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Parameters Of Bone Tissue Metabolism In Women With Rheumatoid Arthritis

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Abstract: ***Osteoporosis is considered as a systemic skeletal disease characterized by decrease in bone mass and micro-architectural violation of bone tissue, resulting in an increased risk of fractures and decline in the quality of life of patients. In rheumatoid arthritis, osteoporosis, as a decrease in bone mineral density is not only formed locally in the area of inflamed joints, but also systemically. The basis of the development of osteoporosis in rheumatoid arthritis is increased production of mediators of bone resorption, including those resulting from the use of glucocorticoids, whereas the impact of the disease on markers of bone formation is not fully established. The aim of the research was to study the concentration of blood osteocalcin and parathormone in women with various clinical variants of rheumatoid arthritis. Study included 74 patients with rheumatoid arthritis of age between 20 to 66 years. Patients had been diagnosed with rheumatoid arthritis according to the ACR/EULAR (2010) criteria. Levels of osteocalcin and parathormone were determined by ELISA. Statistical processing of the data was done using ANOVA with the computation of multiple comparisons test (Student's t-criteria), correlation analysis with the computation of criteria of Spearman and Pearson. Concentration of osteocalcin in rheumatoid arthritis and in the control group correspond to the norm range, but its levels in rheumatoid arthritis was significantly lower than in controls (p = 0.012). Concentration of osteocalcin in blood less than lower normal range was present in 23% of patients. Parameters of parathormone above the upper normal range were revealed in 12.2% of cases. In women with rheumatoid arthritis, disorder of bone tissue metabolism in the form of decrease in the level of marker of bone formation, osteocalcin, associated with duration, activity and functional class of the disease was observed. By this study we conclude that low levels of osteocalcin in rheumatoid arthritis testify to insufficient intensifying of bone formation process in reply to activation of bone resorption. It dictates the necessity of estimation of biochemical markers of bone metabolism for prevention of osteoporosis development.***

Keywords: ***Rheumatoid arthritis, osteocalcin, parathormone, rheumatoid factor, antibody to cyclic citrullinated peptide***

I. INTRODUCTION

Osteoporosis - systemic skeletal disease characterized by decrease in bone mass and disorder in microarchitecture of bone tissue resulting in increased risk of fractures and decline in quality of life of the patients. In the recent years main interests were shown on the secondary osteoporosis, which is a result of many autoimmune diseases, including that of rheumatoid profile. Inflammatory process, underlying as the basis of rheumatoid arthritis (RA), may setoff disorder in

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metabolism of bone tissue and increases risk of developing osteoporosis, which are considered as the indicators of severity and activity of disease .

In RA, osteoporosis manifested as decrease in mineral density of bone tissue, which is formed not only locally in the inflamed joints but also systemic, characterized as frequent non articular manifestation of disease. In patients with RA osteoporosis is seen 1.5-4 times frequently than in general population and odds of its appearance increases regardless of sex and age. Nevertheless, it is supposed that such characteristics as high levels of pro-inflammatory mediators, decreased functional activity of patients, duration of the disease, presence of rheumatoid factor, female sex, status of menopause and intake of non-steroid anti-inflammatory drugs (NSAIDs) and glucocorticoids are more closely related with disorder of metabolism and domination of negative reparative balance of bones.

Metabolism of bone tissue is characterized by two simultaneously occurring multidirectional processes: formation of new bone tissue by osteoblasts and resorption of old bone by osteoclasts. Markers of bone formation are alkaline phosphatase of bone, osteocalcin, parathormone, calcitonin, calcitriol and etc. It is considered that cytokine mediated bone resorption accompanied by hyper activation of osteoclasts, strengthened by the production of markers of bone resorption and the correlating active clinical and laboratory components of RA lies in the basis of osteoporosis on the background of RA. Effect of disease on markers of bone formation is not completely studied, as results of research are often of contradictory character. There is an view on the suppression of formation of bone in RA or expression of a point of view on possible (expected) compensatory increase in formation of bone tissue.

The aim of this research was to study serum concentration of biochemical markers of bone tissue metabolism in women with different variants of RA.

II. MATERIALS AND METHODS

74 patients with RA of the age from 20 to 66 years (mean age 51.03±1.25 years) were examined, who were undergone observation and treatment at rheumatology department and in rheumatologist cabinet of Regional clinical hospital. Inclusion criteria: Patients, female sex of age 18 years and more, diagnosed with RA, consent of participation in research, absence of intake of glucocorticoids up to 3 months until their inclusion in research, continuous intake of NSAIDs in stable doses. Exclusion criteria: presence of other diseases effecting on bone tissue metabolism (hypercorticism, hypogonadism, diseases of parathyroid and thyroid glands, diabetes mellitus, systemic connective tissue diseases, diseases of blood, malignant tumors, malabsorption syndrome, syndrome of prolonged immobilization, chronic renal insufficiency), intake of antiosteoporotic preparations (calcium preparations, vitamin D, estrogen and etc.), recipients of biological preparations for 6 months until their inclusion in research. Control group consisted of 19 healthy women comparable with age, physical condition and concomitant pathology and not diagnosed with RA or any other autoimmune diseases.

