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Key words: *osteoarthritis, metabolic syndrome.*

OSTEOARTHRITIS AND METABOLIC SYNDROME: A CURRENT VIEW OF THE PROBLEM

Osteoarthritis is the most common rheumatologic disorder leading to prolonged disability. However, numerous studies concerning illness pathogenic changes help better understand risk factors and principles of the disease progress. The problem of metabolic syndrome has recently attracted attention of doctors and scientists all over the world due to close relationship between this disease and cardiovascular pathology. Respectively, pathogenetic correlation between osteoarthritis and metabolic syndrome opens a new horizon of the early diagnosis and prevention of this nosology.

Obesity and osteoarthritis (OA) are the most urgent among medical and social problems nowadays (Насонова В.А., Фоломеева О.М., 2001; Дедов И.И., Мельниченко Г.А., 2004). This is due to both their extremely high prevalence and high comorbidity with other conditions and diseases having a significant influence on the life quality of the patients. According to the recent data (Tukker A. et al., 2007; Magliano M., 2008), obesity is a risk factor for OA and many other diseases related to metabolic disorders, dysfunctions and disability limitations, usually accompanied by OA and respectively leading to increased body mass index (BMI) and induce the development of cardiovascular disease and diabetes.

According to the WHO definition, overweight and obesity are excessive fat accumulations leading to health disorders (Aus Tariq Ali, Nigel John Crowther, 2005; Francesco Branca et al., 2009). «Overweight» corresponds to a BMI ⩾25, and «obesity» — to a BMI ⩾30:

$$BMI = \frac{body\ weight\ (kg)}{height^2\ (m^2)}.$$

BMI, a ratio of weight to height, is widely used for classification of the stages of overweight and obesity in adult population. According to WHO data, in 2005 approximately 1.6 billion adults (aged over 15 years) were overweight worldwide and at least 400 million adults suffered from obesity. The results of the sample surveys conducted in Russia indicate that at least 30% of the working-age population is overweight and 25% is obese. By 2015, approximately 2.3 billion adults will have overweighted and more than 700 million adults will have suffered from obesity. From the etiologic and pathogenetic point of view, obesity is considered to be a heterogeneous chronic, progressive disease, associated with a number of genetic, hormonal and neurological factors leading to violations of all kinds of metabolism and energy imbalance.

Numerous studies have demonstrated that obesity results in development of various diseases, high levels of disability and life expectancy reduction in the patients. Risk of their development is progressively increasing along with BMI. People with 40% of excess body weight face twice higher risks of premature death compared to people with an average body weight. The number of diseases caused by obesity is rather high. The diseases commonly associated with obesity are: diabetes mellitus (DM) Type 2, hypertension (HT), dyslipidemia, coronary heart disease (CHD), heart failure (HF), cerebrovascular disease (increased risk of stroke), respiratory disease (sleep apnoea syndrome, asthma), cholelithiasis, non-alcoholic liver cirrhosis and OA (Malnick S.D., Knobler H., 2006; Calza S.et al., 2008).

OA is a heterogeneous group of diseases with different aetiologies but similar in biological, morphological and clinical manifestations, first and foremost, resulting in the destruction of all joint components, for instance, the cartilage and subchondral bone, synovium, ligaments, capsules and arthrous muscles. At present, instead of the term «osteoarthrosis» more common term of «osteoarthritis» is used in many countries. It emphasizes the important role of the inflammatory component in the development and progression of the disease.

Nowadays, the two main forms of OA are distinguished: primary (idiopathic) and secondary, caused by some other diseases (Насонова В.А., Насонов Е.Л. 2003). Primary OA may be topical (localized in one joint) and generalized (three or more joints are involved). There is no clear correlation between clinical symptoms and roentgenology data. Thus, for example, it has been established that old people aged 65–93 years in 33% of cases show radiological signs of OA, but only 9.5% of them experience its clinical manifestations (Felson D.T., Zhand Y., 1998). OA pain characteristics are not detected or minimal radiographic changes can be identified. The classification by Kellgren and Lawrence is the most widely used for diagnosis and assessment of progress of OA. Most epidemiological studies are based on OA radiographic signs and pain syndrome duration in the joint. According to various studies (Sharma L., Berenbaum F. (ed)., 2007), incidence of OA detected in autopsy is significantly higher compared with its clinical manifestations. It ranges 48 to 65%.

The list of diseases complicated by secondary OA is large and includes all chronic inflammatory joint diseases, bone diseases, the effects of trauma, orthopaedic pathology, a range of metabolic diseases. In this case, joints cartilage changes occur not only under the influence of mechanical factors (trauma, orthopae-

dic abnormalities, physical overload to the joint), but also resulting from exposure to endogenous causes (inflammatory joint diseases, certain metabolic conditions, such as homogentisuria, hypothyroidism, hemochromatosis etc.) in which degenerative changes occur in the cartilage altered by the underlying disease (Беленький А.Г., 2006).

