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Osteoarthritis and cardiovascular diseases: etiological and clinical-pathogenetic relationships, treatment and prevention

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In recent years, numerous studies have shown a link between osteoarthritis (OA) and cardiovascular disease (CVD). Comorbidity of one of these diseases is directly and significantly associated with an increased risk of developing another. Objective. Carrying out a critical analysis of the results of studies related to the relationship between CVD and OA, as well as an assessment of the possibilities of their joint prevention and treatment. Methods. Publications from the Google search system, electronic databases PubMed, Scopus, Web of Science and other relevant sources of scientific and medical information were analyzed. The results. The main pathogenetic explanation of the relationship between CVD and OA is the presence of systemic, slowly progressing inflammation, which becomes especially important in patients of older age groups. The similarity of the composition of pro-inflammatory cytokines in the development of both CVD and OA enhances pathological changes in the structure of comorbidity. CVD and OA share common pathological mechanisms, such as oxidative and metabolic stress, molecular factors of endothelial dysfunction, hyperlipidemia, and systemic and local vascular remodeling. At the same time, it was established that OA develops against the background of CVD risk factors and progresses along with their accumulation. Special care should be taken when prescribing non-steroidal anti-inflammatory drugs (NSAIDs). The appointment of systemic forms of NSAIDs is not recommended for patients with high and very high cardiovascular risk. Conclusions. In patients with both conditions, the risk of one is directly related to an increased risk of the other. Further study of the role of comorbidities in the pathogenesis of OA will expand the understanding of the integration of cardiovascular risk factors. These facts provide prospects for further studying the role of comorbidities in the pathogenesis of OA, expanding the understanding of the integration of cardiovascular risk factors and successful cardiovascular prevention and treatment of OA.

В останні роки численні дослідження свідчать про зв'язок між остеоартритом (ОА) та серцево-судинними захворюваннями (ССЗ). Коморбідність одного з цих захворювань прямо та суттєво пов'язана з підвищеним ризиком розвитку іншого. Мета. Провести критичний аналіз результатів досліджень стосовно взаємозв'язку між ССЗ та ОА, а також оцінити можливості їхньої спільної профілактики та лікування. Методи. Проаналізовано публікації з пошукової системи Google, баз даних PubMed, Scopus, Web of Science та інших релевантних джерел науково-медичної інформації. Результати. Основним патогенетичним поясненням взаємозв'язку між ССЗ та ОА є наявність системного повільно прогресуючого запалення, яке набуває особливого значення у пацієнтів старших вікових груп. Схожість складу прозапальних цитокінів у розвитку як ССЗ, так і ОА, посилює патологічні зміни у структурі коморбідності. ССЗ та ОА мають загальні патологічні механізми, такі як окислювальний та метаболічний стрес, молекулярні фактори ендотеліальної дисфункції, гіперліпідемія, а також системне та локальне судинне ремоделювання. При цьому встановлено, що ОА розвивається на тлі факторів ризику ССЗ та прогресує разом із їх накопиченням. При призначенні нестероїдних протизапальних препаратів (НПЗП) слід виявляти особливу обережність. Призначення системних форм НПЗП не рекомендується пацієнтам з високим і дуже високим кардіоваскулярним ризиком. Висновки. У пацієнтів з обома станами ризик одного з них безпосередньо пов'язаний зі збільшенням ризику іншого. Подальше вивчення ролі супутніх захворювань у патогенезі ОА розширить розуміння інтеграції факторів серцево-судинного ризику. Ці факти надають перспективи для подальшого вивчення ролі супутніх захворювань у патогенезі ОА, розширення розуміння інтеграції факторів серцево-судинного ризику та успішної кардіоваскулярної профілактики та лікування ОА. Ключові слова. Остеоартрит, серцево-судинні захворювання, коморбідність.

Keywords. Osteoarthritis, cardiovascular diseases, comorbidity

Introduction

The discovery of universal mechanisms and the role of cardiometabolic factors in the pathogenesis of various diseases led to the formation of a paradigm of joint prevention. It is aimed at preventing cardiovascular diseases (CVD) and related comorbid conditions, which often share common pathogenic mechanisms. The most significant discoveries have been made in the field of studying degenerative-inflammatory joint diseases, including osteoarthritis (OA).

