Düzce Tıp Fakültesi Dergisi 2009; 11(2): 1-8

Relationship between Functional Disability and Bone Loss in Spondyloartropathy Patients

Lina VENCEVIČIENĖ[1], Irena BUTRIMIENĖ[2], Algirdas VENALIS[2]

[1] Vilnius University, Clinic of Internal Diseases, Family Medicine, Gerontology and Oncology, Vilnius,
[2] Vilnius University, Clinic of Rheumatology, Traumatology, Orthopedics and Reconstructive Surgery; Vilnius University Institute of Experimental and Clinical Medicine, Vilnius, Lithuania

Abstract

Objective: To determine the relationship between bone mineral density (BMD) and functional status of spondyloarthropathy (SpA) patients.

Methods: BMD (g/cm ^{2}) of 139 SpA patients was determined at the lumbar spine and the upper part of the left and right femur by dual energy X-ray absorptiometry (DXA). The functional disability in patients with SpA was assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI), the Bath Ankylosing Spondylitis Patient Global Assessment (BAS-G), the Health Assessment Questionnaire Modified for the SpA (HAQ-S); spinal mobility - by measuring metrology indices (tragus-to wall distance, lateral flexion, modified Schober's distance, and intermalleolar distance). Physical activity was measured by amount of time spent exercising per week. In order to find out whether there was a relationship between functional indices and BMD linear regression stepwise selection was employed.

Results: No significant association between frequency of exercise and BMD was detected in SpA patients. Femur BMD was associated with BASFI, HAQ-S and all components of metrology indices, except for tragus to wall distance for left femur. Significant decreases of right and left femur BMD, except for the spine BMD, were associated with cases of severe impairment of lumbar side flexion, and impairment of modified Schober's test and intermalleolar distance. Spinal BMD was associated only with HAQ-S.

Conclusions: Femur BMD of SpA patients was found to be associated with both subjective (BASFI, HAQ-S) and objective (tragus to wall distance, lumbar side flexion, modified Schober's test and intermalleolar distance) functional indices. Prevention of bone loss of SpA patients relies upon preservation and control of functional status of the patient.

Key words: Functional Disability, Bone Mineral Density, Spondyloarthropathies.

INTRODUCTION

Spondyloarthropathies (SpA), including ankylosing spondylitis (AS), reactive arthritis (ReA), psoriatic arthritis (PsA) and arthritis associated with inflammatory bowel disease (EnA) are a group of chronic autoimmune disorders. They share common clinical, radiological and genetic features that are clearly distinct from other inflammatory rheumatic diseases. SpA are characterized by main involvement of axial joints and bilateral sacroiliitis, however peripheral joints and extra-articular organs are often implicated, leading to decreasing mobility in the back and extremities. Some studies reported that functional limitations in AS increase with age and with the duration of symptoms (1-8). Additional risk factors noted in prior studies are the severity of pain and stiffness, peripheral arthritis, and smoking (9-12). In the early stage of the SpA these functional limitations are mostly reversible, whereas in later stages irreversible ossification of ligaments and joint capsules occurs. These ossifications play an important role in the development of functional changes in patients with SpA (13). Since there is no gold standard available for measuring functional limitations and the outcome, many different methods have been developed to assess mobility and disability in SpA patients. For the assessment of functional changes the Assessment in Ankylosing Spondylitis (ASAS) Working Group (14) recommends Bath Ankylosing Spondylitis Functional Index (BASFI) (15), Health Assessment Questionnaire Modified for Spondyloartropathy (HAQ-S) (16), Bath Ankylosing Spondylitis Patient Global Score (BAS-G) (17), and metrology measures for spinal mobility: tragus to wall distance, lumbar side flexion, modified Schobers test,

intermalleolar distance, or the Bath Ankylosing Spondylitis Metrology Index (BASMI) (18).