OA is regarded as one of the most common joint diseases affecting at least 20% of the world population. According to the U. S. and European rheumatologists, the share of the disease is accounted for 69–70% of all rheumatic diseases. OA is registered in all the countries, climatic and geographical zones and affects all race and ethnic groups. According to S. Perrot and C.J. Menkes (1996), OA radiographic manifestations affect 50% of the European population aged over 65 years and clinical signs are relevant to — 12.5%, among the patients older than 80 years OA is mostly diagnosed. It is predicted that by 2020, OA prevalence will potentially reach 57% in population. In addition, OA development is associated with lung and cardiovascular pathology increased incidence and reduces life expectancy in women for approximately 10–12 years. The OA prevalence increases with age and apparent sex differences are characteristic. Females suffer from OA almost two times more commonly compared with males. Females frequently experience knee joints affection (gonarthrosis). Hip joint affection (coxarthrosis) is more frequent among males. Whereas OA is the most common cause of hip and knee joints endoprosthesis. In Europe, every 1.5 minute one affected joint is replaced, approximately 500.000 endoprosthesis operations are performed in the United States annually (Насонова В.А., Насонов Е.Л., 2003; Поворознюк В.В., 2006). However, true prevalence of OA is difficult to assess, as patients admit to the doctor with clinical symptoms of arthropathy, such as pain, stiffness, limitation of movement. Typically, OA radiographic signs have been revealed in patients: namely, irregular narrowing of the joint space, subcartilaginous sclerosis, head bones blooming, isolated or multiple osteophytes. Early stage of OA including collagen framework swelling, increased synthesis of proteoglycans and matrix proteases is usually clinically asymptomatic.

Aetiology of OA remains unknown though the risk factors of the disease development are distinguished. Among genetic features much attention is paid to the defects of type II collagen gene resulting in progressive cartilage degeneration; congenital diseases of bones and joints; and to consider female gender.

Elderly age, excessive body mass, estrogens deficiency in postmenopausal women, acquired diseases of bones and joints, operative interventions on the joints are related to characteristic acquired risk factors. Thus, obesity increases loading on the lower extremities joints. The risk of OA occurrence increases in patients with inborn musculoskeletal system defects by 7.7 times, for individuals with excessive body weight — is twofold higher (Цурко В.В., 2005). According to the data of investigations acquired in twins (middle-aged females), 1 kg body mass gaining is related to increased risk of gonarthrosis development by 9–13% (Cicuttini F. et al., 1996).

OA has been considered as the outcome of an inevitable articular cartilage aging for years. However, it has recently become clear that structural changes process in aging cartilage and in clinical case of OA differ. Proteoglycans aggregation is decreased in aging cartilage, water consumption becomes lower too; the number of protein and hyaluronate chains split by proteolytic enzymes is increased (Wachtel E. et al., 1995). A pathological process in OA differs from these changes, moreover, a number of biochemical processes differs in early and advanced stages of OA. In addition, the range of biochemical processes is determined both in cartilage natural aging, and in development of OA. In this regard, during the study in elderly patients it is prospective to assess the markers for cartilaginous tissue dystrophy in blood and urine, even in the absence of OA clinical manifestations, that may be the occasion to initiate early treatment during primary stages of balance deterioration between the degradation and synthesis processes in a cartilaginous tissue.

Complexity of OA pathogenesis is defined by the particular structure of cartilaginous tissue, where the main function is to adapt the joint to the mechanical loading and accommodate motions. The key role in equilibrium support between anabolic and catastatic processes belongs to chondrocytes — the elements of cartilage. OA pathogenesis is based on the violation of this balance. This pathological process involves all tissues in the joint, including the synovial membrane, arthral capsule, intra-articular copulas, peri-arthral muscles. Loss of proteoglycan integral parts — glycosaminoglycans from the surfaces of cartilage intermediate and deep zones occurs in case of OA. It results in surplus hydratation and splitting of matrix, followed by its dehydration and collagen fibres rupture. Therefore, the principal function of cartilaginous tissue that provides adjusting of degradation and synthesis processes within cartilage matrix components and joint depreciation function is violated (Цурко В.В., 2005).

The damaged chondrocytes excrete stress catabolic enzymes, that destroy collagen (elastase, collagenase, peptidase, etc.) and proteoglycans (metalloproteinase, stromelizyn, cathepsin, interleukins (IL-1, IL-6), tumor necrosis factor (TNF)-α, etc.). Increased production of cytokines contributing to synovial cells proliferation, on the one hand, and collagen and proteoglycans synthesis inhibition with the help of chondrocytes on the other hand, are significant (Цурко В.В., 2005). Chondrocytes cyclooxygenase (COX) — 2 enzyme hyperproduction that induces the synthesis of prostaglandins involved in the development of inflammation occurs in OA. Inflammation has a substantial role in development of OA, with relevance to an evidence of synovial membrane hyperplasia and mononuclear infiltration, not different from those in rheumatoid arthritis; oncoproteins and transcription factor NF-kB increased expression regulating the synthesis of pro-inflammatory mediators; certain connection between the stable increase of CRP levels and progress of OA (Насонов Е.Л., 2001).

Thus, a crucial significance in OA development is related to the insufficient synthesis of proteoglycans by

the chondrocytes, and to quantitative and qualitative violation of proteoglycan aggregates formation. Clinical studies confirm that there is an increase of bone tissue resorption and remodelling rate in OA. Numerous studies of OA on the animal models and samples of subchondral bone and articular cartilage of patients, who undergone endoprosthesis, confirm that the greatest degree of cartilage degradation is observed if intensity and depth of changes in the architectonics of a bone are more pronounced (Bobinac D., 2003).

The diagnosis of OA is made based on the constellation of the clinical and roentgenology data obtained. The principal clinical symptoms of OA are pain, joints defiguration due to exudative component, joints deformation resulting in functional failure. OA symptoms also include such signs as bone excrescences, violations of arthral surfaces congruence, development of subluxations. If the onset pain occurs only intermittently, after considerable physical activity, and fast disappears at rest, whereas with OA progress pain intensity increases, it does not disappear after rest, and may appear at night. The pain is often associated with a morning constraint and is the symptom of inflammation and synovitis. However, the mechanism of OA pain is not fully defined. As an arthral cartilage is not innervated and, therefore, it is not sensitive to pain, its occurrence is associated with the development of pathological changes in the uncartilaginous structures of the joint. Principal causes of pain are probably the trabecular microfractures, bone venous stasis and intra-medullary HT, presence of chronic synovitis, increased pressure on the subchondral bone, periarticular muscle spasm and degenerative changes of intra-articular copulas, damage of surrounding tissues by osteophytes, also psycho-emotional and other factors (Насонова В.А., Насонов Е.Л., 2003; Плаксина Т.В., 2005).

