s. 131-15

Eugen PRYSTUPA, Ludmila PRYSTUPA,
Olexandr OPIMAKH, Vladyslava DYTKO
Lviv State University of Physical Education, Ukraine

The association of osteoarthritis and ohesity

Związek osteoartrozy z otyłością

Abstract

The review of literature about obesity and osteoarthritis association were represent.It is known that osteoarthritis is a common pathology, and one of the factors for its appearance is obesity. Obesity associates with increased risk of cardio-vascular diseases, diabetes mellitus type II, some cancers and osteoarthritis. Impact of obesity on the onset and course of osteoarthritis is less studied, but there is evidence ot the relationship between obesity and knee osteoarthritis, at least - hip osteoarthritis and hands. The role of obesity in the pathogenesis of osteoarthritis as biomechanical and metabolic factors, based on studying the role of low level inflammation in the pathogenesis of degenerative lesions of joints, sensitive marker assessment of which is C-reactive protein. Great importance is attached to obesity as an independent factor limiting physical activity of the pain syndrome and the progression of radiological changes. Detail the influence of leptin on inflammatory and degenerative processes in the association of obesity and osteoarthritis. Proved that leptin is a key regulator of chondrocyte metabolism, provides a relationship between obesity and osteoarthritis by immunological mechanisms and inflammation as well - gender differences in this disease. Sigmficant importance is a study on the role of weight loss and physical activity in this disease associations, in particular - their impact on the probability of occurrence, progression of osteoarthritis and its prognosis.

Key words: osteoarthritis, body weight, obesity, association, leptin, proinflammatory cytokines, exercise.

Streszczenie

W niniejszym artykule przedstawiony został przegląd literatury na temat wzajemnych związków osteoartrozy i otyłości. Wiadomo, ze osteoartroza jest rozpowszechniona patologia, a jeden z czynnikow jej powstawania otyłość. Otylosc wiaze sie z podwyzszonym ryzykiem rozwoju chorob układu sercowo-naczyniowego, cukrzycy 2 typu, niektorymi formami raka i osteoartrozy. Wpływ otylosci na powstanie i przebieg osteoartrozy jest zbadany, jednak istnieja dowody wzajemnego związku miedzy otyloscia a gonartroza, w mniejszym stopniu - koksartroza i osteoartroza rak. Rozpatrzona rola otyłosci w patogenezie osteoartrozy jako biomechanicznego metabolicznego czynnika została oparta na zbadaniu roli malointensywnego zapalenia w patogenezie zwyrodnienia: porażenia stawow, ktorego wrazliwym markerem oceny jest C-reaktywne białko.

Duze znaczenie przypisuje się otylosci jako samodzielnemu czynnikowi ograniczenia aktywnosci fizycznej, powstania syndromu bolowego i wzrastania zmian rentgenologicznych.

Szczegółowo opracowano wpływ leptyny na procesy zapalne i degeneracyjne przy wzajemnym oddziaływaniu otyłosci i osteoartrozy. Udowodniono, ze leptyna jest kluczowym regulatorem metabolizmu chondrocytów, zapewnia wzajemny związek między otyloscia i osteoartroza przez mechanizmy immunologiczne, płciowe roznice danego zachorowania. Wielkie znaczenie nadaje się badaniom na temat roli zmniejszenia masy ciała i wysiłku fizycznego przy polaczeniu osteoartrozy z otyloscią, szczegolnie ich wpływu na prawdopodobieństwo: powstania, rozwoju osteoartrozy i jej prognozy.

Słowa kluczowe: osteoartroza, masa ciała, otyłosc, wzajemny związek, leptyna, przeciwzapalne cytokiny, ćwiczenia fizyczne.

Osteoarthritis is the widespread pathology. It is the most common disease for people of middle and old age, which determines its medico-social importance [1]. The prevalence of osteoarthritis in Ukraine is equal to 3172,6 per 100 thousand people, sickness rate – 607,3 cases per year, which is much lower than in the rest of the world, but this does not show the real state of things, so far as it is difficult to estimate its true spreading because of the fact, that patients go to doctor only in cases of arthropathia symptoms appearance [2]. The rate of osteoarthritis emergence increases as one grows older. Thus, among the people who are under 29 years old the rate of disease cases is equal to 8,4 people per 1000 people, 30-39 years old – 41,2 people; 40-49 years old – 191,9; 50-59 years old – 297,2; 60-69 years old – 879,7 per 1000 people. In population researches the rate and prevalence of falling ill increases in 2-10 times during the age period between 30 and 65 years old and keeps increasing when person grows older. Although, the development of osteoarthritis does not influence the vital prognosis it remains one of the major cause of disability, invalidism and chronic pain syndrome, which decreases the level of patient's life. In connection with essential aging of population, including Ukrainian people, the problems of prevention and medical treatment are of major importance [3].