The term "cardiovascular diseases" unites a wide range of nosologies with various causes, accompanied by damage to the heart, blood vessels, brain and other organs. These diseases are the main cause of death and permanent disability worldwide [1]. The main mechanism underlying the development of CVD is atherosclerosis. Studies show that atherosclerosis in 75 % of cases is responsible for the development of ischemic diseases, chronic heart failure (CHF) and acute cardiovascular events, including sudden coronary death [2]. In addition, infectious (bacterial, viral, fungal) lesions of the cardiovascular system, diseases of autoimmune origin, and oncological processes are distinguished. The most common CVD is arterial hypertension (AH) [1].

The utilitarian approach and increased interest in the issues of cardiovascular comorbidity in the case of OA are due to several factors [3]. First, the significant economic burden that these diseases have on the world economy. Secondly, there are currently no effective conservative treatment methods for OA. Third, the increasing number of publications on the role of cardiovascular factors in the development and progression of OA increases the significance of this comorbidity. Finally, the question of the therapeutic effectiveness of existing methods of cardiovascular prevention and therapy for OA remains unresolved.

In recent years, numerous studies have shed light on the relationship between OA and various risk factors, such as obesity, hypertension, vascular remodeling, lipid metabolism disorders, and hormonal imbalances. However, the causal relationships between risk factors for CVD and OA remain unclear [4, 5].

In other words, the question arises whether certain risk factors for CVD, such as hypertension and dyslipidemia, can be the cause of the development of degenerative joint diseases. The answer to it can help us better understand the pathogenesis of OA and develop effective treatment methods based on the principles of cardiovascular prevention.

Purpose: to conduct a critical analysis of the results of studies that relate to the relationship between cardiovascular diseases and osteoarthritis, as well as to evaluate the possibilities of their joint prevention and treatment.

Material and methods

The study involved an assessment of publications from the Google search engine, scientometric electronic databases PubMed, Scopus, Web of Science and other relevant sources of scientific and medical information. Articles for the last 8 years (from 2017 to 2024) were selected by keywords: osteoarthritis, cardiovascular diseases, comorbidity.

Results and their discussion

Pathogenic features of cardiovascular diseases in patients with osteoarthritis

Currently, there is uncertainty about the nature of the relationship between OA and CVD. However, it is known that the symptoms of OA can be associated with an adverse course of CVD. Pain in large joints significantly limits the mobility of patients with OA, and maintaining physical activity is a key aspect of the management of patients with CVD. In patients suffering from CVD and OA at the same time, the comorbidity of one of these diseases is directly and significantly associated with an increased risk of developing the other [6]. But the relationship between OA and mortality from CVD has not been sufficiently studied.

The mechanisms underlying the relationship between OA and CVD are still poorly defined. This situation is partly explained by the complexity of organizing and conducting studies involving patients with different OA phenotypes, risk factors and treated with different techniques. For example, drugs that are mostly used to treat OA, namely nonsteroidal anti-inflammatory drugs (NSAIDs), cause an increased risk of CVD [5]. In addition, the reduced level of physical activity in patients with OA may be an additional negative factor for those suffering from CVD.

Over the past 30 years, the perception of OA and its impact on the body has changed significantly. Today, it is considered not only as a disease that affects the cartilage of large joints (as it was in the 90s), or as a disease that affects the joint as a whole (as it was at the beginning of the 21st century), but also as a disorder, associated with systemic inflammation of low intensity. It should be noted that such inflammation is also characteristic of CVD and diabetes mellitus (DM). For example, the level of glucose in the blood in the case of diabetes can lead to joint damage,

cartilage destruction and the development of atherosclerosis [7].

Therefore, it is important to consider the presence of systemic inflammation when planning and carrying out treatment measures in patients suffering from OA and CVD. Today, combining information on OA and mortality rates is challenging because this relationship is influenced by multiple mediators and factors, including systemic inflammation. So far, there is not enough information to state a direct relationship between OA and overall mortality. However, there is an association between OA and some joints (such as the hip, knee, and hand) and increased all-cause mortality [3].

