DOI 10.26724/2079-8334-2021-4-78-56-60
UDC 616.72-002-085

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OSTEOARTHRITIS AND METABOLIC SYNDROME: UNITY OF PATHOGENETIC MECHANISMS

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The article presents the results of the examination of the functional state of the joints of 116 people. There was a study of lipid profile, insulin resistance, systemic inflammation activity in patients with osteoarthritis, osteoarthritis in combination with metabolic syndrome. According to the results of the study, significant changes in the above-mentioned predictors were found in patients with osteoarthritis in combination with metabolic syndrome compared to groups of healthy individuals and patients with osteoarthritis. Thus, we found a probable increase in total cholesterol by 1.3 times, triglycerides by 1.4 times, cholesterol of very-low-density lipoproteins by 1.8 times compared with the corresponding values in patients with osteoarthritis. Exceedances in TNF-α and IL-1β indices were found to be 3.6 and 2.5-fold higher, respectively, in patients with osteoarthritis in combination with metabolic syndrome compared with other study groups. With the growing number of patients with osteoarthritis in combination with metabolic syndrome in Ukraine and around the world, the study of the unity of pathogenetic mechanisms and the possibility of finding new treatments is critical.

Key words: dyslipidemia, insulin resistance, atherosclerosis, cytokines, patient's quality of life.

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ОСТЕОАРТРИТ І МЕТАБОЛІЧНИЙ СИНДРОМ: ЄДНІСТЬ ПАТОГЕНЕТИЧНИХ МЕХАНІЗМІВ

У статті наведені результати досліджень функціонального стану суглобів 116 осіб, показників ліпідного профілю, інсулінорезистентності, активності системного запалення у хворих з остеоартритом, остеоартритом в поєднанні з метаболічним синдромом. За результатами досліджень, було виявлені достовірно виражені зміни вищезгаданих показників у пацієнтів з остеоартритом в поєднанні з метаболічним синдромом порівняно з групами здорових осіб і пацієнтів з остеоартритом. Так, встановлено вірогідне зростання загального холестерину у 1,3 рази, тригліцеридів у 1,4 рази, холестерину ліпопротеїдів дуже низької щільності у 1,8 разів порівняно з відповідними показниками у хворих на остеоартрит. Встановлено перевищення концентрації ФНП-α та ІЛ-1β показники у 3,6 та у 2,5 рази відповідно у пацієнтів з остеоартритом в поєднанні з метаболічним синдромом порівняно з іншими групами досліджуваних. В умовах зростання кількості пацієнтів на остеоартрит у поєднанні з метаболічним синдромом не тільки в Україні, а й в усьому світі, вивчення єдності патогенетичних механізмів та можливості пошуку нових методів лікування є дуже актуальним.

Ключові слова: дисліпідемія, інсулінорезистентність, атеросклероз, цитокіни, якість життя пацієнта.

The study is a fragment of the research project "Features of the course, prognosis and treatment of comorbid diseases in the pathology of internal organs, considering genetic, age and gender aspects", state registration No .0118U004461.

Osteoarthritis (OA) is the most common form of arthritis, the prevalence of which is increasing, primarily due to the population ageing and the obesity epidemic [1]. For a long time, OA was considered an inevitable process associated only with age or as a disease of wear and tear of hyaline cartilage, i.e. as a degenerative rather than inflammatory disease. Only recently it has become clear that inflammation plays a significant role in the initiation and progression of OA [2, 3, 4]. The pathogenesis of OA is complex and multidimensional. However, today most experts support the view that degradation of articular cartilage, remodelling of subchondral bone and inflammation are critical pathogenetic mechanisms in OA [5, 6, 7].

Metabolic syndrome (MS) and insulin resistance are also currently attracting much attention from therapists. The prevalence of MS, like OA, increases significantly with age, and on average, reaches 25–30 % of the population and is a severe problem worldwide [6, 7, 8, 11]. Each of the components of MS significantly increases the risk of cardiovascular disease (CVD), and their combination within MS substantially increases the likelihood of developing diseases of this group. There is information about the association of OA and MS [8].

