ORIGINAL ARTICLE

DISORDERS OF STRUCTURAL AND FUNCTIONAL STATE OF BONE TISSUE IN MEN WITH ANKYLOSING SPONDYLITIS, THEIR RELATION TO DISEASE COURSE

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ABSTRACT

The aim: To study the structural and functional state of bone tissue in men with ankylosing spondylitis and to asses its relationship with the course of the disease.

Materials and methods: the study was conducted involving 105 men, aged 40.74 ± 0.87 years and 25 generally healthy individuals of the certain age and sex, who formed the control group. The functional ability was assessed by the BASFI index and the disease activity was calculated by ASDAS-CRP and BASDAI. Laboratory criteria for the activity of the inflammatory process were considered erythrocyte sedimentation rate and C-reactive protein. Bone mineral density of the lumbar spine and femoral neck was determined by dual energy X-ray absorptiometry.

Results: osteoporosis and osteopenic syndrome were identified in men with ankylosing spondylitis in 27,7% and 29,5% consequently. Disorder of the structural and functional state of bone tissue was closely related to the total indicators of inflammatory activity in ASDAS-CRP (r = –0,36), BASDAI (r = –0,51), the functional index BASFI (r = –0,30), C-reactive protein (r = –0,30) and the cumulative dose of glucocorticoids (r = –0.32). The comparative analysis of densitometric parameters in groups of patients depending on the form of the disease has not shown statistically significant differences.

Conclusions: The decrease in bone mineral density in patients with ankylosing spondylitis does not depend on age and duration of the disease, but is associated with the cumulative dose of glucocorticoids and high activity of the inflammatory process.

KEY WORDS: ankylosing spondylitis, osteoporosis, X-ray absorptiometry

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INTRODUCTION

The problem of osteoporosis has been maintaining its relevance over tenths of years due to high frequency and increase in the number of osteoporotic fractures among the population. This disease, according to the WHO, holds fourth place among non-infectious diseases, being inferior only to cardiovascular pathologies, oncologic diseases and diabetes mellitus. Of particular interest is the study of osteoporosis in ankylosing spondylitis (AS), because the unique peculiarity of pathogenesis of this disease is the development of two opposite processes: spine ossification and formation of syndesmophytes as well as loss of bone tissue leading to the development of osteoporosis [1]. It has been established that generalized loss of bone mass may be the consequence of systemic inflammation and high disease activity [2] and due to the fact that disease activity in AS contributes to fast loss of bone mass, osteoporosis is considered to be a symptom of the disease itself and not a comorbidity [3]. However, pathogenesis of osteoporosis still remains controversial even today. It is considered that main reasons of the loss of bone mineral density along with traditional risk factors (age, sex, genetic inclination, low body mass index) are characteristic for this disease – duration of AS, activity of inflammation process, severity of functional disorders, vitamin D deficiency and intake of glucocorticoids (GC). According to the literature data, in case of AS, there is a significant decrease in the BMD in the lumbar spine and in the femoral neck [4]. Regarding the Ukrainian population of patients suffering from the AS we have not discovered any data on the frequency of osteoporosis and osteopenic syndrome. The influence of disease course on the formation of BMD disorders also remains unstudied.

THE AIM

Thus**,** the purpose of the research was to study structural and functional condition of bone tissue in men suffering from AS and to evaluate its connection with the disease course.

MATERIALS AND METHODS

Main group included 105 men suffering from AS aged 40,7±0,87 years, average duration of the disease made 8,7±0,5 years. Control group included 25 practically healthy persons of appropriate age and sex. The diagnosis of AS was based on the ASAS criteria [5]. Age, disease duration, form of AS, intake of GCs, calcium and vitamin D preparations were

Table I. Frequency of osteoporosis and osteopenic syndrome in men suffering from AS