Diagnosis of RA was established according to classification criteria of ACR/EULAR (2010). Clinical characteristics of patients in accordance with classification accepted by association of rheumatologists of Russia were presented in Table1. It can be seen from the table 1 that most of the patients were more than 50 years of age, with late stage of RA and characterized by the presence of rheumatoid factor (RF) and antibody to cyclic citrullinated peptide (ACCP) in blood, and with high activity of the disease. Duration of joint syndrome was from 9.33±0.52 years. Concentrations of RF IgM and ACCP in serum were 131.50±10.08 ME/ml and 242.55±22.52 U/ml respectively. Median value of index DAS28 in patients was 5.22±0.09. Most of the patients were diagnosed with erosive form of the disease, III radiographic stage, II and III functional class. In 23% of the patients, systemic manifestations (especially rheumatoid nodules) were seen. In 2/3 of the patients complication of the disease (secondary osteoarthritis) was seen.

Research was corresponded with the requirements of Helsinki declaration of the world medical association on ethical principles for medical research involving human subjects. All the subjects gave information consent on their participation in the research. Research was approved by ethical committee of the University.

Laboratory examination included the determination of serum level of osteocalcin and parathormone by ELISA.

Results were statistically analyzed using IBM SPSS Statistics ver. 24.0. Quantitative values are characterized, normally distributed and presented in the form of mean ± standard error. Two sample students t-criteria, correlation analysis with evaluation of Pearson were used for the evaluation of differences between groups. In statistical analysis of qualitative values χ^2 criteria with Yates's correction was evaluated. Results are proven reliable with the level of significant difference $p \leq 0.05$.

III. RESEARCH RESULTS

Mean values of osteocalcin and parathormone in women with RA and in the control groups corresponded normal value, however in patients with RA concentration of osteocalcin in blood was significantly lower (p=0.002), but value of parathormone was not differed from the control group (Table II).

Serum concentration of osteocalcin less than the lower limits of norm was seen in 23% of patients (χ^2=3.91, p=0.048) and was 9.63±0.59 ng/ml. This group of patients frequently met high activity of the disease (94.1% and 59.6% respectively; χ^2=5.61, p=0.018) and III functional class (82.4% and 40.4% respectively; χ^2=7.64, p=0.006), than in patients with normal level of this mediator in blood.

Parameters of parathormone higher than upper limit of norm were seen in 12.2% of patients and were 84.55±9.91 pg/ml. Values of osteocalcin higher and values of parathormone lower than the normal range were not present in patents with RA.

Serum concentration of osteocalcin and parathormone were not associated with duration or clinical stage of the disease. Reliable importance of values of bone metabolism

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with the presence or absence of RF and ACCP was not seen, although a tendency for higher levels of parathormone was noted in ACCP positive RA. A positive correlation of parathormone activity with serum quantity of ACCP antibodies was noted (p=0.05).

In cases with high activity of inflammatory process by index DAS28, serum concentration of osteocalcin was significantly lower (p=0.029) than in moderate activity of RA, while the concentration of parathormone were not correlated with the expression of inflammatory component. Parameters of bone tissue metabolism were not correlated with the levels of ESR and C-reactive protein, and were also not depended on the severity of x-ray changes of joints, including the presence or absence of erosions.

High gradation of functional class of the disease was characterized by significant low concentration of osteocalcin in blood (p=0.048) and unchanged serum concentration of parathormone. Presence of systemic effects or complications of RA does not effect on the dynamics of studied mediators in blood.

Analysis of markers of bone metabolism depending on the presence or absence of menopause showed that concentrations of osteocalcin and parathormone were comparable in both group of patients without any significant difference in between groups.

IV. DISCUSSION

The obtained results confirm the thesis that increase in bone resorption in RA is not accompanied with expected compensatory increase in bone formation. At the same time, veraciously lower mean values of osteocalcin were found in patients with RA when compared with control group, and levels of osteocalcin lower than normal range in some patients (23%) shows a subclinical violation in bone remodeling, which subsequently may manifest as systemic effect with the development of generalized osteoporosis.

Osteocalcin is a vitamin K dependent noncollagenous protein, specific for bone tissue and dentine, synthesized predominantly by osteoblasts and is included in extracellular matrix of bone tissue. Osteocalcin is considered as one of the most informative biochemical markers of bone formation and rate of bone turnover. Parathormone increases quantity and activity of osteoclasts, contributing bone resorption, although it may also have some anabolic properties. Therefore the role of parathormone in regulation of balance between formation and resorption of bone still remains unclear.

