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The role of metabolic syndrome in the pathogenesis of knee osteoarthritis: a new view on the problem

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ABSTRACT

Currently, numerous studies undeniably prove the influence of metabolic syndrome on osteoarthritis (OA) progression.

In hyperlipidemia, free fatty acids abnormally accumulate in the cartilage tissue and provoke cell dysfunction and necrosis. Studies show that palmitate and stearate have a pronounced proapoptotic effect on chondrocytes of the articular cartilage.

Mediators of the systemic inflammatory response produced by the adipose tissue act as a significant link in the pathogenesis of metabolic OA in the knee joint. Metabolic disorders, insulin resistance, and dyslipidemia boost production of inflammatory mediators and glycosylated compounds and formation of free oxygen radicals provoking endothelial dysfunction.

A relationship between intra-articular structures (articular cartilage, synovial membrane, subchondral bone, and synovial fluid) and the intra-articular infrapatellar fat pad is a local pathogenetic factor in the metabolic OA of the knee. It is proven that the intra-articular infrapatellar fat pad increases significantly in obese patients. Due to proximity to the articular cartilage and synovial membrane, the adipose tissue is in close contact with them. The influence of systemic metabolites activates the growth of adipocytes, preadipocytes, macrophages, fibroblasts, and other fat body cells which enhance the production and release of adipokines, such as leptin, adiponectin, visfatin, and cytokines, that, in turn, stimulate aseptic inflammation resulting in development of synovitis, cartilage degeneration, and gonarthrosis progression.

Therefore, the metabolic syndrome has a negative impact on the condition of the joint tissues, contributing to the development of gonarthrosis or its progression. It manifests itself both through systemic effects and the local impact of the hypertrophied infrapatellar fat pad on the components of the synovial joint environment.

Key words: metabolic syndrome, osteoarthritis, dyslipidemia, adipokines, oxidative stress, infrapatellar fat pad.

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Роль метаболического синдрома в патогенезе гонартроза. Новый взгляд на проблему.

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РЕЗЮМЕ

На сегодняшний день получены многочисленные данные, неоспоримо доказывающие взаимосвязь остеоартроза (ОА) с метаболическим синдромом.

При гиперлипидемических состояниях свободные жирные кислоты аномально накапливаются в тканях суставов. Это оказывает липотоксическое действие, что приводит к дисфункции клеток и их гибели. Пальмитаты и стеараты вызывают выраженное проапоптотическое действие на хондроциты суставного хряща.

Факторы системной воспалительной реакции, продуцируемые жировой тканью, выступают в качестве значимого звена в патогенезе метаболического ОА коленного сустава. Метаболические нарушения, инсулинорезистентность, дислипидемия способствуют увеличению продукции медиаторов воспаления, гликированных соединений, образованию кислородных радикалов, провоцирующих эндотелиальную дисфункцию.

Локальным звеном в патогенезе метаболического гонартроза является взаимосвязь внутрисуставных структур (суставного хряща, синовиальной оболочки, субхондральной кости и синовиальной жидкости) с внутрисуставной инфрапателлярной жировой клетчаткой. Доказано, что инфрапателлярная жировая клетчатка значительно увеличивается у пациентов с ожирением. Из-за близкого расположения с суставным хрящом и синовиальной оболочкой, жировая ткань находится с ними в тесном контакте. Под влиянием системных метаболитов, разрастаясь, адипоциты, преадипоциты, макрофаги, фибробласты и другие клетки жировых тел усиливают продукцию и высвобождение адипокинов, таких как лептин, адипонектин, висфатин, цитокинов, которые стимулируют асептическое воспаление, приводящее к развитию синовита, дегенерации хряща и прогрессированию гонартроза.

Таким образом, метаболический синдром оказывает негативное влияние на состояние тканей сустава, способствуя возникновению гонартроза или его прогрессированию, реализуясь как через системные эффекты, так и за счет локального воздействия гипертрофируемой инфрапателлярной жировой клетчатки на компоненты синовиальной среды сустава.

