

ROLE OF OSTEOPROTEGERIN IN BONE TISSUE METABOLISM IN PATIENTS WITH OSTEOARTHRITIS AND OBESITY

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SUMMARY. Osteoarthritis (OA) leads to the degeneration of the articular cartilage, and as a cause of disability it ranks first among the diseases of the musculoskeletal system. Currently, a number of researchers believe that OA can be considered in the context of metabolic syndrome, one of the components of which is obesity. According to modern concepts, muscle tissue is one of the most important human endocrine organs, since it produces a large amount of biologically active substances, hormones and special cytokines (myokines). The latter are cellular regulators of growth and degradation, and support the function of muscle mitochondria. Thus, in the course and progression of OA in patients with increased body weight and obesity, two endocrine-dependent organs "compete" – adipose and muscle tissues. In this case, we should expect not a potentiation of their impact, but a new qualitative effect. And this result of the combined course can be considered the formation of secondary osteoporosis.

The aim – to optimize the diagnosis of osteopenic conditions in young people with osteoarthritis occurring against the background of overweight/obesity by determining the role of osteoprotegerin in the formation of complications.

Materials and Methods. The research included the evaluation of osteoprotegerin values in 75 people with osteoarthritis (OA) proceeding against the background of obesity (main group), and 50 patients with isolated OA (comparison group). The control group consisted of 37 apparently healthy individuals. The diagnosis of OA was established based on the order of the Ministry of Health of Ukraine dated 10/12/2006 "On the provision of medical care to patients with osteoarthritis", the unified diagnostic criteria of the Association of Rheumatologists of Ukraine (2004) and the criteria of the American College of Rheumatology. The presence and severity of obesity was assessed according to the criteria of the International Diabetes Federation (IDF, 2005) based on the calculation of the body mass index (BMI) according to the Quetelet index.

Results. When calculating the content of osteoprotegerin (OCG) it was found that in both examined groups this value exceeded the control values: 1.9 times in patients of the main group and 1.4 times in the comparison group. When the BMI changes in all groups of subjects, there was a significant increase in the OCG relative to control indicators. It was also found that the development and course of osteoarthritis in patients with overweight or obesity occurs against the background of increased serum osteoprotegerin.

Conclusions. The course of osteoarthritis is accompanied by a significant increase of serum osteoprotegerin, the level of which increases with increasing body weight. Serum osteoprotegerin indicator correlates with the radiological stage of the disease and has a maximum value at third stage of the disease. The presence of OA in obese patients is an unfavorable background for the formation of osteoporotic conditions, one of the mechanisms of which is an increase in serum osteoprotegerin, a glycoprotein with an apoptotic effect at the level of osteoclasts.

KEY WORDS: osteoprotegerin; bone metabolism; osteoarthritis; obesity.

Introduction. Recent scientific studies have revealed that adipose tissue plays an important part of the endocrine system. The reason for this statement was the discovery the fact that highly active adipose tissue cells (adipocytes) produce a number of hormones (adipokines) and hormone-like substances, mediators, cytokines, chemokines, which act at the local and systemic level, that are para- and endocrine affects [1]. The list of adipokines produced in adipose tissue is very significant (more than 50) and includes the following hormone-like substances: leptin, adiponectin, resistin, tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), visfatin, apelin, omentin, vaspin, retinol-binding protein-4 (RBP-4) and other factors, including lipoprotein lipase, apolipoprotein E, complement factors, tissue factor, plasminogen activator inhibitor-1 (PAI-1), proteins of the renin-angiotensin system. In addition, adipocytes express chemokines such as MCP-1 and RANTES [2]. In addition, adipose

tissue is the main peripheral source of aromatase, which is involved in estrogen synthesis [3]. Adipokines have a variety of biological effects and affect the severity of processes in many organs directly or through neuroendocrine mechanisms, interacting with pituitary hormones, insulin, catecholamines [4, 5]. They play a role in the relationship between obesity and comorbidities [6, 7].

