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THE ROLE OF METABOLIC SYNDROME IN THE DEVELOPMENT OF OSTEOARTHRITIS

ULOGA METABOLIČKOG SINDROMA U NASTANKU OSTEOARTROZE

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Summary

Introduction. Knee osteoarthritis is a progressive degenerative disease of the entire joint that leads to functional limitations and reduced quality of life. The end-stage of the disease is associated with disability and a significant burden both for the patient and the society. **Osteoarthritis and metabolic syndrome.** Metabolic syndrome is a group of cardiovascular risk factors including diabetes and hyperglycemia, abdominal obesity, hypercholesterolemia, and hypertension. The adverse effects of the metabolic syndrome are associated with worsening of the clinical manifestations and disease prognosis through the combined effects of metabolic disorders. It has also been suggested that individual components of the metabolic syndrome may be an independent risk factor for knee osteoarthritis. **Osteoarthritis and diabetes mellitus.** Experimental and epidemiological evidence supports the role of type II diabetes mellitus in the pathogenesis of osteoarthritis. Chronic hyperglycemia leads to oxidative stress and excessive production of proinflammatory cytokines, while insulin resistance can act locally and systemically through chronic low-grade inflammation. **Osteoarthritis and hypertension.** The mechanism that explains the relationship between osteoarthritis and hypertension is unclear. Several potential pathways for subchondral bone damage due to hypertension have been described. **Osteoarthritis and dyslipidemia.** Experimental studies suggest that dyslipidemia may be involved in the pathophysiological process of osteoarthritis, while epidemiological studies show heterogeneous results. **Conclusion**. Patients with knee osteoarthritis require a holistic approach in which the emphasis is not only on symptomatic pain relief, but also on the treatment of metabolic disorders.

Keywords: Metabolic Syndrome; Osteoarthritis; Risk Factors; Diabetes Mellitus, Type 2; Dyslipidemias; Hyperglycemia; Hypertension; Inflammation; Obesity;

Sažetak

Uvod. Osteoartroza kolena predstavlja degenerativno oboljenje kompletnog zgloba koje dovodi do funkcionalnih ograničenja i smanjenog kvaliteta života. Krajnji stadijum bolesti je povezan sa invaliditetom i značajnim opterećenjem kako za samog pacijenta, tako i za društvo. **Osteoartroza i metabolički sindrom.** Metabolički sindrom predstavlja skup nekoliko kardiovaskularnih faktora rizika– dijabetes melitus i hiperglikemija našte, abdominalna gojaznost, hiperholesterolemija i hipertenzija. Glavni efekat metaboličkog sindroma može biti pogoršanje kliničkih manifestacija i prognoze bolesti putem udruženog uticaja metaboličkih poremećaja. Sugerisano je i da bi pojedinačne komponente metaboličkog sindroma mogle biti nezavisan faktor rizika za osteoartrozu kolena. **Osteoartroza i dijabetes melitus.** Eksperimentalni i epidemiološki dokazi podržavaju ulogu dijabetesa melitus tip II u patogenezi osteoartroze. Hronična hiperglikemija dovodi do oksidativnog stresa, te prekomerne proizvodnje proinflamatornih citokina, dok insulinska rezistencija može delovati lokalno i sistemski putem hronične inflamacije niskog stepena. **Osteoartroza i hipertenzija.** Mehanizam koji bi objasnio vezu između osteoartroze i hipertenzije je nejasan. Opisano je nekoliko potencijalnih načina za oštećenje subhondralne kosti usled povišenog krvnog pritiska. **Osteoartroza i dislipidemija.** Eksperimentalne studije sugerišu da bi dislipidemija mogla biti uključena u patofiziološki proces nastanka osteoartroze, dok epidemiološke studije pokazuju heterogene rezultate. **Zaključak.** Pacijenti sa osteoartrozom kolena zahtevaju holistički pristup u kom akcenat neće biti samo na simptomatskom ublažavanju bolova, već i na lečenju metaboličkih poremećaja.

