone mineral density was correlated significantly with disease duration. No correlations were found between low bone mineral density and disease activity parameters, body mass index, peripheral arthritis,age, sex or types of drugs used for management of Ankylosing spondylitis. **Conclusions:** Bone mineral density is significantly decreased at femoral necks of patients with Ankylosing spondylitis. There was a significant association between duration of the disease and low bone mineral density.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease of the axial skeleton which might have peripheral arthritis and extraarticular manifestations [1]. The first symptoms usually arise at an age younger than 30 years. Men are more often affected than women, and 90–95 % of the AS patients are HLA-B27 positive. Typical radiological features of AS are sacroiliitis on X-ray and bridging syndesmophytes of the spine, which usually take many years to develop, and besides that, not all AS patients develop these syndesmophytes. The diagnosis of AS must rest on the combination of clinical features, radiological findings, and laboratory results. The most widely used classification criteria for AS are the modified New York criteria[2-4].

The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a new composite index to assess disease activity in Ankylosing Spondylitis (AS)[5,6].



Bone loss is now a widely acknowledged characteristic of many inflammatory rheumatic diseases[8]. Within the range of chronic inflammatory arthritis, ankylosing spondylitis (AS) - the prototypical disease of the seronegative spondyloarthropathies - raises the dilemma of a disease characterized by new bone formation occurring in parallel with a process of bone loss (Osteoporosis), which is a metabolic disease that is associated with increased bone porosity with increases risk of bone fractures, especially in the wrist, hip, and spine[9-11]. Patients with ankylosing spondylitis display a high prevalence of osteoporosis and run a higher risk for fragility fractures particularly in uncontrolled disease activity[12-13].

Dual energy X-ray absorptiometry (DXA) is considered the best method for diagnosing osteoporosis in AS patients[14]. Dual energy x-ray absorptiometry (DXA) is the most accurate and widely used method in current practice. The radiation exposure is minimal with only 1 to 3 microsieverts (μSv)/site compared with 50 to 100 μSv for one chest radiograph. Bone mineral density (BMD) can also be measured by computed tomography (CT) (50 μSv) and ultrasound (US) (no radiation). Central densitometry (DXA) measurements (spine and hip) are the best predictors of fracture risk and have the best precision for longitudinal monitoring. Peripheral densitometry measurements (heel, radius, hands) are more widely available and less expensive but less accurate[15]. Two types of scores are used to quantify BMD: The *T* score is the number of standard deviations the patient's BMD measurement is above or below the young-normal mean BMD. The *Z* score is the number of standard deviations the measurement is above or below the age-matched mean BMD. The World Health Organization (WHO) defines osteoporosis as a *T* score ≤ −2.5[16].

A low Z-score is predictive of an underlying secondary cause other than age or menopause. The actual BMD expressed in g/cm2. This is the value that should be used to calculate changes in BMD during longitudinal follow-up. Osteoporosis should be diagnosed in any patient who sustains a fragility fracture regardless of BMD T-score. In a patient over the age of 50 years without fractures, the diagnosis can be made based on the BMD T-score at the lowest skeletal site, using the following criteria:

- T-score ≥ −1 Normal
- T-score between −1 and −2.5 Osteopenia
- T-score ≤ −2.5 Osteoporosis

In a premenopausal woman or man under the age of 50 years, the diagnosis can be made based on a BMD Z-score of ≤ −2.0 at the lowest skeletal site[17].

Aims of the study

- Evaluation of BMD in patients with AS and to compare it with matched healthy controls.
- Determination of the correlation of BMD values with the demographic and clinical characteristics of AS.

PATIENTS AND METHODS

In this comparative study, 34 patients (19 male and 15 female) with AS were enrolled, collected from regular attendees of the general hospital/division of Rheumatology at slêmani city from January 2015 to august 2015. Patients diagnosis made according to the modified New York criteria[3].

The control group consisted of 34 age- and sex-matched healthy subjects.