Decreased bone mineral density (BMD) is a typical extra-articular symptom in SpA. Many patients with SpA, despite being either young or male have osteoporosis (OP) and consequent non-traumatic fractures. In subsequent reports, the osteopenia or osteoporosis frequency in AS patients ranges from 50 to 92% (19,20). In our earlier work we already showed statistically significant BMD differences between SpA and healthy control group, irregardless of disease duration at all tested skeletal sites (lumbar spine and both femurs). When comparing patients according to disease duration starting from the appearance of symptoms (up to 5, from 5 to 10 and more than 10 years), BMD differences were found only in femurs, while no significant differences in lumbar spine were found. It is interesting to note that there were no statistical significant changes in the same indices when comparing disease duration starting from the time of diagnosis (21).

The bone density of an individual and risk of developing OP are influenced by a number of common factors, including peak bone mass, race, advanced age, family history of OP, other illnesses, decreased sex-steroid activity, corticosteroid use, certain chronic diseases that affect absorption or vitamin D, smoking, and excessive alcohol use (22-25). The release of inflammatory mediators during the course of chronic autoimmune disorders, use of medications (especially corticosteroids) and decreased mobility of patients are some possible mechanisms for the occurrence of OP (26,27). In our earlier study, when we compared patients with SpA, rheumatoid arthritis, and healthy control group we found statistical significant difference only between patients and control group, however BMD and Z score did not differ among SpA and rheumatoid arthritis patients. Changes in bone mass in patients with disease duration up to 10 years in the spine of patients with SpA were even more expressed than in rheumatoid arthritis patients, while in femur sites no differences were found (28).

A reduced range of movement of the spine in AS patients has been considered as an etiological factor of OP (29-31). Until now, there is still a lack of data that assesses the correlation between BMD and functional limitations in patients not with AS but other SpA.

The objectives of this study were to evaluate functional disability and BMD in patients with different SpA and to determine the relationship between BMD and functional status of the patient.

Materials and methods

A cross sectional study was conducted between 2006 and 2008 at the Department of Rheumatology of Vilnius University Hospital "Santariskiu Klinikos". The study was approved by the National Committee of Ethics. Study sample included 139 SpA patients (96 males, 43 females) aged between 20 and 75 years. Patients suffering from conditions which might alter bone mineral content and/or bone metabolism (alcohol abuse, liver and kidney disease, hypogonadism, hyperthyroidism, hyperparathyroidism, ongoing thyroxin and anti-convulsant therapy) were excluded.

BMD (g/cm^2) was determined at the lumbar spine (first to fourth vertebrae, anteroposterior view) and the upper part of the left and right femur by dual energy X-ray absorptiometry (DXA) (LEXXOS-DMS, France). All participants completed questionnaires covering demographics, medical history and functional status. The functional disability in patients with SpA was assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI) using a range from 0 (easy) to 10 (impossible); the Health Assessment Questionnaire modified for the Spondylo-arthropathies (HAQ-S) using a range from 0 (no difficulty) to 3 (unable to do), Bath Ankylosing Spondylitis Patient Global Assessment (BAS-G) using a range from 0 to 10 (the higher score, the greater perceived effect of the disease on patients well being), and by measuring metrology indices (tragus-to wall distance, lateral flexion, modified Schober's distance, and intermalleolar distance (0-mild, 1-moderate, 2-severe impairment). Physical activity was measured by amount of time spent exercising per week: >140 min. per week; >60-140 min. per week; 20-60 min. per week; no activity.

Statistical analysis

Data was analyzed using SPSS 16.0 software (version for windows). Descriptives for continuous variables were presented as mean

(SD) and tables of frequencies were reported for categorical variables. For comparison of BMD between different SpA, analysis of covariance (ANCOVA) was used when adjustment for confounding factors was made. In order to find out whether there was a relationship between functional indices and BMD linear regression stepwise selection was employed. A variable entered the model if its significance was less or equal to 0.05 and was removed if its significance was greater than 0.1. All presented p values are two sided. Level of significance was set to 0.05.

RESULTS

Characteristics of patients

Clinical characteristics of studied patients are presented in tables 1 and 2. The distribution by gender was not uniform. The average delay in diagnosis of SpA was close to 5 years. Evaluation of patient's exercising per week revealed that about 1/3 of patients were physically inactive, however, in more than 50% of patients only mild impairment of spinal mobility was found according to metrology indices.