Group	BMD, n (%)								
	Patients			Z-score, SD			BMD, g\cm²		
	with osteoporosis	with osteopenia	with preserved BMD	of the lumbar spine	of the femoral neck	proximal part of femur	of the lumbar spine	of the femoral neck	proximal part of femur
Control group n = 25	1 (4,0%)	5 (20%)	19 (76%)	–0,17 ±0,2	–0,13 ±0,1	–0,23 ±0,14	1,052 ±0,02	0,889 ±0,02	1,034 ±0,02
Patients with AS n = 105	30 (28,6%)*	31 (29,5%)	44 (41,9%)*	–1,08 ±0,15*	–0,91 ±0,08*	–0,69 ±0,08*	0,945 ±0,02*	0,747 ±0,01*	0,874 ±0,02*

Note: *- sign indicated credible differences between the patients suffering from AS and the control group

Table II. BMD indexes depending on AS form

Group	BMD, n (%)								
	Patients			Z-score, SD			BMD, g\cm²		
	with osteoporosis	with osteopenia	with preserved BMD	of the lumbar spine	of the femoral neck	proximal part of femur	of the lumbar spine	of the femoral neck	proximal part of femur
Peripheral form n = 32	7 (21,9%)	9 (28,1%)	16 (50%)	–1,05 ±0,24	–0,82 ±0,1	–0,51 ±0,15	0,919 ±0,02	0,751 ±0,01	0,906 ±0,02
Central form n =73	23 (31,5%)	22 (30,2%)	28 (38,3%)	–1,09 ±0,02	–0,95 ±0,01	–0,77 ±0,01	0,957' ±0,02	0,745 ±0,01	0,860 ±0,03

Table 3. Relation between disease duration and BMD indexes in men suffering from AS

Group	BMD, n (%)								
	Patients			Z-score, SD			BMD, g\cm²		
	with osteoporosis	with osteopenia	with preserved BMD	of the lumbar spine	of the femoral neck	proximal part of femur	of the lumbar spine	of the femoral neck	proximal part of femur
<5 years, n = 20	3 (15%)	8 (40%)	9 (45%)	–0,88 ±0,25	–0,56 ±0,15	–0,43 ±0,13	0,960 ±0,02	0,823 ±0,02	0,947 ±0,02
5 – 10 years, n = 44	20 (45,5%)*	13 (29,5%)	11 (25%)	–1,58 ±0,25	–1,09 ±0,11*	–0,86 ±0,11*	0,905 ±0,02	0,726 ±0,01*	0,873 ±0,02*
>10 years, n = 41	7 (17%) #	10 (24,5%)	24 (58,5%) #	–0,64 ±0,25 #	–0,89 ±0,13	–0,63 ±0,15	0,982 ±0,03 #	0,732 ±0,02*	0,840 ±0,05*

Note: sign *- means credible difference with respect to the group of patients having a disease duration of up to 5 years; sign # - means credible difference with respect to the group of patients having a disease duration of 5-10 years

evaluated in all the patients. For each patient, a cumulative dose and the duration of treatment with GCs were determined. A comprehensive clinical and laboratory examination was performed in all the patients. In order to evaluate back pain, morning stiffness as well as to perform general activity evaluation for the patient, a Visual Analogue Scale was used. The determination of clinical activity of AS was based on the BASDAI and ASDAS-CRP index (<1,3 – inactive AS; 1,3-2,1 – moderate activity; 2,1-3,5 – high activity; >3,5 – very high activity). Laboratory examination included the determination of such markers of inflammation process activity as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

BMD of the lumbar spine and femoral neck was determined by using the method of the dual-energy X-ray absorptiometry (DXA) on the device "Hologic Discovery W" (S/N 87227). The diagnosis of osteoporosis in patients aged above 50 years was considered in case of the decrease in BMD according to the T-score ≤–2,5 SD, osteopenia corresponded to the indexes of T-score ranging from –1 to –2,5 SD. For men aged up to 50 years, Z-score was used, its decrease below ≤–2,0 SD or less indicated a significant loss of bone mass.