Exclusion criteria for patients and controls includes {Postmenopausal women, Males older than 60 years, Patients with other forms of spondyloarthropathy, Conditions that might have affected bone metabolism (renal failure, liver diseases, hyperthyroidism, cushings syndrome, hypogonadism, hyperparathyroidism), Treatments that might have affected bone metabolism (corticosteroids, anticonvulsants, heparin and thyroxine), Smokers and heavy alcoholism}.

Demographic and clinical variables were recorded, including age, sex, weight, height, body mass index (BMI = Weight/Height2, kg/m2), disease duration, and peripheral arthritis. Disease duration was defined as the time elapsed from diagnosis. We have also recorded the patients' medication history including non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs) and tumour necrosis factor-alpha (TNFα) blockers (Infliximab and Etanercep).

Laboratory activity was assessed by the Westergren's ESR and serum CRP level .

Disease activity was measured by the ASDAS, (ESR, mm/hr) and the four additional self-reported items included in this index are back pain (1-10 cm,VAS or 0-10, NRS), duration of morning stiffness (VAS/NRS), peripheral pain/swelling (VAS/NRS) and patient global assessment of disease activity (VAS/NRS).

The methodology and the results were debated by ASAS members and four disease activity states were chosen by consensus: "inactive disease", "moderate disease activity", "high disease activity" and "very high disease activity". The 3 cut-offs selected to separate these states were: <1.3 between "inactive disease" and "moderate disease activity", <2.1 between "moderate disease activity" and "high disease activity", and >3.5 between "high disease activity" and "very high disease activity"[7].

BMD was measured at the Antero-posterior (AP) lumbar spine (L1-L4) and femoral neck by means of DXA, using a Lunar –GE medical systems, Madison, WI, USA. The same densitometer was used for all BMD measurements. Results were expressed as BMD in g/cm2, and also as T-score (standard deviation from peak adult BMD). According to the WHO criteria, osteopenia was defined as T-score between -1 and -2.5 and osteoporosis as a T-score ≤ -2.5[8].

STATISTICAL ANALYSIS

The Statistical Package for Social Sciences (SPSS) version 17 was used for all statistical analysis. Descriptive statistics presented as (mean ± standard deviation) and frequencies as percentages. Kolmogorov Smirnov analysis verified the normality of the data set. Multiple contingency tables conducted and appropriate statistical tests performed, Chi-square used for categorical variables (Fishers exact test was used when more than 20% of the cells less than 5). Independent t-test was used to compare between two means. In all

statistical analysis, level of significance (p value) set at ≤ 0.05 and the result presented as tables.

RESULTS

A total of 34 AS patients with 34 healthy controls were included in present study with mean age 34±8 years for cases and 34±9 for controls. Males were more than females with male to female ratio as 1.2:1in both cases and controls. Mean BMI of AS patients was 26.6±4.9 Kg/m^2, 32.3% of them were obese and 26.5% of them were overweight. Mean BMI of controls was 27.5±4.7 Kg/m^2, 23.5% of them were obese and 32.4% of them were overweight. All these findings are shown in table 1.

Table 1: Demographic characteristics of AS patients and controls.

Variable	Cases No.(%)	Controls No.(%)
Age		
20-29 years	13(38.2)	7(20.6)
30-39 years	10(29.4)	20(58.8)
40-49 years	9(26.5)	5(14.7)
≥ 50 years	2(5.9)	2(5.9)
Total	34(100)	100.0
Gender		
Male	19(55.9)	19(55.9)
Female	15(44.1)	15(44.1)
Total	34(100.0)	34(100.0)
BMI		
Normal	14(41.2)	15(44.1)
Overweight	9(26.6)	11(32.4)
Obese	11(32.2)	8(23.5)
Total	34(100.0)	34(100.0)

Peripheral arthritis was present among 11 AS patients. NSAIDs were taken by 16 AS patients, DMARDs in combination with TNF- α blockers were taken by 7 patients and TNF- α blockers as a single therapy were taken by 11 patients. Mean ASDAS of studied patients was 1.4±0.5, 11 patients had active AS disease. All these findings are shown in table 2.

