ORIGINAL ARTICLE

LEVELS OF OSTEOCALCIN AND PROCOLLAGEN I N-TERMINAL PROPEPTIDE (PINP) IN MEN SUFFERING FROM ANKYLOSING SPONDYLITIS

DOI: 10.36740/WLek202110105

Oksana Pavliuk[1], Sergii Shevchuk[1,2]

[1]NATIONAL PIROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSIA, UKRAINE

[2]SCIENTIFIC RESEARCH INSTITUTE FOR REHABILITATION OF DISABLED PERSONS OF THE NATIONAL PIROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSIA, UKRAINE

ABSTRACT

The aim: To evaluate osteocalcin and PINP levels in men suffering from AS and to compare them with structural and functional state of bone tissue and clinical course of illness.

Materials and methods: The study included 82 patients suffering from AS with an average age of 40,9±0,9 years. Osteocalcin level was determined in 82 patients, and PINP level was determined in 79 patients. Control group included 22 apparently healthy persons. Disease activity was assessed through CRP level, ASDAS and BASDAI scores, while functional ability was assessed through the BASFI score. Osteocalcin and PINP levels were determined by immunoenzymatic method for the purpose of evaluating the metabolic state of bone tissue.

Results: Average osteocalcin and PINP levels were not significantly different in patients suffering from AS and patients in the control group and did not show any significant correlation with ASDAS, BASDAI, BASFI and CRP scores. In patients with spinal ankylosis, average osteocalcin values (14,3 ng\ml) and PINP (747,2 pg\ml) were higher compared to patients with single syndesmophytes (11,0 ng\ml; 711,8 pg\ml) and patients without syndesmophytes (10,4 ng\ml; 537,7 pg\ml respectively).

Conclusions: Osteocalcin and PINP levels are not related to age, disease duration, BMI, glucocorticoids load and inflammatory process activity, however, they are closely related to the presence of bone growths.

KEY WORDS: ankylosing spondylitis, bone density, osteoporosis, osteocalcin

Wiad Lek. 2021;74(10 p.I):2384-2391

INTRODUCTION

It is known that the reduction of bone mineral density in the form of osteoporosis/osteopenia is a widely known complication of ankylosing spondylitis (AS) and is frequently observed at early stages of the disease [1]. Loss of bone mass in this cohort of patients significantly increases the risk of compression fractures of vertebrae [2-3]. Over the period of 30 years after establishing the diagnosis of AS this risk makes up 14%-30% which is reliably higher than in practically healthy persons [4-5]. Pathogenesis of the reduction of bone mineral density actively correlates with activity of inflammatory process and, as a result, with intensification of resorption processes in bone tissue (N-telopeptide, C-telopeptide) and the reduction of bone formation markers (osteocalcin, PINP). Remodelling of bone tissue in case of AS is particularly characterized by the fact that in different regions of the skeleton the processes of formation and resorption of bone tissue take place in parallel. Thus, syndesmophytes are formed as a result of local inflammation with increased synthesis of bone matrix by osteoblasts in the points of tendon attachment and the presence of chronic inflammation which is supported by excessive amount of proinflammatory (TNF-alpha, IL-6, IL-7 etc.) cytokines which activate osteoclastogenesis and bone tissue resorption [6]. For this reason, the determination of bone metabolism markers would give us an opportunity to evaluate bone metabolism state in patients suffering from AS. Literary data on this matter are contradictory. A range of studies conducted on patients suffering from AS show an increase in the osteocalcin level in blood serum [7-8], according to the data of other studies, osteoporosis develops on the background of normal osteocalcin level [9], however, some studies show low concentration of the markers of bone tissue biosynthesis [10-11].

As for the Ukrainian cohort of patients suffering from AS, no studies were conducted on this matter. The role of disease course in the formation of bone metabolism disorders is also unknown.

THE AIM

The aim of our study was to examine metabolic state of the bone, in the context of bone formation markers (osteocalcin, PINP), evaluate their connection to the structural and functional state of the bone according to the data of X-ray densitometry and compare the identified disorders with disease course in men suffering from AS.