RESULTS

In men suffering from AS, the decrease in bone mineral density (BMD) at the level of the lumbar spine and the femoral neck was observed in 58,1 % of the persons, while oste-

Table IV. BMD indexes depending on the age of patients with AS

Group	BMD, n (%)								
	Patients			Z-score, SD			BMD, g\cm2		
	with osteoporosis	with osteopenia	with preserved BMD	of the lumbar spine	of the femoral neck	proximal part of femur	of the lumbar spine	of the femoral neck	proximal part of femur
Patients aged up to 35 years n = 28	10 (35,7%)	10 (35,7%)	8 (28,6%)	–1,55 ±0,21	–0,91 ±0,14	–0,68 ±0,14	0,911 ±0,02	0,780 ±0,02	0,914 ±0,02
Patients aged from 35 to 50 years n = 62	18 (29%)	17 (27,4%)	27 (43,6%)	–1,05 ±0,21	–0,92 ±0,10	–0,78 ±0,11	0,948 ±0,02	0,735 ±0,01	0,848 ±0,03
Patients aged up to > 50 years n = 15	2 (13,3%)	4 (26,7%)	9 (60%)*	–0,30 ±0,44 *	–0,87 ±0,19	–0,32 ±0,21	0,998 ±0,05	0,732 ±0,03	0,905 ±0,03

Note: sign *- means a reliable difference regarding the group of patients aged up to 35 years

Table V. Relation between BMD and ASDAS-CRP and BASDAI activity indexes as well as functional BASFI index

Group	BMD, n (%)								
	Patients			Z-score, SD			BMD, g\cm2		
	with osteoporosis	with osteopenia	with preserved BMD	of the lumbar spine	of the femoral neck	proximal part of femur	of the lumbar spine	of the femoral neck	proximal part of femur
(ASDAS 1,3 - 2,1) n = 2	–	–	2 (100%)	1,10 ±1,7	–0,8 ±0,2	–0,35 ±0,2	1,191 ±0,2	0,863 ±0,02	0,947 ±0,01
(ASDAS 2,1 - 3,5) n = 51	6 (11,8%)*	20 (39,2%)*	25 (49%)*	–0,75 ±0,19	–0,8 ±0,1	–0,59 ±0,12	0,986 ±0,02	0,758 ±0,02	0,866 ±0,04*
(ASDAS >3,5) n = 52	24 (46,1%)*#	11 (21,2%)*#	17 (32,7%)*	–1,48 ±0,23 #	–1,01 ±0,11	–0,79 ±0,1 *	0,897 ±0,02 #	0,731 ±0,01	0,879 ±0,01*
Depending on BASDAI									
(BASDAI < 4) n = 33	1 (3%)	7 (21,2%)	25 (75,8%)	–0,02 ±0,26	–0,53 ±0,12	–0,28 ±0,13	1,059 ±0,03	0,797 ±0,02	0,944 ±0,02
(BASDAI > 4) n = 72	29 (40,3%)*	24 (33,3%)	19 (26,4%)*	–1,56 ±0,16*	–1,08 ±0,09*	–0,87 ±0,1*	0,893 ±0,02*	0,724 ±0,01*	0,842 ±0,03*
Depending on BASFI									
(BASFI < 4) n = 37	5 (13,5%)	8 (21,6%)	24 (64,9%)	–0,43 ±0,26	–0,61 ±0,12	–0,31 ±0,12	1,012 ±0,03	0,792 ±0,02	0,944 ±0,02
(BASFI > 4) n = 68	25 (36,8%)*	23 (33,8%)	20 (29,4%)*	–1,43 ±0,18*	–1,07 ±0,09*	–0,89 ±0,1*	0,909 ±0,02*	0,722 ±0,01*	0,836 ±0,03*

Note: sign * means reliable difference with respect to patients with the lowest activity indexes according to ASDAS-CRP, BASDAI and BASFI; sign # - means reliable difference with respect to the group of patients suffering from ASDAS 2,1 - 3,5.

oporosis was found in 28,6% of the patients and osteopenic syndrome was found in 29,5% of the patients (Table I). In practically healthy persons, the decrease of BMD was observed in 24% of the persons, while osteoporosis was found only in 4% of the persons. In control group, Z-score at the level of the lumbar spine and the femoral neck made –0,17±0,2 SD and –0,13±0,1 SD, while in patients with AS it was 7 times lower and made –1,08±0,15 SD and –0,91±0,08 SD respectively.

