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Bone Mineral Density Changes in Patients with Spondyloarthropathies

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1. Introduction

The concept of inflammatory spondyloarthropathies (SpA) as an independent group of diseases was introduced approximately 15-20 years ago, when symptoms distinguishing these diseases from rheumathoid arthritis (RA) were defined precisely. SpA group includes 4 main diseases: ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA) and enteropathic arthropathies (EnA). Global prevalence of these diseases is .2-3.0 percent. Furthermore, SpA incidence in Lithuania is .64 percent (Adomaviciute et al., 2008). The incidence is higher in close relatives of patients with established human leucocyte antigen B27 (HLA B27). SpA is 2-3 times more common in males than in females (Khan, 2002; Sieper, 2002).

Although SpA and RA ethiology and pathogenesis differ, these immune arthritides are similar in their consequences, principles of diagnostic and treatment. Genetic predisposition to the disease and relation with infectious factors is characteristic to both SpA and RA diseases, however, the true causes remain unclear. It is known that tissue damage in these diseases is caused by reactions governed by immune processes. In addition, RA is the most investigated autoimmune, continuously progressing erosive-destructive poliarthritis. The incidence among adults ranges from .35 to 1.0 percent in various populations whilst in Lithuania it is about .55 percent (Adomavičiūtė et al., 2008). In both SpA and RA clinical outcomes depend primarily on various complications: cardiovascular abnormalities, infections, amyloidosis, osteoporosis.

Osteoporosis (OP) is a skeletal disease characterized by low bone mineral density (BMD) and poor bone quality that reduces bone strength and increases the risk of fractures. OP is a major public health concern, affecting approximately 200 million individuals worldwide, including a third of women aged 60 to 70 years. Fractures of the hip and spine are associated with increased morbidity and mortality (Johnell et al., 2005). Despite the high prevalence of OP and the availability of effective drugs to reduce the risk of fracture, it is underdiagnosed

and undertreated (Feldstein et al., 2003). Patients with immune arthritides, who are at very high risk of fracture, are usually not evaluated for OP. It has been reported that in patients with SpA and RA decreased BMD is being diagnosed at a much younger age (Lane at al., 2002). These patients are affected not only by ordinary OP risk factors but also specific disease factors: activity and course of the disease, its duration, treatment with glucocorticoids (GC) and immunosuppressants, reduced mobility (Gratacos, 1999; Kroot, 2001; Baek, 2005).

Most of the publications analyzing BMD changes are related to RA. It was observed that RA is associated with local and systemic loss of bone mineral density (Sambrook, 1995; Gough, 1994) and also with increased risk of osteoporotic fracture (Cooper et al., 1995). The main factors associating RA and decrease of BMD are activity of the disease, physical disability and immobility, disease duration and use of gliucocorticoids (Dequeker, 1995; Kvien, 2000). According to other work in the field, pathologic fractures of spine vertebrae are more common in patients with SpA than RA (despite the formation of syndesmophytes and ossification of longitudinal ligaments that could probably "protect the spine" in SpA case) (Bessant, 2002; Brand, 2008). It is supposed that in both RA and SpA bone tissue is damaged due to reduced mobility, the activity of the disease and, most importantly, similar reactions caused by immune processes, which are characteristic to these diseases (Illei et al., 2000; Pettit, 2001).

Although in most cases SpA are investigated as a whole group of diseases with common clinical, radiological and genetic features, BMD was investigated mostly in patients with AS. According to other studies, the incident of OP in patients with AS is very different and ranges from 50 to 92% (Mitra, 2000; Capaci, 2003). Too little and controversial data concerning changes of BMD in other diseases belonging to SpA group were published (El Maghraoui, 2004; Speden, 2002).

Scientific novelty. This investigation for the first time evaluated and compared BMD at the lumbar spine and upper part of left and right femur in patients with SpA and RA and healthy people. Consistent patterns of BMD changes at the lumbar spine and upper parts of both femurs were assessed in patients with diseases belonging to SpA group (AS, ReA, EnA, PsA) and in SpA patients with various types of joint lesion. Relation between SpA specific factors – duration of the disease, physical disability and immobility, activity of the disease, medications in use and BMD changes at the lumbar spine and upper part of left and right femur was evaluated.

Absolute determination of consistent patterns of BMD changes at the lumbar spine and upper parts of both femurs in patients with various diseases belonging to SpA group (AS, ReA, EnA, PsA) and with various types of joint lesion together with, investigation of distinct clinical risk factors associated with BMD changes in SpA patients would allow to select patients for BMD test precisely, indicate the exact skeleton area for investigation, diagnose changes in bone mass earlier and timely apply effective preventive and/or treatment measures.

Aim of the research – to determine consistent patterns of BMD changes at the lumbar spine and upper part of left and right femur in patients with SpA (AS, ReA, PsA, EnA) and to assess the relation between changes of BMD and specific factors of the disease (duration of

the disease, physical disability and immobility, activity of the disease, medications in use) using noninvasive method of BMD evaluation (dual-energy X-ray absorptiometry (DXA)).

Objectives of the research

- To investigate BMD changes at the lumbar spine and upper part of left and right femur in groups of patients with SpA, Ra and healthy subjects.
- To investigate BMD changes at the lumbar spine and upper part of left and right femur in patients with various diseases belonging to SpA group (AS, ReA, PsA, EnA) and in SpA patients with different type of joint lesions (only axial, only peripheral, both axial and peripheral).
- To analyse relation between the duration of SpA and BMD changes at the lumbar spine and upper part of left and right femur.
- To evaluate influence of physical disability and immobility on BMD changes in patients with SpA.
- To determine influence of medications in use: glucocorticoids and TNF-α blockers on BMD changes in patients with SpA.

Statements defended:

- BMD decrease at the lumbar spine and upper part of left and right femur is similar in patients with inflammatory joint diseases: SpA and RA.
- Impact of various diseases belonging to SpA group on bone mass changes is similar.
- SpA activity and physical disability and immobility are important prognostic factors for BMD decrease.

2. Study subjects and methods

2.1 Study population

Patients treated in the Department of Rheumatology of Vilnius University Hospital "Santariškių klinikos" in the period of December 2006 to June 2008 were invited to participate in this research. Patients arriving at Vilnius University Hospital "Santariškių klinikos" Family Health Center for the prophylactic examination were invited to take part in the control group of the research. A total of 136 patients with SpA, 104 patients with RA and 114 healthy people (control group) matching inclusion criteria, and not having any exclusion criteria stated below were involved in the investigation.

2.2 Inclusion criteria

- Age of subjects ranging from 20 to 75 years;
- People with RA diagnosis established according to rheumatoid arthritis diagnostic criteria of American College of Rheumatology (ARA'87) (diagnosis established by rheumatologist) (Arnett et al., 1988);
- Subjects with SpA diagnosis established according to diagnostic criteria approved by European Spondyloarthropathy Study Group (ESSG) (1991) (diagnosis established by rheumatologist);
- Subjects of control group – healthy individuals (Dougados et al., 1991);
- Subjects signed an *Informed Consent* form approved by Lithuanian bioethics committee. (The permission to perform this investigation was obtained from the Lithuanian bioethics committee (No.60; 2006-12-22)).