Ключевые слова: метаболический синдром, остеоартроз, дислипидемия, адипокины, оксидативный стресс, жировые тела Гоффа.

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INTRODUCTION

Metabolic syndrome (MS) is a complex of metabolic and hormonal disorders that are risk factors for development of cardiovascular diseases. The syndrome classically includes abdominal obesity, insulin resistance, arterial hypertension, impaired carbohydrate metabolism, increased triglycerides, and reduced high-density lipoprotein cholesterol. All these components are predictors of the adverse course of osteoarthritis (OA) [1].

Statistics shows a clear dependence of joint remodeling on metabolic disorders [2]. Each newly manifested component of MS makes the course of OA more severe. Therefore, in on a sample of 482 patients, among individuals with a mono-factor dis-

order, 12.8% had knee OA, while in people with 2 or more MS components, knee OA was registered in 23.2% [3]. Comorbid metabolic and vascular pathologies cause an early progressive course of OA with pronounced clinical and functional disorders. Increased duration of relapses, predominance of generalized forms, frequent development of synovitis and periarthritis, and more intense pain are observed [4].

The combination of MS and OA is more pronounced in young people and decreases with age [5]. Gender predisposition to OA in MS showed a prevailing risk in women of all age groups, which should be associated with peculiarities of the function of reproductive hormones [6].

Development of osteoarthritis, especially in the knee joints, leads to limited physical activity and subsequent progression of obesity. Therefore, a vicious circle forms, where, on the one hand, MS contributes to the development of OA, and on the other hand, the mobility is limited due to degenerative and dystrophic processes in the joint, which contributes to the progression of obesity and MS.

All pathogenetic factors of gonarthrosis in MS can be divided into systemic ones (such as lipotoxicity and endothelial dysfunction), developing as a result of dyslipidemia; activation of oxidative stress against the background of hyperglycemia and insulin resistance; and increased production of active metabolites by adipokines in the conditions of obesity, that induce and promote inflammation in the joints. A number of authors prove the importance of local factors in the pathogenesis of gonarthritis and, in particular, the role of infrapatellar fat pad, which is in direct contact with the synovial membrane of the knee joint, is hypertrophied in the metabolic syndrome, and participates in the implementation of destructive processes in the intra-articular structures.

SIGNIFICANCE OF THE MECHANICAL FACTOR

According to the original concept of OA development in MS, it is the mechanical factor (overweightness) that contributes to hyperextension of the ligamentous apparatus and increases the mobility of the intra-articular structures and the load on the articular surfaces. Therefore, friction increases, which implies constant irritation and development of aseptic inflammation [7]. In addition, obese patients often have big bone mass, which increases the pressure in the subchondral bone and contributes to trophic disturbances, formation of subchondral cysts, and destruction of the cartilage [8]. In this case, the knee joint is the primary target affected by significant biomechanical factors [9]. Numerous studies of women with MS showed that an average weight loss of 5 kg reduced the risk of developing knee OA by 50% [10, 11].

However, overload of the joints cannot explain convincing epidemiological data demonstrating a link between obesity and OA of the upper limb joints that do not carry a significant load. At the same time, patients with obesity and MS have a higher risk of gonarthrosis than patients with obesity without the metabolic syndrome [12].

According to modern data, the mechanical factor in MS plays an aggravating role in progression of OA, but this role is not the primary one. The main systemic pathological processes are dyslipidemia and hypersecretion of proinflammatory mediators and cytokines by the adipose tissue [13]. Accumulation of lipids in chondrocytes and low-grade systemic inflammation (metainflammation) involving adipokines and cytokines disrupt homeostasis, leading to lipotoxicity and degenerative changes in the joint tissues [14].

DYSLIPIDEMIA

Lipid imbalance is a key metabolic disorder associated with metabolic syndrome and obesity. A high-calorie diet affects adversely the barrier characteristics of the gastrointestinal mucosa, contributes to the violation of its integrity, and reduces the production of antimicrobial peptides and mucins. In addition, the intestinal microbial flora changes, and the production of proinflammatory metabolites, in particular, lipopolysaccharides (LPS), increases [15]. The increased permeability of the intestinal wall provides excess supply of LPS to the systemic circulation, which supports low-grade chronic inflammation in the body with the activation of innate immune components via Toll-like receptors (TLR) 4 [16].