When discussing the relationship between OA and mortality, we rely on the results of studies conducted in different countries with different standards of living and health care organization. This means that these data are not completely transferable to our population, but they are an important source of information. For example, R. Birtwhistle et al. indicate that OA is the most common form of arthritis, affecting 1 in 8 (13 %) Canadians and a leading cause of pain and disability in society [8]. This disease is diagnosed at any age, but most often in elderly women. With an aging population and increasing obesity, the prevalence of OA is expected to continue to rise and by 2040 one in four people will be affected. The prevalence of OA in Canada has a significant impact on quality of life and health care costs. It has been proven that the quality of life of people with OA decreases by 10–25 % compared to the general population [9].

An attempt to study the relationship between concomitant diseases and the structural progression of OA was made by C. Roubille et al., during the study of the treatment of patients with symptomatic OA of the knee and/or hip joints without obesity [10]. According to the results of this study, after 5 years, CVDs were significantly associated with radiological progression of both knee and hip OA. This report indicates the need for comprehensive treatment of CVD in patients with OA and emphasizes the specific impact of cardiovascular disorders on the structural progression of OA in non-obese individuals [10].

Overweight and obesity have become important problems of modern society and health care, they are associated with disability, diabetes, hypertension, cardiovascular events and OA [11]. It is predicted that by 2030, up to 38 % of the world's population will be overweight, and 20 % will be obese [12].

Metabolic syndrome (MS), which includes disturbances in carbohydrate and lipid metabolism, hypertension and obesity, results in mechanical stress on the joints and activation of pro-inflammatory compounds produced by adipose tissue. This contributes to the development of OA and the formation of its metabolic phenotype. Adipocytes of adipose tissue have both systemic and local effects on joint tissues. For example, leptin, adiponectin, and lipocalin-2 produced by adipose tissue activate intracellular signaling pathways, leading to changes in the differentiation and phenotype of chondrocytes and synoviocytes [14].

The results of a nationwide study in South Korea involving 8,491 subjects, confirmed a high risk of developing OA in patients with MS, which is 1.664 ($p < 0.001$) [15]. Considering MS as a risk factor for the development of OA, its multicomponent and multivariate nature should be taken into account. Of interest are the results of the Framingham study [16], which showed a different association of components of the metabolic syndrome with symptomatic and radiological OA. After correcting the results of the study for the body mass index or the weight of the patients, a strong correlation of hypertension with the severity of symptomatic and radiological manifestations of OA was found.

The main pathogenic explanation of the relationship between CVD and OA is the presence of systemic, slowly progressing inflammation, which becomes especially important in patients of older age groups [17]. The similarity of the composition of pro-inflammatory cytokines in the development of both CVD and OA enhances pathological changes in the comorbidity structure of aging patients.

Pain plays an important role in the relationship between OA and CVD. Its presence not only increases the risk of mortality in patients with OA and CVD, but also contributes to the destabilization of their condition [18]. Pain triggers sympatho-adrenal reactions that underlie the destabilization of comorbidities. They can enhance endothelial damage, increase blood pressure and lead to episodes of ischemia.

The development and progression of sarcopenia becomes important in the context of the connection between OA and CVD. This aspect of comorbidity is considered from several angles: as an independent risk factor for death in persons over 65 years of age, and as one that contributes to the progression of CVD (including chronic heart failure), and as a factor that reduces the rehabilitation potential, significantly complicating the recovery of elderly patients with CVD and OA. [19]. Special attention should be paid to sarcopenic obesity, when a high level of fat mass is combined with a relatively low level of muscle mass. Recent reviews indicate a significant impact of sarcopenic

obesity on the progression of loss of mobility and autonomy in patients with OA [20].

Patients who suffer from OA in combination with other diseases often lose not only pain tolerance, but also mobility due to a decrease in the level of physical activity. For example, low walking speed, due to OA, significantly affects the risk of developing CVD, even after adjustment for known risk factors [21]. Moreover, OA increases the physical limitations associated with the manifestations of CVD [22], and in patients with different degrees of severity of CVD, progressive OA is accompanied by a gradual deterioration of physical functioning [23].

Thus, the similarity of risk factors between OA and CVD plays a key role in the high prevalence of this polymorbidity. The combination of CVD and OA has serious clinical consequences both in terms of disease progression in elderly patients and in terms of more rapid and severe impairment of physical functionality, which can lead to loss of mobility, increased dependence, and impaired autonomy. This emphasizes the need for more careful selection of therapeutic strategies, prevention of unwanted side effects of drugs, as well as not only ensuring adequate analgesia in patients, but also increasing the level of physical activity and functionality.