2.3 Exclusion criteria

- Subjects after hip joint replacement;
- Patients with other diseases (renal, liver, thyroid and parathyroid, and cancer) influencing calcium metabolism or interfering metabolism of bone tissue;
- Individuals treated with medications (anti-osteoporosis, thyroxin, insulin, anticoagulants, anticonvulsants, hormone replacement therapy, etc.) that may influence bone tissue metabolism, except medications used to treat underlying disease: disease modifiers, TNF-α blockers, GC and non-steroid anti-inflammatory drugs (data obtained from medical records and patient interviews);
- Pregnant women, vegetarians, alcohol addicts.

2.4 Research structure

Primary selection of patients was performed according to patients' medical history and data of clinical investigations (data from the hospital and out-patient records were used under the patients consent). Then, every patient completed one of the three questionnaires depending on the research subgroup he/she belonged to. The following questionnaire data were assessed: socio-demographic data – age, gender, education, profession, work environment; smoking, use of alcohol; bone fractures in subject and his close relatives; previous and current diseases; previously and currently used medications; calcium amount in the diet (mg/d); frequency of physical activities by month (at least 20 minutes physical exercises per day) and the age of the beginning and the end of menstrual cycle in femails.

In patients with SpA and RA: duration of the disease (in months) from the onset of the first symptoms and from the date the diagnosis was established; pain intensity assessment using 10 cm VAS scale; patient's general status assessment using 10 cm VAS scale.

In patients with SpA the following parameters were assessed: disease belonging to SpA group; type of joint lesion: axial, peripheric, both axial and peripheric; physical disability was assessed by completing Health Assessment Questionaire Modified for Spondyloarthropathies (HAQ-S) (Daltroy et al., 1990); immobility was assessed according to Bath Ankylosing Spondylitis Functional Index (BASFI) (Calin et al., 1994) and Bath Ankylosing Spondylitis Patient Global Score (BAS-G) (Jones et al., 1996); assessment of enthesis; movement of spine was assessed according to standardized SpA clinical measurements: lumbar side flexion, modified Schober's test, tragus to wall distance and intermalleolar distance (Jenkinson et al, 1994); activity of the disease according to patients self-assessment using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (Garrett et al, 1994); activity of the disease evaluated by rheumatologist (Landewe et al, 2004). The linguistic and cultural adaptation of these questionnaires was made during the study. Internal consistency was high for functional and disease activity index (Cronbach alpha>/=0.80) and moderate for the Bath Ankylosing Spondylitis Patient Global Score (Cronbach alpha=0.58). High stability in regard to time was characteristic of all three questionnaires (intraclass correlation coefficient >0.95). A significant association between the separate questions of examined instruments, their joint results and other factors reflecting patient's health was established (Venceviciene et al., 2009).

In patients with RA the following parameters were assessed: rheumatoid arthritis functional ARA classes; disease activity index DAS 28 and activity of the disease established by rheumatologist (Arnett et al., 1988).

Anthropometric measurements were performed on all patients: height, weight, BMI; laboratory tests: ESR, CRP, calcium blood level, HLA-B27 (in patients with SpA), RF (in patients with RA). Laboratory tests were performed in the Department of Laboratory Diagnostics of Vilnius University Hospital "Santariškių klinikos".

2.5 Evaluation of the bone mineral density

In all subjects BMD was measured by dual-energy X-ray absorptiometry (DXA) using osteodensitometer LEXXOS-DMS (software: V6, 20a, version of the year 2006). The anterior-posterior view of lumbar spine (L1-L4 vertebrae) and upper parts of both femurs were examined. BMD data were expressed as g/cm^2 and the number of standard deviations from the peak bone mass (T – score), and also the number of standard deviations of any individual result from the age and sex matched population mean (Z – score). Normal ranges were provided by manufacturers of the osteodensitometer. According to ISCD recommendations, BMD deviation was measured as Z-score, since most of the enrolled subjects were males less than 50 years old. Osteodensitometer quality test and measurement error test were performed every morning before work. Indications of the scan of spine vertebrae reference (phantom) fluctuated no more than 2 %, bias of the repeated measurement in spine vertebrae was not higher than 1.5 %, and in the upper part of femur– not higher then 2.1 %. All BMD measurements were performed by the principal investigator.

2.6 Data analysis

Statistical analysis was performed using SPSS 16 software. Mean (M) and standard deviation (SD) were used to describe quantitative characteristics of the research. Frequencies (n) and percents (%) were used for qualitative characteristics. Depending on applicable assumptions Student's t-test for independent samples was used to compare means of a particular qualitative characteristic of different samples. Analysis of variance ANOVA was used to compare quantitative variables of more than two samples (when variances were unequal Welch test statistics was used). When the hypothesis of the equality of means of two or more groups was rejected, pairwise comparison of this characteristic was additionally used. In that case Tukey HSD Post Hoc test was used. Differences of qualitative characteristics of experimental groups were assessed using Chi square test. Selected level of significance $\alpha = .05$.

To analyze relationship between SpA variables: the duration of disease, physical disability and immobility, activity of the disease and treatment with GC and TNF-α blockers and BMD changes linear regression models were developed. Stepwise selection of variables in the linear regression was used. Variables were included in the model when their p was $<.05$ and excluded when their p was $> .10$. When strong association between independent variables was observed (e.g., cumulative dose of GC and duration of use (calculated using Spearman correlation coefficient), only one of them was used for calculations. To assess probability that Z-score will be ≤ -2 in any site of examined skeleton logistic regression analysis was used.

3. Results

3.1 Characteristics of study groups

Three hundred fifty four subjects were enrolled in this research: 136 (38.4%) patients with SpA, 104 (29.4%) patients with RA and 114 (32.2%) healthy people (control group). The subjects of all groups were similar in BMI, physical activity and family history (all $p > .05$). No differences in disease activity determined by rheumatologist were observed between RA and SpA patients ($p > .516$). Subjects' differences in age (SpA patients: M = 42.18 ± 12.92; RA patients: M = 50.09 ± 11.10; $p < .001$), duration of the disease (SpA patients: M = 112.09 ± 94.54; RA patients: M = 148.49 ± 109.60; $p < .007$), and gender were determined. There were more males in SpA group compared with RA group ($p < .001$) and control group ($p < .001$); there were no differences in the number of males in RA group and control group ($p = .119$). No significant differences in the proportion of premenopausal and postmenopausal women in research groups were determined. (SpA vs. control group $p = .550$; SpA vs. RA $p = .112$; RA vs. control group $p = .600$).

3.2 BMD comparison in patients with SpA and RA and in control group subjects

The first objective of our research was to investigate BMD changes at lumbar spine and upper parts of the femurs in groups of patients with SpA, RA and healthy subjects.

BMD values at lumbar spine and upper part of the left and right femur (BMD expressed as g/cm^2 and Z-score) are presented in Table 1.

BMD	Research groups			p	Post hoc
	1	2	3		
	SpA (n = 136)	RA (n = 104)	Control (n = 114)		
BMDS	.873 (.128)	.866 (.125)	1.016 (.121)	< .001	3>1 (p <.001) 3>2 (p <.001)
BMDL	.849 (.121)	.832 (.131)	.998 (.113)	< .001	3>1 (p <.001) 3>2 (p <.001)
BMDR	.837 (.122)	.825 (.122)	.983 (.110)	< .001	3>1 (p <.001) 3>2 (p <.001)
ZS	-1.317 (.998)	-1.061 (1.096)	.045 (.941)	< .001	3>1 (p <.001) 3>2 (p <.001)
ZL	-1.133 (.949)	-1.014 (1.001)	.097 (.842)	< .001	3>1 (p <.001) 3>2 (p <.001)
ZR	-1.222 (.952)	-1.143 (1.161)	-.014 (.838)	< .001	3>1 (p <.001) 3>2 (p <.001)

Table 1. Comparison of BMD (g/cm^2) and Z-score (mean (SD)) between research groups SpA – patients with spondyloarthropathies; RA – patients with rheumatoid arthritis. Bone mineral density (BMD) expressed as g/cm^2 at spine (BMDS), left femur (BMDL) and right femur (BMDR); BMD expressed as Z-score in spine (ZS), left femur (ZL) and right femur (ZR).

