THE MARKERS OF BONE METABOLISM AND SYSTEM INFLAMMATION IN PATIENTS WITH OSTEOARTHRITIS DEPENDING ON BODY MASS, THE INFLUENCE OF SYMPTOMATIC SLOW ACTING DRUGS

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Abstract

Aim. To assess the levels of markers of the bone synthesis and system inflammation in patients with osteoarthritis (OA) in combination with obesity and their dynamic under the influence of basic treatment.

Materials and methods. The research included 40 women with OA, 46–78 years old (mean age – 59,8±1,5 years). Duration of the disease varied from 3 to 36 years (mean duration – 10,0±1,1 years). Mean body mass index (BMI) among patients was 30,6±0,7 [22,3; 39,5] kg/m^2, according to which patients were divided in 3 groups: patients with OA without obesity (n=17), patients with OA with 1 degree of obesity (n=14), patients with OA with 2 degree of obesity (n=9). The level of osteochondral metabolism was assessed using quantitative measuring of the levels of procollagen IC-terminal propeptide (PICP), (CloudCloneCorp. "procollagen IC-Terminal Propeptide", USA) and osteocalcin (Roche Diagnostics «N-MID Osteocalcin», Switzerland) on analyzer «ELECSYS 2010» by the method of immune-enzyme analysis; the level of the system inflammation was assessed by the level of C-reactive protein (CRP) by the method of immunoturbidimetry. The clinical efficacy was assessed by the dynamics of intensity levels of pain syndromes at physical load and at rest by the visual-analogue scale (VAS). The measuring of PICP, osteocalcin and CRP levels and also the assessment of clinical efficacy as to the decrease of pain syndrome were carried out twice – at the beginning and at the end of observation. The period of observation is 2 months.

Results. The presence of direct correlation between PICP and BMI (r=0,62; p=0,008) among patients with OA in combination with the normal body weight was established at the research, whereas among patients with OA in combination with obesity the analogous correlation was demonstrated between SRP and BMI (r=0,43; p=0,04) on the background of correlation of PICP and OC levels (r=0,46; p=0,03).

Obesity in patients with OA was associated with the reliably higher levels of pain at both rest and physical load from the side of knee joints, with maximal intensity of the pain syndrome among patients with OA and 1 degree of obesity.

Statistical analysis did not reveal the reliable dependence of PICP and OC in patients with OA from the initial CRP level on the background of tendency to the higher PICP level and lower OC level among patients with initially increased CRP level comparing with ones with normal CRP level. The therapy with basic preparations at OA during 2 months among patients with OA with increased CRP level led to the reliable decrease of PICP level (p=0,0076) and the tendency to increase of OC level (p>0,05), without the reliably significant difference between the initial and final PICP and OC levels among patients with OA and normal CRP level.

At the end of observation period the maximal analgesic effect was demonstrated as to the articulate pain at rest from the side of knee joints (p<0,001) among patients with OA, who received diacerein, with clinically comparable effect from the side of other aticulate zones (p<0,05), that was associated with reliable decrease of CRP level (p=0,013).

Discussion. The received results testify that the control of the system inflammation level at OA is a target not only relative to the decrease of pain syndrome but also conditions the stable state of subchondral bone (SCB), providing the compensation of processes of destruction and synthesis in bone tissue. The significance of procollagen IC-terminal propeptide (PICP) and osteocalcin (OC) as the markers of bone synthesis that are able to reflect metabolic processes in SCB at OA, and also the discordant influence of CRP level on PICP level at the relative stability of OC level were demonstrated at the research.

The received results allow consider the inflammatory process at OA as a target for preservance of the bone tissue, conditioning the expedience of taking into account the ability of OA basic preparations to realize the control influence on the level of system inflammation. Diacerein that in ESCEO recommendations (2014) is related to the preparations of the 1 step of treatment of patients with OA provides the control on inflammation and stability of osteocalcin level that testifies to the balance of catabolic processes in SCB.

Conclusions. At OA the levels of procollagen IC-terminal propeptide (PICP) and osteocalcin (OC) were not associated with obesity and did not depend on the initial CRP level at the presence of correlation between PICP level and BMI among patients with OA with the normal body weight and BMI and CRP level among patients with OA in combination with obesity.

The absence of reliable dynamics from PICP side and maintenance of the stable OC level on the background of the reliable anti-inflammatory effect at using diacerein in patients with OA can testify to the compensatory adequacy of reparation processes in SCB.

Keywords: osteoarthritis, obesity, procollagen IC-terminal propeptide, osteocalcin, system inflammation, diacerein.

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1. Introduction

According to the modern epidemiological data, osteoarthritis is the most frequent form of arthritis. According to WHO data, 25 % of adult population past 65 years old has clinically symptomatic OA of one or other joint [1]. Besides persisting pain syndrome, OA is also the case of early disablement and high invalidism of population.

The modern conception of OA considers this disease rather as abnormal remodeling of all articulate tissues (articulate cartilage, subchondral bone, synovial tunic, muscles, ligaments, meniscuci), conditioned by the influence of proinflammatory mediators, and not only as degenerative process, conditioned by age, as it was previously considered [2]. Thus, the understanding of OA must be the complex one and take into account not only clinical symptoms but also the degree of structural changes of all components of articulate cartilage that gives a possibility to assess the role of separate pathogenetic factors that have the cross influence on joint and also their contribution in OA progressing [3].

