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PATHOGENETIC AND DIAGNOSTIC ROLE OF OSTEOPROTEGERIN IN THE COMBINED COURSE OF OSTEOARTHRITIS AND OBESITY

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Abstract

In recent years, it has been proven that the formation of OA can occur against the background of impaired bone metabolism.

Bone remodeling is considered as a continuous complex process aimed at eliminating microdamages and updating the bone matrix. A key link in the regulation of this process is the system RANK / RANKL / OPG (osteoprotegerin), which provides a balance of activity of osteoblasts and osteoclasts. It blocks the interaction between RANK and RANKL by intercepting the RANKL ligand, which inhibits osteoclast development and reduces bone resorption.

Thus, these properties of OPG can be considered as one of the pathogenetic factors in patients with dystrophic joint lesions.

Objective: to investigate the content and role of osteoprotegerin in young patients with osteoarthritis, which occurs against the background of changes in body weight.

Materials and methods. The study involved 75 young patients (mean age - 30.92 ± 0.546 years) with overweight or obesity, who in the previous stages of the study was diagnosed with osteoarthritis (main group). The comparison group was represented by 50 patients with osteoarthritis and normal body weight. The age of patients was 30.95 ± 0.545 years; as in the previous group, men predominated - 64% and 36% respectively.

Benchmarks of osteoprotegerin were obtained in a study of 37 relatively healthy individuals of the same age and sex.

The level of osteoprotegerin was determined by enzyme-linked immunosorbent assay using the FineTest EH0247 reagent kit, China.

The outcomes were processed by the methods of variation statistics using the computer program STATISTICA. Results and discussion. When determining the content of OPG in the serum of patients of the main group was found to increase to 124.03 pg / ml, against control - 65.64 pg / ml. In the group of patients with isolated OA, this value was 92.29 pg / ml. Meaning that, in OA, running on the background of altered BMI, the content of OPG is likely to increase, both in relation to the norm and the results of the comparison group ($p < 0,001$).

The formation and course of osteoarthritis is accompanied by an increase in osteoprotegerin, the content of which depends on the degree of obesity and the radiological stage of the process.

Conclusions: The course of osteoarthritis is accompanied by an increase in osteoprotegerin, which is considered a negative regulator of bone resorption.

In osteoarthritis, which occurs against the background of changes in body mass index, a direct correlation with the degree of obesity.

Changes in osteoprotegerin in patients with osteoarthritis depend on the radiological stage of joint damage and are most pronounced in individuals with stage 2 obesity and stage 2 radiological changes

Keywords: obesity; osteoarthritis; osteoprotegerin; osteoporosis.

The most common disease of the human locomotor system and one of the main causes of disability is osteoarthritis (OA) - a disease caused by biological and mechanical factors that destabilize the normal relationship between the degradation and synthesis of chondrocytes, extracellular matrix of the articular cartilage and subchondral bone [1, 2, 3].

The prevalence of osteoarthritis in different regions of the world is 5-30%, and in people over 60 years, it occurs in almost 100% of cases [4].

Osteoarthritis is one of the most costly chronic diseases: almost 55% of patients with OA become disabled. The cost of treatment is more than 20%, and the losses caused by joint pathology in developed countries reach 3% of gross national income. Thus, US economic spending is \$65 billion a year [5].

Until recently, OA was considered an "age-related pathology" due to a long pathological process caused by mechanical damage to the cartilage. However, in recent years there has been a tendency to change the clinical concept of osteoarthritis. Many experts are inclined to the need for diagnostics of an early, radiological stage of OA, when adequate therapy can stop not only the progression but also achieve the reverse structural changes in the joint [6].

It is proved that the development of OA is due to many pathogenetic mechanisms that interact in a genetically predisposed organism. The onset of the disease can be observed after traumatic joint damage, infectious diseases, stress, and other causes. However, attempts to prove these factors as etiological factors remain unsuccessful.