The analysis of densitometric parameters depending on the form of treatment showed no statistically significant differences (Table II). Thus, at the level of the lumbar spine in patients with peripheral form of AS, BMD made up 0,919±0,02 g/cm^2 which corresponds to

Table VI. BMD indexes depending on CRP level in men suffering from AS

Group	BMD, n (%)								
	Patients			Z-score, SD			BMD, g\cm²		
	with osteoporosis	with osteopenia	with preserved BMD	of the lumbar spine	of the femoral neck	proximal part of femur	of the lumbar spine	of the femoral neck	proximal part of femur
Patients with CRP < 6 mg\l n = 47	2 (4,2%)	13 (27,7%)	32 (68,1%)	–0,30 ±0,19	–0,60 ±0,10	–0,26 ±0,11	1,024 ±0,02	0,788 ±0,02	0,903 ±0,04
Patients with CRP 6 – 12 mg\l n = 35	14 (40%)*	14 (40%)	7 (20%)*	–1,67 ±0,22*	–1,21 ±0,11*	–1,08 ±0,11*	0,883 ±0,02*	0,709 ±0,02*	0,842 ±0,02
Patients with CRP > 12 mg\l n = 23	14 (60,9%)*	4 (17,4%)	5 (21,7%)*	–1,77 ±0,39*	–1,10 ±0,18*	–0,96 ±0,17*	0,880 ±0,04*	0,721 ±0,02*	0,865 ±0,03

Note: sign *- means reliable differences with respect to the patients with lower CRP levels

Table VII. BMD level depending on the cumulative dose of GCs

Group	BMD, n (%)								
	Patients			Z-score, SD			BMD, g\cm²		
	with osteoporosis	with osteopenia	with preser ved BMD	of the lumbar spine	of the femoral neck	proximal part of femur	of the lumbar spine	of the femoral neck	proximal part of femur
(Cumulative dose of GCs < 21,6) n = 80	16 (20%)	27 (33,7%)	37 (46,3%)	–0,78 ±0,18	–0,76 ±0,08	–0,62 ±0,09	0,978 ±0,02	0,769 ±0,01	0,884 ±0,03
(Cumulative dose of GCs > 21,6) n = 25	14 (56%)*	4 (16%)	7 (28%)	–2,04 ±0,24*	–1,38 ±0,14*	–0,91 ±0,19	0,841 ±0,02*	0,675 ±0,02*	0,842 ±0,02

Note: sign *- credible differences with respect to the patients with the lowest cumulative dose of GCs.

Table VIII. Correlation coefficients of BMD indexes with risk factors and disease course in men suffering from AS

	BMD at the level of the lumbar spine, SD	BMD at the level of the femoral neck, SD	BMD at the level of the lumbar spine, SD
Age	0,25	0,02	0,12
Disease duration	0,21	0,02	0,11
CRP	–0,30*	–0,21*	–0,27*
ASDAS	–0,36*	–0,21*	–0,16
BASDAI	–0,51*	–0,31*	–0,27*
BASFI	–0,30*	–0,31*	–0,24*
Cumulative dose of GCs	–0,24*	-0,32*	-0,09

Note: sign * - means credible correlation coefficients.

Z-score, i.e. makes –1,05±0,24 SD, in patients with central form it made up 0,957±0,02 g/cm² and –1,09 ± 0,02 SD respectively. BMD at the level of the femoral neck in men with peripheral form made 0,751±0,01 g/cm² which corresponds to Z-score, i.e. –0,82±0,1 SD, in patients with central form it made 0,745±0,01 g/cm² and –0,95±0,01 SD respectively. The share of patients with osteoporosis and osteopenic syndrome remained the same in the groups of patients.

Regarding the duration of disease, the biggest share of 33 (75%) patients with decreased BMD was found in the group of patients with a disease duration ranging from 5 to 10 years. In groups of patients with disease duration up to 5 years, 11 persons (55%) had a decreased Z-score and

17 persons had a disease duration of more than 10 years. Z-score at the level of the lumbar spine and femoral neck was the lowest in the group of patients having the disease duration of 5-10 years, i.e. −1,58±0,25SD and −1,09±0,11 SD respectively. Similar data was obtained during the analysis of the BMD index (Table III).