The question about, are the changes in subchondral bone (SCB) the primary ones as to the injury of cartilage or appear at further OA progressing, remains discussable one. The studies of last decades demonstrate that abnormal remodeling of SCB, namely subchondral osteosclerosis and formation of osteophytes that is conditioned by the appearance of new loci of osteogenesis often go before the changes in articulate cartilage and stenosis of articulate fissure [4–6]. The mediators of inflammation, which level in articulate cartilage increases at OA, can also lead to the destruction of subchondral bone at the expense of intensification of bone remodeling processes [7]. At the same time it is known that the system osteoporosis, attended with the decrease of bone tissue mass, has inducing influence and/or is able to result in OA progressing [8]. Thus, both phenotypes of the bone tissue remodeling (osteosclerosis and osteoporosis) can be considered as the risk factors of OA development. At that, the presence of other risk factors of OA leads to the synergetic influence as to OA initiation.

It is known, that the balance between the bone synthesis and its resorption in SCB is broken at OA that on the background of metabolic processes [9] leads to the defective mineralization of bone and decrease of its biochemical properties [5, 10]. The distinctive feature of the bone tissue remodeling mechanisms at OA is the differences in domination of catabolic or anabolic component depending on the stage of OA development [11]. The study of osteocytes activity invitro demonstrates the bone resorptions at the early OA stages [12, 13], with further decrease of their intensity at further OA progressing [14] that is proved by the results of several researches with measuring the level of bone creation and bone resorption markers in the blood serum of patients with OA [15].

The progressive direction of modern medicine is the study and revelation of biomarkers that in OA context would give a possibility to not only reveal the potentially irreversible changes in the articulate cartilage structure but also to prognosticate the speed of disease progressing. The searches in this branch were started already in 2006 when American society for OA biomarkers offered biomarkers classification «BIPED» (*Burden of Disease, Investigative, Prognostic, Efficacy of Intervention and Diagnostic*) for the widening of possibilities of OA study [16]. According to this classification, 5 markers of OA are separated: burden of disease (CTXII, COMP, leptin, adiponectin, visfatin), prognosis (CTXII, COMP, MMP-3, MMP-1, C2M, C2C, leptin, adiponectin, visfatin), C-reactive protein, interleukin-6), efficacy of intervention, investigative (genetic markers) and diagnostic ones (CTX II, COMP, C2C, PIINP, osteocalcin, FSTL-1, PIIANP, sRAGE) [16, 17].

Despite the series of researches on the study of biomarkers that potentially can be used from the position of diagnostic significance at OA, the problem of distinct "marker algorithm" remains open for today [16]. The last recommendation on this question were offered in instructions of ESCEO (*The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis*) in 2012, according to which the most reliable markers of OA are the structural molecules or their fragments that are the constitutive components of articulate cartilage, SCB or synovial tunic and, according to experts, can reliably reflect the processes of degradation and synthesis in these tissues [18].

Osteocalcin (OC) it is a main non-collagenous protein of the bone matrix that contains hydroxyapatite and is a structural component of the bone organic matrix [18]. It is known, that OC is synthesized by osteoblasts that is why its level in the blood plasma can testify about the osteoblasts metabolic activity, because OC concentration in blood is a result of new synthesis and not the release of it at the resorption of bone tissue. Alongside with it OC has calcium binding effect and takes part in the bone mineralization [17]. The series of researches demonstrated the increase of OC level in patients with OA on the background of intensification of remodeling processes and changes in the process of bone tissue mineralization that was associated with further osteophytosis progressing [19, 20]. Thus, OC can be considered as the specific marker of functional activity of SCB osteoblasts and the sensitive marker of the bone tissue remodeling. The data that demonstrate the decrease of OC level among patients with obesity and its connection with carbohydrate metabolism disorder are also interesting [15].

Alongside with OC there is also the series of other markers of bone metabolism that reflect the synthesis processes in bone tissue. For example, procollagen IC-terminal propeptide (PICP) that is synthesized by osteoblasts as predecessor and is a big molecule that has the partially globular fragment – PICP on C-end, which structure is stabilized by bisulfite connections [4]. Entering in extracellular space, PICP undergoes enzyme hydrolysis and remains in extracellular liquid and the mature collagen 1 molecule takes part in formation of the bone matrix. Although the ratio between collagen that is settled in the bone matrix and PICP quantity that comes into the blood channel is theoretically equal 1, PICP can be used for the assessment of metabolic activity of osteoblasts [21]. The most researches of PICP are concentrated on the study of this marker from the positions of system osteoporosis, where were demonstrated the decrease of its level in the conditions of osteoporosis. Taking into account the fact that osteoporosis not only negatively influences the SCB state and is an unfavorable factor of the development and progressing of OA but is often combined with OA, the study of this marker from OA positions is very topical. Nevertheless the literary data as to the study of PICP with OA are not enough that conditions the topicality of this work.