Preclinical studies showed that LPSs suppress cartilage matrix synthesis, increasing the production of IL-1β by the upregulation mechanism via TLRs present in human articular cartilage [17]. In addition, indirectly through activation of circulating monocytes, synthesis of osteopontin increases,

which is responsible for activation of matrix metalloproteinases (MMR) and regulation of cell migration, has proinflammatory effect, and is able to participate in vascular remodeling, contributing to ischemization of the joints [18]. Accumulation of LPS due to activation of transforming growth factor (TGF)β leads to an increase in ectopic bone formation and enhances inflammation in the synovial membrane due to activation of macrophages [17].

Dyslipidemia in MS leads to abnormal accumulation of lipids in tissues, and hyperinsulinemia occurring against the background of insulin resistance with a compensatory purpose is both direct alternative and mediated in nature [13].

Articular chondrocytes, unlike most other cells, are characterized by significant lipid deposits. Infiltration of excessively high lipid levels in chondrocytes in hyperlipidemia leads to lipotoxicity. Free fatty acids are considered the main factors that have a damaging effect. The obtained data prove that the main mechanism underlying the damaging effect of toxic concentrations of oleate and palmitate in articular chondrocytes is implementation of apoptosis. A quantitative assessment of DNA hypoploidia using flow cytometry revealed accumulation of apoptotic cells with a subdiploid DNA content, and an assessment of nuclear morphology showed that nuclear condensation and fragmentation were significantly increased. In addition, Western blotting showed that oleate induced caspase-3 and -7, and the pan-caspase inhibitor zVAD-fmk completely prevented oleate-induced cytotoxicity [13].

Experiments on a mouse model using a high-fat diet showed that the incidence of OA in the group with the addition of polyunsaturated fatty acids (PUFA) was lower, both for idiopathic and post-traumatic OA. PUFA inhibits apoptosis caused by hyperlipidemia by redirecting saturated fatty acids to triglyceride pools, which are stored as neutral fats [19].

The two central categories of lipid mediators of inflammation are omega-6 and omega - 3 PUFAs. Omega-6 PUFAs, such as arachidonic acid, are precursors of proinflammatory eicosanoids, including prostaglandins, thromboxanes, and leukotrienes. Omega-3 PUFAs, such as eicosapentaenoic and docosahexaenoic acids, on the contrary, inhibit the intensity of inflammation. The experimental model proved that the decrease in the omega-6 / omega-3 PUFA ratio, either through diet or genetically by introducing the fat-1 transgen, which endogenously converts omega-6 to omega-3 PUFA, leads to a reduced risk of developing knee OA [20, 21].

Mediated damaging factors of dyslipidemia are manifested in disturbances of the microcirculatory supply in the cartilage. Increased infiltration of the synovial and subchondral vascular intima by lipids contributes to the activation of lipid peroxidation (LPO), development of endothelial dysfunction, plasmorrhagia, progression of atherosclerosis, and vascular remodeling [13].

HYPERGLYCEMIA AND INSULIN RESISTANCE

Hyperglycemia and glucose toxicity are significant triggers of damage in gonarthrosis. Changes in the function of glucose carriers on the surface of chondrocytes contribute to maintaining the inflammatory and degenerative and dystrophic processes, inhibiting the anabolic effects. Neurotoxic effects of hyperglycemia lead to neuromuscular damage, which worsens the course of OA and leads to destabilization of the joints [22].

Hyperinsulinemia contributes to activation of the sympathetic system; Na retention in the body increases, which leads to additional occlusion of the vascular lumen, development of arterial hypertension, and deterioration of microcirculation [23]. Impaired joint perfusion under vascular remodeling increases the risk of oxidative stress, which is especially unfavorable for the cartilage tissue due to the absence of blood vessels and its initially reduced antioxidant potential [24].