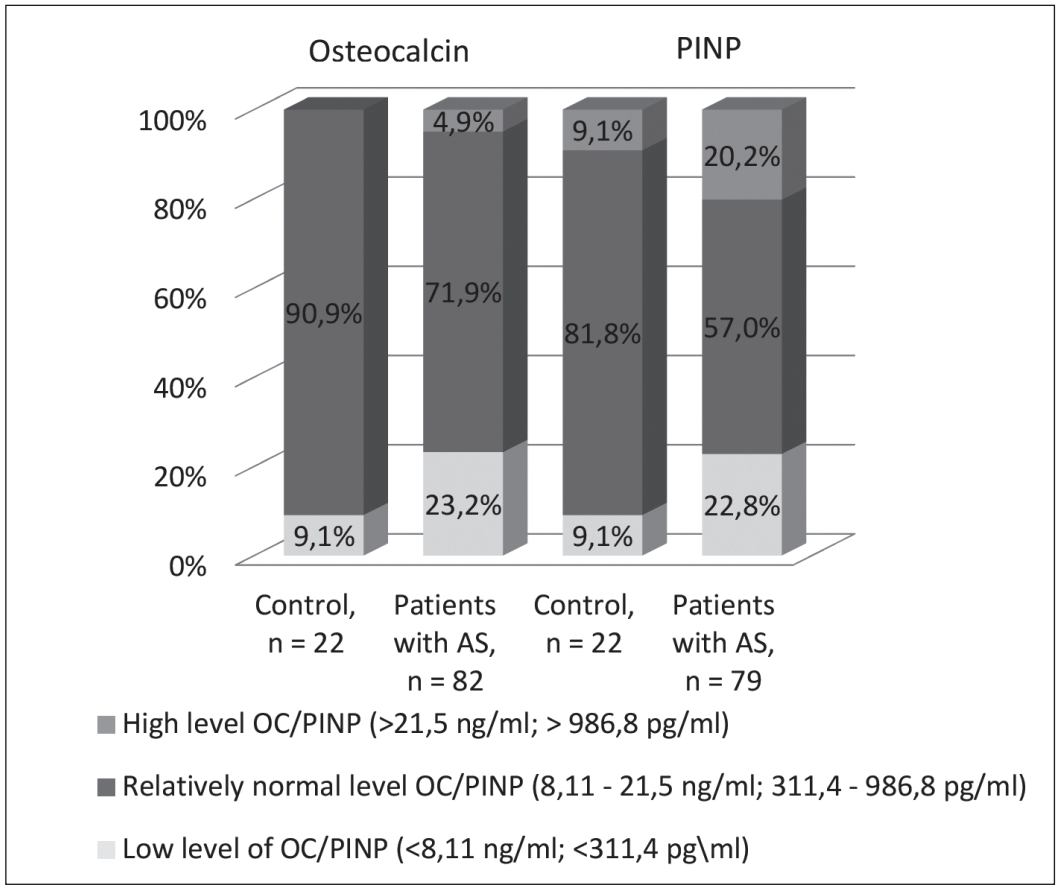

Fig 1. Levels of osteocalcin and PINP in blood serum in men suffering from AS

MATERIALS AND METHODS

The study included 82 patients suffering from AS (100% of them were men), their average age was 40,9±0,9 years, disease duration made 9,02±0,6 years. Osteocalcin level was determined in 82 patients, and PINP level was determined in 79 patients. Control group included 22 practically healthy persons without any rheumatic pathology. As a result of the expert examination conducted by the bioethics committee of Vinnytsia National Medical University it has been established that research methods do not contradict the basic norms of bioethics under the Declaration of Helsinki and do not violate any human rights under current laws of Ukraine. The diagnosis of AS was established on the basis of ASAS criteria [12]. All the patients were assessed on the basis of their age, disease duration, intake of glucocorticoids (GC), calcium preparations and vitamin D. For each patient, cumulative dose and duration of treatment with GC was determined.

Disease activity was evaluated on the basis of BASDAI score and ASDAS-CRP score (<1,3 – inactive ankylosing spondylitis; 1,3-2,1 – moderate activity; 2,1 -3,5 – high activity; >3,5 – very high activity) and functional activity was evaluated using the Bath Ankylosing Spondyloarthritis Functional Index (BASFI). The level of markers of inflammatory process activity, erythrocyte sedimentation rate and C-reactive protein (CRP) were analysed using standard laboratory methods at a medical institution. Markers of bone remodelling (osteocalcin and PINP) were evaluated by an immunoenzymatic method using the sets «N-MID Osteocalcin ELISA Kit» (Immunodiagnostic Systems, Great Britain) and «Human PINP (Procollagen I N-Terminal Propeptide) ELISA Kit» (Ela science, USA).

Bone mineral density (BMD) was measured using dual-energy X-ray absorptiometry on the device «Hologic Discovery Wi» (S/N 87227) at the level of the lumber spine and the femoral neck. For patients aged 50 years old or older, the following terms of the World Health Organization (WHO) were used with respect to osteopenia and osteoporosis: osteopenia, T-score <-1 up to> -2,5 and osteoporosis, T-score ≤ -2,5 SD. For patients aged up to 50 years Z-score ≤ -2,0 SD was considered to be lower than expected for this age [13].