Except for arthralgia symptoms, affected joint crepitus as a result of violations of arthral surfaces congruence, motions limitations in the joint is demonstrable in OA (Насонова В.А., Насонов Е.Л., 2003). With the progression of the disease due to the presence of pain and the muscular spasmodic reflex emergence, limitation of motions in the staggered joint up to the formation of tendon-muscular contractions is possible (Плаксина Т.В., 2005).

Radiological symptoms of OA are divided into obligatory and optional (Смирнов А.В., 2001). Joint space narrowing, the presence of osteophytes and subchondral sclerosis are related to the obligatory symptoms. Narrowing of joint space has a direct correlative connection with pathological changes that take place in a cartilage. Osteophytes — are bony excrescences on the edges of arthral surfaces of bones with different shape and sizes. As OA progresses, osteophytes are enlarged, become more massive. Measurement of osteophytes and their sizes is a sensitive indicator of disease progression. Subchondral osteosclerosis is the bone thickening concentrated directly under the articular cartilage, it is detected in advanced stages of OA, when synovium is narrowed and naked articulated surfaces friction takes place, indicating a profound degenerative process in an integumentary cartilage or its disappearance.

A metabolic syndrome (MS) is a relatively new term that includes the complex of hormonal and metabolic violations, based on insulin resistance (IR) and is a serious medical and social problem of our time. MS is called the «syndrome of the modern world» (Цыганова Е.В., 2000) due to the prevalence of the latter in the adult population. First, in 1988 G.M. Reaven set forth a concept about MS, calling it the «syndrome of X», and suggested that hyperinsulinemia (HI), HT, glucose intolerance, increased concentration of triglycerides in blood and declined level of high density lipoprotein cholesterol may be a manifestation of insulin-mediated glucose uptake violation by peripheral tissues — IR (Reaven G.V., 1988). Later, the term MS has undergone some transformation expanding its practical significance. So in 1989 abdominal obesity was distinguished as a major etiologic factor of IR forming and also a term «deadly quartet» appeared which combines obesity, especially in the upper half of a trunk, glucose intolerance, hypertriglyceridemia and arterial hypertension (AH), thereby indicating the increased mortality from cardiovascular diseases in the specified combination. Later the MS concept was supplemented and specified. So, many authors began to include hyperuricemia in the MS concept taking into account experimental researches that showed direct diabetes risk factors, hypertensive and caffeine-like effects of urinary acid (Аршавский В.В. и соавт., 1978). There are some ideas about the relationship between the level of urinary acid and the morbidity of CHD, HT, index of left ventricular mass increasing. To the term MS also were added: microalbuminuria, hyperandrogenemia in women, myocardial hypertrophy, activation of the sympathetic nervous system, increased concentration of fibrinogen in blood (Juhan-Vague I. et al., 1993). In recent years the MS concept is also suggested to complement with a sleep apnea syndrome, endothelial dysfunction, and insufficient decrease of blood pressure at night. It is also found that MS is quite often accompanied by a polycystic ovary syndrome, hepatosteatosis, erectile dysfunction (De Aquiar L.G. et al., 2006).

Almost all components of MS are independent risk factors of cardiovascular complications development, and a combination of several components significantly increases the risk of their development. Patients with MS have an increased risk of developing DM, cardiovascular diseases, stroke, general and cardiovascular mortality. According to the West of Scotland clinical trial research the risk of CHD in men with 4 or 5 components of MS increases in 3.7 times and the risk of DM type 2 — in 24.5 times. Thus, the prevalence of basic MS components among adult population of the economically developed countries is large: insulin dependent diabetes — 6.8%, HT — 17–22%, IHD — 25%, obesity — 30% (De Fronzo R.A., Ferrannini E., 1991). According G.V. Reaven (1988) 25% of middle-aged people have IR and, as consequence, MS. According to researches the prevalence of MS is 15–20%. According to epidemiological studies in Finland and Sweden MS without carbohydrate metabolism disor-

ders has been detected in 10% of women and 15% of men, during increased glycemia on an empty stomach and/or during impaired glucose tolerance in 42% and 64%, and during DM — in 78% and 84% respectively. In Russia, among the population of adults aged 25–64 years, 2 and more components of MS were found in 40%, with the predominance of MS prevalence among women (De Fronzo R.A., Ferrannini E., 1991).

The leading role in the MS pathogenesis is given to IR and the consequent compensatory HI (Reaven G.V., 1988; De Fronzo R.A., Ferrannini E., 1991). IR is a decrease of insulin-dependent glucose utilization by peripheral tissues, first of all by muscles and liver. Development of IR is contributed both by genetic factors (insulin receptor defect or post-receptor defect) and by external factors. The external factors that increase IR are formation of obesity especially androgenic, lowering of blood volume in the capillaries of skeletal musculature as a result of vasoconstriction, that develop as a result of hypodynamia, hyperhighcalorie feed, increased activity of the sympathetic nervous system — all that are combined in literature as a concept of «Western lifestyle». However due to HI — a compensatory increase of insulin secretion β-cells of the pancreas — the normal level of glycaemia can be maintained for long time. Thus, HI from the one hand is compensated, that is necessary to overcome the IR and to maintain the normal glucose transport into cells. Compensated HI causes weight gain due to the decline of glycaemia and increases appetite, which in turn, strengthens IR of adipose tissue. Thus, a «vicious circle» develops as an «ascending spiral», when every new higher level of compensated HI causes even greater increase of IR, that results in the insulin secretion (Недосугова Л.В., 2005).