The modern conception of OA therapy provides two hypothetic points on influence on OA pathogenetic links: anti-inflammatory therapy that is realized by the use of non-steroid anti-inflammatory drugs and the therapy, directed on deceleration of degradation of articulate cartilage components and disease progressing that is realized by the use of symptomatic slow acting drugs for osteoarthritis – SYSADOA) [22]. At the same time the one of unsolved problems in the treatment of patients with OA remains the absence of pathogenetic model of influence on SCB that, according to the modern notions, can be the "target" at OA. Although the use of biphosphonates in patients with OA remains problematic, taking into account the high risks of side effects, connected with their use, it is expedient to study the ability of basic OA preparations to make the correcting influence on SCB state. According to ESCEO recommendations, symptomatic slow acting drugs are related to the preparations of the 1 step of OA treatment. The representative of this group is diacerein that demonstrated the high clinical efficacy at treatment of patients with OA [23] at the expense of verified anti-inflammatory effect, conditioned by inhibition of interleukin -1 and, according to the results of recent research, can influence the separate catabolic and anabolic mediators of inflammation that participate in OA pathogenesis [24].

2. Aim

To assess the levels of markers of the bone synthesis and system inflammation in patients with OA in combination with obesity and their dynamic under the influence of basic treatment.

3. Materials and methods

The research included 40 women with OA, 46–78 years old (mean age is 59,8±1,5 years), in 31 of them was diagnosed monoosteroartritis and in 8 patients – olygoosteroathritis OA (**Table 1**). In most patients was diagnosed the II stage of OA – 65 %, I and III stage – in 25 % and 10 % respectively. The duration of disease varied from 3 to 36 years (mean duration – 10,0±1,1 years). All patients underwent therapy according to the local protocol of medical help for patients with OA that included symptomatic slow acting drug – diacerein ("Flexerin") and symptom-modifying preparations – non-steroid anti-inflammatory preparations (NAIP) from the group of selective inhibitors of cyclooxigenase-2 (meloxicam, celecoxib and other). Patients received flexerin (PC "Kyiv vitamin factory") according to the scheme: first 2 weeks – 50 mg/day with further increase of dose up to 100 mg/day.

The mean body mass index (BMI) among patients was 30,6±0,7 [22,3; 39,5] kg/m^2, at that BMI >29,9 kg/m^2 was diagnosed in 23 patients with mean BMI value in this group of patients 33,7±0,7 [30,3; 39,5] kg/m^2. To assess the influence of obesity on the bone synthesis processes and system inflammation level all patients with OA were divided in 3 groups: patients with OA without obesity (n=17), patients with OA with 1 degree of obesity (n=14), patients with OA with 2 degree of obesity (n=9).

Table 1

Characteristics of injury of main groups of joints among patients with OA

Joints	Patients with OA (n=40)	%
	Monoosteroarthritis OA (n=31)	
Knee	20	50
Hand joints	9	22,5
Hip	3	7,5
	Olygoosteroarthritis OA(n=8)	
Knee+hand joints	6	15,0
Knee+hip	2	5,0

The level of osteochondral metabolism was assessed using quantitative measuring of the levels of procollagen IC-terminal propeptide (PICP), (Cloud-CloneCorp. «procollagen IC-Terminal Propeptide, USA) and osteocalcin (Roche Diagnostics «N-MID Osteocalcin», Switzerland) on analyzer «ELECSYS 2010» by the method of immune-enzyme analysis; the level of the system inflammation was assessed by the level of C-reactive protein (CRP) by the method of immunoturbidimetry. The clinical efficacy was assessed by the dynamics of intensity levels of pain syndromes at physical load and at rest by the visual-analogue scale (VAS). The measuring of PICP, osteocalcin and CRP levels and also the assessment of clinical effectiveness as to the decrease of pain syndrome were carried out twice – at the beginning and at the end of observation. The period of observation is 2 months.

For the statistical analysis of data the descriptive statistics with calculation of the mean value (M), mean standard mistake (m) was used. The probability of difference was assessed by the parametric methods (on Student t-criterion for unrelated samples) and non-parametric ones (Pirson χ^2 Mann-Whitney, Kholmogorov-Smirnov U-criterion). Interconnection between the studied parameters was revealed using the calculation of Spearmen correlation coefficient. All data are presented as the mean value and its mistake. The difference at $p<0,05$ was considered as significant one. All calculations were realized in Statistica 6.0 program.

4. Results

The mean PICP level among patients with OA was 35,8±3,7 [4,1;78,1] pg/ml, OC – 23,8±1,6 [8,9; 53,3] mcg/ml, CRP – 5,0±0,5 [0,7; 13,8] mg/ml. On VAS the mean pain level at load and at rest from the side of knee joints was– 4,1±0,34 and 5,7±0,38 points, respectively. The mean pain level from the side of other joint zones at rest was 3,6±0,31 points, at physical load – 5,5±0,41 points. Statistical analysis did not revealed the reliable difference between the initial levels of PICP, OC and

CRP in patients with OA depending on BMI. Nevertheless there was demonstrated a tendency to the increase of PICP level among patients with OA and 2 degree of obesity (**Table 2**) that exceeded the level among patients with OA and normal body weight by 18,7 %. The opposite tendency was demonstrated related to OC level – the decrease of it depending on BMI increase with maximal difference between patients with OA and normal body mass and obesity of 2 degree – 24,6 %. At that CRP level was the highest one among patients with OA and 1 degree of obesity without clear tendency as to the change of its level depending on BMI (**Table 2**).