In both SpA and RA patients a similar decrease of BMD (expressed as g/cm^2 and Z-score, unless otherwise stated) (Table 1) at lumbar spine and upper parts of the both femurs was

determined. It was also established that in both SpA and RA patients mean BMD value in all examined skeletal sites was significantly lower than mean BMD value in control group subjects.

3.3 Homogenicity by BMD changes in patients with various diseases belonging to spondyloarthropathy group and with various types of joint lesions

The second objective of our research was to investigate BMD changes at lumbar spine and upper part of the left and right femur in patients with various diseases belonging to SpA group (AS, ReA, PsA, EnA) and in SpA patients with different type of joint lesions (only axial, only peripheral, both axial and peripheral).

Patients with SpA were allocated to the following subgroups: 54 (39.70%) patients with AS, 33 (24.3%) – with PsA, 29 (21.3%) - with EnA and 20 (14.7%) with ReA. The comparison of BMD value between these groups is presented in Table 2.

BMD	Disease belonging to SpA group				p
	AS (n = 54)	PsA (n = 33)	EnA (n = 29)	ReaA (n = 20)	
BMDS	.885 (.149)	.890 (.143)	.837 (.075)	.870 (.096)	.346
BMDL	.837 (.125)	.845 (.135)	.857 (.115)	.877 (.094)	.632
BMDR	.821 (.127)	.830 (.131)	.858 (.118)	.860 (.094)	.463
ZS	-1.301 (1.023)	-1.077 (1.258)	-1.631 (.484)	-1.298 (.868)	.179
ZL	-1.282 (.912)	-.991 (1.069)	-1.157 (.856)	-.928 (.965)	.392
ZR	-1.386 (.933)	-1.120 (1.032)	-1.158 (.891)	-1.040 (.954)	.418

Table 2. Comparison of BMD (g/cm^2) and Z-score (mean (SD)) between patients with various diseases of spondyloarthropathy group patients with ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA) and enteropathic arthropathy (EnA). Bone mineral density (BMD) expressed as g/cm^2 at spine (BMDS), left femur (BMDL) and right femur (BMDR); BMD expressed as Z-score in spine (ZS), left femur (ZL) and right femur (ZR).

Data presented in Table 2 do not demonstrate statistically significant BMD differences at lumbar spine and upper parts of the both femurs of patients with AS, PsA, EnA and ReA.

Patients with SpA were allocated to three subgroups depending on the type of joint lesion: patients with only axial lesion, only peripheral lesions and patients with both axial and peripheral lesion. Twenty five (18.4%) patients were allocated to the axial lesion group, 20 (14.7%) – to the peripheral lesion group, and both axial and peripheral lesion was diagnosed in 91 (66.9) patients. The comparison of BMD in SpA patients with various joint lesion types showed that there are no significant differences in BMD between subgroups at any examined sites of the skeleton (Table 3).

Summarizing data presented in Tables 2 and 3 it might be claimed that no significant differences in BMD mean values were found at any examined sites of the skeleton both comparing patients with various diseases belonging to SpA group and patients with different types of joint lesions. Therefore SpA group could be further analyzed as a homogeneous group without dividing it into subgroups by diseases.

BMD	Type of joint lesion			p
	Axial (n = 25)	Peripheric (n = 20)	Axial and peripheric (n = 91)	
BMDS	.859 (.158)	.846 (.080)	.883 (.128)	.416
BMDL	.836 (.147)	.882 (.100)	.845 (.117)	.391
BMDR	.818 (.149)	.875 (.103)	.833 (.117)	.269
ZS	-1.427 (1.289)	-1.541 (.668)	-1.237 (.952)	.384
ZL	-1.284 (1.122)	-.982 (.874)	-1.124 (.917)	.567
ZR	-1.408 (1.142)	-1.034 (.874)	-1.213 (.913)	.421

Table 3. Comparison of BMD (g/cm^2) and Z-score (mean (SD)) between patients with various types of joint lesions Bone mineral density (BMD) expressed as g/cm^2 at spine (BMDS), left femur (BMDL) and right femur (BMDR); BMD expressed as Z-score in spine (ZS), left femur (ZL) and right femur (ZR).

3.4 Variables associated with bone mineral density changes in patients with spondyloarthropathies

In order to determine variables related to BMD at lumbar spine and upper part of the left and right femur of patients with SpA, 90 models of multiple stepwise linear regression analysis were developed. One of the values of BMD (BMDS, BMDL, BMDR, ZS, ZL, ZR) served as dependent variable, and independent variables were controlled variables: age, gender (when BMD was expressed as g/cm^2), BMI, family history of fractures, various diseases belonging to SpA group, type of joint lesions and physical activity. Each time one of the specific SpA factors was involved into the model: duration of the disease calculated from the time of the manifestation of first symptoms and from the time the diagnosis was established; physical disability and immobility indicators: subjective (HAQ-S, BAS-G, BASFI) and objective (spine movement indicators: lumbar side flexion, modified Schober's test, tragus to wall distance and intermalleolar distance); disease activity indicators: BASDAI, ESR, CRP and disease activity determined by rheumatologist; medications in use: glucocorticoids and TNF-α blockers. Variables with highest determination coefficients of the equations of multiple stepwise linear regression obtained during the assessment of BMD at lumbar spine and upper part of the left and right femur were selected for the final multiple linear regression analysis:

- Age, gender (BMD expressed as g/cm^2), BMI;
- Duration of the disease calculated from the time of the manifestation of first symptoms;
- Indicators of patient's functional status: physical disability and immobility according to HAQ-S questionnaire, and reduction of spine movement assessed by the measurement of intermalleolar distance;
- Activity of the diseases determined by rheumatologist;
- Treatment: cumulative doses of glucocorticoids (g).

The summary of the final linear regression analysis model is presented in Table 4. Coding of the categorical variables is presented in Table 5.