Obesity - the growing epidemic

Together with aging there is another factor that causes osteoarthritis appearance – it is called obesity. No matter whether the country is developed or it is just developing, obesity remains one of the main problems for health protection in the whole world for both adults and children. According to the World Health Organization data more than 1,6 billion people have got overweight and 400 millions – obesity. Almost 30% of the able-bodied population of Ukraine has got obesity and every fourth person has overweight. The prevalence of obesity is 52% for those who are over 45 years old and the overweight is 32%, it means that excessive weight of the body makes up 85% and normal weight – only 13%. Today the emphasis is made on the fact that the increasing of the body weight leads to the growth of sickness and death rate from cardiovascular diseases, insular diabetes of the II type, sleep apnea and some neoplasm [4, 5, 6, 7].

Muskuloskeletal problems linked with obesity

Yet, the influence of obesity on the development of musculoskeletal system diseases remains little-studied [8]. Still, it is known that obesity is the risk factor of musculoskeletal system diseases development: osteoarthritis, back pain, gout, plantar fasciitis, chronic musculoskeletal pain, inflammatory arthritis [9, 10]. The analysis of epidemiologic evidences concerning the association of obesity and osteoarthritis, rheumatoid arthritis and podagra helps to examine the potential role of adipose tissue in pathogenesis of joints affection in a new way. Previ-

ously it was considered that obesity increases the risk of rheumatoid arthritis appearance, but further researches showed that high body weight promotes slower radiological progression of disease and favorable prognosis concerning the survival is observed [9]. On the other hand, obesity is closely connected with gouty arthritis and osteoarthritis, and the presence of obesity in youth correlates with development of these diseases during later period of life [10].

Obesity and osteoarthritis

Association between obesity and osteoarthritis is confirmed by the presence of twice higher pain rate in thigh and knee joints for those who suffer from obesity and twice frequent diagnosis of osteoarthritis [11]. Obesity is the risk factor of osteoarthritis occurrence [8] and especially associates with the development of knee, thigh and hand joints osteoarthritis [12, 13, 14, 15] and also with its progression and development of invalidism [8]. Though, there is an opposite thought that its influence on circuit is probably insignificant [15].

Obesity and knee osteoarthritis

The results of many researches confirm positive association between obesity and osteoarthritis, and especially close with gonarthrosis [16, 17, 18]. The correlation between overweight and knee osteoarthritis is studied [12, 17, 18, 19, 20, 21]. Thus, the development of gonarthrosis for women and men with overweight, in comparison with the patients with normal weight, in the range 30-35 kg/m^2 was 4 and 4,8 times increased, respectively [17]. The risk of gonarthrosis development increased by 15% on each 1 kg/m^2 over 27 kg/m^2 [10], and in the Coggon et al. (2001) research it is determined that the risk for those with overweight $\geq$ 30 kg/m^2 was 6,8 times higher than for those with normal weight [19]. The increase of overweight by 5 kg/m^2 enhances the risk of roentgenologic changes typical for gonarthrosis by two [13, 17, 22, 23]. According to the data given by other authors the rate of roentgenologic changes increases by 4-9 times for women with obesity. It proves the connection between body weight, osteoarthritis and evidence of roentgenologic changes [16, 17, 18, 23].

Some gender differences are determined. Thus, it is determined that healthy women have got strong connection between overweight and high rate of roentgenologic changes which are typical for gonarthrosis [15]. The presence of connection between overweight and knee joint osteoarthritis was proved for middle aged women. For such women with overweight higher than 26,4 kg/m^2 the risk of development of roentgenologic changes in knee joint was twice higher in comparison with women whose overweight was lower than 23,4 kg/m^2 [24]. Other researches determined similar associations and showed that connection between overweight and knee joint osteoarthritis was stronger for women than for men, which proves the role of estrogens in pathogenesis of disease [16, 19, 25, 26, 27]. Yet, positive connection between overweight and gonarthrosis for

both genders was determined in researches of Franklin J. (2009) and [illegible] A.M. (2002) [28, 29].

On the other hand, it is determined that 83% of women with go[illegible] suffer from obesity in comparison with 42% in control group [30].

According to the Magliano M. et al. (2008) data obesity, increasing the [illegible] of roentgenologic changes, influences the progress of disease development [illegible] lesser degree, though, according to the data of other researches the advance [illegible] roentgenologic changes of knee joints increases as the person gains extra body [illegible] weight [9, 20, 21, 31, 32]. And, the higher body weight is, the more evident be-comes its influence on disease progression [20]. Obesity is also the risk factor [illegible] transition of one-sided gonarthrosis into two-sided [18], and it is also the risk factor of two-sided gonarthrosis [21].

Another evidence of the fact that obesity precedes the knee joint osteoarthritis is that connection between knee osteoarthritis and obesity was strong even for those people who did not have any symptoms of gonarthrosis [17]. It is confirmed in Framingham research, where the connection between extra weight of the body in youth and the development of gonarthrosis in senior age was determined. The osteoarthritis morbidity for women, who gained extra body weight during re-search, increased by 1,6 times with each extra 10 pounds of weight [16, 25].