CHRONIC METABOLIC INFLAMMATION

Taking into account the developing hyperlipidemia and constantly increasing adipose tissue mass in the metabolic syndrome, as well as its good vascularization, inflammatory mediators, free fatty acids from the adipose tissue, enter the systemic circulation in a significant amount, subsequently affecting the intra-articular structures. The spectrum of signaling molecules secreted by adipocytes is very diverse. They can be divided into specific molecules, such as leptin, and non-specific ones, such as cytokines, in particular, IL-1β, IL-4, IL-6, IL-8, IL-13, IL-17, IL-18, chemokines (CCL2, MIP-1α), and growth factors (TGFβ, IGF-1, VEGF, TNFα) [25].

There is evidence that leptin is able to act through insulin receptors and components of the insulin cascade, becoming one of the causes of insulin resistance in pathological concentrations [26]. Leptin has a dose-dependent effect on the joints. In the physiological state, small doses of it stimulate formation of the extracellular matrix in the cartilage and expression of TGFβ and IGF-1 by osteoblasts [27]. The concentration is maintained by the relationship between the articular cartilage and the infrapatellar fat pad. The metabolic syndrome is characterized by hyperleptinemia. In addition, most cells of the immune system have receptors for leptin and its antagonist, ghrelin. Leptin is involved not only in metabolic correction, but also in immune processes [28]. In particular, in innate immunity, it activates macrophages and natural killers (NK) and causes neutrophil chemotaxis. In adaptive immunity, leptin affects proliferation and differentiation of T cells, stimulates the formation of Th-1 lymphocytes, and suppresses the concentration of Th-reg [29].

In an experimental mouse model, leptin inhibition led to suppression of inflammatory responses, including symptoms of arthritis. Intraperitoneal injection of leptin resumed the inflammatory process. Therefore, leptin indirectly induced the release of IL-6 via synovial macrophages, which can lead to degradation of proteoglycans, inhibit cartilage regeneration, and enhance MMP13 expression [30]. Under the influence of leptin in chondrocytes, the production of IL-1, one of the key proinflammatory agents that has a catabolic effect through cascade activation of other interleukins, such as MMP9 and MMP13, and attraction of inducible NO-synthetase, increases. Such effects also lead to chondrocyte apoptosis, including p53-dependent apoptosis, and activation of subchondral bone osteoclasts, which causes bone remodeling and lysis with formation of cysts [31]. In addition to inducing proinflammatory cytokines, leptin also contributed to expression of other cartilage catabolic factors, such as IL8, MMP2, cathepsin, and calpain [32]. Moreover, leptin mediated the dose-dependent expression of vascular cell adhesion molecules (VCAM) in the synovial membrane, correlating with severe OA [33].

Adiponectin is considered to be a mediator that has a protective effect on the joint in metabolic OA. However, all new studies characterize it as a proinflammatory agent, the effects of which are largely similar to those of leptin [34]. In progressive obesity, it is a mediator of insulin resistance and tissue inflammation, contributing to the formation and progression of OA [35].

Visfatin is produced constitutively not only by adipocytes, but also by almost all local tissues that are involved in the pathogenesis of OA, to a greater extent by the synovial membrane and chondrocytes. Like other adipokines, it has pleiotropic effects and performs immune, proinflammatory, and enzymatic functions [36]. The concentration of visfatin in the blood plasma in OA significantly increases. Besides, its high content was determined immunohistochemically in the synovial membrane, especially around blood vessels. In the experiment, osteoblasts were as sensitive to visfatin as chondrocytes, since their stimulation induced the expression and production of the same proinflammatory cytokines and chemokines (disintegrin, prostaglandin E2, IL-6, CCL2, and MCP-1), and the prodegradative effects were determined by the release of MMP-3, MMP-13, and involvement of immunocompetent cells. The use of the visfatin inhibitor APO866 showed a decrease in the production of proinflammatory cytokines in various cells from 63 to 94% [37]. A special role in the formation of insulin resistance belongs to recombinant visfatin, which acts through the insulin receptor IR3 [38].