Dependent variable	Independent variable	Regression coefficient (B) (standard error)	Beta	p
BMDS (R^2 =.192; R^2 (adj.) = .168; p < .001)	DAR2	-.124 (.027)	-.459	< .001
	DAR1	-.066 (.026)	-.252	.012
	G2	.064 (.023)	.231	.006
	BMI	.005 (.002)	.189	.022
	constant	.773 (.063)		< .001
BMDL (R^2 =.405; R^2 (adj.) = .382; p < .001)	DAR2	-.122 (.022)	-.480	< .001
	IM2	-.101 (.025)	-.290	< .001
	BMI	.006 (.002)	.244	.001
	DAR1	-.059 (.021)	-.240	.005
	Glucocorticoids	-.001 (.001)	-.141	.045
	Constant	.783 (.047)		< .001
BMDR (R^2 =.443; R^2 (adj.) = .421; p < .001)	DAR2	-.115 (.022)	-.450	< .001
	IM2	-.121 (.024)	-.347	< .001
	BMI	.006 (.002)	.230	.001
	Glucocorticoids	-.002 (.001)	-.163	.017
	DAR1	-.046 (.020)	-.185	.025
	Constant	.775 (.046)		< .001
ZS (R^2 =.294; R^2 (adj.) = .266; p < .001)	BMI	.061 (.015)	.313	< .001
	DAR2	-.919 (.196)	-.441	< .001
	DAR1	-.496 (.185)	-.247	.008
	Duration of the disease from first symptoms onset	.003 (.001)	.252	.003
	Glucocorticoids	-.019 (.007)	-.226	.006
	Constant	-2.608 (.418)		< .001
ZL (R^2 =.388; R^2 (adj.) = .365; p < .001)	DAR2	-.922 (.177)	-.461	< .001
	BMI	.072 (.013)	.384	< .001
	DAR1	-.468 (.165)	-.243	.005
	Glucocorticoids	-.012 (.006)	-.146	.042
	IM2	-.400 (.199)	-.147	.046
	Constant	-2.399 (.373)		< .001
ZR (R^2 =.384 R^2 (adj.) = .360; p < .001)	DAR2	-.853 (.178)	-.425	< .001
	BMI	.068 (.013)	.360	< .001
	IM2	-.550 (.200)	-.201	< .001
	Glucocorticoids	-.013 (.006)	-.160	.007
	DAR1	-.366 (.166)	-.189	.026
	Constant	-2.414 (.376)		< .001

Table 4. Multiple linear regression analysis of BMD (expressed as g/cm² and Z-score) at different sites of measurement (dependent variable), demographic and disease variables (independent variables). Bone mineral density (BMD) expressed as g/cm² at spine (BMDS), left femur (BMDL) and right femur (BMDR); BMD expressed as Z-score at spine (ZS), left femur (ZL) and right femur (ZR). IM – intermalleolar distance; DAR - activity of the disease determined by rheumatologist. The coefficient of determination R^2 and coefficient of determination corrected by the number of independent variables (R^2(adj.)), and p value close to the coefficient of determination is intended to test the hypothesis that regression is absent (hypothesis is discarded when p < .05); standard error determines standard deviation of the coefficient of regression; beta determines coefficient of regression of standardized data.

Variable	Coding	
Gender	**G1**	**G2**
Premonapausal females	0	0
Postmenopausal females	1	0
Males	0	1
Intermalleolar distance	**IM1**	**IM2**
0 – mild limitation of movement	0	0
1 – moderate limitation of movement	1	0
2 – severe limitation of movement	0	1
Activity of the disease determined by rheumatologist	**DAR 1**	**DAR 2**
2 – low activity	0	0
3 – moderate activity	1	0
4 – high activity	0	1

Table 5. Coding of the categorical variables in the regression analysis.

The analysis of Table 4 shows that main variable associated with BMD decrease at all examined sites of the skeleton is moderate and high disease activity which was determined by rheumatologist. Higher BMD values at all examined sites of the skeleton are determined by higher BMI of the patients with SpA (positive coefficient of regression). Spine BMD (expressed as Z-score) and both femurs BMD (expressed as g/cm^2 and Z-score) are significantly negatively affected by glucocorticoids. This means that higher cumulative glucocorticoid dose is associated with lower BMD at the spine and both femurs. Severe limitation of spine movement, assessed by the intermalleolar distance, is the significant negative variable for BMD changes at the upper part of the left and right femur (expressed as g/cm^2 and Z-score). The duration of the disease calculated from the onset of first symptoms was a significant variable associated with the changes in spine BMD (expressed as Z-score). It should be noted that lengthening of the duration of the disease is associated with higher Z-score at the spine (positive coefficient of regression was obtained). Male gender is another causative factor significantly positively affecting spine BMD changes (expressed as g/cm^2).

To summarise, it should be stated that the decrease of spine BMD is significantly associated with moderate and high activity of the disease determined by rheumatologist, and with the increase of cumulative dose of glucocorticoids; the decrease of upper part of both femurs BMD is associated with moderate and high activity of the disease determined by rheumatologist, the increase of cumulative dose of glucocorticoids and severe limitation of spine movement assessed by intermalleolar distance. Based on beta coefficients of significant variables it might be stated that the most precise prognostic variable for the decrease of BMD is increasing activity of the disease in patients with SpA determined by rheumatologist.

Analyzing BMD changes dependence from changes of established significant variables subjects of SpA group were allocated into subgroups according to these factors. Allocation was based on literature data and trends of changes of BMD and specific factors established by our research.

In order to clarify how BMD changes with the increase of the disease duration (assessed from the time of first symptoms) we allocated patients with SpA in three subgroups:

patients with the duration of the disease shorter than 100 months; patients with the duration of the disease from 100 to 200 months; and patients with the duration of the disease of more than 200 months. Results of the comparison BMD (expressed as g/cm² and Z-score) between subgroups presented in Table 6.

BMD	Duration of the disease from the time of first symptoms			p	Post hoc
	1	2	3		
	< 100 months (n = 75)	100-200 months (n = 35)	> 200 months (n = 26)		
BMDS	.878 (.105)	.852 (.158)	.890(.147)	.488	
BMDL	.886 (.100)	.804 (.123)	.803(.140)	< .001	1>2 (p = .002) 1>3 (p = .005)
BMDR	.875 (.096)	.795 (.138)	.782(.128)	< .001	1>2 (p = .002) 1>3 (p = .001)
ZS	-1.311 (.888)	-1.468 (1.163)	-1.131(1.016)	.422	
ZL	-.920 (.893)	-1.432 (.947)	-1.342(.986)	.013	1>2 (p = .021)
ZR	-1.004 (.878)	-1.489 (1.030)	-1.491(.922)	.011	1>2 (p = .031)

Table 6. Comparison of BMD (g/cm²) and Z-score (mean (SD)) between patients with various disease duration (assessed from the time of first symptoms). Bone mineral density (BMD) expressed as g/cm² at spine (BMDS), left femur (BMDL) and right femur (BMDR); BMD expressed as Z-score in spine (ZS), left femur (ZL) and right femur (ZR).

Using analysis of variance (ANOVA) it was established that BMD (expressed as g/cm² and Z-score) at the both femurs significantly decreased when duration of the disease increased (assessed from the time of first symptoms). BMD at the spine not only decreases with the increase of the duration of disease, but even slightly increases, however, not significantly. We suppose that this is only „false-positive" effect occurred due to spine changes specific to SpA: syndesmophytes, calcification of longitudinal ligaments and calcification intervertebral discs and joint ankylosis in long-term SpA patients, and therefore no significant spine BMD (expressed as g/cm² and Z-score) differences between these subgroups were established measuring BMD by DXA anterior-posterior view. No significant BMD differences between subgroups of patients allocated according to the duration of the disease assessed from the time of diagnosis were established in any sites of the skeleton (all $p > .05$. data not shown). According to these data we may assume that the most significant loss of bone mass takes place in the beginning of disease when diagnosis is not established yet. When diagnosis is established, etiopathogenetic treatment starts strongly inhibiting local and systemic inflammation and associated osteoclast activity and demineralization of the bone tissue.

Another variable that allows for the suspected decrease of BMD (expressed as g/cm² and Z-score) at upper parts of both femurs is decrease in spine movement assessed by the intermalleolar distance. When SpA patients were allocated into subgroups according to standardized levels of limitation of movement, it was noticed that with the decline of spine movement (assessed by the intermalleolar distance) BMD decreased not only at both femurs (expressed as g/cm² and Z-score), but also at the spine (expressed as g/cm²). The lowest femur BMD (expressed as g/cm² and Z-score) was determined in SpA patients with severe limitation of spine movement assessed by the intermalleolar distance (Table 7).