Table 2

PICP, ostecalcin, SRP levels in patients with OA depending on presence and degree of obesity

	PICP, pg/ml	Osteocalcin, mcg/ml	CRP, mg/ml
BMI ≤29,9 kg/m^2 (n=17)	36,1±5,2 [5; 78,1]	25,6±2,6 [14,9; 53,3]	5,2±0,7 [0,7; 8,7]
BMI 30–34,9 kg/m^2 (n=14)	29,5±6,7 [4,1; 72,0]	24,6±2,5 [14,5; 48,9]	6,3±0,8 [2,9; 13,8]
BMI 35–39,9 kg/m^2 (n=9)	44,4±8,6 [8,2; 72,0]	19,3±3,0 [8,9; 33,6]	3,9±0,5 [1,8; 6,3]

Note: p<0,05 between data in the groups of comparison

Together with it, the direct correlation between PICP level and BMI was revealed among patients with the normal body weight (r=0,62; p=0,008) (**Fig. 1**), whereas among patients with obesity the analogous correlation was established relative to CRP level and BMI (r=0,43; p=0,04) (**Fig. 2, *b***) on the background of correlation of PICP and OC levels (r=0,46; p=0,03) (**Fig. 2, *a***).

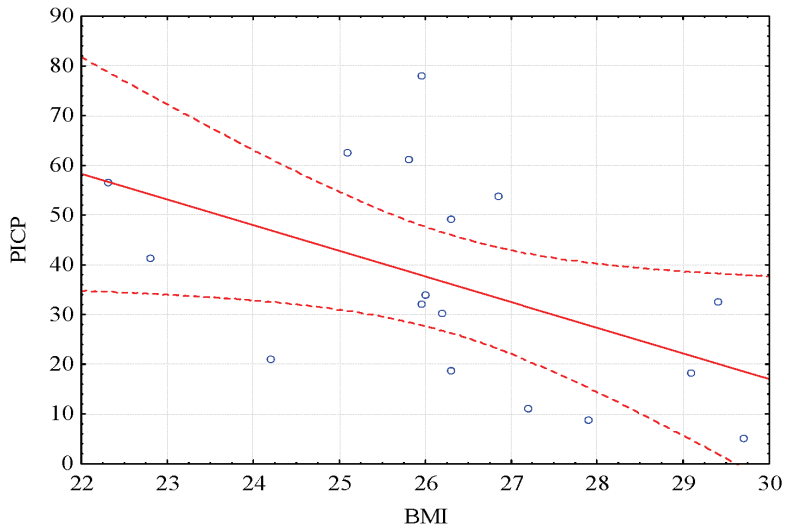


Fig. 1. Correlation between PICP level and BMI among patients with OA and normal weight

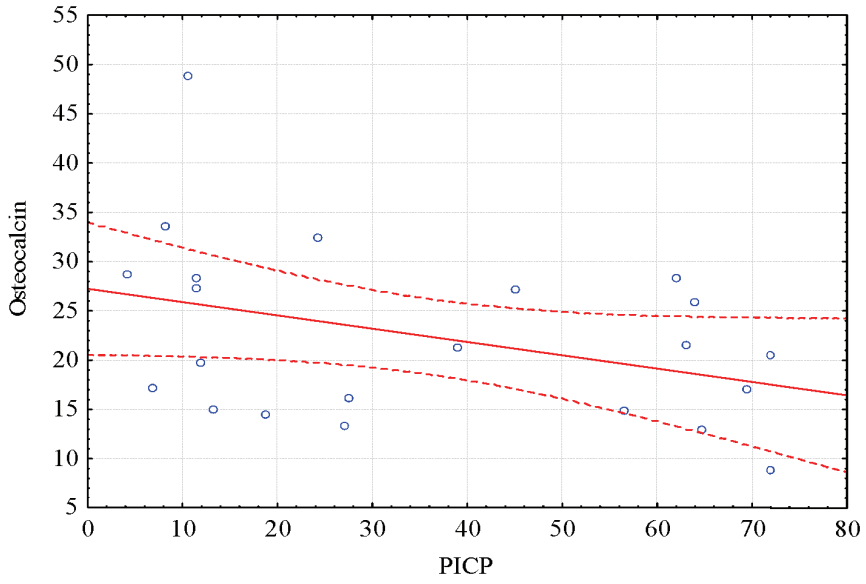
In patients with OA obesity was associated with reliably higher pain levels, both at rest and at physical load from the side of knee joints, with maximal intensity of pain syndrome among patients with OA and 1 degree of obesity (**Table 3**).

Table 3

Intensity of pain syndrome at rest and at physical load in patients with OA depending on BMI

	BMI ≤29,9 kg/m^2 (n=17)	BMI 30–34,9 kg/m^2 (n=14)	BMI 35–39,9 kg/m^2 (n=9)
VAS at rest, points			
Knee joints	3,4±0,5*	4,7±0,7*	4,4±0,6*
Other articulate zones	3,4±0,4	3,9±0,7	3,4±0,4
VAS at physical load, points			
Knee joints	4,8±0,6*	6,5±0,5*	6,0±0,7*
Other articulate zones	5,4±0,7	5,8±0,7	5,1±0,8