Activation of bradykinin, vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs) contributes to a change in the phenotype of chondrocytes, which leads to hypertrophic differentiation and expansion of endothelial cells in the basal zone of joint cartilage. This ultimately causes disruption of biochemical processes in the intercellular matrix and the development of OA [24]. These data indicate a direct effect of arterial hypertension on joint tissues, stimulating ischemia and oxidative stress, which, in turn, triggers angioproliferation processes to adapt to hypoxic conditions. Tissue hypoxia, in response to this, provokes angiogenesis under the influence of VEGF, which leads to pathological differentiation of chondrocytes and the expression of tissue collagenases, which ultimately increases the destruction of the intercellular matrix in joint tissues.

Common mechanisms of CVD and OA development include not only endothelial dysfunction and vascular remodeling, but also lipid metabolism disorders. An important role in understanding the impact of hyperlipidemia on the pathogenesis of OA is played by the Rotterdam study, which showed that hypercholesterolemia is an independent risk factor for OA [25]. Endothelial dysfunction and hyperlipidemia combine in a pathogenetic cascade of vascular remodeling through lectin-like oxidase receptor-1 (LOX-1), which actively binds to low-density lipoproteins (LDL), causing activation of nitric oxide production, arterial intimal thickening, and lipid deposition [26]. Binding of LOX-1 and LDL causes activation of NF-kB and production of reactive oxygen species in chondrocytes [27]. In an animal model of post-traumatic OA, it was convincingly proven that the expression of LOX-1 contributes to the degradation of cartilage tissue and the formation of osteophytes [28].

Lipids directly affect joint tissues, as cholesterol can accumulate in articular cartilage, causing mitochondrial dysfunction and chondrocyte hypertrophy through the production of reactive oxygen species [29]. Experimental studies have established that cholesterol metabolism in chondrocytes is controlled by hydrolases, and their increased activity contributes to the development of OA. In experimental hyperlipidemia, processes of apoptosis, angioproliferation, and pathological ossification are observed in joint tissues [30].

The increased level of cholesterol in LDL, which plays a key role in the development of atherosclerosis, stimulates inflammation of the synovial membrane, activating synovial macrophages and fibroblasts. This leads to the release of growth factors, MMPs and pro-inflammatory cytokines [31]. Inflammation caused by the introduction of oxidized LDL into the joint cavity provokes the destruction of joint cartilage [32]. Thus, the disturbance of lipid metabolism is an important factor in the development of OA, since the accumulation of lipids in articular cartilage causes cellular stress and activates the processes of degradation in joint tissues.

Considering the importance of hypertension and hyperlipidemia in the development of OA, researchers are faced with the question of how the combination of CVD risk factors affects the state of the joints. Its importance is confirmed by the results of scientific research, which demonstrate the high prevalence of comorbid relationships in society. For example, the national study BEACH (Bettering the Evaluation and Care of Health), conducted in Australia with the participation of 8,707 subjects, found that the most frequent combination of comorbidity is a combination of hypertension, hyperlipidemia, and OA [33].

Osteoarthritis and arterial hypertension

Studies show that the combination of OA and hypertension is common in different countries in the range from 30 to 80 % of cases [34]. This wide distribution is due to the similar pathogenic basis and risk factors of both diseases. The risk of developing hypertension in OA is associated with excess body

weight/obesity, insufficient physical activity, and irrational nutrition [35]. Experts single out hypodynamia as the main mechanism of the development of hypertension in OA, caused by impaired mobility of large joints (hip, knee). Hypodynamia leads to disturbances in lipid metabolism, a decrease in the tolerance of the myocardium to physical exertion, a decrease in the elasticity of blood vessels, which ultimately causes an increase in blood pressure [36].

Chronic inflammation in OA affects not only perichondral tissue damage, but also vascular endothelium, which can lead to endothelial dysfunction, which is one of the significant causes of hypertension. The mesodermal origin of subchondral areas of bone, membranes, ligaments, capsules, and periarticular muscles causes mediated injury to the endothelium. The described comorbid association has an inverse relationship characteristic. Long-term hypertension can negatively affect the physical and chemical homeostasis of joints, which provokes disruption of subchondral bone perfusion and ischemia, which, in turn, affects the angiogenic-osteogenic connection and the integrity of the functional unit of bone and cartilage.