OXIDATIVE STRESS

Chronic inflammation affects metabolism in the joint by activating oxidative stress, which is one of the most significant factors of genomic and mitochondrial damage that initiates the processes of cellular aging. The synergistic effect of systemic inflammatory factors on chondrocytes and synovial fibroblasts stimulates synthesis of cytokines and degrading enzymes that induce destruction of proteoglycans and type II collagen (Col2A1), the main structural protein of the cartilage tissue. In addition, impaired regulation of Col2a1 genes is observed, which indicates a decrease in the reparative potential. Adipokines perform their functions by binding to Toll-like receptors (TLRs) on target cell membranes and initiating phosphorylation of the ERK/p38/mitogen-activated protein kinase (MAPK) cascade, which primarily causes changes in the intracellular homeostasis, in particular, increasing the

activity of NADP oxidase (NOX), the main source of ROS generation.

The damaging effect of ROS in physiological conditions is inhibited by the antioxidant system, which is controlled by the transcription factor NRF2 (nuclear related factor 2). Receiving signals, its inactive cytoplasm form KEAP1 (Kelch-like ECH associated protein 1) undergoes hydrolysis with cleavage of the active NF-E2-dependent factor 2 (nuclear factor erythroid 2) and translocation to the nucleus, where it launches biosynthesis of cytoprotective enzymes, such as superoxide dismutase (SOD) and catalase (CAT). During experimental sensitization of chondrocytes and synovial fibroblasts with visfatin, leptin, and resistin, a significant increase in the endogenous superoxide anion, as well as NRF2, catalase, and superoxide dismutase was proved. The latter is explained by an acute adaptive compensatory response. However, given that the potential of antioxidant protection in the cartilage tissue is relatively reduced due to the peculiarities of its histophysiology, the membrane-protective effect is suppressed under conditions of considerable amounts of ROS, which affect the phospholipid bilayer both endogenously, forming inside cells, and exogenously, appearing mainly from targets undergoing apoptosis [39].

Apoptosis is also facilitated by reduced expression of genes of the BCL-2 family proteins, which are some of the regulators of this process intended to increase cell survival. In addition, there is significant positive modulation of the expression of some micro interfering RNA (miRNA) genes, leading to a decrease in the proliferative potential, stoppage of the cell cycle and cellular aging, implementation of apoptosis, and violation of the oxidative balance. The effects of miRNA are enhanced by the synergistic signaling of the NF-kB pathway, which is a family of transcription proteins involved in proinflammatory, immune, and stress responses and activated by the MAP-kinase cascade [40]. Experimental modeling of oxidative and inflammatory stress on synovial fibroblasts and chondrocytes through constant impact of proinflammatory cytokines, in particular, TNFα and H_2O_2, significantly increased the proportion of aging cells among the young population and limited it among the old population. This indicated special susceptibility of young cells to this type of alteration, while the introduction of the antioxidant N-acetylcysteine or fenofibrate suppressed aging and slowed down the progression of OA. Aging cells are characterized by irreversible stoppage of the cell cycle with a shift of the phenotype towards a proinflammatory one, therefore being pathological factors that can independently maintain inflammation in the joint for a long time [41].

VIOLATIONS OF ANGIOGENESIS

Activation of angiogenesis in chronic systemic inflammation is of great importance in metabolic OA. The balance between angiogenic and antiangiogenic factors in the joint regulates the growth of blood vessels, while proinflammatory factors that increase with the metabolic status lead to a balance shift. Inflammation in the joint can promote angiogenesis directly by releasing growth factors from cells, such as macrophages, as well as by stimulating or sensitizing other cells, such as chondrocytes and osteoblasts, which, in turn, release additional angiogenic factors.