The presence of connection between obesity and tibiofemoral osteoarthritis of knee joint is proved [13, 17, 22, 33, 34, 35]. Further researches showed that high initial mass is associated with both tibiofemoral and patellofemoral os-teoarthritis development risk. It is determined that overweight correlated in a positive way with more evident constrictions of joint cavity in medial tibio-femoral junction for patient with genu varum, but not with valgus angulation. Varus deformity together with obesity leads to unfavourable load distribution in comparison with valgus deformity. It is determined that overweight correlated with osteoarthritis severity during varus deformity ($r = -0,29$; $p = 0,0009$), and correlation between overweight and osteoarthritis during valgus deformity was weaker ($r = -0,13$; $p = 0,17$). Thus, overweight was connected with osteoarthritis severity for patients with varus deformity, which is one of the local factors, which can promote the appearance of osteoarthritis against the background of obesity [36].

Obesity and hip osteoarthritis

There are proofs that obesity is the risk factor for coxarthrosis appearance, and that there is positive connection between overweight and coxarthrosis [16, 27, 28]. The connection between overweight and coxarthrosis is disputable because several researches showed its absence [13, 14, 31, 37, 38], and some other proved the presence of this connection [39, 40, 41]. The strongest associations were found between clinical symptoms and not radiological changes [28], although, this asso-ciation is not that strong as it is during gonarthrosis [16, 21, 27]. Obviously obesity brings on the symptoms of coxarthrosis, and weakness of association between

obesity and roentgenologic changes of hip joints is the result of difficulties related to radiographic detection of early changes [42, 43]. It is determined that overweight was the risk factor for coxarthrosis only for healthy men, but not for women [28]. It is also proved in Franklin et al. (2009) researches, which show that association with overweight during coxarthrosis was weaker for women [29].

Researches of the case-control type for men with primary coxarthrosis showed positive connection exactly between osteoarthritis severity of hip joint and overweight, which was proved by huge cohort studies [20, 38, 39].

It will be interesting to mention that obesity in youth is connected with the higher risk of coxarthrosis in comparison with the later period of life [38, 39]. Thus, high body weight for a person under 18 years old increases the risk of coxarthrosis in older age by 7,4 times in comparison with the person with lower body weight [44]. So, connection between obesity and coxarthrosis appearance is moderate; as a rule, though, the risk is higher for those who have extra body weight in youth.

Obesity and hand osteoarthritis

More and more data concerning connection between obesity and osteoarthritis of hand joints appear nowadays. However, unlike gonarthrosis, connection between obesity and hand joints osteoarthritis is not strong [45]. Several cohort studies showed that extra body weight is the independent risk factor for hand joints osteoarthritis, and that there is weak positive connection between obesity and osteoarthritis of hand joints [42].

Roentgenologic changes, typical for hand joints osteoarthritis, are met in 40-50% of people over 50 years old and osteoarthritis morbidity increases with the age. In addition, extra body weight in youth is much weightier predictor of hand joints osteoarthritis appearance than overweight in older age [42]. It is determined that overweight and waist volume are not risk factors of hand joints osteoarthritis especially for old people [45]. Other researches showed disputable data [21] concerning hand joints osteoarthritis and obesity, namely – the presence of connection between osteoarthritis and obesity only for men [46]. Similar research for women did not show the connection between osteoarthritis of hand joints and overweight. Authors consider that obesity can be mechanical and not system risk factor of osteoarthritis, which explains the connection between osteoarthritis of supporting joints and mass of the body in contrast to small hand joints.

Physical activity and working capacity

Osteoarthritis is one of the reasons of physical activity disorders and lasting disability, mostly as a result of gonarthrosis and coxarthrosis [15, 21]. Gonarthrosis and obesity were associated with physical activity descent by 4,3 and 1,7 times, respectively. When obesity and gonarthrosis were put together

physical activity descended by 9,8 times. So, obesity is not only the risk factor of gonarthrosis, but it is also connected with functional disorders.

Obesity is also connected with disability. The presence of extra body weight or obesity increased the risk of disorders of joints functioning by 1,5 times. It is determined that functional disorders in old age grew simultaneously with the weight, and women with obesity have got higher risk of invalidity due to physical activity descent as compared with the women with normal body weight.

Epidemiological researches with the usage of radiological criteria of diagnostics and monitoring of progression showed the absence of correlation between roentgen changes, pain intensity and disability. Only 16% of men and 33,2% of women with roentgenologically confirmed coxarthrosis complained of hip joint pain, and also – 25,4% of men and 34,2% of women with roentgenologically confirmed gonarthrosis. However, pain is the main predictor of joint function disorder. It is confirmed that the risk of development of evident pain in knee joint is 2,7 times higher among patients with obesity in comparison with those who have less than 25 kg/m^2 of overweight, which was proved by other authors.

Mechanisms of correlation of osteoarthritis and obesity

Two main theories explain correlation of osteoarthritis and obesity: biomechanical [33, 34, 47] and system-metabolic, which is intensively developed nowadays and is based on studying of role of low-intensity inflammation in pathogenesis of degenerative affection of joints [13].