*Note: * – p<0,05*



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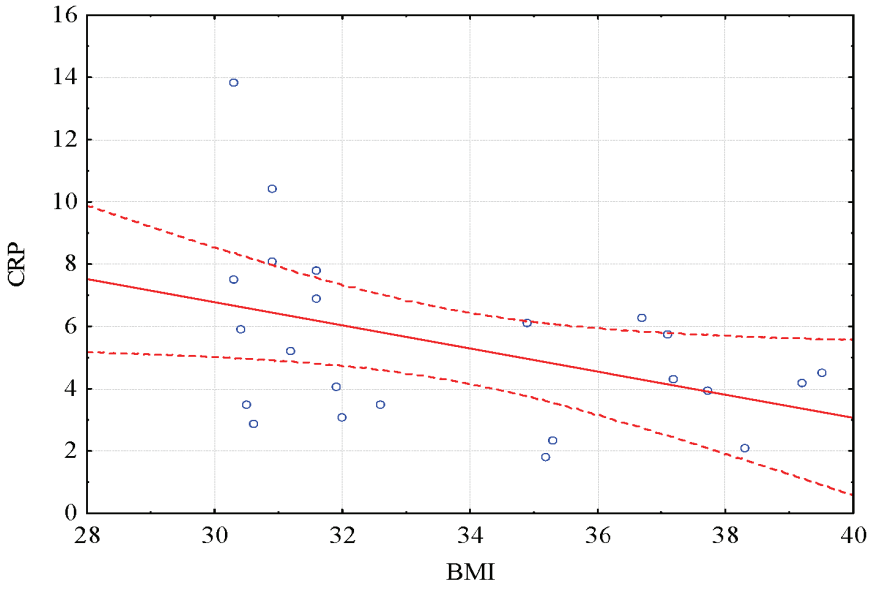

b

Fig. 2. Correlation between PICP, osteocalcin, CRP levels and BMI among patients with OA in combination with obesity: *a* – correlation between PICP and osteocalcin levels; *b* – correlation between CRP level and BMI

The role of system inflammation in the bone metabolism process at OA was assessed depending on the initial CRP level, according to which all patients were divided in 2 groups: patients with normal CRP level (≤6 mg/l), and patients with increased CRP level >6 mg/l (**Table 4**). Analysis of the received results did not reveal the dependence between PICP and OC levels in patients with OA depending on initial CRP level. Nevertheless there was demonstrated that the increased CRP level conditioned the tendency to the increase of PICP level and decrease of OC level comparing with levels of these parameters in patients with OA and the normal CRP level (**Table 4**).

Table 4

PICP and osteocalcin levels in patients with OA depending on CRP level at the beginning of research

Studied parameters	CRP ≤6 mg/l (n=25)	CRP >6 mg/l (n=15)	p
CRP, mg/l	3,2±0,3 [0,4; 5,9]	8,0±0,5 [6,1; 13,8]	p<0,001
PICP, pg/ml	33,3±4,7 [4,1; 78,1]	40,4±6,2 [5,0; 72,0]	p>0,05
Osteocalcin, mcg/ml	24,8±2,1 [8,9; 53,3]	22,1 ±2,4 [12,9; 41,4]	p>0,05

The influence of medical therapy on SCB state and on the sytem inflammation level was assesed on the base of study of the dynamic of PICP, OC and CRP levels among patients with OA, who received "Flexerin" – main group (n=15) and among patients, who received only NAIP – control group (n=25).

Thus, among patients of the main group at the end of observation period the maximal effect as to the decrease of pain syndrome intensity was demonstrated from the side of knee joints, where pain at rest decreased by 37,5 % (p<0,005) and by 39,7 % at physical load (p<0,001) comparing to the initial level. The comparable effect at the end of observation period was attained from the side of other articulate zones, where pain syndrome at rest decreased by 31,3 % and by 36,4 % – at physical load (p<0,05). The decrease of pain syndrome intensity among patients from the control group demonstrated also the reliable decrease as to the pain at rest and at physical load, that decreased by 29,3 % and 31,6 % respectively, from the side of knee joints at the end of 2 month of observation (p<0,05), and from the other articulate zones – by 29,7 % and 27,8 % respectively (p<0,05).

The decrease of pain syndrome among patients from the main group was associated with the reliable decrease of CRP level (p=0,013) comparing with initial levels at the absense of significant dynamics as to PICP and OC levels (**Fig. 3**).