BMD	Level of limitation of spine movement			p	Post hoc
	0 (n = 73)	1 (n = 44)	2 (n = 19)		
BMDS	.899 (.112)	.857 (.124)	.813 (.171)	.019	2<0 (p = .024)
BMDL	.880 (.099)	.849 (.116)	.730 (.139)	< .001	2<0 (p < .001) 2<1 (p < .001)
BMDR	.871 (.100)	.840 (.103)	.698 (.145)	< .001	2<0 (p < .001) 2<1 (p < .001)
ZS	-1.184 (.929)	-1.448 (.877)	-1.522 (1.370)	.234	
ZL	-.980 (.879)	-1.145 (.873)	-1.692 (1.191)	.049	2<0 (p = .009)
ZR	-1.051 (.885)	-1.205 (.794)	-1.917 (1.238)	.002	2<0 (p < .001) 2<1 (p = .014)

Table 7. Comparison of BMD (g/cm^2) and Z-score (mean value (SD)) between SpA patients allocated according to the established limitation of spine movement assessed by the intermalleolar distance

Bone mineral density (BMD) expressed as g/cm^2 at spine (BMDS), left femur (BMDL) and right femur (BMDR); BMD expressed as Z-score in spine (ZS), left femur (ZL) and right femur (ZR); 0 - mild limitation of movement, 1 – moderate limitation of movement, 2 – severe limitation of movement.

Another significant and clinically important factor associated with BMD changes at the spine and both femurs is cumulative dose of GC. It is not known what cumulative dose of GC or duration of use of these medications become risk factors for the decrease of BMD. Therefore patients were conventionally allocated into 4 subgroups according to the following distribution of cumulative doses: untreated patients (n = 46); patients using cumulative dose of less than 1 g (n = 34) corresponding use of 5 mg/day during up to 6 months; patients using cumulative dose from 1 to 10 g (n = 36) corresponding use of 5 mg/day during up to 5 years; and patients using cumulative dose more than 10 g (n = 20) corresponding use of 5 mg/day longer than 5 years.

BMD	Cumulative glucocorticoid dose				p	Post hoc
	1	2	3	4		
	Untreated (n = 46)	< 1g (n = 34)	1-10 g (n = 36)	>10 g (n = 20)		
BMDS	.869 (.102)	.903 (.138)	.869 (.126)	.844 (.167)	.405	
BMDL	.881 (.110)	.873 (.122)	.830 (.106)	.769 (.133)	.002	4<1 (p = .002) 4<2 (p = .010)
BMDR	.868 (.112)	.856 (.113)	.827 (.101)	.747 (.150)	.001	4<1 (p = .001) 4<2 (p = .006)
ZS	-1.320 (.933)	-1.097 (.975)	-1.361 (.960)	-1.602 (1.160)	.333	
ZL	-.871 (.958)	-1.076 (.791)	-1.270 (.847)	-1.586 (1.180)	.028	4<1 (p = .024)
ZR	-.962 (.983)	-1.186 (.737)	-1.291 (.817)	-1.757 (1.226)	.017	4<1 (p = .009)

Table 8. Comparison of BMD (g/cm^2) and Z-score (mean value (SD)) between SpA patients allocated according to the cumulative glucocorticoid dose. Bone mineral density (BMD) expressed as g/cm^2 at spine (BMDS), left femur (BMDL) and right femur (BMDR); BMD expressed as Z-score in spine (ZS), left femur (ZL) and right femur (ZR).

Comparison of BMD (expressed as g/cm^2 and Z-score) between patients allocated according to cumulative glucocorticoid dose is presented in the Table 8. Analysis of the results using Turkey HSD test demonstrated that between first three groups (untreated patients, patients used < 1g and 1-10g cumulative dose of glucocorticoids) there are no statistically significant differences of BMD (expressed as g/cm^2 and Z-score) at the lumbar spine and upper part of the left and right femur. However, differences presented in the Table 8 are caused by the comparison of patients taking a cumulative dose of more than 10 g of glucocorticoids with untreated patients. Summarizing these results it may be said that higher than 10 g cumulative dose of glucocorticoids is associated with the decrease of BMD (expressed as g/cm^2 and Z-score) at the upper part of the left and right femur in patients with SpA.

The most important SpA factor associated with the loss of bone mass is the activity of SpA disease. In SpA group there were no patients with inactive disease determined by rheumatologist (score of activity = 1), and therefore patients were allocated into three subgroups according to the activity of disease: 2 – mild activity, 3 moderate activity, 4 – high activity. Comparison BMD between these subgroups presented in the Table 9.

BMD	Activity of the disease determined by rheumatologist			p	Post hoc
	2 (n = 35)	3 (n = 55)	4 (n = 46)		
BMDS	.937 (.112)	.878 (.116)	.819 (.133)	< .001	4<2 (p < .001) 4<3 (p =.015) 3<2 (p = .026)
BMDL	.927 (.093)	.865 (.110)	.771 (.107)	< .001	4<2 (p < .001) 4<3 (p < .001) 3<2 (p = .007)
BMDR	.909 (.087)	.860 (.109)	.754 (.113)	< .001	4<2 (p < .001) 4<3 (p < .001) 3<2 (p = .034)
ZS	-.809 (.899)	-1.301 (.837)	-1.722 (1.054)	< .001	4<2 (p < .001) 4<3 (p =.025) 3<2 (p = .016)
ZL	-.538 (.735)	-1.054 (.914)	-1.680 (.837)	< .001	4<2 (p < .001) 4<3 (p < .001) 3<2 (p = .005)
ZR	-.683 (.717)	-1.092 (.905)	-1.787 (.881)	< .001	4<2 (p < .001) 4<3 (p < .001) 3<2 (p = .028)

Table 9. Comparison BMD (g/cm^2) and Z-score (mean value (SD)) between SpA patients allocated according to the activity of the disease determined by rheumatologist Bone mineral density (BMD) expressed as g/cm^2 at spine (BMDS), left femur (BMDL) and right femur (BMDR); BMD expressed as Z-score in spine (ZS), left femur (ZL) and right femur (ZR); 2 – mild activity, 3 – moderate activity, 3 – high activity.

Analysis of the comparison data presented in Table 9 demonstrated that disease activity assessment performed by rheumatologist allows to suspect BMD changes in all sites of skeleton. In all analyzed sites (in lumbar spine and both femurs BMD expressed as g/cm^2 and Z-score) in patients with lower disease activity (2) BMD was higher in comparison with

patients with moderate (3) activity of the disease, and in this group of patients BMD was higher than in patients with high (4) activity of the disease.

3.5 Factors predicting Z-score probability of ≤ - 2.0 at any site of skeleton

At the last step of the analysis of the results we performed forward stepwise (Wald) logistic regression analysis intended to find out which variables are the most predictive to event causing Z-score probability of ≤ - 2 at any site of skeleton. Assigning Z-score ≤ - 2.0 as one and Z-score > -2.0 as zero, logistic regression model will predict the probability of the event during which coded variable will obtain valuation of 1; in this case the probability will be designated as θ. Z-score of ≤-2.0 at least in one area of skeleton was determined in 43 patients with SpA (31.6 percent of all patients with SpA).