The main mechanism for osteoarthritis appearance during obesity is overload of hip and knee joints during physical activity [47]. There are moderate and strong evidences of the fact that along with extra body weight, physical activity of hip and knee joints, intensive trainings and their duration are the risk factors of osteoarthritis [1]. It is proved in many researches that biomechanical factors are intermediary of correlation between obesity and osteoarthritis. These factors are realized be means of redistribution of increased body weight on supporting joints [41]. According to the biomechanical theory obesity leads to osteoarthritis by means of growth of axial load on knee joint with further destruction of articular cartilage and subchondral sclerosing. It explains the growth of gonarthrosis rate for those who suffer from overweight, but at the same time obesity is less connected with high coxarthrosis rate [33]. In addition, insignificant growth of osteoarthritis rate of distal interphalangeal hand joints is not explained by mechanical theory [13, 42]. The presence of weak correlation between overweight and hip joint, and hand joints osteoarthritis allows us to think about metabolic/humoral influence of adipose tissue on articular cartilage, and also about role of adipokinins in inflammation pathogenesis during osteoarthritis. The alternative explanation lies in the fact that growth of adipose tissue may have direct influence on metabolism within cartilaginous tissue [9]. There is a thought

that metabolic changes, correlated with obesity e.g. glucose tolerance disorder, hyperglycemia and changes of lipidic profile, may have negative influence on articular cartilage metabolism [34].

These mechanisms are important in osteoarthritis pathogenesis; however, their exact role in this process and correlation with obesity and particularly with adipokinins demands further study due to certain ambiguity.

The set correlation between obesity and osteoarthritis can be explained by means of genetic factors [14]. There are probable confirmations of the fact that genetic factors are of great importance in osteoarthritis appearance, in particular, its appearance is explained by means of genetic factors in 65% of the osteoarthritis disease cases [18]. In addition, obesity also has strong genetic inclination [48]. That's why the researches, aimed at study of common genetic origin of osteoarthritis and obesity, were held. But it turned out that general genetic inclination is hardly probable and strong correlation between overweight and gonarthrosis cannot be explained by means of common genetic origin [15, 46, 49].

Osteoarthritis, obesity and inflammation

Adipose tissue is regarded as active endocrine organ, which produces: leptin, tumor necrosis factor-α (TNF-α), interleukin (IL)-1, IL-6, IL-8, free fatty acids, transforming growth factor-β (TGF-β). The rise of their level leads to development of systemic inflammation of low intensity [50, 51], which increases the risk of development of inflammatory and degenerative illness of joints [52, 53]. Insuloniresistance, for its part, is typical for obesity and closely connected with excessive production of proinflammatory cytokines, that's why as insuloniresistance progresses the inflammation increases [54]. The inflammatory responses during obesity are supported by excessive production of reactive forms of oxygen, which bring on oxidative stress [55]. The derivatives of fatty acids also lead to inflammation [54]. The inflammatory component, obesity related, is confirmed by growth of serum concentration of inflammatory markers, such as proinflammatory cytokines (IL-6, TNF-α) and reagent of inflammation acute phase of C-reactive protein (CRP), which are also higher for those people who suffer from knee and hip osteoarthritis [56, 57]. Besides direct influence on joint, inflammatory mediators may cause the limitation of joint functioning, disease progression, affection of muscular functions and lower pain threshold. So, obesity and osteoarthritis have common physiological component - low-intensity systemic inflammation.

Th1-lymphocytes participation in the process of osteoarthritis development, particularly during synovitis raised levels of Th1-cytokines IL-1β, TNF-α, IL-6, which was accompanied by suppression of Th2-response, was observed. And during remission stage the rise of anti-inflammatory Th2-cytokines was observed [55, 58]. In Clements K.M. et al. (2009) research it is determined that

inflammatory changes in infrapatellaris adipose tissue appear at the initial stage of osteoarthritis monoiodideacetate model and can be the reason of pains at the initial stages of falling ill [59]. It is known that during osteoarthritis osteoblasts, chondrocytes and inflamed synovial membrane produce proinflammatory cytokines and chemokines, by the way some of them (IL-6, IL-8) lead to degenerative processes in cartilage. The examination of CRP, IL-6 and IL-8 contents within synovial fluid showed their growth, which proves the role of inflammation in joints' degenerative changes during osteoarthritis [60].

The experiments in vitro demonstrated potential capability of IL-1β to cause the degradation of cartilaginous tissue, while blockade of this cytokine effectively prevented the destruction of join cartilage. It is determined that inflammatory cytokine IL-1β, which is present in joint tissue of osteoarthritis patients, mediates the inflammation of joints and degeneration of cartilages during osteoarthritis [18, 56, 61, 62].