One of the nosological forms where adipose tissue has a pathogenetic role in the onset and progression of the disease is osteoarthritis (OA). Osteoarthritis is a socially significant pathology of the internal disease, which is associated with both its high prevalence and disability of patients in the early stages. Currently, a number of researchers believe that OA can be considered in the context of metabolic syndrome, components of which - obesity and insulin resistance/diabetes, act as predictors of the pathological process in the joints [8, 9].

Огляди літератури, **оригінальні дослідження**, погляд на проблему, випадок з практики, короткі повідомлення

Osteoarthritis is registered in every fifth inhabitant of the planet. Its occurrence can be observed at any age: in persons over 50 years of age it occurs in 50 % of cases; and after 70 years – in 80-90 %. The incidence of OA in Ukraine is about 607.3 and the prevalence is 3172.6 per 100 thousand population. Thus, the total number of patients in the country exceeds 1,203,000 people and there is a tendency to increase it [10, 11].

Active inflammatory process in OA is associated with the involvement in the pathology of derivatives of the joints: ligaments, muscles, bags and other components. Moreover, according to modern ideas, muscle tissue also acts as one of the most important endocrine organs of man, as it produces a large number of biologically active substances, hormones and special cytokines (myokines). The latter are cellular regulators of growth and degradation, supporting the function of muscle mitochondria [12].

Thus, in the course and progression of OA in patients with overweight and obesity "compete" two endocrine-dependent organs – adipose and muscle tissue. It is not expected to summarize their effects, but a new qualitative result. And this result of the combined course can be considered the formation of secondary osteoporosis.

Objective. Optimization of the diagnosis of osteopenic conditions in young people with osteoarthritis, occurring on the background of overweight/obesity by determining the role of osteoprotegerin in the formation of complications.

Materials and Methods. The study involved 75 young patients (mean age in the group – 30.92±0.55 years) with established in the previous stages of observation osteoarthritis. The formation and course of the disease occurred against the background of overweight or obesity (the main group). To confirm the role of adipose tissue in the progression of the nosology, 50 patients with isolated OA (comparison group) of the same age (30.95±0.55) years were examined. Control parameters were obtained during a survey of 37 healthy individuals of the same age (30.95±0.55) years and sex.

Before starting the study, all patients signed an informed consent recommended by the ethical committees for biomedical research of Ukrainian health legislation, the Declaration of Helsinki 2000 and the

European Society Directive 86/609 on human participation in biomedical research.

Exclusion criteria were: concomitant digestive pathology, cardiovascular and respiratory diseases, endocrine pathology (diabetes, thyroid disease), systemic connective tissue diseases, kidney disease, cancer, mental disorders, pregnancy.

The diagnosis of OA was confirmed by a comprehensive assessment of patients' complaints, history, objective and instrumental examination (X-ray examination of the affected joints) in accordance with "Protocols for the management of patients with osteoarthritis."

The diagnosis of obesity was established taking into account the recommendations and classification criteria of the WHO (1997); the severity of obesity was assessed according to the criteria of the International Diabetes Federation (IDF, 2005) with the calculation of body mass index (BMI) according to the Quelet index: $BMI = \text{body weight (kg)} / \text{growth (m}^2\text{)}$.

Osteoprotegerin (pg/ml) (bone glycoprotein) was examined in fasting serum by enzyme-linked immunosorbent assay (ELISA) using FineTest EH0247 reagents, China.

The prevalence of osteoporotic conditions was assessed during dual-energy X-ray absorptiometry (DEXA) [13], HOLOGIC Explorer QDR W Series Bone Densitometer (USA).

Statistical processing of the results was performed by the method of variation statistics using the licensed software Statistica 10.0 and Excel 2010.

Results and Discussion. When assessing BMI in the main group of individuals, it was found that overweight was registered in 29 % of cases (22 patients); first stage obesity – in 31 patients (42 %) and second stage obesity – in 22 people (29 %).

Taking into account the duration of the anamnesis of the disease, patients with OA were divided into 3 groups (Table 1).