Table 2: Associated symptoms, disease duration of AS patients and Medications of AS patients.

Variable	No.	%
Peripheral arthritis		
Yes	11	32.4
No	23	67.6
Total	34	100.0
Disease duration mean±SD (7±5.3 years)		
≤ 5 years	19	55.9
> 5 years	15	44.1
Total	34	100.0
Medications		
NSAIDs	16	47
DMARDs + TNF-α blockers	7	20
TNF-α blockers	11	33
Total	34	100.0
ASDAS mean±SD (1.4±0.5)		
Active	11	32.4
Inactive	23	67.6
Total	34	100.0

No significant differences were observed between cases and controls regarding their age and gender (p>0.05). There was no significant difference between cases and controls regarding BMI (p=0.7). All these findings are shown in table 3.

Table 3: Distribution of demographic characteristics according to cases and controls.

Variable	Case		Control		χ^2	P
	No.	%	No.	%		
Age					6.7	0.09
20-29 years	13	65.0	7	35.0		
30-39 years	10	33.3	20	66.7		
40-49 years	9	64.3	5	35.7		
≥ 50 years	2	50.0	2	50.0		
Gender					0.00	1.0
Male	19	50.0	19	50.0		
Female	15	50.0	15	50.0		
BMI					0.7	0.7
Normal	14	48.3	15	51.7		
Overweight	9	45.0	11	55.0		
Obese	11	57.9	8	42.1		

There was no significant differences between cases and controls regarding lumber BMD and lumber T-score means (p>0.05). There was a significant association between each of low right femoral neck BMD and T-score means with AS cases (p≤0.05). A significant association was observed between low left femoral neck BMD and T-score means with AS cases (p≤0.05). table 4.

Table 4: Distribution of DXA scan results according to cases and controls.

Variable	Case	Control	t-test	P
	Mean±SD	Mean±SD		
Lumber BMD	1.15±0.16	1.18±0.11	0.9	0.3
Lumber T-score	0.3±1.3	0.56±0.86	0.8	0.4
RT.femoral neck BMD	0.97±0.16	1.05±0.12	2.4	**0.01**
RT.femoral neckT-score	0.03±1.2	0.5±0.9	1.9	**0.05**
LT.femoral neck BMD	0.95±0.16	1.03±0.13	2.3	**0.02**
LT.femoral neckT-score	-0.2±1.2	0.4±0.9	2.4	**0.01**

No significant differences were observed between AS patients with normal and low BMD regarding age, BMI, ESR and ASDAS (p>0.05). There was a significant association between long duration of AS and low BMD (p=0.001), table 5.

Table 5: Distribution of age, BMI, duration, ESR and ASDAS results according to BMD of AS patients.

Variable	Normal	Low	t-test	P
	Mean±SD	Mean±SD		
Age (years)	33.7±8.1	33.7±8.5	0.04	0.9
BMI ($Kg/m^{2)}$	27.1±5.03	25.2±4.5	1.1	0.2
Duration (years)	5±3.2	11±6.5	3.6	**0.001**
ESR (mm/hr)	18.2±14.4	19.2±14.4	0.1	0.8
ASDAS	1.3±0.49	1.3±0.57	0.06	0.9

No significant differences were observed between AS patients with normal and low BMD regarding clinical symptoms, medications and CRP (p>0.05), table 6.

Table 6: Distribution of clinical symptoms, medications and CRP according to BMD of AS patients.