Comparison of different SpA with respect to BMD

No differences between SpA with respect to BMD were found while comparing SpA diseases (Table 3). Using analysis of covariance (ANCOVA) when adjustments were made for the following factors: age, BMI, gender, physical activity, time from first symptoms, time from clinical diagnosis, cumulative dose of glucocorticoids (mg) used and family history of OP also did not revealed significant BMD differences between studied SpA. All patients (n=139) with ankylosing spondylitis, psoriatic arthritis, entheropatic arthritis and reactive arthritis had axial involvement. 91 patients of 139 had axial and peripheral articular involvement. No BMD differences were observed between patients with and without peripheral involvement (p>0,05).

Table 1. Characteristics of studied patients*.

Age	42.439 (12.925)
BMI	26.072 (5.057)
Time from first symptoms to diagnosis (in months)	54.752 (64.06)
Cumulative dose of glucocorticoids (mg)	5341.784 (13170.894)
Gender (%)	
Female, premenopausal	15 (10.8%)
Female, postmenopausal	28 (20.1%)
Male	96 (69.1%)
Physical activity (%)	
>140 min per week	34 (24.5%)
>60-140 min. per week	16 (11.5%)
20-60 min. per week	41 (29.5%)
No activity	48 (34.5%)
family history of OP	40 (28.8%)
BMD (right femur)	0.840 (0.123)
BMD(left femur)	0.853 (0.122)
BMD (spine)	0.883 (0.144)
BAS-G	6.040 (1.994)
BASFI	4.576 (2.779)
HAQ-S	0.901 (0.711)

* For continuous data "mean (SD)" is presented; for categorical data "number (%)" is presented; percent is calculated from total number of patients.

Table 2. Distribution of patients by metrology indices

Metrology indices*	Mild (0)	Moderate (1)	Severe (2)
Modified Schober's test	79 (56.8%)	41 (29.5%)	19 (13.7%)
Lumbar side flexion	79 (56.8%)	44 (31.7%)	16 (11.5%)
Intermalleolar distance	73 (52.5%)	46 (33.1%)	20 (14.4%)
Tragus to wall distance	106 (76.3%)	27 (19.4%)	6 (4.3%)

* In parenthesis percent from total number of patients is presented

Table 3. Comparison of SpA diseases with respect to BMD

	AS (n=57)	PsA (n=33)	EnA (n=29)	ReA (n=20)	P value*
BMD (right femur)	0.830 (0.129)	0.830 (0.131)	0.858 (0.118)	0.860 (0.094)	0.685
BMD (left femur)	0.847 (0.129)	0.845 (0.135)	0.857 (0.115)	0.877 (0.094)	0.750
BMD (spine)	0.908 (0.177)	0.89 (0.143)	0.837 (0.075)	0.870 (0.096)	0.358

* - p value indicates differences between AS, PsA, EnA and ReA groups

Functional disability and BMD

To accomplish the task of assessing the possible relationship between BMD and functional status, linear regression was used. A total of 21 models were constructed. In each of the models one of BMD measures (BMD of right, left femur or spine) acted as a dependent variable. The list of independent variables included the confounding factors, i.e. age, BMI, gender, physical activity, time from first symptoms, time from clinical diagnosis, cumulative dose of glucocorticoids used, family history of OP; and also one of seven functional indices (BAS-G, BASFI, HAQ-S, modified Shober's test, lumbar side flexion, intermalleolar distance, tragus to wall distance). Categorical variables attaining more than 2 values were recorded using the common method of binary indicators. Coding schemes are presented in table 4. Stepwise selection was used. Results of the last step for each model are presented in table 5. Femur BMD was associated with BASFI, HAQ-S and all components of metrology indices, except for tragus to wall distance for left femur. However, spinal BMD was associated only with HAQ-S.

Table 4. Coding of categorical variables.