Statistical analysis of the results was performed using personal computer applications Microsoft office, in particular, Microsoft Excel 2010 and using the program "SPSS-10.0.5 for Window" (licensed № 305147890). The following statistical characteristics were used: the number of observations (n), the arithmetic mean (M), standard error of the mean (m), median range (maximum-minimum), relative values (abs.,%). The normality of the distribution of indicators was determined by the Shapiro-Wilk test. In our studies, there was a normal distribution of indicators, so the significance of the differences was determined by Student's t-test, to determine the relationships between indicators – Pearson's correlation analysis (r). P-value ≤ 0,05 was considered significant statistically. To compare the

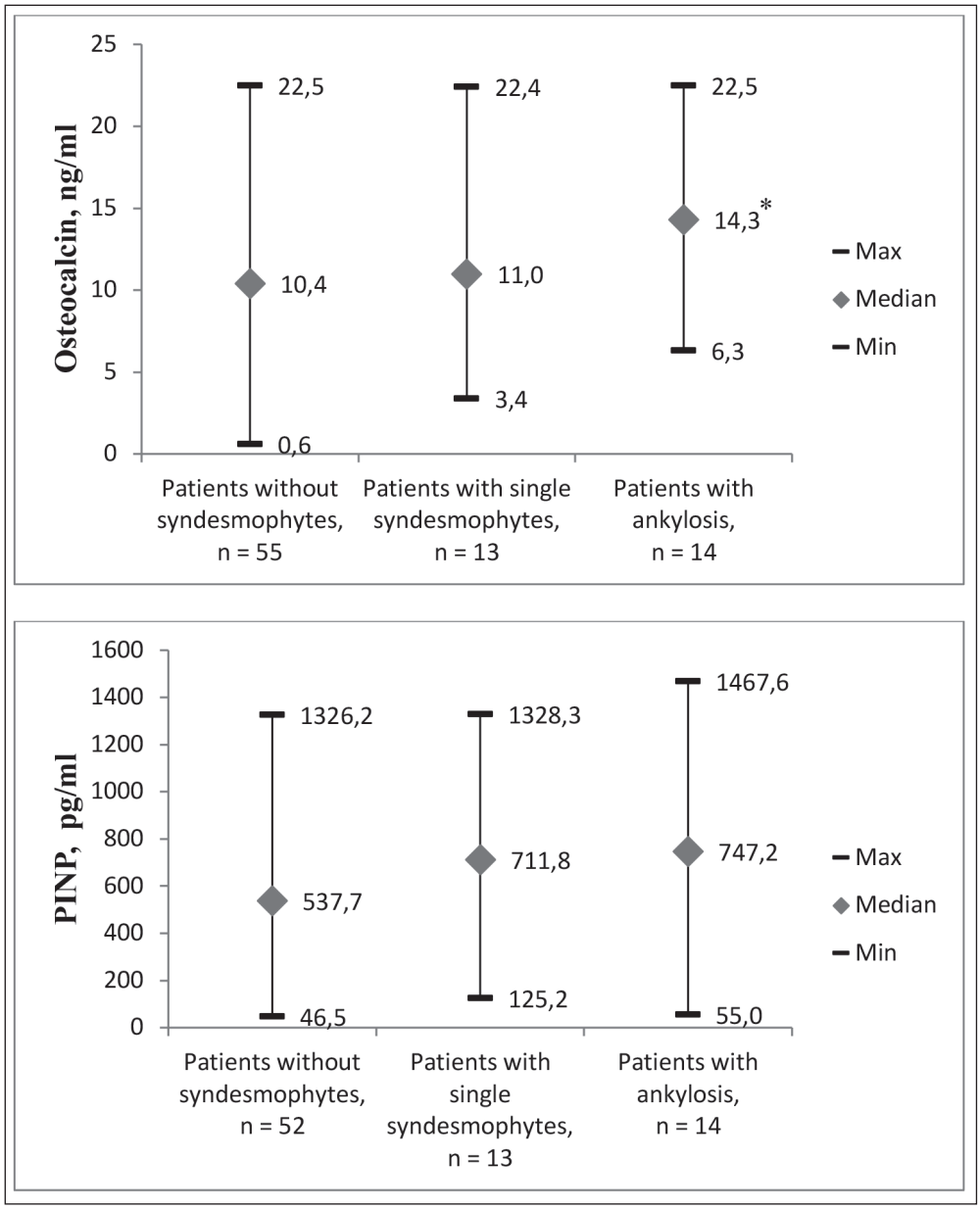

Fig 2. Osteocalcin and PINP levels depending on the presence of syndesmophytes
Note: symbol * – means reliable differences when compared to a group of patients without syndesmophytes,
t-test was used for intergroup comparison.

significance of the differences between the relative values used the exact Fisher method. The percentile method was used to establish standards for laboratory test results, such as the level of osteocalcin, the N-terminal propeptide of type I procollagen.