What is more, hypoxia in the inflamed tissues is a powerful stimulant of angiogenesis. Due to hypoxia, a compensatory increase in the expression of the *VEGF* (vascular endothelial growth factor) gene is observed. Recent studies confirm the significant role of TNFα, which induces accumulation of leucine-rich alpha-2-glycoprotein 1 (LRG1) in the articular cartilage and subchondral bone, as a powerful stimulator of pathological angiogenesis and mesenchymal cell migration, which contribute to aberrant osteogenesis [42]. In turn, progressive angiogenesis aggravates the course of chronic inflammation and leads to endochondral ossification and formation of osteophytes in the region of the bone-cartilage junction. Increased permeability of newly formed blood vessels contributes to the development of edema [43]. Adhesion molecules, such as E-selectin, are highly expressed by new vessels, facilitating inflammatory cell infiltration [44].

SIGNIFICANCE OF INFRAPATELLAR FAT PAD

All systemic processes in the metabolic syndrome, directly or indirectly affecting the joint, change the relationship between its structures, such as cartilage plates, synovial membrane, and intra-articular adipose tissue. Lately, special attention has been paid

to the infrapatellar fat pad (Hoffa's fat pad), which is intracapsular but extrasynovial, performs the cushioning function, and acts as a local paracrine apparatus. It is well supplied with blood and innervated, like subcutaneous fat, and also has a strong connective tissue framework [45]. Due to its location between the articular cartilage and the meniscal surface, the Hoffa's fat pad reduces the load on the knee joint and protects it in physiological conditions or at an early stage of OA [46]. The infrapatellar fat pad improves distribution of fluid in the joint by increasing synovial membrane area and reducing friction, thus enhancing stability in the joint [47].

The main functional unit of this structure is the adipocyte which determines the ability to secrete specific adipocytokines (such as leptin and adiponectin), that have anti-catabolic effects on the cartilage tissue (increase the production of proteoglycans, type II collagen, expression of TGFβ and IGF-1) in physiological concentrations or the ones slightly exceeding them, and, therefore, prevent the development of OA at early stages [48]. Consequently, the infrapatellar fat pad can be defined as an independent formation that regulates the metabolic processes in the joint and counteracts the pathogenesis of OA at initial stages.

However, against the background of a gradual increase in proinflammatory systemic factors in the body in the metabolic syndrome, the first response is usually given by the synovial membrane. Findings of knee joint MRI in patients with gonarthritis demonstrated thickening of the synovial membrane in 73% of patients with early OA, which corresponds to development of chronic synovitis. Histological changes were characterized by massive lymphohistiocytic infiltration. Chronic inflammation in the synovial membrane activated proliferation of fibroblasts and blood vessels and migration of macrophages. At the same time, the inability of synovial macrophages to switch from the proinflammatory M1 subtype to the anti-inflammatory M2 subtypes was observed, which can contribute to the initiation and maintenance of synovitis in OA, and cellular apoptosis is enhanced. M1 macrophages contribute to inflammatory microenvironment and OA progression by interacting with synovial fibroblasts and chondrocytes, thereby increasing MMP secretion [49].

Many authors believe that the Hoffa's fat pad is involved in the catabolic processes with a change in their proinflammatory profile [50]. In this case, the infrapatellar fat pad is able to produce the same proinflammatory mediators and growth factors directly into the synovial fluid as distantly located adipocytes in the blood [51]. In MS, the infrapatellar fat pad secretes higher levels of inflammatory factors and adipokines than subcutaneous fat [52].

On the other hand, chronic hypertrophy of the Hoffa's fat pad and concomitant damage to the soft tissues of the joint lead to ischemia, inducing abnormal distribution of the neurotransmitter SP in the afferent fibers of nerve endings inside the adipose tissue, which ultimately leads to chronic neurogenic tissue inflammation, associated with increased paraarticular pain by some authors [53].

The progression of gonarthrosis in MS leads to changes in the infrapatellar fat pad, that increases in size and becomes denser, which is confirmed by MRI studies [54]. At initial stages of the disease, this change is associated with the development of edema, and at later stages – with hyperplasia caused by the growth of the connective tissue, in which Hoffa's fat pad is a complex, well vascularized, layered structure with fat lobules and foci of lymphohistiocytic infiltration [55].

CONCLUSION

The metabolic syndrome is characterized by low-grade systemic inflammation with the development of obesity, dyslipidemia, insulin resistance, hyperglycemia, and oxidative stress. Each component of MS is involved in the pathogenesis of osteoarthritis (Figure).