The analysis of age characteristics did not show a reliable relation between a decrease of BMD and the age of patients suffering from AS. Thus, in the age group of up to 35 years the decrease of BMD was found in 20 (71,4%) of the patients, in the age group of 35-50 years it was found in 35 (56,4%) patients and in the group aged above 50 years it was found in 6 (40%) patients. Similar data was obtained regarding BMD index and Z-score which were the lowest in patients aged up to 35 years (Table IV).

The study has established (Table V) that the decrease in BMD was closely associated with disease activity evaluated by ASDAS-CRP and BASDAI activity indexes. Thus, in the group of patients with high level of activity (ASDAS 2,1-3,5), the decrease of BMD was found in 51% of the patients, in the group of patients with very high activity (ASDAS >3,5) it was found in 67,3% of the persons, while in the group of patients with moderate activity of AS (ASDAS < 2,1) no patients suffering from osteopenia and osteoporosis were found. In men with high and very high activity, BMD at the level of the lumbar spine was, on the average, 20,6% lower than in persons with moderate activity, while at the level of the femoral neck it was 13,5% less. Similar data were observed with respect to Z-score in both examined areas. Similar regularities were observed only for the BASDAI activity index. Specifically, if in the group of patients with the BASDAI lower than 4 points, a share of persons with osteopenia and osteoporosis was found in 24,2% of the patients, while in the group with BASDAI higher than 4 points it was found in 73,6% of the patients. The number of patients suffering from osteoporosis was reliably higher in the group with low functional ability determined by the BASFI index.

Decrease in BMD and the respective increase in the number of persons suffering from osteoporosis and osteopenia was also closely associated with the level of CRP in blood serum (Table VI). Thus, in patients with optimal CRP level, average indexes of Z-score at the level of the lumbar spine made −0,30±0,19 SD and in persons with high and very high level of CRP these indexes made −1,67±0,22 SD and −1,77±0,39 SD respectively. Similar data were found at the level of the femoral neck. Among the patients with optimal CRP level, 31,9% of the persons had signs of decreased mineral bone density, while 80% of the patients with threshold CRP level had such signs. In men with high activity of inflammatory process (CRP >12) the number of patients suffering from osteoporosis and osteopenic syndrome made 78,3%.

Increase of the cumulative dose of glucocorticoids (GCs) also had a negative influence on the BMD in men suffering from AS (Table VII.) Specifically, in group with a cumulative dose of glucocorticoids lower than 21,6 g, Z-score at the level of the lumbar spine and femoral neck made −0,78±0,18 SD and −0,76±0,08 SD, and in the group with the cumulative dose of glucocorticoids higher than 21,6 g Z-score was 2,6 and 1,8 times lower and made up −2,04±0,25 SD and −1,38±0,14 SD respectively. Along with an increase in the cumulative dose of GCs, the share of patients suffering from osteoporosis became bigger. Thus, in persons with high dose of GCs such patients made 56% and in patients with a low dose it made only 20%.

The additional confirmation of the relation between the disease course and BMD condition was achieved due to the paired correlation analysis (Table VIII). It was established that between the clinical laboratory markers of inflammatory process activity and the dose of GCs, on the one side, and the disorder of BMD, on the other side, reliable correlation relationships were established. And namely, BMD at the level of the lumbar spine and of the femoral neck is closely associated with cumulative activity indexes and the severity of the disease of ASDAS, BASDAI, BASFI indexes (r= –0,36, r= –0,51, r= –0,30 respectively). Probable relations existed also between BMD with CRP level and cumulative dose of GCs. The relationship of the indexes of BMD with the age of patients and the disease duration was not found.