RESULTS

The conducted study has shown that the content of bone metabolism markers, i.e. osteocalcin (OC) and procollagen I N-terminal propeptide (PINP), was not significantly different in men suffering from AS and in persons from the control group. In the control group, the level of osteocalcin was 12,9±0,9 ng/ml, while in men with AS was 12% lower and made 11,3±0,6 ng/ml. As for PINP level, in the control group they made 622,6±46,9 pg\ml and in the main group they made 606,7±42,1 pg\ml, i.e. were 2,5% lower. Ranging the levels of bone formation markers showed (Figure 1) that low levels of osteocalcin and procollagen type 1 N-terminal propeptide were found in 9,1% of persons in the control group, while 81,8-90,9% persons had a relatively normal level of these markers. Low levels of bone metabolism markers were found in 23% of patients suffering from AS and relatively normal levels were found in 57-71,9% of patients. The study showed that from 4 to 20% of patients suffering from AS had relatively high levels of osteocalcin and procollagen type 1 N-terminal propeptide, while the control group had no patients with such levels of OC and only 9,1% of patients with such level of PINP.

The study did not find a connection between the age and changes in levels of markers of bone tissue synthesis (Table I). Thus, the highest share of patients with low level of osteocalcin was found in the age group of 35-50 years and included 16 patients (30,8%), in the group aged up to 35 years, low level of OC was registered in 31,6% of patients and in the group of patients older than 50 years it was registered in 27,3 % of patients. Similar results were obtained after analysing PINP levels,

Table I. Levels of osteocalcin and PINP depending on the age of patients, disease duration, BMI and glucocorticoids load

Group	Bone metabolism markers			
	Osteocalcin, n (%)		PINP, n (%)	
	M±m	Low level (<8,11 ng\ml)	M±m	Low level (<311,4 pg\ml)
Control, n=22	12,9±0,9	2 (9,1%)	622,6±46,9	2 (9,1%)
Patients with AS, n=82/79	11,3±0,6	19 (23,2%)	606,7±42,1	18 (22,8%)
Depending on the age				
<35 years n=19/19	11,0±1,0	6 (31,6%)	520,5±75,8	6 (31,6%)
35-50 years n=52/49	11,2±0,8	16 (30,8%)	588,9±52,7	14 (28,6%)
>50 years n=11/11	11,5±1,4	3 (27,3%)	811,6±132,6	2 (18,2%)
r	0,07		0,23	
Depending on disease duration				
up to 5 years n=13/13	12,6±1,0	1 (7,7%)	653,8±104,6	2 (15,4%)
5-10 years n=42/41	10,5±0,9	15 (35,7%)	558,9±56,5	13 (31,7%)
> 10 years n=27/25	11,5±1,1	9 (33,3%)*	650,4±81,0	7 (28%)
r	0,14		0,11	
Depending on BMI				
BMI<25 n=45/44	10,8±0,9	15 (33,3%)	545,9±58,0	17 (38,6%)
BMI > 25 n=37/35	11,7±0,8	10 (27,02%)	675,8±60,5	5 (14,3%)#
r	0,19		0,19	
Depending on glucocorticoids load				
Cumulative dose of GC < 21,6 g (n=55/53)	11,1±0,7	17 (30,9%)	611,3±50,5	12 (22,6%)
Cumulative dose of GC > 21,6 g (n=27/26)	11,4±1,2	8 (30,7%)	587,5±78,6	10 (38,4%)

Note: symbol * means reliable difference from the group of patients with disease duration of up to 5 years;
symbol # means reliable difference from the group of patients with BMI < 25.
n - the number of observations, M - the arithmetic mean, m - standard error of the mean (m), M ± m means - mean ± standard error of the mean (SEM), r- Pearson's correlation analysis. To compare the significance of the differences between the relative values used the exact Fisher method.

as the largest share of patients (28,6%) with low level was also found in the age group of 35-50 years. Disease duration also had no influence on OC and PINP levels in blood serum. In the group of patients with disease duration of 5-10 years and more than 10 years, low levels of osteocalcin and PINP were found practically in each second patient.

The study did not show any significant connection between bone metabolism markers and BMI, however, there was a distinct tendency towards a decrease of OC and PINP levels in proportion to the reduction of body mass. Levels of osteocalcin and PINP also had no relation to glucocorticoids (GC) load. Specifically, practically similar share of patients with low level of OC was registered in patients with cumulative dose of GC > 21,6 g when compared to patients with GC dose < 21,6 g. It should be also noted that in patients with cumulative dose of GC > 21,6 g, the average content of PINP as well as the share of patients with low levels of the studied index were not also reliably different.