Some preclinical experimental publications describe the positive effect of β-blockers and calcium channel blockers on the course of OA [37]. There is also information indicating the connection of metabolic syndrome and hypertension with the development of OA of the knee joints [38], which confirms the perspective of studying the effect of drugs used in the treatment of these nosologies on the course of OA.

OA and coronary heart disease (CHD)

Regular use of nonsteroidal anti-inflammatory drugs is associated with the risk of developing acute ischemic cardiovascular complications. Disturbance of the balance of prostacyclin and thromboxane A2 can lead to increased adhesion and aggregation of platelets, as well as increased thrombus formation. According to the meta-analysis of M. Bally et al. [39], regular use of NSAIDs increases the risk of developing acute ischemic cardiovascular complications. The ratio was 1.24 (95% confidence interval 0.91–1.82) for celecoxib; 1.48 (1.00–2.26) — ibuprofen; 1.50 (1.06–2.04) — diclofenac; 1.53 (1.07–2.33) for naproxen and 1.58 (1.07–2.17) for rofecoxib. The risk increases with increasing drug dosage [40]. This effect, according to experts, is due to an imbalance of prostaglandins and subsequent deterioration of vascular elasticity. According to the available data, diclofenac has the most pronounced atherothrombotic effect [40].

Chronic joint inflammation causes involuntary hypodynamia, closely associated with obesity, diabetes/insulin resistance, and dyslipidemia, which are known risk factors for the development and progression of CHD. Diabetes mellitus/insulin resistance and dyslipidemia also affect the progression of joint destruction in OA, leading to deterioration of its functionality. Patients with this diagnosis develop the so-called diabetic osteoarthropathy. Chronic disruption of microcirculation in the case of diabetes causes the progression of the destruction of bone and cartilage structures. Decreased mobility due to OA due to hypodynamia and disease progression, in turn, is negatively correlated with the risk of developing acute cardiovascular complications in patients with already stable CAD [41, 42]. Considering the above, it can be assumed that patients with coronary heart disease and OA should be classified as a special risk group that requires the development of an individual approach to the treatment of OA in order to minimize the risk of cardiovascular complications.

OA and chronic heart failure

One of the significant negative effects of OA on the course of CHF is chronic pain syndrome. Pain caused by muscle strain, injuries and inflammatory processes of the bone and joint system stimulates the release of catecholamines into the bloodstream, which, in turn, leads to an increase in the concentration of norepinephrine in the plasma. This process causes increased heart rate, sodium retention, vascular spasm, increasing the load on the myocardium. Such mechanisms inevitably lead to myocardial remodeling and progression of already existing CHF [43, 44]. The presence of chronic pain syndrome due to OA determines the need for constant use of NSAIDs. However, one of the side effects of NSAIDs is fluid retention in the body and destabilization of blood pressure.

According to European meta-analyses for the period 2000–2010, during the use of non-selective NSAIDs (diclofenac, ketorolac, naproxen), especially in the case of increased dosages, the risk of CHF decompensation and re-hospitalization increases significantly. Taking NSAIDs is also associated with inhibition of glomerular filtration, increased tubular reabsorption of sodium, and increased vascular resistance due to inhibition of cyclooxygenase 1 and 2 activity, which, in turn, regulates prostaglandin production. Prostaglandins and prostacyclin are responsible for vasodilation and regulation of platelet adhesion. Suppression of these mechanisms provokes an increase in peripheral vascular resistance, deterioration

of microcirculation, and disruption of vascular hemostasis [45–47].

The importance of early assessment of the risk of decompensation of the underlying cardiovascular pathology in patients with OA, especially CHF, is emphasized in the light of possible negative consequences. In addition to the need to use echocardiographic research and analysis of the level of brain natriuretic peptide or its N-terminal fragment (BNP/NT-proBNP), the possibility of using immunological markers to assess the risk of decompensation before the appearance of clinically pronounced symptoms is actively discussed. Of particular interest is the use of galectin-3, a galactose-binding protein that regulates cell cycle activation, inflammation, fibrosis, and myocardial remodeling. This protein plays a key role in the regulation of the immunological cascade in OA [48]. Experimental studies show that galectin-3 is one of the main regulators of myocardial remodeling processes in CHF [49]. An increase in the level of galectin-3 is associated with an increased risk of mortality and re-hospitalization [50].

