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Structural and functional state of bone tissue in young people with a combined course of osteoarthritis and obesity

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Abstract: In recent years, an increase in the number of patients with osteoarthritis (OA) against the background of obesity is considered not from the point of view of mechanical stress on the joints by an overweight patient but by the active synthesis of hormone-like substances by adipose tissue, which have a metabolic effect on all processes in the body. A large number of different chemical compounds (calcium, phosphorus, magnesium, uronic acids, tartrate-resistant bone phosphatase, and a number of others) are involved in the remodeling of bone tissue, the balance between which determines the strength and mobility of the bone. Among such biochemical markers, the glycoprotein osteoprotegerin is considered. The osteoprotegerin inhibits the differentiation of osteoclast precursors into osteoclasts and also regulates their resorption in vitro and in vivo. It works by binding to RANKL on osteoblast / stromal cells, thereby blocking the RANKL-RANK ligand interaction between osteoblasts / stromal cells and osteoclast precursors.

The aim of our study to establish the content of osteoprotegerin in the blood serum of young patients with osteoarthritis and obesity and to analyze its role in the formation of structural and functional changes in bone tissue. The work was performed on 75 young patients (average age - 30.92 ± 0.55 years) with OA, which was established in patients with various stages of obesity; for the comparison group, 50 individuals with an isolated course of OA of the same age (30.95 ± 0.55 years) and duration of anamnesis were selected; control indicators were obtained when examining 37 apparently healthy individuals. The diagnosis of OA was confirmed by a comprehensive assessment of patients' complaints, anamnesis data, objective and instrumental studies (X-ray examination of the affected joints) while focusing on the "Protocols for the management of patients with osteoarthritis." The presence and severity of obesity were assessed according to the criteria of the International Diabetes Federation (IDF, 2005) based on the calculation of body mass index (BMI) according to the Kettle formula. The indicator of osteoprotegerin (pg / ml) (bone tissue glycoprotein) was investigated in fasting blood serum by enzyme-linked immunosorbent assay (ELISA) using FineTest EH0247 reagents, China. The prevalence of osteoporotic conditions was assessed by dual-energy X-ray absorptiometry (DEXA) using the HOLOGIC Explorer QDR W Series Bone Densitometer (USA). The content of osteoprotegerin in blood serum was studied as a biochemical marker of damage to the bone and cartilage tissue. The data obtained allowed us to say that in both groups - patients with OA (92.3 ± 1.68 pg / ml) and patients with a combination of OA with obesity and increased body weight (124.03 ± 3.2 pg / ml) - there was an increase in this glycoprotein when compared with the control values (65.64 ± 0.64), ($p < 0.001$). The performed densitometric study allowed us to obtain the following results: osteopenia

was identified in 15% of patients in main group and in 36% - in comparison group; osteoporosis was identified in 24% of patients in main group and in 10% - in comparison group. The course of osteoarthritis in young people is accompanied by the formation of osteoporotic conditions, which more often (24% versus 10%), with the addition of obesity, lead to the development of osteoporosis. The development of osteoporotic changes in patients with osteoarthritis and in combination with obesity is accompanied by an increase in the synthesis of osteoprotegerin, a glycoprotein involved in the processes of bone tissue remodeling.

Key words: [body mass index](#), [obesity](#), [osteoarthritis](#), [osteoblasts](#), [osteoclast](#), [osteoprotegerin](#).

Introduction

Bone tissue is considered as a mobile, metabolically active formation that performs a large number of functions in the body, the main of which is the supporting one, due to the structuring of the spine and bones. The ratio of the processes of synthesis and catabolism of the main cellular elements (osteoblasts and osteoclasts) allows maintaining bone homeostasis. Bone metabolites are calcium (the main element), phosphorus, and magnesium (Hunter, & Bierma-Zeinstra, 2019; Oliveira, Vullings, & van de Loo, 2020).

The ratio of these macronutrients determines its state, structure, and architectonics, thereby ensuring strength, mobility, and relative stability. At the same time, a large number of diseases have been established, the so-called. calcium-dependent, in which an increased requirement is imposed on the main element of its structure - consumption for the implementation of various functions of the body. These nosologies include: diseases of the digestive tract, cardiovascular (arterial hypertension, ischemic heart disease), endocrine diseases (diabetes mellitus), kidney disease, and a number of others. The development and course of such nosological forms increase the body's need for calcium, thereby contributing to its leaching from the bones. Among such diseases are osteoarthritis (OA) and obesity (OB) (Thijssen, van Caam, & van der Kraan, 2015).