Systemic exposure to inflammatory mediators produced in MS, such as adipokines, cytokines, adiponectin, and visfatin, stimulates aseptic inflammation in the joint, leading to the development of synovitis and cartilage degeneration.

Hyperlipidemia and oxidative stress have lipotoxic and proapoptotic effects, which leads to chondrocyte dysfunction and death.

Of the local factors in the pathogenesis of metabolic gonarthrosis, an important role is assigned to the intra-articular infrapatellar fat pad. New studies demonstrated that the Hoffa's fat pad is a substrate that performs not only a cushioning function, but also produces proinflammatory factors directly into the synovial fluid and is significantly hypertrophied in the MS.

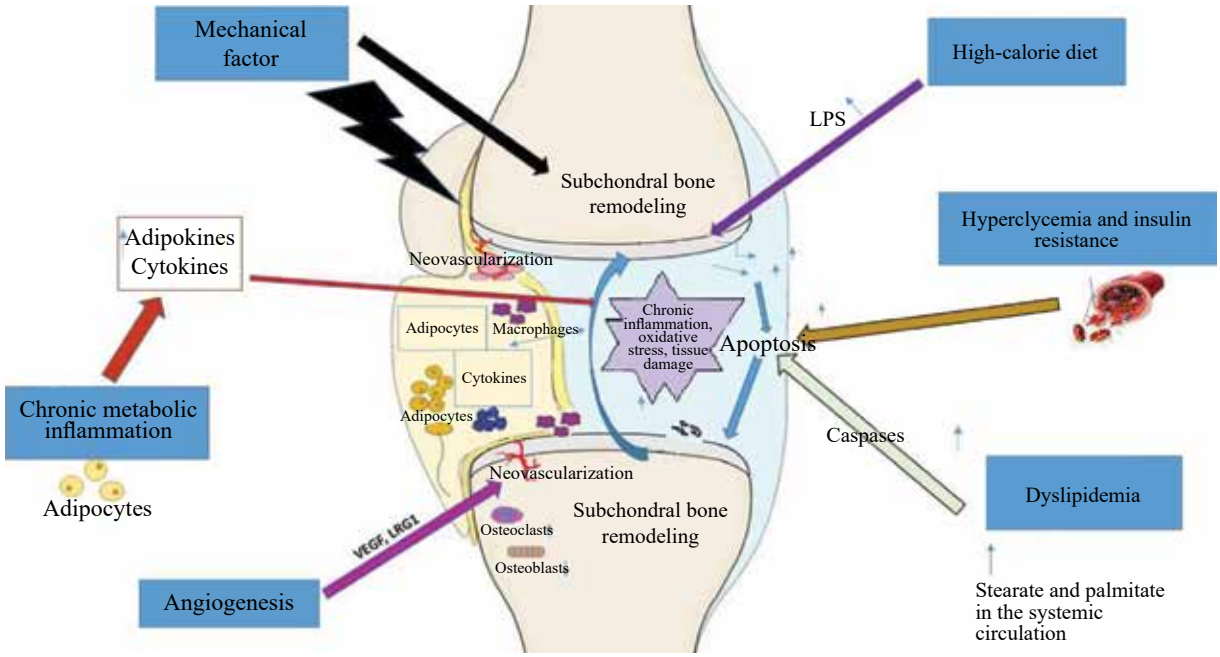

Figure. Components of the metabolic syndrome in the pathogenesis of osteoarthrosis

Therefore, MS leads to development of gonarthrosis or contributes to its progression and is manifested through systemic effects as well as through the induced local effect of hypertrophied infrapatellar fat pad on the components of the synovial environment of the joint. Products of tissue degradation and local and systemic inflammatory mediators form a vicious circle that supports chronic inflammation associated with impaired microcirculation, neovascularization, and vascular sprouting into the cartilage tissue with activation of foci of osteogenesis around the vascular channels, which causes irreversible changes in the joint and contributes to progression of gonarthritis.

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