Levels of markers of bone tissue synthesis grew in parallel to the increase in the activity of inflammatory process (Table II). Specifically, in patients with very high activity of inflammatory

Table II. Connection of OC and PINP with activity indices based on ASDAS-CRP and BASDAI scores, BASFI functional index and CRP

	Level	Bone metabolism marker			
		Osteocalcin, n (%)		PINP, n (%)	
		M±m	Low level (<8,11 ng/ml)	M±m	Low level (<311,4 pg\ml)
ASDAS	<3,5 (n=42/41)	10,3±0,9	15 (36,5%)	583,9±59,4	13 (31,7%)
	> 3,5 (n=40/38)	12,1±0,7	10 (26,3%)	624,5±61,1	9 (23,7%)
	r	-0,15		-0,19	
BASDAI	<4 (n=24/23)	10,9±1,2	8 (33,3%)	596,9±78,0	7 (30,4%)
	> 4 (n=58/56)	11,3±0,7	17 (30,3%)	597,9±50,7	15 (26,8%)
	r	-0,12		-0,10	
BASFI	< 4 (n=23/22)	11,5±1,2	7 (30,4%)	688,1±72,5	5 (22,7%)
	> 4 (n=59/57)	11,1±0,7	18 (30,5%)	570,8±51,3	17 (29,8%)
	r	-0,18		-0,08	
CRP	< 5,4 (n=20/19)	10,3±1,4	8 (40,0%)	571,4±98,3	6 (31,6%)
	5,4-13,4 (n=41/40)	11,4±0,8	12 (29,3%)	602,1±59,3	10 (25,0%)
	> 13,4 (n=21/20)	11,5±1,1	5 (23,8%)	627,5±76,3	6 (30,0%)

n - the number of observations, M ± m means mean ± standard error of the mean (SEM), r- Pearson's correlation analysis.

process (ASDAS >3,5), a share of patients with low level of osteocalcin and PINP was 8-10% lower than in the group of patients with moderate activity of inflammatory process (ASDAS < 3,5). Similar trends were observed also with respect to BASDAI score. Average levels of OC and PINP in the group of patients with high activity (BASDAI > 4) were practically comparable to patients with low activity (BASDAI < 4). A share of patients with low levels of bone tissue synthesis was not also reliably different in groups depending on the functional ability determined on the basis of BASFI score. While performing correlation analysis, no reliable correlations were found between high activity of inflammatory process (based on ASDAS-CRP and BASDAI scores) and low functional ability (BASFI score) with metabolic state of bone tissue determined on the basis of OC and PINP levels.

Ranging CRP levels as optimal, high and very high it was shown that in the group of patients with optimal level of CRP a share of patients with low levels of markers of bone tissue synthesis probably no different than in the groups of patients with high and very high CRP. Based on average values of OC and PINP, there were also significant differences in groups of patients. In groups with very high levels of CRP, concentration of OC and PINP was practically 9-11% higher than in the group with optimal level of CRP.

The study showed that serum levels of OC and PINP in patients suffering from AS were associated with presence of osteophytes (Figure 2). Thus, average level of OC in patients with syndesmophytes made 11,0±1,4 ng/ml and in patients without syndesmophytes it made 10,4±0,7 ng/ml, i.e. it was 5,5% lower. Such trend was also observed with respect to PINP level where in the group of patients without syndesmophytes, low level of PINP was found in 17 patients and in the group with syndesmophytes it was found only in 3 patients (23,1%), while the average level of PINP was 24,5% higher. In patients with compete spinal ankylosis, average levels of the mentioned markers of bone tissue synthesis were even higher, and with respect of OC level in blood serum, in general, the values were reliable when compared to patients without syndesmophytes.

In the next part of the study, we tried to analyse the differences between patients depending on X-ray changes (ankylosis, syndesmophytes) in the spine (Table III). It was found that in patients with complete spinal ankylosis, besides reliably higher levels of OC and PINP, the average age of the patient was also reliably higher when compared to patients without syndesmophytes. Patients with spinal ankylosis when compared to patients without spinal ankylosis showed a tendency towards an increase in disease duration as well as activity of inflammatory process and cumulative GC dose was higher. It was established that patients with complete ankylosis had a higher BMD index of the lower spine when compared to patients without ankylosis and, on the contrary, they had a lower BMD index of the femoral neck, which can be obviously connected to the place (trabecular or cortical part of the vertebral bodies) of BMD

Table III. Peculiarities of AS disease course in patients without syndesmophytes, with single syndesmophytes and spinal ankylosis