In recent years, it has been proven that the formation of OA can occur against the background of impaired bone metabolism. The main biochemical markers of bone metabolism include: parathyroid hormone, calcitonin, calcitriol, osteocalcin, and alkaline phosphatase. They create a single homeostatic mechanism for regulating the metabolism of calcium and phosphorus.

Bone remodeling is considered a continuous complex process aimed at eliminating microdamages and renewal the bone matrix. A key role in the regulation of this process has the RANK / RANKL / OPG (osteoprotegerin) system, which balances the activity of osteoblasts and osteoclasts. It blocks the interaction between RANK and RANKL by intercepting the RANKL ligand, which inhibits osteoclast development and reduces bone resorption. With age, the synthesis of osteoprotegerin decreases, which contributes to the development of osteoporosis [7, 8].

Osteoprotegerin (OPG), also known as osteoclast-inhibiting factor (OCIF) or osteoclast-binding factor, is a glycoprotein 11b of the tumor necrosis factor receptor superfamily (gene name TNFRSF11B). The OPG is synthesized as a monomer with a length of 380 amino acid residues and is collected as a homodimer inside the cell, and then secreted mainly as a disulfide-bound homodimer in the extracellular space [9, 10].

The OPG is produced by many tissues and cell types (e.g., heart, lung, kidney, bone, liver, placenta, brain), including osteoblasts. It is known to be a negative regulator of bone resorption, acting as a receptor trap for RANK ligand (RANKL), thereby neutralizing its function in osteoclastogenesis: activation of RANK (osteoclast activation and differentiation receptor) on the osteoclast membrane and osteoclast proliferation and activation. This glycoprotein is also involved in the regulation of vascular calcification [11].

Thus, these properties of OPG can be considered as one of the pathogenetic factors in patients with dystrophic joint lesions.

Objective: to investigate the content and role of osteoprotegerin in young patients with osteoarthritis, which occurs against the background of changes in body weight.

Materials and methods. The study involved 75 young patients (mean age - 30.92 ± 0.546 years) with overweight or obesity, who in the previous stages of the study were diagnosed with osteoarthritis (main group). The comparison group was represented by 50 patients with osteoarthritis and normal body weight. The age of patients was 30.95 ± 0.545 years; as in the previous group, men predominated - 64% and 36%, respectively.

Control values of osteoprotegerin were obtained in the examination of 37 relatively healthy individuals of the same age and sex.

Prior to joining, all patients signed informed consent to participate in the study, recommended by the Ethical Committees for Biomedical Research of Ukrainian health legislation, the Helsinki Declaration of 2000, and the European Society Directive 86/609 on human participation in biomedical research.

Patients with diseases of the digestive, cardiovascular and pulmonary systems, pathological changes in the endocrine organs, kidneys, systemic connective tissue diseases, and cancer were not involved in the research.

The diagnosis of OA was agreed upon in the comprehensive assessment of patients' complaints, anamnesis data, objective and radiological examination of the affected joints, based on "Protocols for the management of patients with osteoarthritis."

The WHO classification criteria (1997) with the determination of body mass index (BMI) were used to diagnose obesity (OB) and determine its degree. Anthropometric measurements also included the determination of waist circumference (OT), hip circumference (OS) with the calculation of the ratio of OT to OS.

The stage of joint damage was determined by X-ray examination and interpreted according to the classification of J.H. Kellgren and J.S. Lawrence.

The level of osteoprotegerin was determined by enzyme-linked immunosorbent sandwich method using the FineTest EH0247 reagent kit, China.

The obtained results were processed by the methods of variation statistics using the computer program STATISTICA.

Results and discussion. The frequency of involvement of various joints in the development of OA was assessed. Thus, the examined patients more often observed lesions of the knee joints: gonarthrosis was registered in 30 patients; its unilateral lesion was found in 10 people, bilateral - in 20 people. Slightly less often (12 cases) were found lesions of the hip joints with the same distribution by location - 6 people. Combined lesions of the knee and hip joints were observed in 25 patients; simultaneous involvement in the pathology of many joints was determined in 8 people.