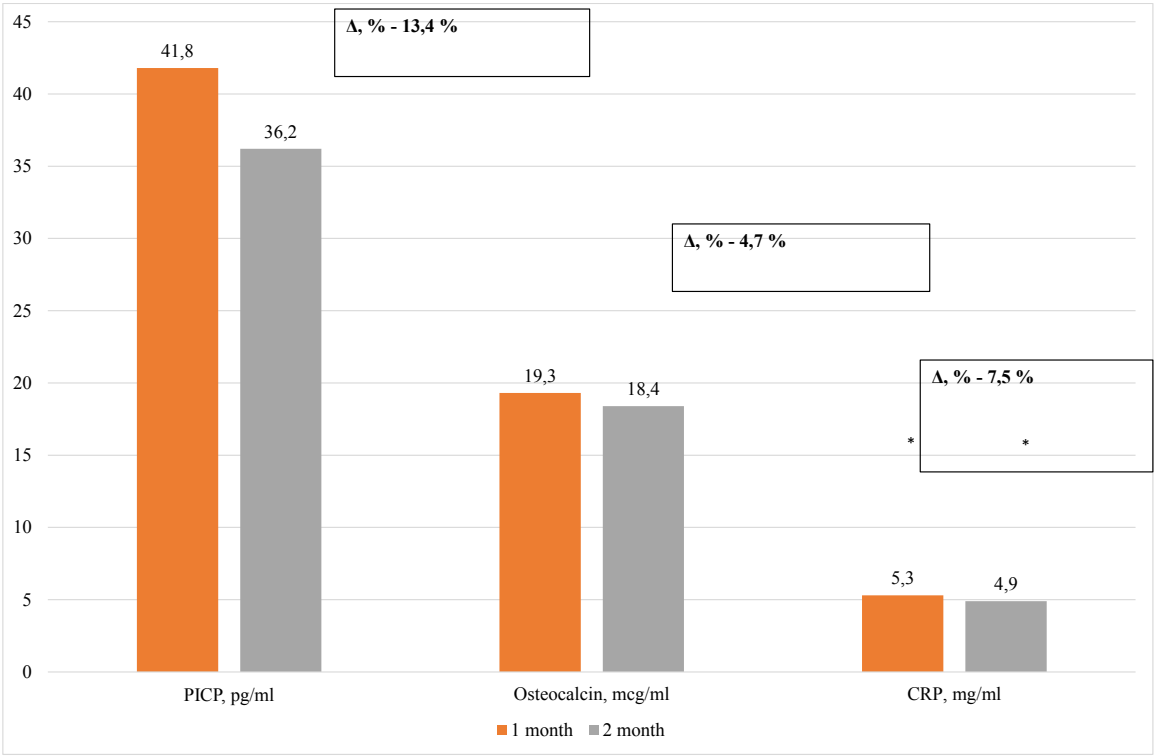

Fig. 3. Dynamics of PICP, osteocalcin and CRP levels among patients of the main group (* – p=0,013)

Instead of it, among patients of control group there was observed only tendency to the decrease of PICP, OC and CRP levels on the background of the received therapy at absence of the reliable difference between initial and final levels (**Fig. 4**).

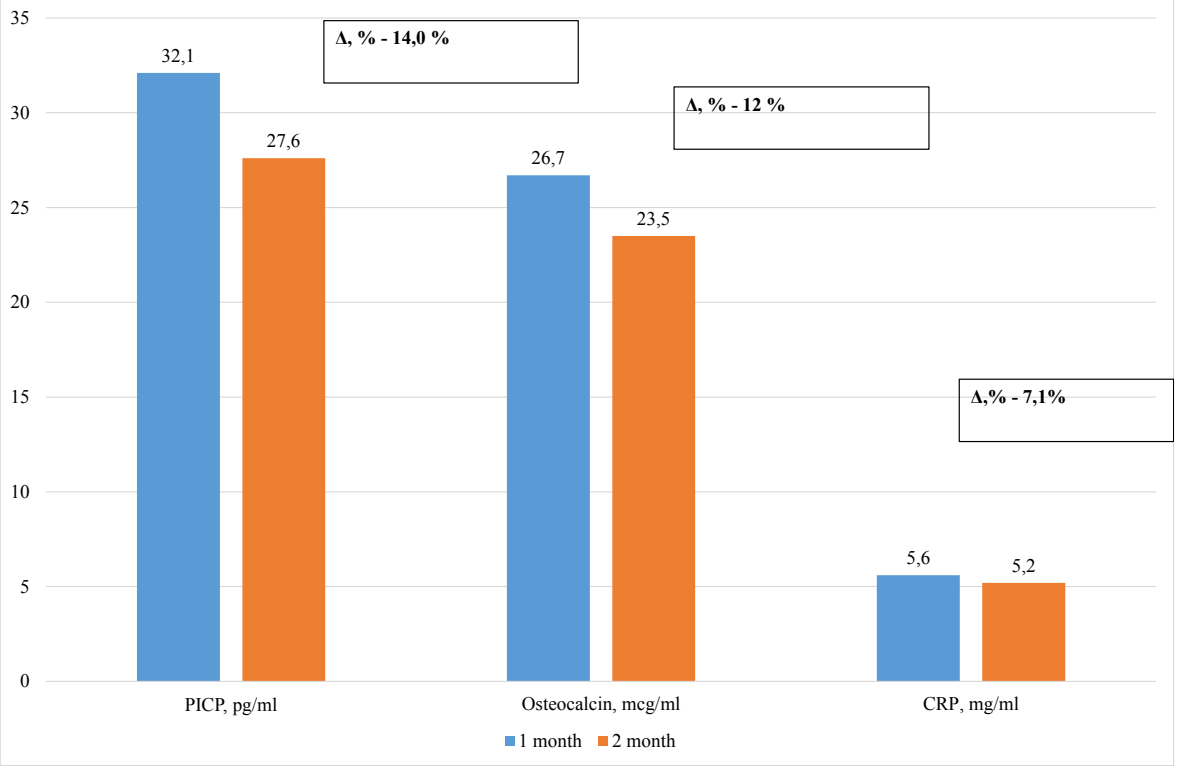

Fig. 4. Dynamics of PICP, osteocalcin and CRP levels among patients of the control group

The research demonstrated that CRP level conditioned the certain features in the type of reacting of the bone tissues on the therapy with basic preparations (**Table 5**).