Indexes	Patients without syndesmophytes, n= 55	Patients with single syndesmophytes, n = 13	Patients with spinal ankylosis, n=14
OC levels, ng/ml	10,4±0,7	11,0±1,4	14,3±1,5*
PINP levels, pg/ml	537,7±48,5	711,8±116,9	747,2±105,2
Age, years	38,6±1,2	48,3±1,3*	43,5±1,5*#
Disease duration	7,7±0,6	9,7±1,3	9,7±1,3
Cumulative GC dose,g	14,5±1,8	16,7±2,7	16,0±2,9
ASDAS, points	3,5±0,1	3,4±0,1	3,5±0,2
BASDAI, points	5,2±0,2	5,3±0,4	5,6±0,4
BASFI, points	4,9±0,3	5,6±0,5	5,2±0,4
CRP levels, mg/l	10,7±0,9	11,5±1,8	14,7±2,8
ESR levels, mm/h	23,1±1,4	23,1±4,6	26,2±3,4
BMD of the lumbar spine, g/cm^2	0,93±0,02	0,95±0,04	0,98±0,04
Z- score of the lumbar spine, SD	-1,38±0,2	-0,68±0,4	-0,36±0,6
BMD of the femoral neck, g/cm^2	0,75±0,02	0,73±0,03	0,73±0,04
Z-score of the femoral neck, SD	-0,87±0,01	-1,07±0,2	-1,14±0,1

Note: symbol * means reliable differences when compared to the group of patients without syndesmophytes,
symbol # means reliable differences when compared to the group of patients with single syndesmophytes.

determination. As for Z-score, in the region of the femoral neck it was reliably higher in patients with complete spinal ankylosis when compared to patients without syndesmophytes.

DISCUSSION

Thus, by analysing metabolic state of bone tissue (levels of bone synthesis markers), it was established that an insignificant reduction of osteocalcin and PINP levels were observed in men suffering from ankylosing spondylitis when compared to patients from the control group. And specifically, average concentration of osteocalcin in patients suffering from AS was 12% lower than in practically healthy persons and made 11,3±0,6 ng/ml in comparison to 12,9±0,9 ng/ml. Average values of PINP in the main group made up 606,7±42,1 pg/ml and 622,6±46,9 pg/ml in the control group which was only 2,5% more. Literary data on this matter are contradictory. Thus, according to the data of Ö. Altindag et al [14], average level of OC in patients suffering from AS was 43% lower than in the control group. Osteocalcin concentration of blood serum was lower than in the study by Huang WN et al [15]. However, there also exist such studies, where OC levels in patients suffering from AS in comparison to patients from the control group were not different or were even 57% higher [16]. The opinion of researchers on the bone formation marker PINP is contradictory. Thus, in the study by Perpétuo IP et al [17], serum level of P1NP was lower in patients suffering from AS when compared to the control group, and, on the contrary, in the study by Pnar Borman et al [18], PINP level was significantly higher in patients suffering from AS and grew in proportion to the disease activity.

The study did not show any influence of age and disease duration on the concentration of bone metabolism markers in blood serum. However, the study by Huang J et al [9] found a correlation between osteocalcin and disease duration in patients suffering from AS (r = 0,323, p = 0,034).

Levels of the mentioned bone formation markers also had no relation to BMI and GC load. According to the data of Yushina SA et al [19], patients who systematically took GC showed stable reduction of osteocalcin level.

It is known that one of the unfavourable pathogenic factors of bone metabolism is a systemic inflammatory process related to excessive activation of proinflammatory factors, such as tumour necrosis factor alpha (TNF-α), interleukin-1 (IL-1), IL-6 and IL-17 which lead to excessive destruction of bone tissue, primarily, due to hyperactivation of osteoclasts and decreased synthesis of osteoblasts [20]. Ankylosing spondylitis is uniquely characterized by the fact that due to multiple inter-relations and interactions of bone tissue and the immune system, active inflammation, on the one hand, contributes to bone resorption by way of intensified differentiation of osteoclasts and, on the other hand, leads to local bone formation, primarily, through TNF-alpha and IL-17 hyperproduction which cause excessive activation of osteoblasts and synthesis of pathologically new bone formations and in the future lead to the formation of syndesmophytes and spinal ankylosis [21-22].

We did not find any reliable associative connection between the activity of inflammatory process evaluated on the basis of ASDAS-CRP, BASDAI scores and the concentration of bone metabolism markers. Thus, in case of very high activity of the disease and low functional ability (ASDAS >3,5; BASDAI >4; BASFI>4), levels of osteocalcin

and PINP in blood serum were practically comparable to moderate activity and functional ability of the patient. Bone formation markers also had no relationship to the CRP level. Similar results were obtained in the study by Park MC et al [23] where average level of osteocalcin in blood serum was not different in patients and in the control group and showed no significant correlations with BMD and BASDAI scores. No significant connection of disease activity to OC level was also found in the study by Muntean L et al [24]. However, the study by Bugrova OV et al [25] showed reliable associative connections between the level of osteocalcin and ASDAS-CRP score.