Variable	Value	Dummy1	Dummy2	Dummy3
Modified Schober's test, lumbar side flexion, intermalleolar distance, tragus to wall distance	Score = 0	0	0	Not needed
	Score = 1	1	0	
	Score = 2	0	1	
Gender	Male	0	0	
	Female, premenopausal	1	0	
	Female, postmenopausal	0	1	
Physical activity	No activity	0	0	0
	20-60 min. per week	1	0	0
	>60-140 min. per week	0	1	0
	>140 min per week	0	0	1

It was found that prominent impairment of metrology indices (lumbar side flexion, modified Schober's test and intermalleolar distance) is linked to a lower femur BMD, since decreased femur BMD was observed only when moving from score 0 to score 2 (see table 4 for coding and table 5 for results). Other significant predictors of lower BMD were BMI and cumulative dose of used glucocorticoids (Table 5).

DISCUSSION

Our study did not reveal any significant differences by measuring BMD in different SpA. Thus irregardless of some differences, SpA do share common clinical, genetic, and pathophysiological features.

Data about the relationship between BMD and functional ability of SpA patients is scarce. Some authors found low bone density in AS patients despite taking regular exercise therapy (32). Our data also showed no association between frequency of exercise and BMD in all SpA group.

Table 5. Association of BMD and evaluated independent variables (results of linear regression)

	Functional Index used in the model	Model summary (R^2;ANOVA p)	Independent variable	Regression coefficient (SE)	Beta	P value
BMD right femur	BAS-G	0.114;<0.001	BMI	0.006 (0.002)	0.251	0.002
			glucocorticoids	<0.001 (<0.001)	-0.254	0.003
	BASFI	0.209;<0.001	BASFI	-0.014 (0.003)	-0.313	<0.001
			BMI	0.007 (0.002)	0.301	<0.001
			glucocorticoids	<0.001 (<0.001)	-0.216	0.006
	HAQ-S	0.212;<0.001	HAQ-S	-0.055 (0.014)	-0.321	<0.001
			BMI	0.008 (0.002)	0.316	<0.001
			glucocorticoids	<0.001 (<0.001)	-0.219	0.005
	modified Schober's test	0.163;<0.001	Schober's test (2)*	-0.079 (0.028)	-0.223	0.006
			glucocorticoids	<0.001 (<0.001)	-0.234	0.004
			BMI	0.005 (0.002)	0.223	0.006
	lumbar side flexion	0.192;<0.001	lumbar side flexion (2)	-0.107 (0.030)	-0.280	<0.001
			BMI	0.005 (0.002)	0.227	0.004
			glucocorticoids	<0.001 (<0.001)	-0.224	0.005
	intermalleolar distance	0.287;<0.001	intermalleolar distance (2)	-0.147 (0.026)	-0.421	<0.001
			BMI	0.007 (0.002)	0.281	<0.001
			glucocorticoids	<0.001 (<0.001)	-0.190	0.011
	tragus to wall distance	0.173;<0.001	BMI	0.006 (0.002)	0.234	0.004
			glucocorticoids	<0.001 (<0.001)	-0.226	0.006
			tragus to wall distance (1)	-0.056 (0.024)	-0.183	0.023
			tragus to wall distance (2)	-0.109 (0.048)	-0.181	0.026
BMD left femur	BAS-G	0,134;<0,001	BMI	0.007 (0.002)	0.273	0.001
			glucocorticoids	<0.001 (<0.001)	-0.204	0.012
			Time**	<0.001 (<0.001)	-0.168	0.038
	BASFI	0,184;<0,001	BMI	0.008 (0.002)	0.320	<0.001
			BASFI	-0.012 (0.003)	-0.284	<0.001
			glucocorticoids	<0.001 (<0.001)	-0.170	0.032
	HAQ-S	0,220;<0,001	HAQ-S	-0.059 (0.013)	-0.346	<0.001
			BMI	0.008 (0.002)	0.345	<0.001
			glucocorticoids	<0.001 (<0.001)	-0.169	0.029
	modified Schober's test	0,161;<0,001	Schober's test (2)	-0.083 (0.028)	-0.235	0.004
			BMI	0.006 (0.002)	0.245	0.003
			glucocorticoids	<0.001 (<0.001)	-0.185	0.021
	lumbar side flexion	0,188;<0,001	lumbar side flexion (2)	-0.110 (0.030)	-0.288	<0.001
			BMI	0.006 (0.002)	0.249	0.002
			glucocorticoids	<0.001 (<0.001)	-0.175	0.026
	intermalleolar distance	0,222;<0,001	Intermalleolar distance (2)	-0.137 (0.026)	-0.394	<0.001
			BMI	0.007 (0.002)	0.292	<0.001
	tragus to wall distance	0,134;<0,001	BMI	0.007 (0.002)	0.273	0.001
			glucocorticoids	<0.001 (<0.001)	-0.204	0.012
			Time**	<0.001 (<0.001)	-0.168	0.038
BMD spine	HAQ-S	0,160;<0,001	BMI	0.006 (0.003)	0.205	0.026
			Gender (2)	-0.112 (0.035)	-0.314	0.002
			Age	0.003 (0.001)	0.289	0.005
			HAQ-S	-0.037 (0.018)	-0.182	0.038
	All other indices***	0,160;<0,001	BMI	0.006 (0.003)	0.219	0.018
			Gender (2)	-0.139 (0.034)	-0.390	<0.001
			Age	0.003 (0.001)	0.266	0.009
			glucocorticoids	<0.001 (<0.001)	-0.167	0.039