Insulin resistance (IR), as the main pathogenetic component of MS, is associated with an imbalance of critical cytokines, mediators of inflammation: increased levels of IL-6, TNF-α and decreased IL-10, IL-4. Activation of the cytokine system plays an essential role in the pathogenesis of IR syndrome, starting from the early stages of its formation. Moreover, it is considered a marker of IR and its severity. It has been proven that chronic subclinical inflammation is part of the IR syndrome, and the levels of these cytokines are predictors of vascular complications. The IRAS study found that IR causes significant quantitative and qualitative changes in the lipid spectrum that promote atherogenesis.

In patients with OA in the presence of MS, significant changes in cartilage structure are registered, and recurrent synovitis is noted [9, 10]. The main component of MS (abdominal obesity) provokes excess production of several proinflammatory cytokines by visceral adipose tissue, including tumour necrosis

factor-α (TNF-α), which also significantly complicates the clinical picture of OA [9, 10]. Several studies have also demonstrated an increased risk of OA of the knee and/or wrist joints in patients with hypertension and/or atherosclerosis. Thus, this supported the hypothesis of impaired subchondral bone perfusion due to widespread atherosclerosis [10, 12]. This hypothesis is confirmed by the results of studies that have established an association between elevated cholesterol levels and triglycerides with the prevalence of bone lesions in magnetic resonance imaging of the knee joints [12].

The purpose of the study was to evaluate the features of the clinical and functional state of patients with osteoarthritis in the presence of metabolic syndrome and assess the effects of dyslipidemia, oxidative stress, systemic inflammation, and insulin resistance in patients with osteoarthritis combined with metabolic syndrome.

Materials and methods. 116 people were examined. Under the purpose, patients were distributed as follows: Group I – control (36 practically healthy individuals), Group II – (32 patients with OA); Group III – 48 patients with OA in combination with MS. The mean duration of the disease in patients of Group II was 7.8±2.5 years, in patients with OA in combination with ankylosing spondylitis and MS – 12.7±3.4 years.

To perform the clinical study of the functional state of the musculoskeletal system (Richie's joint indexes, Lequesne, WOMAC, visual analogue scale indicators) and to access the quality of life of patients with OA, we used the EuroQol-5D questionnaire. It contains questions about difficulties in walking, self-care, daily activities, pain/discomfort, anxiety/depression, the visual analogue scale of pain. We also performed biochemical and enzyme-linked immunosorbent assays for lipid profile (total cholesterol (TH), triglycerides (TG), high-density lipoprotein cholesterol (HDL cholesterol) and low-density cholesterol (LDL cholesterol), atherogenicity index), the state of free radical oxidation of lipids (concentration of TBA reactants, activity of superoxide dismutase (SOD), catalase), insulin resistance (IR) (concentration of leptin, adiponectin, C-peptide, glucose, followed by determination of the IR index – HOMA2IR), systemic inflammatory activity (TNF-α, IL-1, βC-reactive protein).

Anthropometric research methods included measurements of height (cm), weight (kg), waist circumference (WC, cm) and hips (HC, cm). The body mass index (BMI) was calculated based on the measurements. Abdominal obesity was determined by BMI and WC/HC index (WC over 102 cm in men and more than 88 cm in women, WC/ HC index over 1.0).

Statistical analysis was performed on a personal computer using Excel Microsoft Office spreadsheets – 2017 (USA). To prove the reliability of the results obtained, a mathematical and statistical analysis was carried out; the search for correlative patterns between various indicators and their changes was carried out in order to generalize the data obtained for further development of an algorithm for examining patients. Correlation analysis of indices was performed using calculating a simple linear Pearson correlation.

Results of the study and their discussion. The analysis of the obtained results revealed that in patients with osteoarthritis with metabolic syndrome (group III), BMI was by 1.4 times higher compared to healthy individuals and 1.2 times higher than in group II patients. Similar changes are found in determining the volume of the waist, hips and their ratio. In patients with OA with MS, the WC was probably 1.2 times higher than in practically healthy people and by 1.14 times higher than in group II patients. Similar changes were found in determining the WC/HC index in the subjects of group II, which was confirmed by significantly higher rates (by 1.3 times) than healthy individuals and patients of group II.

Assessment of quality of life occupies an important place in modern rheumatology. On the one hand, this reflects the emergence of new treatment technologies that do not sufficiently affect the life expectancy of patients but significantly improve the quality of life of patients, and on the other – increase patient activity, increase its role in choosing diagnostic and treatment methods.