The radiological stage of the disease was determined based on the classification of J.H. Kellgren and J. S. Lawrence. So, in the main group of patients first radiological stage was found in 21 cases (28 %); second stage was registered in 38 patients (51 %) and third stage – in 16 (21 %). In the comparison group, these changes corresponded to: 9 (18 %), 34 (68 %) and 7 (14 %) cases.

Table 1. Distribution of patients with osteoarthritis based on the duration of the anamnesis

Patients examined (n=125)		Comparison group (n=50)		Main group (n=75)	
		Absolute value	%	Absolute value	%
Duration of osteoarthritis history	Up to 5 years, (n=81)	32	64	49	65
	6–10 years, (n=35)	13	26	22	29
	More than 10 years, (n=9)	5	10	4	6
Total, (n=125)		50	100	75	100

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X-ray densitometric examination (DEXA) revealed the following changes in bone tissue: osteopenia was registered in 11 patients (15 %) of the main group and 8 patients (16 %) of the comparison group. Manifestations of osteoporosis were diagnosed in 18 (24 %) and 5 (10 %) patients, respectively.

When calculating the content of osteoprotegerin (OPG), the indicator of bone resorption, it was found that in both examined groups this value exceeded the control values: 1.9 times in patients of the main group and 1.4 times in the comparison group (Table 2).

Thus, the content of OPG in the main group of individuals exceeded the control indicators and a

similar indicator in patients with isolated OA. There is an assumption that the state of bone tissue is largely determined by the local ratio of OPG to the receptor activator of nuclear factor kappa B (RANK) RANKL/OPG [14]. Therefore, a significant increase in this indicator both in patients with OA and in combination with obesity can be regarded as a risk factor for the formation of osteopenic conditions. The content of OPG was studied taking into account gender features: this indicator in men was 122.3 ± 3.5 pg/ml, in women – 127 ± 6.4 pg/ml. In addition, we studied of the OPG content taking into account the BMI (table 3).

Table 2. The level of osteoprotegerin (pg/ml) in patients with osteoarthritis and its comorbidity with obesity

Groups of subjects	The content of OPG pg/ml
Control	65.64 ± 0.64
Main	$124.03 \pm 3.2^*$
Comparison	$92.29 \pm 1.68^{*\wedge}$

Note: $p < 0.001$ * – compared with the control group; $p < 0.001$ ^ – compared with the main group.

Table 3. The content of osteoprotegerin (pg/ml) in the serum of patients with OA and obesity

BMI	Contents OPG
Overweight (n=22)	$111.4 \pm 1.45^*$
Obesity of the first degree (n=31)	$110.58 \pm 2.41^*$
Obesity of the second degree (n=22)	$155.61 \pm 6.54^{*\wedge''}$
Control (n=37)	65.64 ± 0.64

Note: $p < 0.001$ * – relative to the control group; $p < 0.001$ ^ – relative to the group of patients with OA and overweight; $p < 0.001$ '' – for a group of patients with OA and obesity of the first degree.

Thus, against the background of changes the BMI in all groups of subjects there was a significant increase in OPG in comparison to control indicators, but the differences between this indicator in persons with overweight and obesity first stage have

not detected. This result is probably due to the protective effect of the initial stages of BMI changes on bone tissue.

We studied the OPG value, taking into account the radiological stage of the disease (table 4).

Table 4. The serum OPG level value in the examined patients, taking into account the radiological stage of the disease

X-ray stage of OA	Serum osteoprotegerin, pg/ml
I (n=21)	$110.01 \pm 2.71^*$
II (n=38)	$116.78 \pm 3.27^*$
III (n=16)	159.65 ± 7.27

Note: $p < 0.05$ * – in relation to the group of patients with OA with III radiological stage.

Thus, the onset and course of osteoarthritis in patients with overweight or obesity occurs against the background of increased serum osteoprotegerin, which can be considered as a marker of the formation of osteopenic conditions.