Variable	Normal		Low		χ^2	P
	No.	%	No.	%		
Peripheral arthritis						
Yes	8	72.7	3	27.3	0.1	0.6
No	15	65.2	8	34.8		
Extra-articular manifestation						
Yes	6	85.7	1	14.3	1.3	0.2
No	17	63.0	10	37.0		
Medications						
NSAIDs	10	52.6	9	47.4	3.8	0.1
DMARDs	6	85.7	1	14.3		
TNF-α blockers	14	77.7	4	22.3		
CRP						
Positive	5	55.6	4	44.4	0.8	0.3
Negative	18	72.0	7	28.0		

DISCUSSION

AS is a chronic inflammatory disease of the axial skeleton manifested by back pain and progressive stiffness of the spine. It characteristically affects young adults with a peak age of onset between 20 and 30 years[1].

Bone loss and osteoporosis are amongst the important complications of AS [18]. Bone inflammation in AS leads to severe changes in bone turnover, which is the main cause of osteoporosis and the susceptibility to fractures[19]. The frequency of osteoporosis in AS was 18.7% to 62%[12,13,20]. Bone loss is common in patients with long duration of AS; however, the prevalence of decreased BMD in patients with short disease duration is also high[21].

In this comparative study 34 cases of AS compared with 34 healthy controls with matched age and sex for BMD of lumbar spine and femoral necks.

In our study we found a significant reduction of BMD and the corresponding T-score in the right and left femoral neck in patients with AS as compared with controls (all *p-values* < 0.05). All controls had normal values of BMD at right, left femoral neck and lumber spine.

The results showed that 14.7% of cases had osteopenia while 85.3% had normal value at right femoral neck, in the left femoral neck 23.5% of patients were osteopenic while 76.5% had normal value, these results are comparable with the results of Laura Muntean et al[22], carried out on 29 cases of AS, found a reduction of BMD in the femoral neck in patients with ankylosing spondylitis (p-value =0.015) and also close to results concluded by Franck et al[23], when examined 190 males with AS, found a significant BMD reduction in AS patients' group only in the femoral neck and total hip.

At lumber spine we observed 2.9% of cases had osteoporosis and 8.8% had osteopenia while 88.2% had normal value, the figures didn't reach statistically significant compared with controls (p-value=0.1), Franck et al[23], also demonstrated no significant BMD reduction in lumber spine. In contrast a study by Simona Rednic et al[24], who concluded a high prevalence of osteopaenia 22.7% and osteoporosis 25% at the lumbar spine. In another study by Mermerci Baskan B et al[25], who assessed 100 AS patients and 58 healthy controls with both AP and lateral lumbar DXA, the authors reported that lumbar spine BMD was significantly lower in AS patients compared with healthy controls when measured by lateral projection DXA, but not when measured by AP DXA. In our study AP lumber DXA is used only which may be the cause of the non significant results.

The results showed a statistically significant relation between disease duration and low BMD (p-value=0.001), a similar conclusion made by Donelly *et al*[26], found that patients with AS had significantly lower femoral neck BMD in proportion to disease duration, although Toussirot et al[27], who worked on a cohort of 71 patients with early disease, showed that only the femoral neck was correlated with disease duration but in the study of Hatinder et al[28], was observed that there was no significant alteration in BMD with duration of the disease.

In this study among AS patients there was no correlation between low BMD and disease activity parameters(ASDAS,ESR or CRP), Özlem Altindag et al[29], also didn't find any relation between disease activity parameters and BMD values in patients with AS.

Consistent with previous studies,[26,30,31,32] we found no relation between peripheral joint involvement and low BMD.

In this study among AS patients there was no correlation between low BMD and type of drugs used for management of AS. These results are consistent with a study done by Mehmet Ali Ulu et al[30], who found no significant difference between patients using TNF-alpha inhibitor therapy and those receiving NSAIDs alone or with SSZ with regard to BMD levels and low BMD or osteoporosis rates.

In this study, BMD values of AS patients were similar in case of both males and females. These findings are consistent with Capaci K et al[33] study who found that there is no difference with regard to BMD between male and female AS patients.

In the present study, we didn't find any correlation between low BMD and the age of the AS patients, Juanola et al[34] did not find significant variation in BMD values between pre-menopausal women with AS and controls.