In several researches the association of osteoarthritis transition severity and disorders of joints' function with inflammation markers' growth in blood, as well as association of raised serum levels IL-6, TNF-α with loss of knee joint cartilaginous tissue, was determined. It is ascertained that high level of TNF-α of blood serum is the predictor of radiographic progression of gonarthrosis [10, 18, 57, 58, 63, 64]. TNF-α and IL-1β were found in osteoarthritis patients' synovial fluid and they were involved in degenerative process by means of oppression of extracellular matrix synthesis and stimulation of MMP catabolic activity [62]. In addition, cytokines are able to slow down the synthesis of enzymes' inhibitor and block the synthesis of matrix main elements – collagen and proteoglycans. Inhibitors' level lowering and enzymes' growth leads to degeneration of cartilage and arthrosis development. In response to cartilage damage various growth factors, TGF-β1 and IGF-1 including, stimulate chondrocytes to restoration of damaged extracellular matrix by means of cell-clusters formation and rise of their anabolic activity [61].

IL-6 is produced not only by adipocytes, but with the help of various kinds of lymphoid and non-lymphoid cells, chondrocytes and osteoblast [62, 64]. During osteoarthritis the involvement of IL-6 in degenerative process is confirmed by raised level of IL-6 in the cartilages of affected joints [60], IL-6 and its soluble receptor – in synovial fluid, in subchondral bone, osteophytes. IL-6 stimulates the production of CRP in liver. The positive correlation between CRP and intensity of visceral obesity, which would let us foresee that obesity could be the risk factor of inflammatory arthritis, was ascertained. On the other hand it is proved that IL-6 can depress catabolic processes, which participate in cartilage degeneration, but may cause inflammation itself [65].

It is ascertained that estrogen loss leads to IL-6-mediated stimulation of osteoblastogenesis, amplification of bone catabolism, and also association of IL-6 level with gonarthrosis intensity, joint cavity narrowing and osteoarthritis pro-

gression for women.. As the stimulator of IL-6 production in synovial fibroblasts stand adiponektin, TNF-α, IL-1α, thrombin and bradykinin [65].

The sensitive marker of system inflammation response estimation of low intensity is CRP [38]. While interpreting the CRP levels one should take into consideration factors, which have an influence on its contents. Thus, each 10 years of life increase CRP by 10%, each growth of the body weight by 5 kg/m^2 increase CRP by 22,3%. CRP increases by 25,9% for women in comparison with men, it also increases by 34% during regular usage of diuretic and against the background of smoking [66].

Appraising of connection between CRP and osteoarthritis patients' degree of severity did not show the difference between CRP levels under III and IV stage according to Kelgren [38]. Although, it is ascertained that high level of blood serum CRP is the predictor of gonarthrosis radiographic progression strengthening during next 5 years [56, 57, 62] and it is also connected with pain intensity. And each pain growth by 10 mm according to VAS is connected with 5,7%, and addition of pain in one or more joints – with 17% growth of serum CRP. The serum level of CRP correlates with CRP in osteoarthritis patients' synovial fluid. Spector T.D. et al. (1997) observed higher values of CRP for women with radiographic confirmation of osteoarthritis during last 4 years. The mean levels of CRP in these researches make up 2,4-2,5 mg/l and differ from such in general population by 36% ($p \leq 0{,}001$) [18, 38].

In Wolfe F. (1997) research it is also ascertained that quantity of affected joints and pain are correlated with CRP level augmentation for patients with clinically determined osteoarthritis of hip or knee joints [10]. Mean CRP level in this research was more than twice higher (5.9 mg/l) in comparison with Spector T.D. data [18], which is probably connected with including of patients with synovitis presence and inflammation of other origin. The majority of examined had two-sided osteoarthritis, correlated with insignificant rise of CRP, and 25% of generalized osteoarthritis is connected with more evident rise of CRP level [38]. The correlation between CRP level and IL-6 ($r=0{,}64$; $p=0{,}0006$), overweight ($r = 0{,}31$; $p = 0{,}02$), CRP during gonarthrosis is determined. Osteoarthritis patients' feeling of pain may be the result of inflammatory processes, which is proved by correlation between pain intensity and CRP level, and not with roentgenologic changes. Pain is subjective and is under a chain of factors, which are connected with pain perception. It is connected more with systematic inflammation indexes than any other of the objective osteoarthritis factors [56]. In Imhof A. et al. (2001) research the connection between usage of nonsteroidal anti-inflammatory drugs (NSAID) and CRP was not observed, and association between VAS and CRP was practically independent from usage of NSAID [66]. Thus, transition severity, functional changes, pains and roentgenologic progression, at least partly connected with the level of chronic inflammation for osteoarthritis patients. CRP estimation in dynamics is criterion of monitoring and prognostication of osteoarthritis clinical passing [38]. Obesity presence is able to raise the level of

inflammatory markers. That's why study of immune inflammation mediators, connected with inflammation in blood serum and synovial fluid for osteoarthritis patients is considered to be urgent for understanding of inflammation role in osteoarthritis pathogenesis in general and its association with obesity.

Role (or function) of leptin

Leptin is a system factor, which connects osteoarthritis and obesity [31, 66, 68]. It is the key establisher of adipose tissue that takes part in cartilaginous tissue degradation. Leptin level directly correlates with adipose tissue mass [52], and also with level of inflammation [69].