A substantial role in the formation and development of hyperglycemia is given to resistance of adipose tissue to insulin. Many studies observed that in obesity development and progression of IR and its manifestations can be the reflection of lipotoxic effects of free fatty acids and disbalance of adipokines. Furthermore it is known that the sensitiveness of tissues to insulin is reduced by more than 40% in excess of ideal weight by 35–40%. Thus, in obesity there is the «Vicious circle» of hormonal and metabolic violations that contribute to the maintenance and progression of obesity. Nowadays adipose tissue is considered as an independent secretory organ that participates in regulation of metabolism (Савельева Л.В., 2007).

AH is one of the most frequent manifestations of MS and in most cases is connected with the various components of MS. Untreated for a long time or badly treated AH causes deterioration of peripheral circulation, that results in the decline of tissue sensitiveness to insulin and, eventually, in the relative HI and IR, and IR causes already known effects from the endothelium, metabolic disorders. But a significant impact on the development of cardiovascular diseases in MS has obesity. The most significant manifestation of obesity is is the left ventricle hypertrophy (LVH). The probability of LVH development in patients with normal body weight is 5.5%, and in patients with obesity 29.9% (Gottdiener J.S. et al., 1994). Even a small increase of arteriotony in patients with obesity causes pronounced LVH. High blood pressure increases post-load on LV that results in the thickness increase of its walls and the formation of LVH.

Of particular interest is the relationship of OA and MS. Thus, the connection proofs of OA with metabolic violations are obtained. IR, the key link of MS, assisting the increase production of glycosylated connections, causes an increase formation of oxygen radicals that trigger endothelial disfunction. The increase of acid radical formation by neutrophils is also found in patients with OA, complicated by synovitis of the knee joint (Kurygin A.G., Kratnov A.E., 2001). It is known that the damages caused by free radicals have a substantial contribution to development of both atherosclerosis and joint diseases. The close correlation is found between the content of TG and the ability of phagocytes to synthesize TNF-α, which local products in inflammation provides neutrophil chemotaxis, strengthening of phagocytosis, their degranulation, products and secretion of their reactive oxygen forms. The important role of IR in the development of OA is provided by the high level of triglycerides in patients with the complete loss of cartilage according the arthroscopy data and its correlation with the CEC. A.E. Kratanov with a coauthor (Кратнов А.Е. и соавт., 2006) supposed that IR can be a crucial pathogenetic link not only in DM type 2 and HTN but also in OA. The relationship has been detected between dyslipidemia and oxidative stress with erosive changes in cartilage, MS associations with more severe lesions of articular cartilage, according to arthroscopy in patients, with OA complicated by secondary synovitis (Кратнов А.Е. и соавт., 2006).

Early diagnostics of MS has a great practical value, as it helps to reveal patients with an increased risk of cardiovascular disease and DM type 2. This was the prerequisite for the creation of standardized MS criteria that could be used in a wide clinical practice. First MS criteria were formulated by a working group of the WHO (Alberti K.G., Zimmer P.Z., 1998). However, some drawbacks of the criteria for MS proposed by WHO soon became apparent. It was found that frequency of microalbuminuria in the patients with MS is not too large, but in patients with HTN the degree of IR does not correlate with microalbuminuria. Therefore the conclusion was made that using of WHO criteria it is possible to underestimate the MS prevalence in the populations and not to identify patients in the early stage of the disease. All of these triggered the further review of MS criteria. The expert committee of the National Cholesterol Education Program (NCEP ATPIII, 2001) set forth the MS criteria if three and more of the established ongoing features (The report of the National Cholesterol Education program, 2001):

1. Abdominal obesity — waist circumference (WC) >102 cm for men; from >88 cm for women.
2. Level of triglycerides ⩾1,7 mmol/l (⩾150 mg/dl).
3. LDL-HDL <1 mmol/l (<40 mg/dL) for men, <1.3 mmol/l (<50 mg/dL) for women.
4. HT (BP ⩾130/85 mm Hg).
5. Indicators fasting glucose ⩾6,1 mmol/l (⩾110 mg/dl).

OA AND OBESITY METABOLIC DISORDERS

Obesity is one of the most serious risk factors for development and progression of OA (Malnick S.D., Knobler H., 2006; Zhang Y., Jordan J.M., 2010). This initially refers to the primary knee-joint OA, which reveals a clear connection between the level of BMI and the risk of OA. Numerous studies (Framingham, Chingford, Baltimore) (Spector T.D. et al.,1994; Hochberg M.C. et al.,1995; Felson D.T. et al.,1997) and studies done in other countries (Gelber A.C. et al.,1999; Manek Nisha J. et al., 2003) have demonstrated the correlation between the obe-sity (BMI >30) and the presence of radiographic signs of knee-joint OA. According to the information from Medical Research Council's Epidemiology Resource Centre Southampton University (England), the risk of knee OA progressively increases along with BMI, correspondently (Osteoarthritis And Obesity. A report by the Arthritis Research Campaign). This conclusion has been based on analyzing BMI impact on knee OA severity of 525 men and women aged from 45 years old: people with a BMI> 30 kg/m^2 were at risk of knee OA progression; the probability was proved to be 4 times higher than for those with a BMI 25 kg/m^2. People with a high level of obesity (BMI ⩾36 kg/m^2) were 14 times more likely to suffer from knee OA than people with normal BMI. In addition, obesity was associated with both symptomatic OA and OA without clinical manifestations, but with radiographic changes. Dual controlled study by F. Cicuttini (1996) showed that the weight gain per kilogram increases the risk of knee OA radiographic signs.