In the current study among AS patients we found no correlation between the patients with low BMD and BMI., this is inconsistent with Felson et al[35], Nguyen et al[36] and Baheiraei et al[37] which reported that lower BMI was associated with lower BMD. This could be attributed to that the patients in the present study were all either normal body weight, overweight or obese and non of them underweight.

REFERENCES

1. Collantes E, Zarco P, Muñoz E, et al. Disease pattern of spondyloarthropathies in Spain: description of the first national registry (REGISPONSER) extended report. Rheumatology (Oxford) 2007; 46: 1309.
2. Braun J, Sieper J Ankylosing spondylitis. Lancet 2007; 369: 1379–1390.
3. 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: 361–368.
4. Khan MA Epidemiology of HLA-B27 and arthritis. Clin Rheumatol 1996; 15(Suppl 1): 10–12.
5. Lukas C, Landewé R, Sieper J, Dougados M, Davis J, Braun J, van der Linden S, van der Heijde D. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis 2009; 68: 18-24.
6. van der Heijde D, Lie E, Kvien TK, Sieper J, van den Bosch F, Listing J, Braun J, Landewé R. ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis 2009; 68: 1811-8.
7. Machado P, Landewé R, Lie E, Kvien TK, Braun J, Baker D, van der Heijde D. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. Ann Rheum Dis (In Press) 2010.
8. Walsh NC, Crotti TN, Goldring SR, Gravallese EM. Rheumatic diseases: the effects of inflammation on bone. Immunol Rev 2005; 208: 228-251.
9. Wendling D. Bone loss in ankylosing spondylitis: Can we put the puzzle together ?. J Rheumatol 2005; 32: 1184-1186.
10. Resnick D, Niwayama G. Osteoporosis. In: Resnick D, editor. Diagnosis of Bone and Joint Disorders. 3rd ed. Vol. 4. Philadelphia: Saunders; 1995; 1781–923.
11. Center for Disease Control and Prevention. Calcium and Bone Health. 2012. [Last updated on April 2011, Last access on July 2012]. Available from: http://www.cdc.gov/nutrition/everyone/basics/vitamins/calcium.html .
12. Bessant R, Keat A. How should clinicians manage osteoporosis in ankylosing spondylitis? J Rheumatol 2002; 29: 1511-1519.
13. Toussirot E, Wendling D. Bone mass in ankylosing spondylitis. Clin Exp Rheumatol 2000; 18(Suppl 21): S16-S20.
14. Geusens P, Vosse D, van der Linden S. Osteoporosis and vertebral fractures in ankylosing spondylitis. Curr Opin Rheumatol 2007; 19: 335-339.
15. STERLING G. Rheumatology secrets, 3rd edition; 2015; 393-394.
16. John H. Primer on the Rheumatic Diseases, Thirteenth edition; 2008; 577.
17. STERLING G. Rheumatology secrets, 3rd edition; 2015; 393.
18. Sinigaglia L, Varenna M, Girasole G, Bianchi G. Epidemiology of osteoporosis in rheumatic diseases. *Rheum Dis Clin North Am.* 2006; 32(4): 631–58.
19. Gilgil E, Kacar C, Tuncer T, Butun B. The association of syndesmophytes with vertebral bone mineral density in patients with ankylosing spondylitis. *J Rheumatol.* 2005; 32(2): 292–4.
20. Vasdev V, Bhakuni D, Garg MK, Narayanan K, Jain R, Chadha D. Bone mineral density in young males with ankylosing spondylitis. *Int J Rheum Dis.* 2011; 14(1): 68–73.
21. Singh HJ, Nimarpreet K, Das S, Kumar A, Prakash S, Ashima.. Study of bone mineral density in patients with ankylosing spondylitis. *J Clin Diagn Res.* 2013; 7(12): 2832–5.
22. Laura MUNTEAN, Siao-pin SIMON, Calin R. BOLOSIU, Simona REDNIC, Laura DAMIAN, Horatiu D. BOLOSIU. Bone mineral density in patients with ankylosing spodylitis.Medica.2006; 1(1): 7-12.
23. Franck H, Meurer T, Hofbauer LC. Evaluation of bone mineral density, hormones, biochemical markers of bone metabolism, and osteoprotegerin serum levels in ankylosing spondylitis. J Rheumatol 2004; 31: 2236-2241.
24. Simona Rednic, Ruxandra elena Schiotis, Maria-Magdalena Tamas. Relative value of the lumbar spine and hip bone mineral density and bone turnover markers in men with ankylosing spondylitis. ARTICLE in CLINICAL