The prevalence of obesity is so high that the World Health Organisation (WHO) has declared an epidemic of this condition. For example, from 1975 to 2020, the number of obese people worldwide more than tripled. In 2020, there were over 1.9 billion adults (39%) over 18 years old who were overweight, including 39% of men and 40% of women. Over 650 million (about 13%) were obese (11% of men and 15% of women). In

2020, due to quarantine and limited movement, the number of obese people in Ukraine increased by 40% (Vina & Kwoh, 2018; Yakovenko et al., 2019).

At the same time, the prevalence of osteoarthritis in different countries of the world reaches 29%, and in people over 60 years old - 97%. In the United States, rheumatic joint diseases have been diagnosed in more than 30 million people over 35 years old. Due to the fact that age is considered the most important independent risk factor for the development of osteoarthritis (OA), then, given the global trend towards aging in the population, a significant increase in this pathology in the structure of the population's morbidity is expected (Llorente, García-Castañeda, Valero, González-Álvaro, & Castañeda, 2020).

In recent years, an increase in the number of patients with OA against the background of obesity is considered not from the point of view of mechanical stress on the joints by an overweight patient but by the active synthesis of hormone-like substances by adipose tissue, which have a metabolic effect on all processes in the body (Oliveira, Vullings, & van de Loo, 2020). The next important factor of an unfavorable combination of OA and obesity is a change in the structure of bone tissue - the formation of osteoporotic conditions as a result of a disturbance in the equilibrium processes in the synthesis and catabolism of the bone matrix (Thijssen, van Caam, & van der Kraan, 2015).

A large number of different chemical compounds (calcium, phosphorus, magnesium, uronic acids, tartrate-resistant bone phosphatase, and a number of others) are involved in the remodeling of bone tissue, the balance between which determines the strength and mobility of the bone. Among such biochemical markers, the glycopro-

tein osteoprotegerin (OPG) is considered (Cawley et al., 2020).

Osteoprotegerin is a cytokine member of the tumor necrosis factor (TNF) receptor superfamily that can suppress osteoclast synthesis. It is a major glycoprotein consisting of 401 amino acid residues organized into 7 structural domains (Greenhill, 2020).

The OPG inhibits the differentiation of osteoclast precursors into osteoclasts and also regulates their resorption in vitro and in vivo. It works by binding to RANKL on osteoblast / stromal cells, thereby blocking the RANKL-RANK ligand interaction between osteoblasts / stromal cells and osteoclast precursors (Stejskal et al., 2001). Thus, bone remodeling processes are the site of OPG application.

Aim

The aim of our study: to establish the content of osteoprotegerin in the blood serum of young patients with osteoarthritis and obesity and to analyze its role in the formation of structural and functional changes in bone tissue.

Methods

The work was performed on 75 young patients (average age - 30.92 ± 0.55 years) with OA, which was established in patients with various stages of obesity. For the comparison group, 50 individuals with an isolated course of OA of the same age (30.95 ± 0.55 years) and duration of anamnesis were selected. Control indicators were obtained when examining 37 apparently healthy individuals.

The condition for inclusion in the study was the signing of an informed consent recommended by the ethical committees for biomedical research of Ukrainian legislation on health protection, the Declaration of Helsinki 2000, and the directives of the European Society 86/609 on the participation of people in biomedical research.

Exclusion criteria: concomitant pathology of the digestive system, cardiovascular and respiratory systems, diabetes mellitus, thyroid disease, systemic connective tissue diseases, kidney disease, oncopathology.

The diagnosis of OA was confirmed by a comprehensive assessment of patients' complaints, anamnesis data, objective and instrumental studies (X-ray examination of the affected joints)

while focusing on the "Protocols for the management of patients with osteoarthritis." (Hochberg et al., 2012; Kellgren & Lawrence, 1957).

Obesity was diagnosed based on 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 the body mass index (BMI) according to the Quetelet formula: $BMI = \text{body weight (kg)} / \text{height (m}^2\text{)}$.

The indicator of osteoprotegerin (pg / ml) (bone tissue glycoprotein) was investigated in fasting blood serum by enzyme-linked immunosorbent assay (ELISA) using FineTest EH0247 reagents, China.