There are publications on conflicting data on the level of osteocalcin and parathormone in patients with RA: reports of reduced, normal and increased levels of serum mediator concentrations that apparently because of heterogeneity in involvement of bone tissue in RA or due to the differences in duration and activity of the disease.

So, concentration of serum osteocalcin and parathormone in women with active RA, including premenopausal, was lower and the levels of interleukin-6 and carboxy-terminal telopeptide type 1 collagen (marker of bone resorption) were higher than in patients with non-active form of the disease and healthy individuals. Presence of RA in postmenopausal women was characterized by reduced levels of osteocalcin, which was correlated negatively with the activity of the disease, values of ESR, and positively with duration of the disease, platelets in blood, and were independent on the intake of glucocorticosteroids, whereas markers of bone tissue resorption, on the other hand were increased especially in patients receiving glucocorticosteroids. Decreased serum concentration of osteocalcin in RA in difference with normal activity of parathormone, correlated with quantity of bone erosions. Debut of the disease at elderly age was associated with significant lower levels of osteocalcin, than when started at young age.

On the other hand, there were opinions that metabolism of bone tissue is undisrupted in RA and also does not depend on age and sex of the patients, which emphasizes the normal level of activity of osteoblasts. From the data published by S.M. Antonova et al. concentration of serum osteocalcin in early RA was in normal range, unlike increased levels of markers of bone resorption regardless of activity, serological constituents and anatomical stage of the disease. But in 22.6% of the cases reduced level of the mediators, especially in women of premenopause stage was determined. In the research of Batmaz et al. unchanged levels of osteocalcin and bone alkaline phosphatase in postmenopause women with RA were not correlated with x-ray changes and activity of the disease. Normal levels of parathormone in patients with RA were independent of sex, age of patients, activity of the disease and intake of glucocorticosteroids, which according to the authors indicates the low possibility of developing secondary hyperparathyrosis on the background of RA [15].

In contrary, even being in the normal range, serum concentrations of osteocalcin and alkaline phosphatase in men with RA were increased in comparison with control group regardless of activity, functional class and presence of systemic manifestations [16]. From the data of I.N. Totrov, in most of the patients with RA (80.5%), level of osteocalcin was increased. And only in 19.5% cases normal level of this mediator was determined. Significant increase in serum concentrations of osteocalcin with progressive joint destruction according to x-ray examination was noticed [16]. In the view of some authors, active inflammatory process has no significant effect on mediators of bone tissue metabolism, but on the secondary intensification of bone formation (increased levels of osteocalcin) as a response to activation of its resorption, which shows high level of bone metabolism in men with RA. Similarly, increased concentration of serum osteocalcin in women with RA was characterized by a tendency in increase of its values in cases of post-menopause women, whereas increased activity of parathormone in women with RA after menopause correlated with the number of erosions.

Increased serum concentrations of osteocalcin and parathormone combined with reduced serum levels of calcitonin, total and ionized calcium indicates an adverse ratio of calciotropic hormones in RA. Prescription of NSAIDs and glucocorticosteroids led to even more increase in the levels of parathormone and decrease in serum concentration of osteocalcin, calcitonin, total calcium, which characterizes the possibility of latent progression of the disease despite of anti-inflammatory therapy.

In some studies it was determined that the correlation of levels of octeocalcin with the activity of RA may be due to the involvement of cytokines in regulation of bone tissue remodeling. Progression of inflammation and osteoporosis in RA has common pathogenetic mechanisms, in which the main role is assigned to the disbalance of pro- and anti-inflammatory cytokines, and also imbalance in ratio of pro-inflammatory cytokines and their soluble receptors, blocking activity of the mediators. Thus, interleukin-6 acts as a mediator of osteoclast-mediated bone resorption in postmenopausal osteoporosis. Moreover, it indirectly increases the expression of receptor activator of nuclear factor kappa-B ligand (RANKL), which is necessary for the activation, differentiation and functioning of osteoclasts. Interleukin-1intensify osteoclastogenesis and reduces cell apoptosis, and tumor necrosis factor alpha (TNF-α) induces the differentiation of osteoclasts.

On the other hand, TNF-α inhibits the differentiation and maturation of osteoblasts, interrupt the expression of runt-related transcription factor-2 (RUNX2), osteocalcin, alkaline phosphatase and intensifies apoptosis of osteoblasts. Interleukin-1 not only affects negatively on the differentiation of osteoblasts but also interrupts the synthesis of collagen in bone tissue, and interleukin-6 and interleukin-17 suppresses formation of osteoprotegrin by osteoblasts, which is a major antagonist of RANK for binding to its ligand, leading to intensified activation of osteoclasts.