Leptin is cytokinelike hormone with pleiotropic effects, which participates in control of different physiological processes: lipidic homeostasis, insulin secretion, reproductive function, thermogenesis, angiogenesis, immune reactions. Leptin may be enabled in modulation of immune system activity [53, 70, 71, 72], promotes activation of phagocytal function, causes synthesis of eicosanoids and production of proinflammatory cytokines, monocyte and macrophage by means of STAT-3 [73] or NF-kβ [74] activation. In addition, leptin stimulates production of growth hormone by means of mononuclear cells [75], increases interferon-dependent production of nitric oxide synthase by macrophage [76], stimulates endotheliocytes and angiogenesis, causes chemotaxis of neutrophils and liberation of oxygen active forms [77], has an influence on growth, differentiation and T-cell activation [78], polypheration, differentiation, activation and cytotoxicity of natural killers [79], modulates activity of T-helpers in cellular immune response, regulates hypothalamo-pituitary-adrenal axis and slows down cortisol synthesis [53]. Glucocorticoids in vitro and in vivo showed stimulatory effect on synthesis on leptin secretion, the level of which had inverse dependence with cortisol and adrenocorticotropic hormone [80, 81].

Leptin activates Th1-cells and stimulates production of proinflammatory cytokines [52, 72, 82], and in such way, disturbs adequate balance between Th1- and Th2-cells. It is ascertained that leptin level correlated negatively with $CD4^+$ $CD25^+$ regulating T-cells, which is of great importance in pathogenesis of autoimmune diseases [72, 83, 84], and osteoarthritis as well [68]. Reduction of leptin contents leads to secretion growth of IL-4 [85], and its introduction leads to growth of inflammatory infiltration and production of interferon-γ by peripheral T-cells [86]. Leptin as proinflammatory mediator prevents secretion of proinflammatory androstenedione, which may cause persistence of chronic inflammatory diseases [87].

Proinflammatory stimuli (IL-1β, IL-6, TNF-α) regulate mRNA of leptin and its circulating levels [87, 88]. In addition, leptin is produced by inflammatory cells para- or autocrine mechanisms [86]. Evident expression of leptin can be found in all joint tissues: osteophytes, chondrocytes, subchondral bone, osteoarthritis patients' synovial fluid as compared to healthy ones [89]. It is ascertained that osteoblasts and chondrocytes are able to synthesize and secrete leptin [89] and its receptors [90]. And the contents of leptin in cartilage correlated with overweight

[89]. In addition, hyperexpression of leptin was found in fibrotic mesenchymal tissue of the upper zone of osteophytes, where consequent process of pluripotential cells' differentiation leads to formation of new cartilaginous outgrowths, which in the end may ossify. Taking into consideration functional activity of leptin receptors in articular cartilages, leptin has an influence on metabolic changes of chondrocytes [90]. New experimental data indicate the evident influence of leptin on chondrocytes, which are able to produce lots of anti-inflammatory mediators that are connected with inflammation and lead to loss of cartilaginous tissue structure [62]. Besides, leptin expression increases in osteoarthritic chondrocytes and also in joints after leptin's exogenous injection [89].

Direct influence of leptin on chondrocytes is realized synergistically together with interferon-γ and IL-1β by means of nitric oxide synthesis procurement [53], which induces wide spectrum of anti-inflammatory cytokines joints' cartilages and stimulates activation of MMP and chondrocytes' apoptosis [62]. Capability of increasing of proinflammatory cytokines production by leptin is realized through NF-kβ activation [74]. These data prove the theory that leptin works as anti-inflammatory cytokine with direct influence on immuneinflammatory reactions and may be connecting element between obesity and inflammation, which is connected with changes of cartilaginous homeostasis.

Appraising of leptins' role in osteoarthritis pathogenesis by means of leptins' level in synovial fluid and tissue samplings of cartilages detection, which were got from human's joints during operative interventions or arthroscopy, had shown the excessive expression of leptin in cartilages and osteophytes, while in unaffected cartilages leptin was produced by solitary chondrocytes only. Leptin concentration in men's synovial fluid ranged 0,60-17,40 mg/l (average 8,16±5,50 mg/l) an in women's – 5,38-28,50 mg/l (average 12,95±8,92 mg/l) and correlated with overweight ($r = 0,572$; $p \leq 0,01$) [89]. And it is ascertained that average level of leptin in synovial fluid for osteoarthritis patients was the same as in blood serum, though some researches showed that its level was higher in synovial fluid than in blood [91].

Positive correlation of leptin contents and osteoarthritis roentgenological severity and negative correlation between leptin level and overweight with cartilaginous tissue volume is ascertained. Magnetic resonance imaging procedure showed that overweight correlates positively with cartilaginous tissue defects [60].