There are no sufficient studies devoted to studying the properties and dynamics of galectin-3 levels in patients with OA. However, separate works and reviews confirm the active expression and release of galectin-3 by the inflamed synovial membrane in patients with OA [51, 52]. In an experimental study, it was shown that galectin-3 contributes to the dysfunction and damage of articular cartilage by activating the transcription factor NF-κB and mitogen-activated protein kinases [53].

The progression of OA results in a decrease in the physical activity of patients, which, in the presence of CHF, is a negative prognostic factor. Considering the biological properties of galectin-3 as a cytokine that regulates the processes of myocardial remodeling, fibrosis, and apoptosis, it can be assumed that this marker may be useful in assessing the risk of CHF decompensation in patients with OA, since an increase in its level is associated with such a risk. Despite the lack of large studies evaluating the role of galectin-3 in patient groups, this direction is of considerable interest and may be promising for future research.

Therapeutic strategies in patients with OA and CVD

To date, there are no clear recommendations for the development of specialized strategies for the treatment of OA in patients with CVD. However, it is worth mentioning the recommendations of OARSI (2019) [54], highlighting the phenotype of OA with CVD and restrictions on the use of NSAIDs and the expansion of non-drug treatment programs.

Programs of non-drug therapy include the following components:

1. Training on the main aspects of the development and progression of OA, management of pain syndrome, prevention of pain catastrophizing and motivation to perform complex exercises;
2. Structured sets of strengthening exercises;
3. Ordered complexes of cardio exercises;
4. Developed sets of exercises for training balance and equilibrium;
5. Structured exercise programs to improve the condition of the musculoskeletal system;
6. Tai Chi exercises;
7. Other forms of yoga;
8. Diet — for weight control or with high anti-inflammatory potential.

Recent studies confirm the anti-inflammatory potential of prebiotics and probiotics for the treatment of OA [55, 56]. The possibility of their influence on the composition of the intestinal microbiota is considered as a potential strategy for anti-inflammatory therapy of OA and is recommended for most patients [57], primarily considering the amount of information on the beneficial effect of certain types of microbiota on vascular aging.

In the case of prescribing NSAIDs, special caution should be exercised. Their use can cause an imbalance between the synthesis of prothrombotic (thromboxane) and antithrombotic (prostacyclin) factors due to unbalanced blockade of cyclooxygenase-1 and cyclooxygenase-2, which increases the overall vascular risk and can lead to acute cardiovascular events. The appointment of systemic forms of NSAIDs is not recommended for patients with high and very high cardiovascular risk [58].

A recent cardiovascular case analysis of NSAIDs for the treatment of OA and back pain indicated that topical forms of NSAIDs (NSAID patches) were better in elderly patients, but the risk of acute myocardial infarction was comparable to that of oral administration [59]. Therefore, it is recommended to take NSAIDs, including local forms, with caution, especially for patients in this category and for persons with an increased risk of developing CVD.

Prospects for joint prevention of OA and CVD

The results of the conducted studies clearly demonstrate that CVD and OA have common pathological mechanisms, such as oxidative and metabolic stress, molecular factors of endothelial dysfunction, hyperlipidemia, as well as systemic and local vascular remodeling. At the same time, it was established

that OA develops against the background of CVD risk factors and progresses along with their accumulation. These facts provide prospects for successful cardiovascular prevention and treatment of OA.

Research shows that aerobic exercise for 30 minutes a day, 5 days a week, can reduce the level of joint pain and the concentration of initially elevated atherogenic lipids, including total cholesterol, LDL cholesterol, and triglycerides [33]. A cholesterol-restricted diet and dietary supplements containing long-chain omega-3 fatty acids also reduce atherogenic lipids in patients with OA and metabolic syndrome [61]. Despite the lack of reliable information regarding its effect on the development and progression of OA, it can be assumed that exercise and diet may play a key role in the joint prevention strategy of CVD and OA.