An initial examination of patients with OA and patients with concomitant pathology found that the joint syndrome was more pronounced among the latter, which is confirmed by probably higher values of visual analogue scale, Lequesne index and WOMAC.

Lequesne indices remain one of the most reliable for assessing the severity of OA in patients with large joint lesions. This index in patients of group III exceeded by 2.7 times, the WOMAC index – by 1.4 compared to patients of group II.

According to the data obtained, patients have a negative dynamics of quality of life values: patients with OA and MS have an increase in self-service indicators by 1.3 times ($p<0.05$), the degree of pain/discomfort by 1.4 times ($p<0.001$), anxiety/depression by 1.2 times ($p<0.05$) and, accordingly, the overall EuroQol-5D index by 1.2 times ($p<0.001$) compared to the corresponding index of group II (table 1).

The obtained results on the lipid profile indicate that patients of group III showed an increase in the content of TH by 1.4 times ($p<0.01$), the content of HDL cholesterol decreased by 1.15 times ($p<0.01$) against the background of an increase in the concentration of TG by 1.4 times, LDL cholesterol by 1.6

times (P<0.05) and the atherogenicity index by 1.6 times compared to practically healthy individuals. There was also a significant increase in TH by1.3 times, TG by 1.4 times, LDL cholesterol by 1.8 times compared to the respective values in patients with OA. The results show that MS is a predictor of atherosclerosis, contributing to the development of atherogenic dyslipidemia.

Table 1

EuroQol-5D scale indices in patients with OA and OA in combination with MS

Index	Group II	Group III
Walking, points	1.08±0.05	1.23±0.07
Self-care, points	1.04±0.05	1.18±0.03
Daily activity, points	1.16±0.07	1.33±0.09
Pain/discomfort, points	1.12±0.04	1.55±0.09
Anxiety/depression, points	0.98±0.06	1.14±0.05
EuroQol-5D index, points	5.38±0.12	6.43±0.17

In patients of all groups, compared with almost healthy ones, the concentration of TBA reactants in the blood serum increased significantly by 1.2 times, 1.5 times and 1.7 times (10.03±0.58 mmol/L; 12.54±0.36 mmol/L; 14.21±0.42 mmol/L against 8.36±0.49, respectively; p<0.05). In the subjects of group III the activity of oxidative stress was higher than in patients of group II, as evidenced by a 1.2-fold increase in the concentration of TBA reactants in the serum. The accumulation of products of peroxidation processes occurred against the background of a decrease in SOD in patients of group II by 1.2 times compared with the control (2.88±0.10 CU/L vs 3.46±0.18 CU/L; p<0.05), group III – by 1.5 times (2.30±0.08 CU/L).

Insulin resistance (IR), as the main pathogenetic component of MS, is associated with an imbalance of critical cytokines, mediators of inflammation: increased levels of IL-6, TNF-α and decreased IL-10, IL-4. It has been proven that chronic subclinical inflammation is part of the IR syndrome, and the levels of these cytokines are predictors of vascular complications. The IRAS study found that IR causes significant quantitative and qualitative changes in the lipid spectrum that promote atherogenesis.

Analysing glycemic parameters, it was found that the content of fasting blood glucose exceeded normal. In patients of group III – by 3.2 times (p<0.001) and group II – by 1.9 times (p<0.02), which confirmed the presence of type 2 diabetes in this group of examined patients.

In patients with OA in combination with MS with impaired glucose tolerance, a significant increase in leptin content was found by 3.1 times compared to practically healthy individuals and by 2.7 times – with patients with OA (table 2).

Table 2

IR values in patients with OA and OA in combination with MS

Index	Group I	Group II	Group III
Fasting blood glucose, mmol/L	3.38±0.76	4.02±0.62	6.49±0.94***
Leptin, ng/mL	5.48±0.52	6.31±0.78	13.7±1.18***
Adiponectin, ng/mL	10.28±1.94	9.16±1.25	6.18±1.05***
C-peptide, ng/mL	1.06±0.05	1.12±0.08	2.54±0.12***
HOMA2 % B	110.2±7.15	119.4±6.48	148.9±8.1***
HOMA2 % S	155.4±11.2	99.6±10.8	79.15±6.2***
HOMA2 IR	0.71±0.04	1.19±0.11	1.88±0.09***

Notes: *– p<0.05 between indexes in practically healthy individuals and patients of the corresponding groups; *** – p<0.05 between values in patients of group I and group II or group III of the examined patients.