RHEUMATOLOGY · MAY 2011, 10.1007/s10067-010-1648-3 ·

25. Mermerci Baskan B, Pekin Dogan Y, Sivas F, Bodur H, Ozoran K; The relation between Osteoporosis and Vitamin D level and disease activity in ankylosing spondylosis. *Rheumatol Int.* 2010; 30: 375-81.
26. Donnelly S, Doyle DV, Denton A, et al – Bone mineral density and vertebral compression fracture rates in ankylosing spondylitis. *Ann Rheum Dis* 1994; 53: 117-121.
27. Toussirot E, Michel F, Wendling D. Bone density, ultrasound measurements and body composition in early ankylosing spondylitis. J Rheumatol 2001; 40: 882-888.
28. Hatinder Jeet Singh1, Kaur Nimarpreet2, Ashima3, Sibadatta Das4, Ashok Kumar5, Shesh Prakash6; Study of Bone Mineral Density in Patients with Ankylosing Spondylitis. Journal of Clinical and Diagnostic Research. 2013 Dec, Vol-7(12): 2832-2835.
29. Özlem Altindag, Mehmet Karakoç1, Neslihan Soran, Hasan Tabur2, Ahmet Demirkol, Bone Mineral Density in Patients with Ankylosing Spondylitis. Rheumatism 2008; 23: 42-5.
30. Mehmet Ali Ulu, İbrahim Batmaz, Banu Dilek and Remzi Çevik, Prevalence of osteoporosis and vertebral fractures and related factors in patients with ankylosing spondylitis. *Chin Med J 2014; 127(15).*
31. Van der Weijden MAC, van Denderen JC, Lems WF, Heymans MW, Dijkmans BAC, 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.
32. Muntean L, Rojas-Vargas M, Font P, Simon SP, Rednic S, Schiotis R. Relative value of the lumbar spine and hip bone mineral density and bone turnover markers in men with ankylosing spondylitis. Clin Rheumatol 2011; 30: 691-695.
33. Capaci K, Hepguler S, Argin M, Tas I. Bone mineral density in mild and advanced ankylosing spondylitis, Yonsei Med J 2003; 44: 379-384.
34. Juanola X, Mateo L, Nolla JM, Roig-Vilaseca D, Campoy E, Roig Escofet D. Bone mineral density in women with ankylosing spondylitis. J Rheumatol 2000; 27(4): 1028-1031.
35. D. T. Felson, Y. Zhang, M. T. Hannan, and J. J. Anderson, "Effects of weight and body mass index on bone mineral density in men and women: the Framingham study," Journal of Bone and Mineral Research, vol. 8, no. 5, pp. 567–573, 1993.
36. T. V. Nguyen, J. R. Center, and J. A. Eisman, "Osteoporosis in elderly men and women: effects of dietary calcium, physical activity, and body mass index," Journal of Bone and Mineral Research, vol. 15, no. 2, pp. 322–331, 2000.
37. A. Baheiraei, N. A. Pocock, J. A. Eisman, N. D. Nguyen, and T. V. Nguyen, "Bone mineral density, body mass index and cigarette smoking among Iranian women: implications for prevention," BMC Musculoskeletal Disorders, vol. 6, article 34, 2005.