The prevalence of osteoporotic conditions was assessed by dual-energy X-ray absorptiometry (DEXA) using the HOLOGIC Explorer QDR W Series Bone Densitometer (USA).

Statistical analysis was performed using the software package "Statistica 10.0" and Excel 2010. Quantitative and order changes were compared using the Mann-Whitney test. In all procedures of statistical analysis, the level of significance and p were taken to be equal to or less than 0.05 ($p < 0.05$).

Results and discussion

The clinical picture of the disease was characterized by the predominant inclusion of large joints of the lower extremities in the process. Thus, the damage of the hip joints was registered in 16% of cases. The involvement of the knee joints in the process was noted in 40% of patients; changes in the small joints of the hands were registered somewhat less frequently. In patients of the comparison group, the localization of the process corresponded to that (Table 1).

Moreover, in the main group, the X-ray stage of the articular changes met the following criteria. So, stage 1 was registered in 28% of cases; stage 2 was observed in 51% of patients and stage 3 of the disease was inherent in 21% of patients. In the comparison group, these changes corresponded to 18%, 68%, and 14% of patients.

The assessment of the structural and functional state of bone tissue was carried out when interpreting the indicators of bone mineral density (BMD) obtained during instrumental studies. The

performed densitometric study allowed us to obtain the following results (Table 2).

The content of osteoprotegerin in blood serum was studied as a biochemical marker of damage to the bone and cartilage tissue. The data obtained allowed us to say that in both groups - patients with OA (92.3 ± 1.68 pg / ml) and patients with a combination of OA with obesity and increased body weight (124.03 ± 3.2 pg / ml) - there was an increase in this glycoprotein when compared with the control values (65.64 ± 0.64), ($p < 0.001$).

In the main group of individuals, the OPG activity was determined taking into account the dynamics of BMI (Table 3).

The content of OPG was evaluated taking into account the state of bone mineral density. Thus, in patients of the main group with osteopenia, the content of OPG in the serum corresponded to 108.43 ± 0.48 pg/ ml, in the comparison group - 84.86 ± 0.87 pg / ml. In the development of osteoporosis, this value exceeded the control values, but was slightly lower than with osteopenia: 99.94 ± 1.1 and 73.57 ± 1.66 pg/ml, respectively.

Thus, the course of osteoarthritis can be accompanied by the formation of osteoporotic conditions, which is facilitated by the formation of

Localization of the affected joints	Groups of patients with OA			
	main group (n=75)		comparison group (n=50)	
	aбс.	%	aбс.	%
Knee	30	40	32	64
Coxal	12	16	10	20
Knee+ coxal	25	33	4	8
Simultaneous involvement of many joints	8	11	4	8

Table 1. Frequency of involvement of limb joints in patients with OA

biologically active substances by adipocytes and an increase in the content of osteoprotegerin (Litvynova 2022).

Conclusions

The course of osteoarthritis in young people is accompanied by the formation of osteoporotic conditions, which more often (24% versus 10%), with the addition of obesity, lead to the development of osteoporosis.

The development of osteoporotic changes in patients with osteoarthritis and in combination

Patients with osteoarthritis			Structural and functional state of bone tissue according to DEXA data					
			osteopenia		osteoporosis		without changes	
Quantity	aбс.	%	aбс.	%	aбс.	%	aбс.	%
Main group	75	100,0	11	15	18	24	46	61
Comparison group	50	100,0	8	16	5	10	37	74

Table 2. Frequency and nature of absorptiometrically verified disorders of the structural and functional state of bone tissue in patients with osteoarthritis

BMI indicator (n=37)	BMI indicator			
	normal (n=50)	overweight (n=22)	obesity stage 1 (n=31)	obesity stage 2 (n=22)
$65,64 \pm 0,64$	$92,29 \pm 1,5^*$	$111,4 \pm 1,45 \text{ *#}$	$110,58 \pm 2,41 \text{ *#}$	$155,61 \pm 6,54 \text{ *#}^{\wedge}$

Notes: * statistical significance of differences relative to the control group $p < 0.0001$; # statistical significance of differences relative to the main group $p < 0.0001$; ^ statistical significance of differences relative to the group of patients with OA and increased body weight $p < 0.0001$;” Statistical significance of differences relative to the group of patients with OA and OB 1 $p < 0.0001$.

Table 3. The content of osteoprotegerin (pg / ml) taking into account BMI in patients with osteoarthritis

with obesity is accompanied by an increase in the synthesis of osteoprotegerin, a glycoprotein involved in the processes of bone tissue remodeling.