Ključne reči: metabolički sindrom; osteoartroza; faktori rizika; dijabetes melitus, tip 2; dislipidemije; hiperglicemija; hipertenzija; inflamacija; gojaznost

Introduction

Osteoarthritis (OA) is a progressive degenerative disease of the entire joint, since it affects the articular cartilage, meniscus, ligaments, bone, and synovium [1–4]. This rheumatic disease most often has a multifactorial etiology and affects peripheral joints (knee, hip, hand) and/or spine, but it can affect any other joint [5, 6]. The OA involves molecular, anatomic, and/or physiologic disorders such as abnormal joint metabolism, cartilage degradation, bone remodelling, osteophyte formation, and inflammation [2,

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Abbreviations

OA – osteoarthritis
MetS – metabolic syndrome
HDL – high-density lipoprotein
LDL – low-density lipoprotein
DM II – diabetes mellitus type II
BP – blood pressure
BMI – body mass index

4]. Pain, stiffness, and limited mobility are common functional limitations in patients with OA, which affect the ability to perform daily activities [7, 8] and reduce the quality of life [9]. Knee OA affects about 250 million people worldwide, and this number is expected to increase due to the obesity epidemic and population aging [1, 9]. Mechanical pressure is considered to be the primary cause of knee OA. It mostly affects the elderly population, obese people, and women are at higher risk of developing knee OA than men [9]. Also, it has been reported that women with knee OA have a poorer functional status and a more pronounced functional decline compared to men [10].

The pathophysiological mechanisms leading to OA are still unclear, although there is general agreement on the impact of biomechanical and excessive mechanical loading to the joints [11]. Early changes that affect the osteochondral junction play an important role considering the fact that they represent possible mediators of pain and structural progression of OA. The loss of osteochondral integrity removes the barrier between intra-articular and subchondral compartments, exposing subchondral bone and its innervation to unbalanced biochemical and biomechanical influences [12]. Other risk factors that may contribute to an increase in the incidence of OA include genetic, metabolic and neuroendocrine factors, [11] and it is currently considered that there are several disease phenotypes: post-traumatic, age-related OA, genetic, and metabolic syndrome (MetS)-related OA [13].

The incidence and prevalence of OA increase with age, while prolonged life expectancy also increases the need for knee arthroplasty, so the rate of these interventions in the United States is expected to increase by 143% by 2050 [14]. Data on the incidence and prevalence of OA in Serbia are limited. In the period from 2013 to 2014, the waiting list for total hip and knee arthroplasty increased by 20%, and the demand for such procedures is expected to rise [15]. Total knee arthroplasty is an effective treatment for OA, but in conditions of limited access to health care, less expensive therapy options are needed. Treatment of metabolic disorders could be one of the potential ways to slow down the progression of knee OA [16].

Osteoarthritis and metabolic syndrome

Most patients with knee OA are overweight or obese. The risk of developing OA is twice as high in obese individuals compared with individuals with a normal body mass index (BMI) (< 25) odds ratio 1.98, [17] and obesity is the main risk factor for OA [18–20]. Its strongest association is with knee OA, followed by hip OA [18] while the link between high BMI and hand OA remains unclear [19]. A combination of disorders that constitute the MetS has also been reported to be associated with an increased risk for knee, hand, and lumbar spine OA [18]. Hypertension, dyslipidemia, and hyperglycemia are more common in obese patients, indicating that these metabolic disorders are inseparably linked [16]. According to the International Diabetes Federation (IDF) consensus, MetS implies central obesity and any of the following two criteria: elevated triglycerides ≥ 150 mg/dL (1.7 mmol/L) or prior specific treatment, reduced high-density lipoprotein (HDL) cholesterol < 50 mg/dL (1.29 mmol/L) in women/< 40 mg/dL (1.03 mmol/L) in men or previous specific treatment, high blood pressure (BP) - systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg or treatment of previously diagnosed hypertension, raised fasting plasma glucose (FPG) ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type II diabetes mellitus (DM II) [21]. The MetS is a significant public health problem that continues to grow rapidly due to urbanization and sedentary lifestyle, as well as increased caloric intake and consequent increased incidence of obesity [12]. It has been estimated that MetS affects 10 - 40% of the population, depending on diagnostic criteria, sex, age, lifestyle, diet and physical activity [2]. The main effect of MetS may be the worsening of the disease, especially in terms of clinical manifestations. Also, promoting the progression of structural damage through the cumulative impact of metabolic disorders may worsen the prognosis [18].