Chondrocytes during osteoarthritis hyperexpress anabolic insulinlike growth factor (IGF) and its specific receptors (IGFRI), express TNF-α, which stimulates apoptosis of chondrocytes. Intra- or periarthric injection of leptin in experiment induces expression of insulin growth factor (IGF-1) and transforming growth factor (TGF-α) in chondrocytes both at mRNA and protein levels [92]. The level of growth factors in osteoarthritis patients' chondrocytes depends on degree of cartilage damage and leptin quantity [89, 90]. IL-1β or E2 prostaglandins also stimulate liberation of growth factors [93]. There is a thought that mechanical loads also stimulate expression of leptin in joints.

High level of IGF-1 and TGF-β during osteoarthritis was observed not only in cartilages but also in synovial fluid [61, 94, 95, 96]. The presence of obesity during osteoarthritis is accompanied by elevation of leptin level, which increases the synthesis of osteophytes' formative stimulator - TGF-β in joint [94]. As well as leptin regulates synthesis of growth factors, inducing expression of IGF-1 and TGF-β at mRNA and protein levels, then it may lead to pathologic process, typical for osteoarthritis. For osteoarthritis patients chondrocytes demonstrated the production of leptin and growth factors against the degree of severity. These factors have certain role in corresponding processes within cartilage [94, 97]. But, besides their protective role relative the destruction of cartilage, they can also cause degeneration of connective tissue. Specifically, excessive and/or lasting influence of TGF-β in mice's knee joints caused the development of osteophytes [98]. So, growth factors (especially TGF-β) have double influence on cartilaginous tissue, and leptin may lead to formation of osteophytes indirectly by means of stimulation of TGF-β expression or directly – by means of induction endochondral ossification [99].

Leptin may be enabled in regulation of chondrocytes' anabolic activity during osteoarthritis, especially in the early stages of disease, which are characterized by increased synthetic activity of chondrocytes [98]. Leptin regulates the growth of bones, influencing by means of neuronal net or secreting indefinite osteogenous factor [100, 101], or directly stimulating proliferation of osteoblasts, collagen synthesis, bone mineralization [102, 103] and endochondral ossification [99].

Role of leptin in osteoarthritis pathogenesis is supported by its hyperexpression in cartilage and correlation with degree of cartilage destruction,- synthesis of leptin by osteophytes also explains high level of leptin in joints during osteoarthritis [104]. So, leptin may have double influence on joint: its low level regulates proliferation of chondrocytes and their anabolic functions under the influence of growth factors, and high level increases production of IL-1β, MMP-9 and MMP-13, COG-2 expression, E2 prostaglandin level, IL-6, IL-8, nitric oxide, which induces apoptosis, activates MMP, slows down proteoglycans [53], which promotes inflammation, accelerates cartilage degradation and osteophytes formation.

Leptin has system and local effects, which can be mediators and provide metabolic and inflammatory connection between obesity and osteoarthritis, and can partly provide gender unequality of this disease as well [68]. Obesity and female sex present considerable risk factor of osteoarthritis development [68]. So far as, in general population adult women, who demonstrate higher level of leptin concentration as compared to men, suffer from obesity more often, it stipulates gender unequality concerning osteoarthritis development. So, hyperosteoarthritis for women may by conditioned by their high level of circulating leptin in comparison with men [68, 91]. It is marked that leptin secretion is slowed down by testosterone and can be accelerated under the influence of women's steroids, which proves gender peculiarities of leptin contents regulation.

So, participation of obesity in osteoarthritis pathogenesis of supporting and non-supporting joints can be explained by means of leptin hyperproduction and its influence on immune system, and development of inflammation by means of:

- activation of NF-kappa β;
- activation of monocytes/macrophages leading to release of tumour necrosis factor (TNF)-α and Il-6;
- promotes differentiation of Th-naïve T-cells into Th1 phenotype;
- stimulation of anabolic activity of chondrocytes;
- stimulation of endothelial cells and angiogenesis;
- amplification of nitric oxide synthesis;
- stimulation of TGF-β and IGF-1 and, of course,- anabolic functions of chondrocytes and formation of osteophytes [9].

So, these peripheral functions of leptin as the key regulator of chondrocytes' metabolism, indicate that it plays significant part in osteoarthritis pathophysiology with the help of above-mentioned mechanisms of inflammatory development and degeneration.

Osteoarthritis and ohesity - the recommendations

EULAR congress in 2003 and 2005 proposed new recommendations concerning osteoarthritis treatment. These recommendations presuppose the usage of non-pharmacological measures (extra weight loss, physical exercises, orthopedic means, balneotherapy etc.), pharmacological measures (paracetamol, NSAID, opioid analgesics, sex hormones, symptomatic slow-acting preparations: chondroitin sulfate, avocado compounds, diacerein, glycosamine, psychoactive drugs, local NSAID); intra-articular preparations (corticosteroids, hyaluronic acid, lavage); surgical treatment (osteotomy, endoprosthesis replacement) [recom].