Pharmacological agents also play a significant role in controlling CVD and OA. In light of the urgency of the problem of OA and CVD, a fixed combination of amlodipine and celecoxib was created. It has systemic anti-inflammatory and vasodilating effects, specially developed for the treatment of OA and hypertension [62].

The results of a six-year prospective study (2004–2010) are promising in the context of joint prevention of OA and hypertension. It proved a reduction in the incidence of OA in patients with hypertension who took ≥ 3 antihypertensive drugs (odds ratio 0.4; 95 % confidence interval: 0.1–1.0) [63]. In an experimental study on a model of obese rats, it was convincingly proven that treatment with the mineralocorticoid receptor antagonist eplerenone slowed down the remodeling of joint tissues under the influence of metabolic syndrome components [64].

Research is also underway into the potential effects of beta-blockers for the treatment of OA. For example, nebivolol, a known beta-blocker, reduces the transcriptional activity of NF-kB in chondrocytes, which prevents the development of OA [65]. Thus, there is reason to believe that treatment of cardiovascular disease may provide potential benefit by correcting comorbidity factors and direct effects on joint tissue. Therefore, large clinical studies are needed to evaluate the effectiveness of combined therapy for OA and CVD. However, it is already clear that active management of comorbid diseases and risk factors for their development can change the course of OA progression.

There are suggestions about the potential benefit of statins in the treatment of OA. A number of experimental studies showed that atorvastatin is able to inhibit the dysmetabolic effects of lipids on joint tissue [66]. The supposed positive effect of statins on joint tissues is associated with inhibition of lipid peroxidation, some intracellular signaling pathways, and apoptosis [67]. A multicenter study established that taking statins reduces the rate of joint space narrowing by 46 % [68]. However, the key drawback of this work is the lack of consideration of the dosage and use of different statins.

Mixed results were obtained in a four-year study involving 4,448 patients. According to it, taking statins for more than five years reduces the risk of developing joint pain. Controversies lie in the fact that the use of atorvastatin reduces the likelihood of OA symptoms, while the use of rosuvastatin increases it [69].

An interesting approach to the use of statins in the therapy of OA is the intra-articular injection of simvastatin. An experimental study proved that in mice that received intraosseous injections of simvastatin-conjugated hydrogel, there was a decrease in the tissue expression of pro-inflammatory cytokines and MMP-13, as well as an increase in the expression of type 2 collagen [70]. These experiments and clinical developments provide a basis for the integration of hypolipidemic therapy strategies used in cardiovascular prevention, treatment of OA. It is obvious that further study of the therapeutic properties of different treatment regimens, optimal doses of various statin molecules and other hypolipidemic drugs for the prevention and treatment of OA is needed.

Conclusions

The analysis of experimental, clinical and large-scale studies allows researchers to consider joint tissues as target organs for a number of cardiovascular factors. Hypertension, hyperlipidemia, and obesity are among the most significant risk factors for the development of degenerative joint diseases. In some studies, the primary importance of these factors in the pathogenesis of OA has been confirmed.

Although the nature of the relationship between OA and CVD is not fully understood, OA symptoms are known to be associated with adverse CVD events. In patients with both conditions, the risk of one is directly related to an increased risk of the other. Further study of the role of comorbidities in the pathogenesis of OA will expand the understanding of the integration of cardiovascular risk factors. Understanding the importance of the vascular aspects of OA contributes to the improvement of pathogenic approaches in conservative treatment.

Currently, there are reasons to believe that active correction of cardiovascular factors using

non-pharmacological and pharmacological methods may be useful in the treatment of OA. The development of new methods for early diagnosis of the risk of CVD decompensation in patients with OA is a promising direction. Immunomodulatory cytokines may be the most effective markers for the diagnosis of such cases.

Experimental studies confirm the positive effect of β-blockers and calcium channel blockers on the course of OA. The analysis of publications confirms the existence of a number of pathogenic associations of OA with diseases of the cardiovascular system, which should be taken into account during the management of such patients in clinical practice.

Conflict of interest. The authors declare no conflict of interest.

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OSTEOARTHRITIS AND CARDIOVASCULAR DISEASES: ETIOLOGICAL AND CLINICAL-PATHOGENETIC RELATIONSHIPS, TREATMENT AND PREVENTION

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