Adipose tissue is not a passive energy storage, it is the active metabolic and endocrine organ that produces hormones and biologically active substances, and plays a key role in the obesity progression, MS, diabetes type 2, and other diseases. Adipose tissue is proved to produce a large number adipokine or adipocytokine — peptide hormones. Adipokine has a variety of biological effects. Moreover, it influences the severity of processes in many organs either directly or through neuroendocrine mechanisms, that is, interacting with pituitary hormones: insulin and catecholamine. They also act in the relationship with obesity and related diseases. Adipokine, produced by fat cells (adipocytes) and stroma vascular fraction of white adipose tissue cells can be divided into 3 types: the first type is cytokines: TNF-α, interleukins (IL-1, IL-6, IL-8, IL-10), transforming growth factor (TGF), interferon (IFN), leptin, adiponectin, resistin, angiotensinogen; the second type includes the factors of the complement system: an plasminogen activation inhibitor-1 (PAI-1), fibrinogen, angiopoietin protein, complement factor — 3 3rd type — chemoattractant (chemotactic molecules): monocytic chemoattractant protein-1 (MCP-1), macrophage inflammatory protein (MIP-α1) (Matt C. Cave et al., 2008). The fact that adipose tissue produces and cumulates a number of antiphlogistic cytokines, gives reason to regard obesity as a slight inflammatory condition (Das U.N., 2001). It also combines obesity with OA, which is also regarded as slight inflammatory status: both of these diseases are determined by high levels of biomarkers of inflammation-IL-6, TNF-α, TNF-α receptors sTNFR1 and sTNFR2, C-reactive protein (CRP) (Miller G.D. et al., 2008).

Adipokine, such as leptin and adiponectin, should be taken into consideration, as they affect cartilage, bone tissue and vascular wall. Adiponectin is a decisive mediator of IR concerning obesity and tissue inflammation (Matt C. Cave et al., 2008). The effect of adiponectin is aimed at reducing inflammation and increasing tissue sensitivity to insulin. Obese people's content of adiponectin is markedly reduced in comparison with normal body weight ones' (Guerre-Millo M., 2002). Adiponectin reduces the response of macrophages to TLR4 activation by ADIPOR1 (Yamaguchi N. et al., 2005). Thus, adiponectin suppresses TLR4-induced activation NFαB and inhibits secretion of interferon-α, produced by LPS (Wolf A.M. et al., 2004). By inhibiting the expression of adhesion molecules, adiponectin reduces adhesion of macrophages, phagocytic ability and transmigration.

Leptin is a peptide cytokine line. The structure is similar to proinflammatory cytokines such as IL-6 and IL-12. Being produced by white adipose tissue, leptin circulates through blood in two forms: free and bound to a specific protein. The level of leptin in serum is proportional to total fat mass. Leptin regulates neuroendocrine function, energy homeostasis, hematopoiesis and angiogenesis. Leptin modulates food intake and energy balance due to appetite control. The effect of leptin is based on its receptor (LR) innervating. Leptin + LR binding activates factor JAK, affecting a number of hypothalamic neuropeptides manifestation: neuropeptide U, regulating hypothalamic-pituitary-gonadal axis, thyroid-stimulating hormone, and corticotropin functions. Leptin inhibitory effects on neuropeptides U release leads both to loss of appetite, increased sympathetic nervous system activity and energy expenditure, and metabolic, peripheral tissues and organs changes (Mantzoros C., 1999). In addition, leptin plays a significant role in the inflammatory response. Leptin may increase proinflammatory cytokines outlet due to macrophages (TNF-α, IL-6 and IL-12) (Matt C. Cave et al., 2008).

According to T. Saito et al. (2010), the leading role is that of hypoxia inducing factor (HIF-2α) in OA pathogenesis, which accumulates as a result of various stresses, inflammation, biomechanical disorder and leads to chondrocytes hypertrophy. A high level of HIF-2α increases proteases that cause the degradation of cartilage respectively, meanwhile HIF-2α deficiency protects cartilage from osteophytes degradation and formation.

OA being at an early stage, chondrocytes hypertrophy is a key progression factor.

Hypertrophy of chondrocytes is connected with mitogen-activated protein kinase, modulated by chromoendoscopy ½ and p38 (Richette P., Funk-Brentano T., 2010).

As a result of osteoblast subchondral bone mechanical compression, IL-6 release increases and osteoprotegerin outlet reduces respectively.

The ratio of osteoprotegerin/RANKL (Receptor Activator of Nuclear Factor Kappa B Ligand (NF)-κβ) leads both to bone and cartilage lesion.

Intraperitoneal and intraarthrous osteoprotegerin injections prevent cartilage from degrading (Richette P., Funk-Brentano T., 2010).

Kwan Tat et al. (2009) showed that chondrocytes also express osteoprotegerin, RANK, RANKL. Researchers found that osteoproteheryn/RANKL ratio reducing drastically accelerates OA progressing.

The recent studies have indicated that there are common and mutually bound interaction mechanisms between the bone and the cartilage.

The violation of WNT/beta-catenin path contributes to the subchondral bone destruction and leads to t bone tissue restoration (Richette P., Funk-Brentano T., 2010).

The recent studies of the British, Chinese and Japanese scientists have confirmed OA genetic aspects: namely, gene growth factor and differentiation (GDF)-5 is directly connected with the risk of OA hand and knee joint developing, with the risk of fractures in elderly women and with low height (Valdes A.M. et al., 2009).