The examination of osteoprotegerin in the blood serum of patients with osteoarthritis can be used as a marker of osteoporotic conditions.

Financing

This study was not funded.

Conflict of interest

There was no conflict of interest during the study.

Consent to publication.

Litvynova Anastasiia agree to the publication.

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of article

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Структурно-функціональний стан кісткової тканини у людей молодого віку з комбінованим перебігом остеоартриту та ожиріння

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Анотація: В останні роки збільшення кількості хворих на остеоартрит на тлі ожиріння розглядається не так з позиції механічного навантаження на суглоби хворих із зайвою вагою, скільки активного синтезу гормоноподібних речовин жирової тканини, які надають метаболічний вплив на всі процеси в організмі. Велика кількість різноманітних хімічних сполук (кальцій, фосфор, магній, уронові кислоти, тартратрезистентна кісткова фосфатаза та ряд інших) бере участь у ремоделюванні кісткової тканини, баланс між якими визначає міцність і рухливість кістки. Серед таких біохімічних маркерів розглядається глікопротеїн остеопротегерин. Остеопротегерин пригнічує диференціацію попередників остеокластів в остеокласти, а також регулює їх резорбцію *in vitro* та *in vivo*. Він діє шляхом зв'язування з RANKL на остеобластах / стромальних клітинах, блокуючи тим самим взаємодію ліганду RANKL-RANK між остеобластами / стромальними клітинами та попередниками остеокластів. Мета нашого дослідження: встановити вміст остеопротегерину в сироватці крові молодих пацієнтів з остеоартритом та ожирінням та проаналізувати його роль у формуванні структурно-функціональних змін кісткової тканини.

Робота виконана на 75 пацієнтів молодого віку (середній вік – $30,92 \pm 0,55$ років) з ОА, який був встановлений у пацієнтів з різними стадіями ожиріння; для групи порівняння відібрано 50 осіб з ізолюваним перебігом ОА такого ж віку ($30,95 \pm 0,55$ року) та тривалості анамнезу; контрольні показники отримано при обстеженні 37 умовно здорових осіб. Діагноз ОА підтверджено комплексною оцінкою скарг пацієнтів, даних анамнезу, об'єктивних та інструментальних досліджень (рентгенологічне дослідження уражених суглобів) з акцентом на «Протоколи ведення хворих на остеоартрит». Наявність та тяжкість ожиріння оцінювали за критеріями Міжнародної діабетичної федерації (IDF, 2005) на основі розрахунку індексу маси тіла (ІМТ) за формулою Кеттла. Показник остеопротегерину (пг/мл) (глікопротеїну кісткової тканини) досліджували в сироватці крові натще методом імуноферментного аналізу (ІФА) з використанням реагентів FineTest EH0247, Китай. Поширеність остеопоротичних станів оцінювали за допомогою подвійної рентгенівської абсорбціометрії (DEXA) з використанням кісткового денситометра HOLOGIC Explorer QDR серії W (США).

Досліджено вміст остеопротегерину в сироватці крові як біохімічного маркера ураження кістково-хрящової тканини. Отримані дані дозволили стверджувати, що в обох групах – хворих на ОА ($92,3 \pm 1,68$ пг/мл) та пацієнтів із поєднанням ОА з ожирінням та підвищеною масою тіла ($124,03 \pm 3,2$ пг/мл) – спостерігалось збільшення цього глікопротеїну при порівнянні з контрольними значеннями ($65,64 \pm 0,64$), ($p < 0,001$). Проведене денситометричне дослідження дозволило отримати наступні результати: остеопенія була встановлена у 15 % пацієнтів в основній групі та 36 % у групі порівняння; остеопороз встановили у 24 % пацієнтів в основній групі та 10 % пацієнтів у групі порівняння. Перебіг остеоартриту у молодих людей супроводжується формуванням остеопорозних станів, які частіше (24% проти 10%), на фоні ожиріння, призводять до розвитку остеопорозу. Розвиток остеопоротичних змін у хворих на остеоартрит та в поєднанні з ожирінням супроводжується збільшенням синтезу остеопротегерину – глікопротеїну, що бере участь у процесах ремоделювання кісткової тканини.

Ключові слова: індекс маси тіла, ожиріння, остеокласти, остеоартрит, остеобласти, остеопротегерин.