Table 5

PICP and osteocalcin levels in patients with OA depending on CRP level at the end of research

Studied parameters	CRP ≤6 mg/l (n=28)	CRP >6 mg/l (n=12)	p
CRP, mg/l	3,5±0,3 [0,6; 5,6]	7,5±0,5 [6,1; 12,0]	p<0,001
PICP, pg/ml	36,8±4,2 [3,2; 70,6]	15,8±5,1 [2,3; 57,4]	p=0,0076
Osteocalcin, mcg/ml	20,5±1,1 [11,6; 31,8]	24,3±2,4 [13,4; 38,3]	p>0,05

Thus, in the group of patients with increased CRP level was observed the reliable (p=0,0076) decrease of PICP level (40,4 pg/ml vs 15,8 pg/ml) on the background of tendency to the increase of OC level (22,1 mcg/ml vs 24,3 mcg/ml) at the end of 2 month of observation (p>0,05). Instead of it, in patients with the normal CRP level the reliable difference between the initial and final PICP and OC at the present tendency to the increase of PICP level (33,3 pg/ml vs 36,8 pg/ml) and the decrease of OC level (24,8 mcg/ml vs 20,5 mcg/ml) on the background of therapy with OA basic preparations was not demonstrated.

5. Discussion

The received results testify that the control of the system inflammation level at OA is a target not only relative to the decrease of pain syndrome but also conditions the stable state of subchondral bone (SCB), providing the compensation of processes of destruction and synthesis in bone tissue.

The significance of procollagen IC-terminal propeptide (PICP) and osteocalcin (OC) as the markers of bone synthesis that are able to reflect metabolic processes in SCB at OA was demonstrated at the research. PICP and OC levels do not demonstrated the reliable dependence from the obesity and system inflammation level. At the same time there was demonstrated the discordant influence of CRP level on PICP level in patients with OA, that determines the reliable decrease of its level under conditions of the increased CRP level and the tendency to the increase of the level under conditions of referent CRP values at the relative stability of OC levels. Thus in the conditions of control over the system inflammation the positive changes in the aspect of PICP and OC levels were observed, characterized with the balance of catabolic and anabolic processes in SCB.

Nevertheless the received results allow consider the inflammatory process at OA as a target for preservance of the bone tissue, conditioning the expedience of taking into account the ability of OA basic preparations to realize the controling influence on the system inflammation level. Diacerein that in ESCEO recommendations (2014) is related to the preparations of the 1 step of treatment of patients with OA provides the control on inflammation and stability of osteocalcin level that testifies to the balance of catabolic processes in SCB. It was not demonstrated at using NAIP. This advantage can be prospective in the aspect of further study of SCB state in patients with OA under conditions of treatment with basic preparations, recommended by international organizations that deal with this problem (OARSI 2014, EULAR 2003, 2007, ESCEO 2012).

We understand that the results of our research can have certain limitations that is conditioned by the little number of patients in groups of observation and the further studies of presented problem are needed.

6. Conclusions

1. At OA the levels of procollagen IC-terminal propeptide (PICP) and osteocalcin (OC) were not associated with obesity and did not depend on the initial CRP level at the presence of correlation between PICP level and BMI among patients with OA with the normal body weight and BMI and CRP level among patients with OA in combination with obesity.

2. The absence of reliable dynamics from procollagen IC-terminal propeptide (PICP) side and maintenance of the stable osteocalcin (OC) level on the background of the reliable anti-inflammatory effect at using diacerein ("Flexerin") in patients with OA can testify to the compensatory adequacy of reparation processes in SCB. But the tendency to the decrease of PICP and OC levels and the absence of reliable influence on the system inflammation level at using only NAIP can reflect decompensation in the processes of synthesis and destruction in the bone tissue with the shift of balance to the predominance of catabolic processes in SCB at certain comparability from the side of the results of analgesic effect at using diacerein and NAIP.

References

[1] Castañeda, S., Roman-Blas, J. A., Largo, R., Herrero-Beaumont, G. (2012). Subchondral bone as a key target for osteoarthritis treatment. Biochemical Pharmacology, 83 (3), 315–323. doi: 10.1016/j.bcp.2011.09.018

[2] Lotz, M., Martel-Pelletier, J., Christiansen, C., Brandi, M.-L., Bruyère, O., Chapurlat, R. et. al. (2013). Value of biomarkers in osteoarthritis: current status and perspectives. Annals of the Rheumatic Diseases, 72 (11), 1756–1763. doi: 10.1136/annrheumdis-2013-203726

[3] Golovach, I. Yu. (2014). Osteoartrit: fundamentalnyie i prikladnyie aspekty ietiopatogeneza zabolevaniya. Nichego ne stoit na meste. Ukrayinskiy revmatologIchniy zhurnal, 56 (2), 4–11.