Weight reduction and osteoarthritis

So far as, body weight control is influential measure in prophylaxis of joint degeneration against the background of obesity [14], the osteoarthritis treatment recommendations include body weight reduction [21? 105]. Researches concerning positive influence of body weight reduction towards gonarthrosis showed that loss of 5,1 kg during 10 years reduces the risk of osteoarthritis development by 50% or more [16], and reduction of body weight by 5 kg or until normal value help to avoid 24% of cases of surgical interventions because of gonarthrosis [13, 16, 19].

No evidences at the level of randomized control tests of body weight reduction positive influence on transition of coxarthrosis were found yet the degree of disability decreases when body weight reduces more than by 5%. With that it is ascertained that 27% of hip arthroplasty cases are conditioned by obesity influence [16, 21].

Combination of diet and physical exercises leads to significant weight loss, IL-1β levels, which associated with pain rate reduction and growth of working capacity [105]. Miller G.D. et all. (2008) proved correlation between proinflammatory markers (sTNFR1, sTNFR2) and physical activity against the body weight loss background [106]. Intensive body weight reduction for gonarthrosis elderly patients lead to reduction of inflammatory biomarkers levels, which associated with physical function. And, more evident improvement of joints' functions had those who lost more body weight [106].

Framingham research had shown that extra body weight loss by 2 units for women decreased probability of knee osteoarthritis development by 50% and more. Pain rate reduction in knee joints was ascertained after gastrorrhaphy and weight loss by 45 kg. It is also ascertained that for patients with knee join osteoarthritis and obesity, which had auriculopuncture, the feeding control and aerobic exercises were held and together with the body weight loss the pain reduction and improvement of Liken index was observed.

Role of physical exercises

It is obvious that combination of dietotherapy and physical exercises is the most effective for body weight reduction. The study of reasonability of physical exercises usage during osteoarthritis showed following:

For activity of daily life (ADL), the OASIS group states with a moderate level of scientific evidence, that ADL are a risk factor for knee OA and that risk increases with intensity and duration of activity.

The group concludes that healthy subjects as well as OA patients in general can pursue a high level of physical activity, provided the activity is not painful and does not predispose to trauma (grade B).

Radiographic or clinical OA is not a contraindication to promoting activity in patients who have a sedentary lifestyle (grade C).

For exercises and other structured activities pursued with a goal of health improvement, the group states with a high level of scientific evidence that they have a favourable effect on pain and function in the sedentary knee OA patient. The OASIS group recommends the practice of exercises and other structured activities for the sedentary patient with knee OA (grade A).

Static exercises are not favored over dynamic exercises, availability, preference and tolerance being the criteria for the choice of an exercise (grade A).

As results deteriorate when exercises are stopped, they should be performed at a frequency of between one and three times per week (grade B).

Professional assistance can be useful in improving initial compliance and perseverance (grade B).

There is no scientific argument to support halting exercise in case of an OA flare-up (grade C).

For sports and recreational activity, the group states with a high degree of scientific evidence, that these activities are a risk factor for knee and hip OA and that the risk correlates with intensity and duration of exposure. The group also states, with a high degree of scientific evidence, that the risk of OA associated with sport is lesser than that associated with a history of trauma and overweight. No firm conclusion could be drawn about the possible protective role of sports such as cycling, swimming or golf. The OASIS group recommends that athletes should be informed that joint trauma is a greater risk factor than the practice of sport (Grade A).

The high level athlete should be informed that the risk of OA is associated with the duration and intensity of exposure (Grade B).

The OA patient can continue to engage regularly in recreational sports as long as the activity does not cause pain (Grade C).

The OA patient who practices a sport at risk for joint trauma should be encouraged to change sport (Grade C).

For occupational activity, the OASIS group states with a high level of scientific evidence that there is a relationship between occupational activity and OA of the knee and hip. The precise nature of biomechanical stresses leading to OA remains unclear but factors such as high loads on the joint, unnatural body position, heavy lifting, climbing and jumping may contribute to knee and hip OA. The group recommends that taking an occupational history should always be part of managing the OA patient (Grade B).

In the knee or hip OA patient, work-related activity that produces or maintains pain should be avoided (Grade B).

Physicians should be alerted by the early knee and hip signs and symptoms in workers exposed to stresses that are known or supposed to favour knee or hip OA (Grade C) [107].

In that way the problem of obesity and ostheoarthrosis is very actual and need to be study more.

References

1. Bierma-Zeinstra S.M., Koes B.W.: Risk factors and prognostic factors of hip and knee osteoarthritis. Nat. Clin. Pract. Rheumatol., 2007. 3, 2. 78–85.
2. Коваленко В.М., Корнацький В.М.: Хвороби системи кровообігу: динаміка та аналіз. Київ, 2008. 66–79.
3. Коваленко В.Н., Борткевич О.П: Остеоартроз. Практ. руководство. 3-е изд., перераб. и доп. Киев: Морион, 2010. 608с.
4. Chin R.; Miyazaki S.: Criteria of obesity and obesity disease in Japan, 2009. 67, 2. 297–300.
5. Aronne L.J., Isoldi K.K.: Overweight and obesity: key components of cardiometabolic risk. Clin Cornerstone, 2007. 8, 3. 29–37.