All variables analyzed in this research were entered into a forward stepwise logistic regression model: age, gender, BMI, family history of fractures, disease belonging to SpA group, type of joint lesion and physical activity; duration of the disease assessed from the time of the onset of first symptoms and from the time of the diagnosis; physical disability and immobility indicators: BAS-G, BASFI, HAQ-S, lumbar side flexion, modified Schober's test, tragus to wall distance and intermalleolar distance; indicators of the activity of the disease: ESR, CRP, BASDAI and disease activity determined by rheumatologist; cumulative dose of glucocorticoids and treatment with TNF-α blockers.

The following significant variables for event θ remained in the logistic regression model: moderate and high activity of the disease determined by rheumatologist, low BMI and positive family history of fractures. The results of the last step of logistic regression model are presented in Table 10.

Indices of the relevance of model	Regressor*	Coefficient of regression (B), (standard error)	Wald statistics	p	Exp (B)
χ^2 model compatibility criterion p < .001	DAR		17.852	<.001	
	DAR (2)	3.922 (1.091)	13.384	<.001	54.179
	DAR (1)	2.610 (1.077)	5.877	.015	13.602
Hosmer and *Lemeshow* χ^2 compatibility criterion p = .771	BMI	-.156 (.052)	9.025	.003	.856
	Positive family history of fractures	1.167 (.543)	4.618	.032	3.212
Coefficient of determination: *Negelkerke* R^2 = .407	constant	-.528 (1.607)	.108	.743	.590

Table 10. Logistic regression analysis of the event when Z-score probability at any site of skeleton will be ≤ - 2.0 at the analysis of SpA patient data. * DAR – activity of the disease determined by rheumatologist; coding of variables described in the Table 5.

The analysis demonstrated that correct probabilities for Z-score at any sites of the skeleton were established in 75.7 % of respondents.

4. Discussion

Skeletal remodeling in bone growth, maintenance, and repair is tightly regulated by a dynamic interaction between osteoclasts and osteoblasts. Recent advances in immunopathological mechanism of chronic inflammatory rheumatic disease highlighted the altered balance between bone loss and production by inflammation. T cells, natural killers, and cytokines that are involved in inflammatory process may also be responsible for the bone loss (Ritchlin et al., 2003). Many investigators have observed decreased BMD of the whole skeleton and increased femoral and vertebral fracture risk in patients suffering from both RA and SpA in comparison with healthy persons (Lodder, 2004; Huusko, 2001; Grisar, 2002). Up till now BMD changes were not being compared between SpA and RA patients.

An interesting observation from our study is that there was no statistically significant difference of BMD in any examined part of skeleton between the two groups of diseases, i.e. RA and SpA but the BMD difference between the control group and RA and SpA groups was statistically significant, the BMD being higher in all examined parts of skeleton of the control group. Analyzing BMD of SpA, RA and control groups the Z-score of the three groups were compared in order to exclude influence of age and gender, known OP risk factors, on BMD. The Z-score in all examined parts was similar for both RA and SpA groups while the Z-score difference in the same parts examined between the control group and both patient groups was statistically significant, the Z-score being higher in the control group. The findings support the hypothesis that inflammatory environment not only in joint synovial tissues but also in bone caused by autoimmune changes in RA and SpA patients induces a lot of molecular changes, RANKL and OPG equilibrium derangement and is one of the causes provoking not only local but also systemic osteoclastogenesis and related bone resorbtion (Suda, 1992; Franck, 2004; Golmia, 2002). The reduced BMD in case of both RA and SpA may also be explained by worsened mobility function (Szejnfeld, 1997; Faus-Riera, 1991), disturbances of calcium and vitamin D metabolism because of intestine injury and adverse effect of GC on bone tissue (Lange, 2005; Mielants, 1989).

Data on comparison of the BMD between healthy persons and patients diagnosed with SpA are scarce. As it was mentioned above the BMD of SpA patients was mostly investigated in AS. Several researchers have observed decreased BMD in AS patients compared with healthy persons (Will, 1989; Devogelaer, 1992; Sampaio-Barros, 2005). *K. Dheda* and colleagues, having examined 20 PsA patients, have not observed any statistically significant BMD reduction in PsA patients compared with healthy persons either in lumbar spine or in femur (Dheda et al., 2004). On the contrary *B. Frediani* and colleagues have found statistically significant BMD reduction both in vertebra and femur of PsA patients compared with corresponding skeleton parts of the control group (Frediani et al., 2001). Data on statistically significant BMD reduction in entire skeleton of EnA patients compared with the control group was published by several authors. (Frei, 2006; Reffitt, 2003). *J. Grisar* and colleagues investigated bone metabolism markers and BMD of AS, PsA and ReA patients. The investigators found statistically significant BMD decrease in the proximal femur of AS patients compared with PsA patients. There was no statistically significant difference of vertebral BMD of AS patients and both vertebral and proximal femoral BMD of PsA and ReA patients compared with the BMD of the control group. *J. Grisar* and colleagues conclude that in all forms of the above mentioned spondyloarthropathies accelerated resorbtion of bone tissue prevails regardless of the fact that decreased BMD was not

observed in all examined disease patients compared with the control group (Grisar et al., 2002). We have not found any statistically significant BMD difference in AS, PsA, EnA and ReA patients in any part of the skeleton examined.

In our study we tried to define a correlation between BMD changes in lumbar spine and proximal femur and duration of the SpA.The SpA duration was calculated by the two following ways: from manifestation of the first symptoms and from the moment of clinical diagnosis statement. The results revealed that lenghthening disease duration calculated from manifestation of the symptoms is related to vertebral BMD growth and femoral BMD reduction. Agreeing with other authors (Donnelly, 1994; Reid, 1986; Mullaji, 1994), we think that vertebral BMD readings of patients with long disease duration measured by anterior-posterior view of DXA method are merely „deceptive". The lumbar spine often shows misleading high BMD values due to bridging syndesmophytes and ankylosis, which might mask osteoporosis in AS patients with an advanced disease (Donnelly, 1994; Karberg, 2005; Mullaji, 1994; Muntean, 2011).

Our previous investigations showed that SpA patients both with long and short disease duration have statistically significant lower proximal femoral and lumbar vertebral BMD compared with the control group (Venceviciene et al., 2008). Lengthening disease duration calculated from the moment of clinical diagnosis statement had no significant correlation to changes of vertebral and proximal femoral BMD. *R. Will* and colleagues have not found significant difference in the average lumbar vertebral BMD between patients suffering from AS longer than 10 years and the control group (Will et al., 1990). *E. S. Meirelles* and colleagues observed positive correlation between disease duration and changes of proximal femoral and lumbar vertebral BMD (Meirelles et al., 1999). Until now only one study that quantifies the magnitude of osteoporosis in population of early SpA patients is available (Van der Weijden et al., 2011). In this study all patients had a BMD measurement at a median of period 6.6 months after diagnosis. This study showed a high prevalence (47%) of low BMD in both femur and lumbar spine in SpA patients with early disease. In contrast with our study, no significant differences between the two groups with low and normal BMD were found in regard to time since diagnosis and disease duration (median of 6.3 years), counting from the very first symptoms of axial manifestations (Van der Weijden et al., 2011). Unfortunately the above mentioned study has some limitations: the BMD of patients was not compared with healthy persons. More to the point, a BMD and Z-score should be used instead of T-score to assess BMD changes in males under 50 years of age. The fact that low BMD is encountered in a young population with an early disease is very interesting. In most other studies, "early" often refers to patients who have not yet developed ankylosis or other radiological progression signs, or that these studies made use of disease durations as time since diagnosis and then referred to a disease duration of <10 years (Gratacos, 1999; Toussirot, 2001, Will, 1989). The issue of defining disease duration has been often debated in the AS literature. Today, the onset of the first symptoms is considered to be most important criteria (Davis et al., 2006). Taking into account the fact that AS is usually diagnosed 6-8 years after manifestation of the first symptoms we think that the most prominent decrease of the BMD takes place in the early pre-diagnosis period of the disease. Etiopathogenetic treatment begun after diagnosing the disease suppresses local and systematic inflammation and related activity of osteoclasts together with demineralization of the bone tissue.