Indirect evidence of the effect of rheumatoid arthritis activity on bone tissue metabolism can be the fact of the relationship of bone mediators with the severity of radiographic manifestations. Thus, reduced concentration of osteocalcin in the blood or increased parathyroid hormone activity correlated with the amount of bone erosions. A significant increase in serum levels of osteocalcin with progression of articular destruction in men with RA indicates an increase in bone formation in response to activation of its resorption and a high level of bone metabolism.

The question of the influence of menopause on the parameters of bone metabolism in rheumatoid arthritis remains open. According to the results of our study, reduced content of osteocalcin and normal levels of parathyroid hormone in the blood are independent of menopause. At the same time, there are data on reduced serum concentrations of osteocalcin and parathyroid hormone in pre- or postmenopausal women and a trend toward further increase in the elevated concentration of osteocalcin in blood of postmenopausal women with rheumatoid arthritis.

Revealed relationship of osteocalcin with functional class of the disease was apparently due to the decreased functional activity in III functional class of the disease (restriction in professional and non-professional activities), which is an important risk factor for disorders of bone remodeling.

V. CONCLUSION

In women with RA, disorder of bone tissue metabolism in the form of decreased concentration of serum osteocalcin, associated with disease activity and functional class was observed. Reduced concentrations of osteocalcin indicates lack of amplification in the process of bone formation in response to activation of its resorption in RA, necessitating the assessment of biochemical markers of bone metabolism as a predictor of early development of osteoporosis for the corresponding corrections in treatment.

Parameters	No. of patients, % (Abs.)
Age:	
< 50 years	39,2 % (29)
≥ 50 years	60,8 % (45)
Clinical stage:	
Early	1,4 % (1)
Progressive	16,2 % (12)
Late	82,4 % (61)
Immunological characteristics:	
Seropositive (RF present)	87,8 % (65)
Seronegative (RF absent)	12,2 % (9)
ACCP-positive	75,7 % (56)
ACCP- negative	24,3 % (18)
Degree of activity (by index DAS28):	
Moderate	32,4 % (24)
Severe	67,6 % (50)
Anatomical (x-ray) stage:	
Stage I	2,7 % (2)
Stage II	13,5 % (10)
Stage III	68,9 % (51)
Stage IV	14,9 % (11)
Presence of bone erosions:	
Erosive RA	89,2 % (66)
Non erosive RA	10,8 % (8)
Functional class:	
I	1,4 % (1)
II	48,6 % (36)
III	50,0 % (37)
Systemic manifestations:	
Present	23,0 % (17)
Absent	77,0 % (57)
Complications:	
Present	66,2 % (49)
Absent	33,8 % (25)

Table 1: Clinical characteristics of the patients with Rheumatoid arthritis

Examined groups	Parameters	
	Parathormone (pg/ml)	Osteocalcin (ng/ml)
Control group, n=19	47,87±2,73	29,05±1,31
Rheumatoid arthritis, n=74	40,91±2,65	22,04±1,07 *
Early & progressive stage RA, n=13	46,16±10,69	22,46±2,04
Late stage RA, n=61	39,80±2,32	21,95±1,23
Seropositive RA, n=65	41,36±2,92	21,53±1,07
Seronegative RA, n=9	37,73±5,83	25,77±4,07
ACCP-positive RA, n=61	43,05±3,25	22,16±1,24
ACCP-negative RA, n=13	34,29±3,76	21,69±2,13
Moderate activity RA, n=24	44,25±3,67	25,37±1,70
Severe activity RA, n=50	39,31±3,51	20,44±1,30 *

Anatomical (x-ray) stage I/II, n=12 Anatomical (x-ray) stage III, n=62	48,81±11,26 39,39±2,32	23,50±1,91 21,76±1,22
Non-erosive form RA, n=8 Erosive form RA, n=66	40,33±6,24 40,99±2,89	22,16±2,31 22,03±1,17
Functional class I/II, n=37 Functional class III, n=37	43,10±4,39 38,72±2,99	24,14±1,31 19,94±1,63 *
Systemic manifestations RA (-), n=57 Systemic manifestations RA (+), n=17	41,27±3,23 39,73±4,15	21,73±8,97 23,10±2,46
Complications RA (-), n=25 Complications RA (+), n=49	42,50±5,98 40,11±2,64	22,41±1,79 21,86±1,34
RA (premenopause), n=29 RA (postmenopause), n=45	37,10±3,51 43,38±3,71	20,61±1,75 22,97±1,34

Note: * - p<0.05 between examined groups

Table 2: Concentrations of parathormone and osteocalcin in patients with Rheumatoid arthritis

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