DISCUSSION

Thus, the study has shown that only in 41,9% the values of BMD were normal (by Z-score), osteopenia was found in 29,5% and osteoporosis was found in 28,6% of the patients. In control group, osteoporosis was diagnosed in 4%, osteopenia was found in 20% and normal values of Z-score were found in 76% of the examined patients. Modern literature describes a significant number of studies dedicated to the research of changes of BMD in AS. On the whole, the results were similar. Thus, in the study conducted by Klingberg E. et al, osteoporosis and osteopenia was found in 21% and 44% of the patients suffering from AS [6]. According to the data of Singh HJ, osteoporosis was found in 27% of the patients, while osteopenia was found in 47% of the patients [7]. However, there exists a study where osteoporosis was found more rarely than in our patients. According to the data of Van Der Weijden M., osteopenia at the level of the lumbar spine was found in 54% of the patients, osteoporosis was found in 13% [8]. In the study of Wang D. et al, osteoporosis was found only in 5,7% and osteopenia was found in 62,8% of the patients [9]. In our opinion, such variability of results probably depends on the peculiarities of the examined populations (age, sex, duration of AS), different approaches to the evaluation of the level of decrease in BMD and methods of its determination.

We found no statistically significant differences based on the average values and on the share of patients with changes in BMD indexes depending on the disease form. The study by Raskina T. did not find them either [10]. However, according to the data of Landge U., in patients with peripheral form of the disease, deeper changes of BMD were observed, while a share of persons with osteoporosis and osteopenia was higher than in patients with central form of AS [11].

The study has established that the biggest share of patients with osteodeficiency was found among the patients of the young age. Entirely opposite data was obtained by E. Klingberg [12]. According to the data of Smiian S., no differences were found in the share of the patients with osteoporosis among different age groups of the patients suffering from AS [13].

No influence of the disease duration on the condition of BMD was found. Instead, in the study by E. Toussirot et al, the decrease in BMD indexes at the level of the femoral neck was associated with an increase in the duration of AS [14].

The majority of scientists came to the conclusion that one of the factors of osteoporosis development is high disease frequency [15; 16]. We have established that close associative relations are formed between inflammatory process activity based on the levels of CRP, ASDAS and BASDAI and decrease in BMD at the level of the lumbar spine and femoral neck. Specifically, if in the group of patients with an optimal level of CRP, a share of persons with osteoporosis was equal to 4,2%, then in the group with high level it made up 40% and in the group with very high level it made up only 60,9%.

The role of inflammatory process markers in the formation of disorders of structural and functional bone condition was also reflected in other scientific works. According to the data of Ulu M., BMD of the femoral bone was associated with high BASFI index and did not have a relation with CRP [17]. In the study of Vasdev V. in patients suffering from early AS, no correlation was found between the decrease in BMD and the levels of ESR and CRP as well as disease activity based on the BASDAI index [18].

Along with high activity of AS, a decrease of the functional status due to limited spine mobility is of great significance for the development of osteoporosis and its complications [19]. Our study showed that the disorder of functional ability determined by using the BASFI score correlated negatively with BMD in the region of the femoral neck and the lumbar spine.

It is known that long-term use of GCs leads to a decrease in BMD and the rate of its loss is maximum during the first year of the disease and may achieve 30% during the first 6 months of the intake of preparations. The results obtained give us grounds to affirm that the loss of bone tissue is closely associated with an increase in the cumulative dose of GCs. It is confirmed by that fact that the group of patients with a cumulative dose of GCs higher than 21,6 g includes twice as many persons suffering from osteoporosis in comparison to the group of the patients in which the dose of GCs was lower than 21,6 g. Literature data also show the existence of the close associative relationship between the GCs load and BMD [20].

Thus, in men suffering from AS with high frequency, there is a decrease in BMD associated with high disease activity, high dose of GCs and decreased functional status which evaluated on the basis of the BASFI index and was not related to form, age or disease duration.

CONCLUSION

1. In men suffering from AS, osteoporosis is found in 28,6% of the persons, osteopenia is found in 29,5% of the patients and normal indexes of bone mineral density are found in 41,9% of the patients.
2. Decrease in bone mineral density in men suffering from AS does not depend on the age, disease duration and form of AS, however, it is closely associated with inflammatory process activity (levels of CRP, ASDAS, BASDAI), low functional status evaluated on the basis of the BASFI index and the cumulative dose of GCs.

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The Authors declare no conflict of interest.

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