In recent years, the leading role in OA pathogenesis of superoxide oxygen radicals, inducible NO synthase (iNOS), NF-κβ has been highlighted.

Except superoxide oxygen radicals in the pathogenesis of OA a significant role is played by inducible NO synthase.

At present three isoforms of NO synthase are known:

- Neuronal NO synthase (nNOS), which performs metabolic processes in the nervous tissue;
- Endothelial NO synthase (eNOS), which plays a basic role in vasodilation;
- Inducible NO synthase (iNOS), which plays a significant role in phagocytosis implementation and in inflammation.

In recent years, the role of nitric oxide (NO) in the pathogenesis of OA has been established (Lotz M., 1999), namely:

iNOS through NO can result directly in pathological changes in joints.

In chondrocytes iNOS is induced by cytokines, especially IL-1β and TNF-α, stimulating their own products, which leads to progressive destruction of articular cartilage.

Excessive NO production in the joint inhibits matrix synthesis and causes its destruction.

NO causes cell damage due to the formation of peroxynitrite ($ONOO^-$), and also due to apoptosis of chondrocytes.

Application of NOS inhibitors in experimental arthritis caused synovia inflammation reduction, cartilage and bone destruction.

Taking into account the substantial role of non-steroidal anti-inflammatory drugs (NSAIDs) in patients treatment of OA, that is elimination of pain and inflammation, particularly essential is NSAIDs choice taking into account their safety and influence on the cartilaginous tissue.

Taking into consideration non-COX-dependent mechanisms of nimesulide, namely blocking of superoxide oxygen radicals, iNO synthase activity and, consequently, the formation of NO and $ONOO^-$, inhibition of IL-6, which are key mediators in the cartilage destruction, inflammation development and also abolition of chondrocytes apoptosis, blocking collagenase and stromelysin that results in type II collagen reduction and proteoglycans, ie nimesulide chondroprotective action can be considered the choice drug for OA.

As OA is diagnosed more often in the elderly with concomitant cardiovascular disorders, then such nimesulide properties as activation synthesis inhibitor of tissue plasminogen activator, blocking platelet-activating synthesis factor are extremely important in preventing thromboembolic complications (Rainsford K.D., 2006).

The third significant factor in OA — NF-kB — one of the principal inflammation process regulators in various tissues in case of different pathologies. It controls the expression of the genes of inflammation, immune response and apoptosis. NF-kB is concentrated in the cytoplasm in a dormant form, but under the effect of IL-1β, TNF-α activation of the superoxide radicals and NF-kB translocation into the nucleus occur. NF-kB changes the translocation of over 150 genes, and this results in inflammation, apoptosis and autoimmune diseases (Du Souich P. et al., 2009).

In the recent research (Dumond H. et al., 2003) it has been established, that adipokins can accompany the changes associated with OA and, furthermore, may be potentially involved into the local regulation of metabolism in the arthroidal cartilage. Leptin, resistin and adiponectin are detected in the synovial fluid of the patients with OA. Leptin is found out both inside of osteophytes and in cartilage tissue of the patients with OA with increase of its expression in the area of matrix emaciation, fibrillation and chondrocytes aggregation. Leptin level in the articular tissues correlates with BMI. Leptin expression and production are elevated in the subchondral osteoblasts in the episode of compared with the normal. Leptin induces the growth factors expression, stimulates the synthesis of proteoglycans and collagen, increases the proinflammatory cytokines stimulating effect on nitrogen nitrite production in chondrocytes. D. Mainard and coauthors (Mainard D. et al., 2008) experimentally demonstrated the principal leptin role in OA pathogenesis through effects on the synthesis of insulin-like growth factor (IGF_1) and TGF-β_1. Presence of leptin, IGF_1 and TGF-β_1 in cartilage tissue (osteophyte) has been immunologically established in case of OA (Lajeunesse D., 2004). The patients with OA demonstrated a high level of leptin in synovial fluid and subchondral bone. Normally leptin is not detected in cartilage tissue. As established IGF_1 and TGF-β_1 are produced by the chondrocytes in OA. Expression of of TGF-β_1 is strongly associated with osteophytes. TGF-β_1 induces fibrotic changes on the synovial membrane, bone sclerosis, stem cells differentiation within the periosteal layer with osteophytes formation (Chevalier X., Tyler J.A., 1996). The study experimentally confirmed that leptin injections into the joint of healthy rats tend to mimic the signs of OA. G. Miller and coauthors (Miller G.D. et al., 2008) studied the relationship between the serum leptin content, obesity and progress of the knee joint OA (patients aged over

60 years with a BMI of 28.0 kg/m^2 or more have been included into this study). The results obtained allowed the authors to conclude that serum leptin reduction may be one of the mechanisms by which weight loss slows down the progress of OA.

Thus, at present OA can be viewed as a systemic disease where lipid homeostasis deregulation may be one of the principal pathophysiological mechanisms resulting in OA development (Aspden R. et al., 2001). Vicious cycle connects obesity and OA in the patients: obesity is a risk factor for OA development and many other diseases associated with metabolic disorders whereas OA is usually accompanied by dysfunctions and disability, consequently leading to BMI increase and resulting in DM and cardiovascular diseases development. According to some data available, OA is most commonly associated with HT and other cardiovascular diseases (atherosclerosis, CHD) (Kadam U.T. et al., 2004; Hochberg M.C., 2008; Gabriel Sh.E., Michaud K., 2009; Денисов Л.Н. соавт., 2010; Мендель О.И. и соавт., 2010). Cardiovascular disease is observed in more than 50% of patients with OA. In the research conducted by L.N. Denisov and V.A. Nasonova in 2010, 298 patients with OA of the knee and hip joints were included. Relationship between obesity and incidence of other diseases, lipid metabolism disorders and progress of OA with various localization was studied. With increase of BMI clear increase in prevalence of cardiovascular disease and DM has been detected. Among the patients group with obesity (BMI >30–35 kg/m^2) OA of the II-III stage prevailed (97%); OA of the III–IV stage has been diagnosed in 80% of patients in the group with a BMI >40 kg/m^2 (Денисов Л.Н. и соавт., 2010).