In SpA, especially AS, other potential risk factors for bone loss occur, such as inflammation and mechanical factors -rigidity of the spine resulting in limited mobility and reduced physical activity due to pain and stiffness. Data about these risk factors, high disease activity variables such as ESR, CRP, BASDAI in relation with low BMD levels in different studies are not consistently reported (Karberg, 2005; Gratacos, 1999; Toussirot, 2001).

Acknowledging that high SpA activity is one of the most important risk factors for BMD reduction (Gratacos, 1999; Kim, 2006) and there being no currently standardized indicators of SpA activity we aimed to define which of the accessible disease activity indicators most frequently used in clinical practice might reflect BMD changes in SpA patients. We assessed disease activity on the basis of active disease diagnosis rated by the same rheumatologist, acute inflammatory phase indicators, ESR and CRP, and by subjective patient's evaluation of the disease activity using results of BASDAI questionnaire (Landewe et al., 2004). We found statistically significant association between decreased vertebral and both femoral BMD and moderate or hight SpA activity rated by the rheumatologist. There was no significant correlation between CRB, ESR, BASDAI and BMD changes in the examined skeleton parts.

On the contrary, *E. S. Meirelles* and colleagues have found no correlation between disease activity rated by the rheumatologist and BMD changes (Meirelles et al., 1999). *K. Capaci* and colleagues has proved that disease activity rated by physician on the basis of radiological signs of vertebral and hip destruction extent has no influence on the bone mass of AS patients (Capaci et al., 2003). Other authors have made similar conclusions to proving that acute inflammatory phase markers found once do not forecast either progression of radiological signs of SpA or reduction of BMD in different parts of skeleton. (Karberg, 2005; Toussirot, 2001; Muntean, 2011). Nevertheless, *J. Gratacos* and colleagues having carried out a two year perspective study and assessing AS disease activity by ESR, CRP and IL-6 blood concentration found that the subgroup of active disease patients had statistically significant reduction of BMD of femoral neck and lumbar spine but there were no significant BMD changes in the examined parts of the subgroup of non-active disease patients. (Gratacos, 1999). In another study disease activity parameters such as increased CRP and high BASFI and BASMI scores, correlated significantly with low bone mass in femoral neck as well as in lumbar spine (Van der Weijden et al., 2011). However, at the 12-month follow-up study hip bone loss was found to be associated with raised baseline C-reactive protein levels (Haugeberg et al., 2010).

Based on the previous research, as well as on the results of the present study, we conclude that active course of the disease and pronounced systemic inflammatory process without question has negative influence on BMD by different mechanisms which are insufficiently researched up to this time. We think that the contradiction that exists between our data and presented by other authors about the influence of disease activity on BMD changes may result from the difference in the groups of patients (the other authors mostly studied only AS patients) and methods used to assess disease activity. Furthermore, the role of pro-inflammatory cytokines might be important for the onset of osteoporosis because increased TNF-alpha levels have been found in patients with AS compared with subjects with non-inflammatory back pain, and correlations have been found between disease activity and markers associated with an increased bone metabolism (Lange et al., 2000). We, together with other authors think that cross-sectional laboratory acute inflammatory markers such as

CRP or ESR and results of BASDAI questionnaire which reflects the main SpA symptoms during the last week can not predict BMD changes (Karberg, 2005; Speden, 2002; Muntean, 2011). Only a physician rheumatologist's assessment of the entire case history including clinical, laboratory, radiological signs and taking regular care of the patient may accurately determine disease activity in the long course of disease activity. Disease activity according to our research data has a significant correlation with bone mass loss both in lumbar vertebral and femoral proximal regions.

We also tried to determine the influence of physical disability and disturbances of mobility function on BMD changes in lumbar vertebral and femoral proximal regions. Like other investigators we have found that patient's mobility function worsens with increasing duration of the illness (Falkenbach, 2002; Wei, 2007; Karatepe, 2005). It is known that SpA standardized indicators of spine mobility correlate with radiological changes such as impairment in sacroiliac joints and spine and the latter is an independent factor for the prediction of femoral BMD changes (Speden et al., 2002). We have established that the decrease of spine mobility determined by the modified Shober test shows possible reduction of femoral BMD. *H. J. Baek* and colleagues, having divided AS patients into two groups by spine flexibility index according to Schober test (correspondingly > 5cm and < 5cm), the group of patients with good mobility and the group of patients with bad mobility, have not found any BMD difference in lumbar spine between the groups while the proximal femoral BMD was statistically significantly lower in the bad mobility group in comparison with the good mobility group (Baek et al., 2005). We have obtained similar results by dividing SpA patients according to tragus-to-wall distance and lumbar lateral flexion measurement, then assessing the decrease in spine flexibility and comparing it's BMD. Statistically significant BMD difference was obtained only in the femur. Differently, the decrease in spine flexibility was determined by intermalleolar distance measurement, showed significant BMD reduction not only in femur but in spine too. We failed to find studies assessing correlation between spine flexibility indices such as lateral flexion, tragus-to-wall distance, intermalleolar distance (measuring spine flexibility in different parts of spine) and BMD changes.

It is worthy to note that many studies assessing mobility and physical disability of SpA patients are being carried out all over the world (Bostan, 2003; Zochling, 2006; Ward, 2002) but the research data about dependence of bone mass changes in different regions of skeleton on physical disability and disturbances of mobility are scarce and controversial. Several scientists insist that disturbances of mobility function have no influence on lowering BMD in AS patients (Mitra, 1999; Maillefert, 2001). *J. Gratacos* and colleagues failed to find the correlation between BMD reduction and the results of HAQ-S questionnaire evaluating physical disability of SpA patients. (Gratacos et al., 1999). Nevertheless *H. Franck* and colleagues found that patients having decreased BMD in different parts of the skeleton had significantly poorer mobility function indices (Schober index and results of BASFI questionnaire) in comparison with the group of patients having normal BMD (Franck et al., 2004). The results of our study however show that lessening of mobility function has no influence on spinal BMD. Changes in femoral BMD are best reflected by the physical disability of SpA patients assessed using HAQ-S questionnaire and disturbances of mobility function assessed by the BASFI questionnaire.

In agreement with other authors (Will, 1989; Mullaji, 1994) we have found that frequency of exercise of the patient had no significant influence on BMD changes in the parts of skeleton examined.

Summing up the results it is possible to state that reduction of BMD correlates with disturbances of mobility function that lessens during disease course as demonstrated by the results presented above. On the other hand, comparativelly good spine BMD results are probably „misleading". We as other researchers (Donnelly, 1994; Reid, 1986) support the statement that in the course of the disease, impairment of the spine begins in the form of calcification of longitudinal ligaments and intervertebral discs, formation of syndesmophytes and joint ankylosis. Apparently the decrease in spine mobility caused by changes in the spine may be associated with proximal femoral BMD changes.