[4] Couchourel, D., Aubry, I., Delalandre, A., Lavigne, M., Martel-Pelletier, J., Pelletier, J.-P., Lajeunesse, D. (2009). Altered mineralization of human osteoarthritic osteoblasts is attributable to abnormal type I collagen production. Arthritis & Rheumatism, 60 (5), 1438–1450. doi: 10.1002/art.24489

[5] Hamann, N., Zaucke, F., Dayakli, M., Brüggemann, G.-P., Niehoff, A. (2012). Growth-related structural, biochemical, and mechanical properties of the functional bone-cartilage unit. Journal of Anatomy, 222 (2), 248–259. doi: 10.1111/joa.12003

[6] Herrero-Beaumont, G., Roman-Blas, J. A., Largo, R., Berenbaum, F., Castaneda, S. (2011). Bone mineral density and joint cartilage: four clinical settings of a complex relationship in osteoarthritis. Annals of the Rheumatic Diseases, 70 (9), 1523–1525. doi: 10.1136/ard.2011.151233

[7] Berenbaum, F. (2013). Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis and Cartilage, 21 (1), 16–21. doi: 10.1016/j.joca.2012.11.012

[8] Bellido, M., Lugo, L., Roman-Blas, J. A., Castañeda, S., Calvo, E., Largo, R., Herrero-Beaumont, G. (2011). Improving subchondral bone integrity reduces progression of cartilage damage in experimental osteoarthritis preceded by osteoporosis. Osteoarthritis and Cartilage, 19 (10), 1228–1236. doi: 10.1016/j.joca.2011.07.003

[9] Sharma, A., Jagga, S., Lee, S.-S., Nam, J.-S. (2013). Interplay between Cartilage and Subchondral Bone Contributing to Pathogenesis of Osteoarthritis. International Journal of Molecular Sciences, 14 (10), 19805–19830. doi: 10.3390/ijms141019805

[10] Chan, T. F., Couchourel, D., Abed, **É.,** Delalandre, A., Duval, N., Lajeunesse, D. (2011). Elevated Dickkopf-2 levels contribute to the abnormal phenotype of human osteoarthritic osteoblasts. Journal of Bone and Mineral Research, 26 (7), 1399–1410. doi: 10.1002/jbmr.358

[11] Castañeda, S., Roman-Blas, J. A., Largo, R., Herrero-Beaumont, G. (2012). Subchondral bone as a key target for osteoarthritis treatment. Biochemical Pharmacology, 83 (3), 315–323. doi: 10.1016/j.bcp.2011.09.018

[12] Felson, D. T. (2009). Developments in the clinical understanding of osteoarthritis. Arthritis Research & Therapy, 11 (1), 203. doi: 10.1186/ar2531

[13] Burr, D. B., Gallant, M. A. (2012). Bone remodelling in osteoarthritis. Nature Reviews Rheumatology, 8 (11), 665–673. doi: 10.1038/nrrheum.2012.130

[14] Mastbergen, S. C., Lafeber, F. P. J. G. (2011). Changes in subchondral bone early in the development of osteoarthritis. Arthritis & Rheumatism, 63 (9), 2561–2563. doi: 10.1002/art.30306

[15] Zanatta, L. C. B., Boguszewski, C. L., Borba, V. Z. C., Kulak, C. A. M. (2014). Osteocalcin, energy and glucose metabolism. Arquivos Brasileiros de Endocrinologia & Metabologia, 58 (5), 444–451. doi: 10.1590/0004-2730000003333

[16] Rousseau, J. C., Garnero, P. (2012). Biological markers in osteoarthritis. Bone, 51 (2), 265–277. doi: 10.1016/j.bone.2012.04.001

[17] Dolgova, E. A., Sorotskaya, V. N., Rakita, D. R. (2012). Biomarkery iosteoartrita (obzor literaturyi). Vestnik novyih meditsinskih tehnologiy, XIX (1), 227–230.

[18] Lotz, M., Martel-Pelletier, J., Christiansen, C., Brandi, M.-L., Bruyère, O., Chapurlat, R. et. al. (2013). Value of biomarkers in osteoarthritis: current status and perspectives. Annals of the Rheumatic Diseases, 72 (11), 1756–1763. doi: 10.1136/annrheumdis-2013-203726

[19] Guntur, A., Rosen, C. (2012). Bone as an Endocrine Organ. Endocrine Practice, 18 (5), 758–762. doi: 10.4158/ep12141.ra

[20] Csifo, E., Katona, T., Arseni, J., Nagy, E., Gergely, I., Nagy, Ö. (2014). Correlation of Serum and Synovial Osteocalcin, Osteoprotegerin and Tumor Necrosis Factor-Alpha with the Disease Severity Score in Knee Osteoarthritis. Acta Medica Marisiensis, 60 (3). doi: 10.2478/amma-2014-0021

[21] Netiukhailo, L. H., Ishcheikina, L. K. (2014). Metabolizm kistkovoi tkanyny v normitaprypatolohii (ohliadliteratury). Molodyivchenyi, 6 (09), 152–158.

[22] Kuryata, A. V., Cherkasova, A. V. (2016). Insulinorezistentnost i sistemnoevospalenie u patsientov s osteoartrozom v sochetanii s ozhireniem: effektivnost simptomaticheskih preparatov zamedlennogo deystviya. Travma, 1 (17), 47–54.

[23] Kuryata, A. V., Cherkasova, A. V. (2015). Klinicheskaya effektivnost i dinamika sistemnogo vospaleniya u patsientov s osteoartrozom; vliyanie ozhireniya // Simeynameditsina, 5 (61), 171–180.

[24] Shuba, N. M., Voronova, T. D., Krylova, A. S., Danishevska, H. V. (2015). Vyvchennia efektyvnosti strukturno-modyfikuiuchykh preparativ u khvorykh na honartroz. Liky Ukrainy, 4 (190), 66–70.