Thus, modern scientific data allow considering OA as a disease pathogenetically related to obesity, cardiovascular diseases and other metabolic states which suggest a complex approach to selection of treatment methods.

PRINCIPLES OF TREATMENT FOR PATIENTS WITH OA WITH INCREASED BODY WEIGHT AND COMORBID INDIVIDUALS

Medical literature describes more than 50 methods of non-pharmacological, pharmacological and surgery treatment for OA in peripheral joints, mainly the knee and hip joints. Common schemes for OA treatment are based on the recommendations developed by the leading scientific organizations engaged in study of all aspects of OA, including its therapy in terms of evidence-based medicine. OA patient treatment of is performed according to international guidelines established by OARSI (Osteoarthritis Research Society International) and EULAR (European League Against Rheumatism). According to the guidelines, OA treatment must be conducted based on risk factors: common risk factors — age, comorbidity (obesity, cardiovascular disease, etc.), pain intensity and functional impairment parameters, the presence or absence of inflammation signs, localization and expression of structural changes. Optimal therapy for OA should include a combination of non-pharmacological and pharmacological methods of treatment.

Non-pharmacological methods for OA treatment include regular nursing and education for the patients, regular medical physical exercises and aerobics, use of special orthopaedic devices, dietary recommendations. The positive impact of medical physical exercise therapy to reduce pain in the joints in OA was established in a range of studies. Medical physical training complex should be individually selected according to available patient's diseases and severity degree of diseases. From the standpoint of joints mechanical unload and cardiovascular pathology prevention patients must be oriented at normal body weight maintaining.

Medical physical exercises to decrease overall body mass is a priority goal for the OA patient with obesity both in terms of mechanical physical exercises and in terms of cardiovascular diseases prevention. Body mass reduction is recommended if BMI >25 kg/m^2. Appropriate body mass correction will reduce the pain syndrome intensity in the affected joints, will contribute to slow down the progression of OA significantly reducing the potential risks of cardiovascular complications. Systematic review of literature devoted to the study of the obese individuals with diagnosed knee joints OA, allowed to make a conclusion that OA induced disability can be significantly diminished after body mass decrease by 5.1% (Christensen R. et al., 2007). The study by D. Felson and coauthors (Felson D.T. et al., 1992) which included 800 women, demonstrated that BMI decrease of 2 kg/m^2 for 10 years reduced the risk of developing OA by more than 50%. The most effective is a combination of diet with physical exercises. G. Miller and coauthors (Christensen R. et al., 2007) investigated the relationship between serum leptin levels, obesity and overall disease progress in the patients with knee OA. The study included the patients with symptoms of knee OA aged over 60 years, BMI 28.0 kg/m^2 or more. Total duration of study made up 18 months. All patients with OA were randomized into 4 groups depending on the method of body mass reducing: a control group — those leading a healthy way of life, a diet group, a physical exercise group and a group combining physical exercise with diet. The greatest weight loss was achieved in groups «diet» and «diet + physical exercise» — by 5.3 and 6.1%, respectively, «physical exercise» group reduced body mass to a lesser extent — 2.9%. Decrease in serum leptin after 6 and 18 months were reliable in the groups «diet» and «diet + physical exercise» compared with the other two groups (β=0,245; $p<0,01$). The results achieved indicate that serum leptin levels reduction may be one of the mechanisms by which weight loss may slow down the progression of OA. OA patients are recommended a diet including fish products (at least 2 times a week), which contain omega-3 poly-unsaturated fatty acids (omega-3 PUFAs). Omega-3 poly-unsaturated fatty acids are not produced in the human body, but are vitally demanded by the organism: they can inhibit inflammatory reactions in human body, stabilizing fat metabolism, positively affecting the vascular walls and blood rheology properties (MacLean C.H. et al., 2004). In order to fully compensate omega-3 PUFA deficit and to contribute to physiological correction of lipid metabolism omega-3 PUFAs medical preparations are recommended.

The main objectives for pharmacological treatment of OA are effective pain relief, reduction of joint inflammation, improving joint functional capacity and inhibition of disease progress. Pain relief in OA is possible by several groups of drugs which differ in mechanism of action, rate of analgesic effect onset and strength; safety profile and medical drug tolerability. The fact that patients with OA tend to simultaneously have several systemic diseases, especially cardiovascular disease was taken into consideration, this necessitates a strict assessment for anticipated benefits and possible risks of anti-arthrosis therapy prescribed. Amid the comorbidity, excessive and irrational prescription of medicines without consideration of their interaction properties leads to a sharp increase in probability of adverse therapeutic effects and complications of the disease course.