In the comparison group, changes in the knee joints were determined in 32 patients (unilateral lesion - in 26, bilateral - in 6 people); hip joints were involved in the process in 10 patients (7 and 3, respectively). Combined lesions of the knee and hip joints - in 4 patients; simultaneous involvement of many joints was found in 4 people.

Taking into account the radiological stage of the process, patients were divided as follows (table 1).

Table 1. Distribution of patients with OA taking into account radiological changes in the joints (according to the classification of J.H. Kellgren and J.S. Lawrence)

Patients examined (n=125)		Comparison group		Main group	
		aбс.	%	aбс.	%
X-ray stage	I (n= 30)	9	18	21	28
	II (n=72)	34	68	38	51
	III (n=23)	7	14	16	21
	Total (n=125)	50	100	75	100

The presence of overweight and obesity in the main group allowed us to identify the following groups. Thus, overweight was inherent in 22 people (29.3%); obesity of 1st stage was registered in 31 cases (41.3%), obesity of the 2nd stage was detected in 22 patients (29.3%).

At the same time, when comparing the stage of obesity and radiological changes in the joints, the following results were obtained (table 2).

Table 2. Distribution of patients of the main group taking into account the stage of obesity and radiological changes

Patients examined (n=75)		BMI					
		overweight (n=22)		obesity stage 1 (n=31)		obesity stage 2 (n=22)	
		абс.	%	абс.	%	абс.	%
Radiological stage of osteoarthritis	I (n=21)	5	23,8	13	61,9	3	14,3
	II (n=38)	17	44,7	18	47,4	3	7,9
	III (n=16)	-	-	-	-	16	100

That is, the vast majority of patients were located in the group with the second radiological stage of osteoarthritis.

When determining the content of OPG in the serum of patients of the main group was found its increase to 124.03 pg/ml, against control - 65.64 pg/ml. In the group of patients with isolated OA, this value was 92.29 pg/ml. That is, in OA, running on the background of altered BMI, the content of OPG is likely to increase, both in relation to the norm and the results of the comparison group ($p < 0,001$).

The study of osteoprotegerin content taking into account the stage of obesity (table 3).

Table 3. The content of osteoprotegerin (pg/ml) in patients of the examined groups, taking into account BMI

BMI	overweight (n=22)	obesity stage 1 n=31	obesity stage 2 n=22
Кількість хворих	n=22	n=31	n=22
OPG	111,4 ± 1,45	110,58 ± 2,41	155,61 ± 6,54 ^{^*}

Note: $p < 0,001$ [^] - a significant difference compared with the group of patients with OA with overweight; $p < 0,001$ ^{*} - a significant difference compared with the group of patients with OA and obesity stage 1.

The content of osteoprotegerin was determined, taking into account the radiological stage of joint damage and indicators of the fat component (table 4).

Table 4. The content of osteoprotegerin (pg/ml) in the serum of patients of the main group depending on the radiological stage of the disease and BMI

Radiological stage of osteoarthritis	BMI		
	overweight (n=22)	obesity stage 1 (n=31)	obesity stage 2 (n=22)
I	111,3 ± 3,65	106,57 ± 2,7	122,78 ± 13,08*
II	111,43 ± 1,6	113,47 ± 3,6^	166,89 ± 19,1
III	-	-	159,65 ± 7,3^

Note: p <0.05 * - a significant difference compared with the group of patients with OA and overweight; p <0,05 ^ - a significant difference compared with the group of patients with OA stage II and obesity stage 2.

Thus, the formation and course of osteoarthritis are accompanied by an increase in osteoprotegerin, the content of which depends on the degree of obesity and the radiological stage of the process.

Conclusions. The course of osteoarthritis is accompanied by an increase in osteoprotegerin, which is considered a negative regulator of bone resorption.

In osteoarthritis, which occurs against the background of changes in body mass index, a direct correlation with the degree of obesity is determined.

Changes in osteoprotegerin in patients with osteoarthritis depend on the radiological stage of joint damage and are most pronounced in individuals with stage 2 obesity and stage 2 radiological changes.

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