Analysis of bone formation markers depending on X-ray changes in the spine showed that in the group of patients with complete spinal ankylosis, OC values were reliably 37,5% higher than in the group without syndesmophytes. Also, in the last group, PINP levels were lower than in the group with single syndesmophytes and complete spinal ankylosis. The study showed that patients with complete spinal ankylosis had a reliably higher age than patients without osteophytes. However, bone mineral density was determined on the basis of BMD score which was calculated in the region of the lumbar spine, and it was found to be lower in the last group when compared to the group with spinal ankylosis; simultaneously, BMD level in the region of the femoral neck was lower in the group of patients with syndesmophytes and spinal ankylosis than in the group without syndesmophytes. As for Z-score, it was slightly higher in the region of the femoral neck in patients with complete spinal ankylosis when compared to patients without syndesmophytes. The data provided by other studies are also contradictory. According to the data of Arends S et al [26], increased levels of OC and PINP in patients suffering from AS were associated with reduced bone mineral density. In the study by Gamez-Nava et al [27], patients with marked syndesmophytes had a higher level of OC than patients without syndesmophytes.

That is, such different results can be explained by the fact that measurement of bone mineral density in the region of the lumbar spine using X-ray absorptiometry is normally performed in anteroposterior projection. For this reason, any type of spinal lesion related to AS, and namely: presence of osteophytes, calcifications, degenerative changes of facet joints, hyperostosis and lesion of the posterior arch of vertebrae can influence the measurement of bone mineral density, i.e. increase BMD value and, thus, BMD levels can be normal or high in patients with osteoporosis as previously shown in studies [28-29]. In our opinion, determination of bone mineral density in the region of the femoral neck is a more sensitive method of osteoporosis evaluation in case of AS in patients with single syndesmophytes as well as in patients with complete spinal ankylosis.

Thus, when analysing our own data and the results of literary data it should be notated that in men suffering from AS, concentration of bone formation markers does not significantly differ from practically healthy persons. OC and PINP levels have no relation to age, disease duration, BMI and GC load. Inflammation process activity also did not significantly affect the synthesis of OC and PINP. In men suffering from AS, a pathologically new formation of bone tissue is observed which shows itself first in the form of syndesmophytes and later in the form of complete spinal ankylosis which is confirmed by credible increase of bone formation markers.

CONCLUSIONS

1. In men suffering from ankylosing spondylitis the level of OC and PINP in blood serum do not significantly differ from patients in the control group. OC and PINP levels have no relation to age, disease duration, BMI and GC load. Inflammation process activity also did not significantly affect the levels of markers of bone tissue synthesis.
2. Patients suffering from AS show pathologically new formation of bone tissue in the form of syndesmophytes and spinal ankylosis which is closely connected to the elevated level of bone formation markers, and is not associated with the course of the disease.

REFERENCES

1. Briot K., Durnez A., Paternotte S. et al. Bone oedema on MRI is highly associated with low bone mineral density in patients with early inflammatory back pain: results from the DESIR cohort. Ann Rheum Dis. 2013;72(12):1914-1919.
2. Malochet-Guinamand S., Pereira B., Tatar Z. et al. Prevalence and risk factors of low bone mineral density in spondyloarthritis and prevalence of vertebral fractures. BMC Musculoskelet Disord. 2017;18(1):357.
3. Leone A., Marino M., Dell'Atti C. et al. Spinal fractures in patients with ankylosing spondylitis. Rheumatol Int. 2016;36:1335–46.
4. Prieto-Alhambra D., Muñoz-Ortego J., De Vries F. et al. Ankylosing spondylitis confers substantially increased risk of clinical spine fractures: a nationwide case-control study. Osteoporos Int. 2015; 26: 85–91.
5. Bessant R., Keat A. How should clinicians manage osteoporosis in ankylosing spondylitis? J Rheumatol. 2002; 29 (7): 1511–9.
6. Weitzmann M.N. Bone and the Immune System. Toxicol Pathol. 2017; 45(7): 911-924.
7. Kwon S.R., Lim M.J., Suh C.H. et al. Dickkopf-1 level is lower in patients with ankylosing spondylitis than in healthy people and is not influenced by anti-tumor necrosis factor therapy. Rheumatol Int. 2012; 32(8): 2523–2527.
8. Visvanathan S., van der Heijde D., Deodhar A. et al. Effects of infliximab on markers of inflammation and bone turnover and associations with bone mineral density in patients with ankylosing spondylitis. Ann Rheum Dis. 2009; 68:175–182.
9. Huang J., Song G., Yin Z. et al. Alteration of Bone Turnover Markers in Canonical Wingless Pathway in Patients With Ankylosing Spondylitis. Arch Rheumatol. 2016; 31(3): 221–228.
10. Korczowska I., Przepiera-Bedzak H., Brzosko M. et al. Bone tissue metabolism in men with ankylosing spondylitis. Adv Med Sci. 2011; 56(2): 264–269.
11. Franck H., Keck E. Serum osteocalcin and vitamin D metabolites in patients with ankylosing spondylitis. Ann Rheum Dis. 1993;52(5):343–346.
12. Rudwaleit M., van der Heijde D., Landewé R. et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009; 68(6): 777–783.