Within the International guidelines for OA treatment (EULAR, 2003; OARSI, 2008) non-steroidal anti-inflammatory drugs (NSAIDs) are listed as drugs of choice for pain relief in OA patients. NSAIDs, both non-selective and selective, have a pronounced anti-inflammatory and analgesic properties, but in patients with OA and metabolic disease or high risk of developing (obesity, HT, CHD, etc.) they can induce a range of side effects which aggravate the cardiovascular disease course (Насонов Е.Л., Каратеев А.Е., 2003; Antman E.M. et al., 2007). NSAIDs administration may cause destabilization of AH and progress of HF. It has been determined that NSAIDs administration by the patients with heart disease history 10 times increases likelihood of hospitalization with HF (OR=10,5) compared with patients not taking NSAIDs (OR=1,6) (Page J., Henry D., 2000). Also one should note that NSAIDs can reduce the effectiveness of drugs used in standard CVD therapy (β-blockers, diuretics, ACE inhibitors, and to a lesser extent — calcium channel antagonists).

Nowadays symptomatic drugs with possible structure-modifying effect (SYSODOA) take more important place in treatment of OA. They, alike NSAIDs, are included into EULAR (Jordan K.M. et al., 2003; Jordan K.M. et al., 2005) and OARSI (Zhang W. et al., 2008) recommendations for treatment of OA. These include glucosamine (GA) and chondroitin sulfate (CS), hyaluronic acid preparations for intra-articular injections. The mechanism of therapeutic action of chondroitin sulfate (CS) and glucosamine (GA) in OA is associated with their ability to inhibit the catabolic (degenerative) and activate anabolic (renewable) processes in cartilage, provide anti-inflammatory and anaesthetic effect (Насонова В.А., Насонов Е.Л., 2003). Thus, chondroitin sulfate depending on the dose inhibits IL-1 stimulated prostaglandin synthesis by synovial fibroblasts, repealing hyaluronic acid synthesis inhibition associated with IL-1; decreases the synthesis of collagenase dependent on IL-1, that is an evidence of possibility of reducing collagenolytic activity and increasing the matrix components production. In addition, chondroitin sulfate (CS) inhibits NO-induced apoptosis of chondrocytes, improves subchondral bone microcirculation by inhibiting lipids synthesis, mobilization of fibrin, lipids and cholesterol in the subchondral bone blood vessels. Glucosamine (GA) has properties to inhibit gene expression and cyclooxygenase-2 (COX-2) proteins synthesis, selectively through COX-1, therefore, preventing the release of prostaglandin PGE2. Effect of NFκB is inhibited by GA at the level of both chondrocytes and synoviocytes, thus, the parallel reduction of protein synthesis of COX-2, release of prostaglandin E2, NO release in chondrocytes are provided. In addition, GA sequentially decreases synthesis of matrix proteinases caused by IL-1 in both types of cells (Alvarez-Soria M.A. et al., 2005). It has been established that CS and GA do not take quite identical pharmacological action, they complement and reinforce the effects of each other, which determines the prospects of their combined use in treatment of OA. Recent double-blind, placebo-controlled trial «Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT)» in assessing the impact of different treatment regimens for pain (WOMAC) after 6 months of therapy, determined that OA patients with severe pain in the knee joints (WOMAC 301–400 mm) the effectiveness of CS and GA combined therapy was significantly higher (79.2%, p=0,002 *vs* placebo) than in the case of separate administration of CS or GA (Clegg D. et al., 2006).

With consideration of data suggested, conclusion is that the therapy for clinical manifestations of OA in patients with obesity and other metabolic diseases (HT, CHD, etc. or their high risk) must be carefully considered by the doctor. In establishing the scheme of treatment significant attention should be paid to non-medical therapeutic methods — physical exercises, diet aimed at reducing BMI, organization of work and leisure regimens. The whole course of treatment requires strict control of blood pressure, ECG. With regard to drug therapy, in patients with OA who are at high risk of cardiovascular complications NSAIDs administration should be suggested with greater caution, following the accepted guidelines. With account of the confirmed clinical efficacy, higher safety and tolerance of CS and GA medical drugs, they can be considered as the most preferable medicines for treatment of OA clinical manifestations in patients with comorbid diseases.

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ОСТЕОАРТРОЗ И МЕТАБОЛИЧЕСКИЙ СИНДРОМ: СОВРЕМЕННЫЙ ВЗГЛЯД НА ПРОБЛЕМУ

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Резюме. *Остеоартроз — наиболее распространенное ревматическое заболевание, приводящее к длительной нетрудоспособности и инвалидизации. При этом многочисленные исследования в отношении патогенетических изменений при заболевании позволяют по-новому взглянуть на факторы риска и принципы развития болезни. Проблема метаболического синдрома в последнее десятилетие привлекает пристальное внимает врачей и ученых всего мира в связи с тесной взаимосвязью данной патологии с сердечно-сосудистыми заболеваниями. В свою очередь, патогенетические взаимосвязи между остеоартрозом и метаболическим синдромом открывают новые горизонты в ранней диагностике и профилактике данных нозологий.*

Ключевые слова: остеоартроз, метаболический синдром.

ОСТЕОАРТРОЗ І МЕТАБОЛІЧНИЙ СИНДРОМ: СУЧАСНИЙ ПОГЛЯД НА ПРОБЛЕМУ

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Резюме. *Остеоартроз — найбільш поширене ревматологічне захворювання, що призводить до тривалої непрацездатності та інвалідизації. При цьому численні дослідження щодо патогенетичних змін при захворюванні дозволяють по-новому поглянути на фактори ризику і принципи розвитку захворювання. Проблема метаболічного синдрому останнім часом привертає пильну увагу лікарів і вчених усього світу в зв'язку з тісним взаємозв'язком цієї патології з серцево-судинними захворюваннями. У свою чергу, патогенетичні взаємозв'язки між остеоартрозом та метаболічним синдромом відкривають нові горизонти в ранній діагностиці та профілактиці цих нозологій.*

Ключові слова: остеоартроз, метаболічний синдром.

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