* Number in parenthesis stands for number of dummy variable (see table 4.);
** Time (in months) from first symptoms till clinical diagnosis;
*** All other indices did not enter final model and it were always the same.

Maillefert et al. did not find any relation between bone loss and baseline functional index or spinal mobility (33). Gratacos et al. in a longitudinal cohort study did not observe any relationship between bone loss and vertebral mobility, clinical disability (HAQ-S), or even daily physical activity (34). Speden et al. found that only metrology indices correlated with radiological severity whereas the radiological severity of sacroiliac disease was an independent factor in predicting femoral neck BMD (35). Donnely et al. reported that BMD at the proximal femur decreased in proportion to clinical disease severity (based on the Schober index), while BMD at the lumbar spine increased in the severe disease group as opposed to the mild disease group (36). It is important to note that a decrease in femur BMD, (but not in the spine) found in our study was observed only in cases with severe impairment of lumbar side flexion, modified Schober's test and intermalleolar distance. We also found that femur BMD was associated with BASFI and HAQ-S. Our other data clearly showed no correlations between BAS-G and BASFI, HAQ-S, metrology indices (data to be published). It follows that BAS–G as indicator of patient's well being is not sensitive enough to describe function impairment. This could explain why we did not find any correlation between BAS-G and BMD measurements at tested sites.

Our other study comparing patients according to disease duration, starting from the appearance of symptoms (up to 5, from 5 to 10, and more than 10 years), determined that BMD differences appeared only in femurs, and no significant differences in lumbar spine were found (21). It is evident that pathological changes in patients with SpA occur predominantly in the spine leading to structural alterations. Thusly, formation of syndesmophytes and ossification of ligaments led not only to reduced spinal mobility, but to an overestimation of spinal BMD. It is likely therefore, that the spinal BMD in our study was associated only with HAQ-S and associations between spinal BMD and other functional indices were not detected. It can be stated with some certainty that prevention of bone loss of SpA patients relies not only upon reducing the inflammation but also on the preservation and control of functional status of the patient.

The studies results may be of clinical importance and could provide additional understanding of the relationship between the impairment of function and bone loss in patients with SpA. In combining the findings of our earlier study and literature (37,38) we can state that bone mass at the lumbar spine, as measured by DXA, does not reflect the real progression of bone loss in SpA patients. Our data supports the position that more accurate assessment of lumbar BMD in patients with SpA can be done by using quantitative computer tomography and lateral lumbar spine DXA (39). However the results found allows us to agree with the position that measurements of femur BMD can be more accurately assessed using DXA examination (19,20).

Conclusions

1. The left and right femur BMD are associated with subjective (BASFI, HAQ-S) and objective (tragus to wall distance, lumbar side flexion, modified Schober's test and intermalleolar distance) functional indices in SpA patients.
2. Significant decreases of right and left femur BMD are observed only in cases with severe impairment of reduced spinal mobility measured by lumbar side flexion, modified Schober's test and intermalleolar distance.
3. Spinal BMD is associated only with functional disability measured by HAQ-S.
4. Our study did not reveal associations between frequency of exercise and BMD in patients with SpA.