Conclusions. The course of osteoarthritis is accompanied by a significant increase in the content of osteoprotegerin in the serum, the level of which has a direct correlation with BMI.

Serum osteoprotegerin level correlates with the radiological stage of joint damage and it is maximal in the third stage of the disease.

The presence of osteoarthritis in obese patients is an unfavorable factor in the formation of osteoporotic conditions, one of the mechanisms of which is an increase in serum osteoprotegerin – a glycoprotein with apoptotic action at the level of osteoclasts.

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РОЛЬ ОСТЕОПРОТЕГЕРИНУ В МЕТАБОЛІЗМІ КІСТКОВОЇ ТКАНИНИ У ХВОРИХ ІЗ ОСТЕОАРТРИТОМ І ОЖИРІННЯМ

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РЕЗЮМЕ. Остеоартрит (ОА) призводить до дегенерації суглобового хряща, і, як причина інвалідності, посідає перше місце серед захворювань кістково-м'язової системи. На сьогодні ряд дослідників вважає, що ОА можна розглядати в контексті метаболічного синдрому, однією із складових якого є ожиріння. Згідно з сучасними уявленнями, м'язова тканина також є одним із найбільш значущих ендокринних органів людини, оскільки виробляє велику кількість біологічно активних речовин, гормонів та особливі цитокіни (міокіни). Останні є клітинними регуляторами росту та розпаду, підтримують функцію м'язових мітохондрій. Таким чином, у перебізі та прогресуванні ОА у хворих із підвищеною масою тіла та ожирінням «конкурують» два ендокринно-залежних органи – жирова та м'язова тканини. При цьому слід очікувати не підсумування їх ефектів, а нового якісного результату. І таким результатом поєданого перебігу можна вважати формування вторинного остеопорозу.

Мета – оптимізація діагностики остеопенічних станів у осіб молодого віку з остеоартритом, що перебігає на тлі підвищеної маси тіла/ожиріння, шляхом визначення ролі остеопротегерину у формуванні ускладнень.

Матеріал і методи. До роботи було залучено 75 хворих із остеоартритом (ОА), який перебігав на тлі ожиріння (основна група). У 50 пацієнтів ураження суглобів спостерігали при збереженому індексі маси тіла в межах норми (група порівняння) та 37 практично здорових осіб, які увійшли до контрольної групи. Усі групи обстежених були репрезентативні за віком та статтю. Діагноз ОА встановлювали на підставі наказу МОЗ України від 12.10.2006 року «Про надання медичної допомоги хворим із остеоартрозом», уніфікованих діагностичних критеріїв Асоціації ревматологів України (2004) та критеріїв Американської колегії ревматологів. Наявність та тяжкість ожиріння оцінювали згідно з критеріями International Diabetes Federation (IDF, 2005) на підставі розрахунку індексу маси тіла (ІМТ) за формулою Кетле.

Результати. При підрахунку вмісту остеопротегерину (ОПГ) встановлено, що в обох обстежених групах ця величина перевищувала контрольні значення: в 1,9 раза у хворих основної групи і в 1,4 раза в групі порівняння. При зміні ІМТ у всіх групах обстежених зазначено достовірне підвищення ОПГ щодо показників контролю. Також виявили, що розвиток та перебіг остеоартриту у хворих із підвищеною масою тіла або ожирінням відбувається на тлі підвищення остеопротегерину сироватки крові.

Висновки. Перебіг остеоартриту супроводжується достовірним збільшенням вмісту остеопротегерину у сироватці крові, рівень якого ще більше зростає із збільшенням маси тіла. Рівень остеопротегерину сироватки крові корелює з рентгенологічною стадією захворювання та має максимальне значення при третій стадії захворювання. Наявність ОА у хворих із ожирінням є несприятливим фоном для формування остеопоротичних станів, одним із механізмів якого є збільшення остеопротегерину сироватки крові – глікопротеїну з апоптичною дією на рівні остеоцитів.

КЛЮЧОВІ СЛОВА: остеопротегерин; метаболізм кісткової тканини; остеоартит; ожиріння.

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