Similar changes were found in the study of the content of C-peptide, which was probably higher in patients of group II by 2.4, respectively, compared with almost healthy individuals.

The increase in leptin and C-peptide occurred against the background of decreasing adiponectin content. Thus, it was 1.7 times lower compared to practically healthy people in patients of group III and 1.5 times lower than those examined in group II. This was confirmed by a probable decrease in adiponectin content in the serum by 1.9 times compared with almost healthy individuals and 1.7 times – in patients with OA.

To assess the degree of IR, the Noma2 index was calculated, which includes HOMA2 % B (pancreatic β-cell activity), HOMA2 % S (tissue sensitivity to insulin) and HOMA2 % IR (IR level).

The obtained data showed a likely increase in HOMA2 IR in patients with combined pathology was established. This index in the patients exceeded the control values in patients of group II – by 2.6 times, which confirms the presence of IR and its increase in combination with other diseases, namely, OA and MS.

The function of immune surveillance, which is aimed at neutralising pathogens, viral, bacterial, and tumour nature, is performed by TNFα– a potent pro-inflammatory cytokine of systemic action. It is synthesised mainly by macrophages, Kupffer cells, monocytes, lymphocytes, and fibroblasts, epithelial, endothelial and other specialised cells. Possessing the ability to initiate apoptosis, TNF-α also causes

generalisation in the cell membrane of reactive oxygen species, superoxide radicals, and nitric oxide. It affects the endothelium, increasing the expression of adhesion molecules on it, activates macrophages, neutrophilic granulocytes and stimulates proteins of the acute phase of inflammation. TNF-α receptors are present in almost all nucleated cells of the human body, so they are involved in various processes. In inflammation, one of the functions responsible for TNF-α is mobilising inflammatory cells. Once in the bloodstream, TNF-α activates endothelial cell genes through receptors responsible for synthesising "sticky" molecules. They adhere to the endothelium in the area of inflammation of circulating in the blood polymorphonuclear and mononuclear leukocytes, followed by their migration into the site of inflammation. In inflammatory reactions and lesions, synoviocytes and chondrocytes secrete IL-1, which stimulates matrix catabolism, inhibits the synthesis of adhesive molecules, and enhances the synthesis of enzymes – metalloproteinases, especially collagenases.

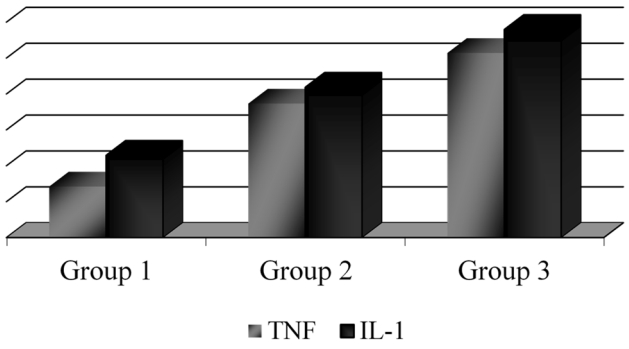

Fig. 1. Indexes of TNF-α and IL-1β content, pg/ml

Higher values of proinflammatory cytokines were found in patients with comorbid pathology: the concentration of TNF-α and IL-1β in group III exceeded the control values by 3.6 and 2.5 times (102.8±9.4 pg/mL vs 28.4±6.7 pg/mL; $p<0.001$) and (115.9±4.9 pg/mL vs 45.8±7.2 pg/mL; $p<0.01$), respectively (fig. 1).

Similar dynamics was established at the content of C-reactive protein. Thus, in patients of group III, it exceeded the control data by 1.5 times.

According to the results of the study of systemic inflammation, we found an increase in the content of pro-inflammatory cytokines in all groups of patients, but the highest rates were in patients with combined pathology. The lipid profile in patients with OA and OA comorbid with MS was characterised by an increase in cholesterol content and its fractions (TG). This is characteristic of atherogenic dyslipidemia, which developed due to MS, and the activation of oxidative stress, a universal damaging factor [10]. We found that oxidative stress, endogenous inflammation, and dyslipidemia significantly affect the course of osteoarthritis and metabolic syndrome [6]. Free radical oxidation of lipids is accompanied by the formation of oxidatively modified LDL, which contributes to the formation of foamy cells and the development of autoimmune reactions [4, 8, 12].