Corresponding author: Lina VENCEVICIENĖ,
Santariškių 2, Family Medicine Center,
Vilnius University Hospital,
Santariskiu Klinikos", LT-08661 Vilnius, Lithuania
Tel.: +3705 2365034;
Fax: +3705 2365302
E-Mail: linaven@gmail.com

REFERENCES

1. Ward MM: Health-related quality of life in ankylosing spondylitis: a survey of 175 patients. Arthritis Care Res. 12: 247-55, 1999.
2. Guillemin F, Briancion S, Pourel J, Gaucher A: Long-term disability and prolonged sick leaves as outcome measurements in ankylosing spondylitis: possible predictive factors. Arthritis Rheum. 33: 1001-6, 1990.
3. Gran JT, Skomsvoll JF: The outcome of ankylosing spondylitis: a study of 100 patients. Br J Rheumatol. 36: 766-71, 1997.
4. Taylor AL, Balakrishnan C, Calin AL: Reference centile charts for measures of disease activity, functional impairment, and metrology in ankylosing spondylitis. Arthritis Rheum. 41: 1119-25, 1998.
5. Zink A, Braun J, Listing J, Wollenhaupt J, and the German Collaborative Arthritis Centers. Disability and handicap in rheumatoid arthritis and ankylosing spondylitis: results from the German rheumatological database. 27: 613-22, 2000.
6. Falkenbach A, Franke A, van Tubergen A, van der Linden S: Assessment of functional ability in younger and older patients with ankylosing spondylitis: performance of the Bath Ankylosing Spondylitis Functional Index. Am J Phys Med Rehabil. 81: 416-20, 2002.
7. Falkenbach A, Franke A, van der Linden S: Factors associated with body function and disability in patients with ankylosing spondylitis: a cross-sectional study. J Rheumatol. 30: 2186-92, 2003.
8. Ward MM: Predictors of the progression pf functional disability in patients with ankylosing spondylitis. J Rheumatol. 29: 1420-5, 2002.
9. Doran MF, Brophy S, MacKay K, Taylor G, Calin A: Predictors of longterm outcome in ankylosing spondylitis. J Rheumatol. 30: 316-20, 2003.
10. Wordsworth BP, Mowat AG: A review of 100 patients with ankylosing spondylitis with particular reference to socio-economic effects. Br J Rheumatol. 25: 175-80, 1986.
11. Bakker C, van de Linden S, van Santen-Hoeufft M, Bolwijn P, Hidding A: Problem elicitations to assess patient priorities in ankylosing spondylitis and fibromyalgia. J Rheumatol. 22: 1304-10, 1995.
12. Averns HL, Oxtoby J, Taylor HG, Jones PW, Dziedzic K, Dawes PT: Smoking and outcome in ankylosing spondylitis. Scand J Rheumatol. 25: 138-42, 1996.
13. Heikkila S, Ronni S, Kautiainen H.J, Kauppi M.J: Functional impairment in spondyloarthropathy and fibromyalgia. J Rheumatol 29: 1415-9, 2002.
14. van der Heijde D, Calin A, Dougados M, Khan M, van der Linden S, Bellamy N: Selection of instruments in the core set for DC-ART, SMARD, physical therapy, and clinical record keeping in ankylosing spondylitis. Progress report of the ASAS Working group. J Rheumatol. 26: 951-4, 1999.
15. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, Jenkinson T: A new approach to defining functional ability in anklosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol. 21: 2281-5, 1994.
16. Daltroy LH, Larson MG, Roberts WN, Liang MH: A modification of the Health Assessment Questionnaire for spondyloarthropathies. J Rheumatol. 17: 946-50, 1990.
17. Jones SD, Steiner A, Garrett SL, Calin A: The Bath Ankylosing Spondylitis Patient Global Score (BAS-G). Br J Rheumatol. 35: 66-71, 1996.
18. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A: Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. J Rheumatol. 21: 1694-1698, 1994.
19. Meirelles ES, Borelli A, Camargo OP: Influence of disease activity and chronicity on ankylosing spondylitis bone mass loss. Clin Rheumatol. 18: 364-8, 1999.
20. El Maghraoul A, Borderie D, Cherruau B, Edouard R, Dougados M, Roux C: Osteoporosis, body composition, and bone turnover in ankylosing spondylitis. J Rheumatol. 26: 2205-9, 1999.
21. Venceviciene L, Venalis A, Sapoka V, Butrimiene I: Bone mineral density in patients with spondyloarthropathies. Medicinos teorija ir praktika. 14(3): 275-282, 2008.
22. Deodhar AA, Woolf AD: Bone mass measurement and bone metabolism in