Numerous studies have recently been conducted to investigate the association between MetS and OA [9, 11, 22–24] but the association between MetS and OA remains controversial. While some studies suggest an association rather than a causal link, others point out that there is no association between MetS and OA [18, 22, 23]. There is still a consideration that OA is exclusively a consequence of the increased load on the joints due to excess weight [25]. It is undisputed that the mechanical effect caused by increased body weight can affect the development of knee OA in patients with MetS, but in recent years the emphasis has been on the metabolic effects of MetS [9]. The strongest epidemiological association between OA and MetS is found in knee OA, since higher body weight leads to a greater load on the supporting joints. However, obesity increases the risk of developing OA on joints that do not carry weight, like the hand [8, 9].

Systemic adipose tissue includes subcutaneous adipose tissue, visceral adipose tissue, intramuscular and intermuscular adipose tissue. An excess in visceral adipose tissue which is known as central obesity [26] plays an important role in the pathogenesis of OA, since it can promote systemic and local inflammation [24, 27]. Increased amount of adipose tissue in the body leads to metainflammation through the production of adipokines and cytokines which can modulate the immune system and

induce the synthesis of proinflammatory and catabolic mediators. This process may lead to chondrocyte dysfunction and accelerated progression of OA [27]. "Metabolic inflammation" was described by Hotamisligil et al. [28] in the late 1990s. They found that adipose tissue in obese mice and humans released higher amounts of tumor necrosis factor-α than in non-obese mice and humans. It remains unclear whether metainflammation is the cause or consequence of metabolic diseases or both considerations are true [25]. In addition to chronic inflammation, it is important to emphasize the influence of insulin resistance and the production of abnormal adipokines (tumor necrosis factor-α, interleukin-1, interleukin-6, leptin, and adiponectin) [22]. Adipokines, which are mainly secreted by white adipose tissue, have shown a systemic pro-inflammatory effect in many diseases [29]. Several studies compared adipokine levels in synovial fluid and blood in patients with and without OA. Good correlations were found between adipokines levels in synovial fluid and BMI. Higher levels of adipokines in synovial fluid and serum in OA patients were associated with disease severity and progression [25, 30].

The heterogeneity of results in current literature may be due to methodological differences, such as differences in the definition of MetS, different criteria for the diagnosis of OA, different age, gender and ethnicity of respondents [11]. Some studies did not consider the influence of factors that may contribute to the outcome such as smoking, physical activity level, or use of medications like antihypertensives and statins [13, 29]. Two reasons related to the design of the study are cited as a common lack of studies that have reported the association between MetS and OA. The first is the non-adjustment of results for body weight or BMI, while the second is the fact that most published studies were designed as cross-sectional studies [22].

Osteoarthritis and dysglycemia

Metabolic processes play an important role in the physiological turnover and remodelling of synovial joint tissue in both healthy and affected joints. Persistent hyperglycemia promotes oxidant production, which results in increased catabolism of the osteoarthritic cartilage matrix [17]. It is considered that the link between the two diseases is related to the adverse role of glucose excess due to accumulation of advanced glycation end products, oxidative stress and promotion of systemic inflammation [31]. Due to the accumulation of advanced glycation end products, the brittleness and stiffness of collagen increase, and the joint becomes additionally sensitive to mechanical stress [32]. It has been reported that cartilage is softer in diabetics and consequently submissive to damage [17]. Increased insulin resistance may contribute to the development of osteophytes and sclerosis of the subchondral bone [31].