Conclusions

1. According to the data obtained, patients have a negative dynamics of quality of life: patients with osteoarthritis and metabolic syndrome have an increase in self-service indicators by 1.3 times, the degree of pain/discomfort by 1.4 times, anxiety/depression by 1.2 times compared to patients with osteoarthritis.

2. Activation of oxidative stress, progression of atherogenic dyslipidemia, growth of IR indexes (leptin, C-peptide, HOMA2 IR), proinflammatory cytokines are observed at a combination of osteoarthritis with a metabolic syndrome. This indicates an essential pathogenetic role of the latter in the progression of systemic manifestations of comorbid conditions.

Prospects for further research. Changing our perceptions of the OA development, understanding that OA is a heterogeneous state and metabolic disorders play a significant role in the development and progression of the disease, provide an opportunity to find new treatment approaches.

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Стаття надійшла 10.10.2020 р.

DOI 10.26724/2079-8334-2021-4-78-60-65
UDC 616-001.4-022.1-085-037

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COMBINATION OF ULTRAVIOLET RADIATION OF AUTOLOGOUS BLOOD, NEGATIVE PRESSURE WOUND THERAPY, AND ENDOLYMPHATIC ANTIBACTERIAL THERAPY IN THE TREATMENT OF POST-TRAUMATIC WOUND INFECTIONS

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The doctrine of the wound process is one of the current problems of surgery. It reflects the level of theoretical and practical medicine development. The purpose of this work was to study the improvement of treatment outcomes in patients with post-traumatic wound infections. A set of tools was used to treat patients: endolymphatic antibacterial therapy, ultraviolet irradiation of autologous blood and topical application of vacuum therapy. At the present stage, the best topical treatment method in bulky infected and purulent wounds is vacuum therapy using special technical equipment. The proposed complex of treatment reduces the severity of the disease and accelerates the debridement and regeneration of wounds. As a result, it allowed reducing the course of antibiotic administration by 1.8 times and the duration of inpatient treatment by 3.5 days compared to the traditional treatment methods.

Keywords: intoxication index, negative pressure wound therapy, endolymphatic administration of drugs, blood irradiation.

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КОМБІНАЦІЯ УЛЬТРАФІОЛЕТОВОГО ОПРОМІНЕННЯ АУТОКРОВІ, ВАКУУМНОЇ ТЕРАПІЇ ТА ЕНДОЛІМФАТИЧНОЇ АНТИБАКТЕРІАЛЬНОЇ ТЕРАПІЇ У ЛІКУВАННІ ПІСЛЯТРАВМАТИЧНОЇ ІНФІКОВАНІ РАНИ

Вчення про рановий процес відноситься до числа актуальних проблем хірургії та відображає рівень розвитку теоретичної і практичної медицини. Метою даної роботи було вивчення покращення результатів лікування хворих на післятравматичні інфіковані рани. При лікуванні хворих був застосований комплекс засобів: ендолімфатична антибактеріальна терапія, ультрафіолетове опромінення аутокрові та місцеве застосування вакуумної терапії. На сучасному етапі кращим методом місцевого лікування при наявності об'ємних інфікованих та гнійних ран є вакуумна терапія з використанням спеціального технічного оснащення. Запропонований комплекс лікування зменшує тяжкість перебігу захворювання, прискорює процеси очищення та регенерації ран. І в результаті, дозволив скоротити курсову дозу антибіотика у 1,8 рази та термін стаціонарного лікування на 3,5 діб в порівнянні з традиційними методами лікування.

Ключові слова: індекс інтоксикації, ВАК-терапія, ендолімфатичне ведення препаратів, опромінення крові.

The study is a fragment of the research project "Improvement of diagnosis and treatment tactics in purulent-inflammatory soft tissue diseases, acute and chronic surgical pathology of the abdominal cavity. Prediction of complications and their prevention, prediction of the course of wound healing in patients with allergic reactions to antibiotics", state registration No. 0118U006953.

The doctrine of the wound process is one of the current problems of surgery. It reflects the level of theoretical and practical medicine development [6]. Among the various areas of modern clinical surgery, the problem of treating patients with purulent, including wound infection, attracts special attention and is intensively studied in Ukraine and abroad [4, 9].