rheumatoid arthritis: a review. British Journal of Reumatology. 35: 309-22, 1996.
23. Kanis JA: Osteoporosis. Victoria, Blackwell Science Ltd. Pp. 1-254, 1994.
24. Nishimura J, Ikuyama S: Glucocorticoid-induced osteoporosis: pathogenesis and management. Journal of Bone and Mineral Metabolism. 18: 350-2, 2000.
25. Bonnick SL, Johnston CC Jr, Kleerekoper M, Lindsay R, Miller P, Sherwood L, Siris E: Importance of precision in bone density measurements. J Clin Densitom. 4: 105, 2001.
26. Illei GG, Lipsky PE: Novel, non-antigen-specific therapeutic approaches to autoimmune/inflammatory diseases. Curr Opin Immunol. 12: 712-718, 2000.
27. Rehman Q, Lane NE: Therapeutic approaches for preventing inflammatory bone loss in inflammatory arthritis. Arthritis Res. 3: 221-227, 2001.
28. Venceviciene L, Venalis A, Butrimiene I: Loss of bone mass: when it begins in immune arthritides. Gerontologija. 9(2): 71-78, 2008.
29. Will R, Bhalla AK, Palmer R, Ring R, Calin A: Osteoporosis in early ankylosing spondylitis: a primary pathological event? Lancet. II: 1483–5, 1989.
30. Mitra D, Elvins DM, Speden DJ, Collins AJ: The prevalence of vertebral fractures in mild ankylosing spondylitis and their relationship to bone mineral density. Rheumatology. 39: 85-89, 2000.
31. Bikle DD, Halloran BP: The response of bone to unloading. J Bone Miner Metab. 17: 233-44, 1999.
32. Mullaji AB, Upadhyay SS, Ho EKW: Bone mineral density in ankylosing spondylitis: DEXA comparison of control subjects with mild and advanced cases. J Bone Joint Surg Br. 76: 660-5, 1994.
33. 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. 12: 605–9, 2001.
34. Gratacos J, Collado A, Pons F, Osaba M, Sanmarti R, Roque M, Larrosa M, Munoz-Gomez J: Significant loss of bone mass in patients with early, active ankylosing spondylitis. J Rheumatol. 41: 2319-2324, 1999.
35. Speden DJ, Calin AI, Ring FJ, Bhalla A: Bone mineral density, calcaneal ultrasound, and bone turnover markers in women with anlylosing spondylitis. The Journal of Rheumatology. 29(3): 516-521, 2002.
36. 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. 53: 117-121, 1994.
37. Devogelaer JP, Maldague B, Malghem J, Nagant de Deuxchaisnes C: Appendicular and vertebral bone mass in ankylosing spondylitis. A comparison of plain radiographs with single-and dual-photon absorptiometry and with quantitative computed tomography. Arthritis Rheum. 35: 1062-1067, 1992.
38. Lee YS, Scholtzhauer T, Ott SM, van Vollenhoven RF, Hunter J, Shapiro J, Marcus R, McGuire JL: Skeletal status of men with early and late ankylosing spondylitis. Am J Med. 103: 233-241, 1997.
39. Bronson WD, Walker SE, Hillman LS, Keisler D, Hoyt T, Allen SH: Bone mineral density and biochemical markers of bone metabolism in ankylosing spondylitis. J Rheumatol. 25: 929-35, 1998.