The aim of our study was to clear up whether GC and TNF-α blockers can influence BMD changes for SpA patients. The effect of GC on bone mass of SpA patients is not sufficiently investigated. Some authors are of the opinion that GC cumulative doses is not a factor in the successful prognosis of BMD decrease [Bjarnason, 1997; Habtezion, 2002; Millard, 2001). Several clinical studies have shown that GC in doses of less than 7,5 mg/d does not incite more pronounced bone resorbtion (Bijlsma, 2000; Nishimura, 2000). *O. A. Malysheva* and colleagues have proved that the therapeutic GC dose of 7,5 mg/d has negative influence on BMD when being used longer than 48 weeks (Malysheva et al., 2008). Still A. Savickienė and colleagues have found that duration of GC use and their cumulative dose significantly correlated with lumbar spine BMD reduction in SpA patients (Savickienė et al., 2003). Negative GC influence on bone mass was also described by German researchers having determined that cumulative GC dose negatively correlates with BMD changes and serves as an independent factor for prognosis of BMD reduction in all parts of skeleton (Pollak, 1998; De Jong, 2002).

Considering the fact that GC treatment schemes (dose and duration of presciption) were changed several times we have conditionally divided SpA patients into 4 subgroups according to cumulative GC doses. We have compared BMD among the subgroups. We have not found statistically significant femoral and vertebral BMD difference among the first three subgroups (patients who have not used GC, used cumulative GC doses of <1g and 1-10g). Proximal femoral BMD of patients who used more than 10g of GC was statistically significantly less than BMD of patients who have not used GC. Similar results were obtained by the other group of researchers who proved that only cumulative GC doses exceeding 10 g has significant influence on BMD reduction in all parts of skeleton (Silvennoinen, 1995; Von Tirpitz, 1993).

A new group of drugs blocking cytokin TNF- α used for SpA treatment are called TNF- α blocking agents. This drug is effective in reducing disease symptoms, inflammatory processes and joint destruction (Braun, 2002; Brandt, 2000; Baeten, 2001; Breban, 2002 ; Gorman, 2002). It has been shown that TNF-blocking agents not only reduce signs and symptoms of disease activity in SpA, but also arrest hip and spine bone loss (Marzo-Ortega, 2003; Marzo-Ortega, 2005; Demis, 2002).

We compared BMD readings of patients treated with TNF-α blockers and patients who did not received TNF-α blockers and found no statistically significant BMD difference between the groups in all examined parts of the skeleton. While statistically significant influence of

TNF-α blockers on bone mass was not found it is still not possible to state that these drugs have no positive effect on suppression of bone tissue resorbtion. This cross-sectional study was not designed as an observation of TNF-α blockers effectiveness. On the other hand these drugs are only used to treat SpA of high activity after treatment with other disease modifying drugs and in cases with pronounced joint impairment. On the basis of the results of this study showing statistically significant negative influence of high disease activity on the BMD changes and „deceptive" BMD spine readings conditioned by long disease duration it is possible to assume that these factors could „hide" positive effect on bone caused by the TNF-α blockers. We hope that the further long term longitudinal studies with bigger observational cohort will prove the beneficial effect of TNF-α blockers for not merely reducing local and systemic inflammation but also their positive influence on the bone tissue of SpA patients.

Summing up all the results it is possible to state that only moderate or high SpA activity rated by the rheumatologist and GC cumulative dose are statistically significant specific factors which can predict reduction of BMD of lumbar spine in SpA patients.. It is important to note that the lengthening disease duration counted from the beginning of the first symptoms relates to augmentation of spinal BMD. Reduction of BMD of both proximal femurs was associated with moderate or high SpA activity rated by the rheumatologist, severe reduction of spine flexibility assessed by intermalleolar distance measurement and GC cumulative doses. The BMI is the only significant variable out of all other factors related to spinal and femoral BMD changes. It is necessary to point that increased BMI is related to higher vertebral and femoral BMD readings. The data of this study are in agreement with the data presented by the other authors that low BMI (< 19 kg/m^2) is related to possible nutritional deficiencies of vitamin D, calcium and protein and therefore, to BMD reduction (Ravn, 1999; Edelstein, 1993; Cetin, 2001). We have also determined the prognostic factors for SpA patients that need to be included into the group of reduced BMD (when the Z-score is ≤–2.0 in any part of the skeleton). Results of our study show that SpA patients whose disease activity rated by the rheumatologist is moderate or high and who have positive family history of OP fractures have a Z-score of ≤–2.0 found in any investigated part of the skeleton.

We have proved that SpA disease activity rated by the rheumatologist, spine flexibility assessed by intermalleolar distance measurement, cumulative GC doses, BMI, disease duration measured from the manifestation of symptoms and family history of OP fractures are important for evaluating the risk of BMD reduction for SpA patients. It is valuable for identifying those who should undergo testing for BMD and for what specific region of skeleton, and also for prescribing effective means for prevention and/or treatment.

5. Conclusions

- In patients with spondyloarthropathies BMD (expressed as g/cm^2 and Z-score) is the same as in patients with rheumatoid arthritis and is significantly lower in comparison with BMD of healthy subjects measured at the lumbar spine and upper part of left and right femur.
- Similar BMD changes at the lumbar spine and upper part of left and right femur are characteristic to SpA patients with various diseases belonging to SpA group.

- In SpA patients BMD changes do not depend on the predominant type of joint lesion.
- Duration of the disease reflects changes in BMD better when it is calculated not from the time of the establishment of clinical diagnosis, but from the time of onset of first clinical symptoms. Relations between the duration of the disease and BMD changes at the lumbar spine and upper part of left and right femur are different: BMD decreases at the upper parts of both femurs and increases at the spine with longer duration of the disease.
- High and moderate activity of the disease (established by rheumatologist) is associated with the elevated bone resorption at the lumbar spine and upper part of left and right femur. The relation between disease activity (which measured by ESR, CRP level and BASDAI questionnaire) and BMD decrease in any investigated area of skeletal system was not observed.
- BMD reduction at the lumbar spine and upper parts of both femurs is associated with the decrease of mobility of a SpA patient. Intermalleolar distance is the most precise indicant reflecting the relation between decrease of physical ability and mobility and BMD changes in all investigated areas of skeletal system: at the spine (BMD expressed as g/cm^2) and at the upper parts of both femurs (BMD expressed as g/cm^2 and Z-score); the lowest BMD at upper parts of both femurs is measured when reduction of spine movement is defined as severe.
- Significant negative association between cumulative dose of glucocorticoids and BMD changes at the lumbar spine and upper part of left and right femur were observed: BMD at the lumbar spine and upper parts of both femurs decrease with the increase of cumulative dose of glucocorticoids.

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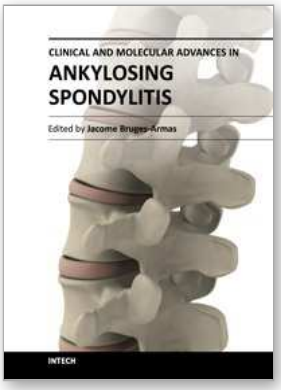

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The first section of the book entitled Clinical and Molecular Advances in Ankylosing Spondylitis is a review of the clinical manifestations of Ankylosing Spondylitis (AS) and Spondyloarthritis (SpA). The book includes chapters on Bone Mineral Density measurements, two chapters on the temporomandibular joints, axial fractures, clinical manifestations, diagnosis, and treatment. Molecular genetics and immune response are analyzed in the second section of the book; information on HLA-B*27, other MHC genes and the immune response of AS patients to bacteria is reviewed and updated. Two chapters are dedicated to recent information on non-MHC genes in AS susceptibility, and to new data on disease pathways generated from gene expression studies on peripheral blood.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

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