13. Baim S., Binkley N., Bilezikian J.P. et al. Official Positions of the International Society for Clinical Densitometry and executive summary of the 2007 ISCD Position Development Conference. J Clin Densitom. 2008;11(1):75-91.
14. Altindag Ö., Karakoç1 M., Soran N. et al. Bone Mineral Density in Patients with Ankylosing Spondylitis. Rheumatism. 2008; 23: 42-5.
15. Huang W.N., Tso T.K., Kuo Y.C., Tsay G.J. Distinct impacts of syndesmophyte formation on male and female patients with ankylosing spondylitis. Int J Rheum Dis. 2012; 15(2):163–168.
16. Chi-Chien Niu, Song-Shu Lin, Li-Jen Yuan et al. Correlation of blood bone turnover biomarkers and Wnt signaling antagonists with AS, DISH, OPLL, and OYL BMC Musculoskeletal Disorders. 2017; 18: 61.
17. Perpétuo I.P., Caetano-Lopes J., Vieira-Sousa E. et al. Ankylosing Spondylitis Patients Have Impaired Osteoclast Gene Expression in Circulating Osteoclast Precursors. Front Med (Lausanne). 2017;4:5.
18. Borman P., Bodur H., Bingöl N. et al. Bone mineral density and bone turnover markers in a group of male ankylosing spondylitis patients: relationship to disease activity. J Clin Rheumatol. 2001; 7(5): 315–321.
19. Yushina S.A., Bugrova O.V., Ovchinnikova N.A., Aleksandrova I.A. Osobennosti metabolizma kostnoy tkani u bolnykh ankiloziruyushchim spondiloartritom. Osteoporosis and Bone Diseases. 2011;14(2):15-18.
20. Perpétuo I.P., Raposeiro R., Caetano-Lopes J. et al. Effect of Tumor Necrosis Factor Inhibitor Therapy on Osteoclasts Precursors in Ankylosing Spondylitis. PLoS One. 2015; 10(12): e0144655.
21. Briot K., Roux C. Inflammation, bone loss and fracture risk in spondyloarthritis. RMD Open. 2015;1(1):e000052.
22. Coury F., Peyruchaud O., Machuca-Gayet I. Osteoimmunology of Bone Loss in Inflammatory Rheumatic Diseases. Front Immunol. 2019;10:679.
23. Park M.C., Chung S.J., Park Y.B., Lee S.K. Bone and Cartilage Turnover Markers, Bone Mineral Density, and Radiographic Damage in Men with Ankylosing Spondylitis. Yonsei Med J. 2008; 49(2): 288-294.
24. Muntean .L, Rojas-Vargas M., Font P. et al. Relative value of the lumbar spine and hip bone mineral density and bone turnover markers in men with ankylosing spondylitis. Clin Rheumatol. 2011;30(5):691–695.
25. Bugrova O.V., Nagornova K.A., Artemova N.E. Bone metabolism and its regulation in patients with ankylosing spondylitis. Nauchno-Prakticheskaya Revmatologiya. 2016; 54(5) 527-529.
26. Arends S., Spoorenberg A., Bruyn G.A. et al. The relation between bone mineral density, bone turnover markers, and vitamin D status in ankylosing spondylitis patients with active disease: a cross-sectional analysis. Osteoporos Int. 2011; 22(5): 1431-1439.
27. Gamez-Nava J.I., de la Cerda-Trujillo L.F., Vazquez-Villegas M.L. et al. Association between bone turnover markers, clinical variables, spinal syndesmophytes and bone mineral density in Mexican patients with ankylosing spondylitis. Scand J Rheumatol. 2016;45(6):480–490.
28. Deminger A., Klingberg E., Lorentzon M. et al. Which measuring site in ankylosing spondylitis is best to detect bone loss and what predicts the decline: results from a 5-year prospective study. Arthritis Res Ther. 2017;19(1): 273.
29. Van der Weijden M.A., van Denderen J.C., Lems W.F. et al. Low bone mineral density is related to male gender and decreased functional capacity in early spondylarthropathies. Clin Rheumatol. 2011;30(4):497-503.

ORCID and contributionship: :
Oksana Pavliuk: 0000-0002-5582-3800 [A-D]
Sergii Shevchuk: 0000-0002-5649-2775 [A,C,E,F]

Conflict of interest:
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Sergii Shevchuk
National Pirogov Memorial Medical University
56 Pirogova st.,, 21018 Vinnytsia, Ukraine
tel: +380961119123
e-mail: shev.sv76@gmail.com

Received: 15.10.2020
Accepted: 02.08.2021

A – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article