Type II diabetes mellitus is a highly prevalent metabolic disorder with multifactorial etiology caused by an inadequate β-cell response to progressive insulin resistance [27, 33]. The incidence and prevalence of DM II have almost doubled within the last two decades, and a high incidence of DM II has been reported among patients with knee OA [27, 34]. It was reported that 47.3% of patients with DM II have some form of arthritis. Although an association between DM and OA has been shown, a causal link has not been well established [33]. Increased incidence of musculoskeletal diseases in patients with DM may be explained by common risk factors [27].

The association between DM II and OA has been investigated in several meta-analyses [31, 32]. Epidemiological and experimental evidence suggests that DM II may be an independent risk factor for the development and progression of the DM-induced OA phenotype [35]. The DM has also been reported to be a strong predictor of severe OA, regardless of age and body mass index [34]. Veronese et al. [33] found that after adjustment for age, BMI, and other potential risk factors, the DM II doubles the risk of severe OA which requires arthroplasty (hazard ratio = 2.1; 95% confidence index 1.1,3.8; p = 0.023). Additionally, DM II may harm the outcome of arthroplasty as it leads to an increased risk of postoperative mortality, reduces functionality, and increases the risk of infection and the need for revision arthroplasty [33]. To the contrary, the results of other studies did not support the link between DM and OA [22, 23].

Osteoarthritis and hypertension

Knee OA and cardiovascular disease are tightly associated with sedentary lifestyle and obesity, [17] but less attention has been paid to the association between hypertension and OA [25]. The mechanism that would explain the association between OA and hypertension is unclear. Both diseases have a high incidence and one of the possible explanations is common risk factors such as aging, obesity and chronic inflammation [29, 36]. It has been shown that multiple genes are involved in both OA and hypertension. It has also been reported that polymorphism in vitamin D receptors may be linked with decreased bone mineral density, OA, and hypertension [29]. Additionally, the proinflammatory cytokine interleukin-6 plays a significant role in the pathogenesis of both diseases [29, 37, 38]. The prevalence of hypertension is higher in patients with OA compared to the population without OA, and poorly regulated hypertension is related to the severity of OA. It has been suggested that hypertension may favour OA through its proatherogenic influence on the subchondral bone [25]. In their meta-analysis, Zhang and al. [29] found a significant relationship between hypertension and both radiographic and symptomatic knee OA. Also, a recent longitudinal study has shown that after adjustment for several confounders, patients with knee OA had a 13% higher chance of developing hypertension (hazard ratio 1.13; 95% confidence index: 1.01–1.26; p = 0.03) [39, 40].

Bone tissue is well supplied with blood vessels, and vascularization is closely related to growth, re-

newal and metabolic processes. There are several ways in which vascular pathology leads to damage to the integrity of the subchondral bone resulting in the development of OA [12]. A few mechanisms have been proposed to explain the association between OA and hypertension, [39] including the promotion of microvasculature remodelling [36]. It is considered that blood vessels are narrowing over time, which results in restriction of blood flow to the subchondral bone. Due to impaired blood flow, nutrient delivery is reduced and cartilage begins to deteriorate [39]. In addition to subchondral bone ischemia and osteocyte apoptosis, a decreased blood flow may induce osteoclastic bone resorption [41]. It should be emphasized that hypertension confers a prothrombotic state and microvascular thrombosis further exacerbates the already damaged subchondral bone perfusion [36].

Osteoarthritis and hyperlipidemia

While experimental studies suggest that lipid disorders may be related to the pathophysiology of OA, epidemiological studies show heterogeneous results [13]. Low-density lipoprotein (LDL) cholesterol may be involved in the pathophysiological processes associated with OA through the induction of synovial inflammation, cartilage destruction and ectopic bone formation [42]. The accumulation of cholesterol in cartilage can disrupt the efflux function of cartilage, leading to OA [25, 29]. It has been shown that dietary cholesterol intake leads more frequently to spontaneous cartilage damage in mice [42]. Study in ApoE knockout mice has shown that higher levels of LDL cholesterol in serum correspond to higher levels of pro-inflammatory cytokines [43]. On the other hand, in vivo studies have shown that reduced HDL cholesterol levels play a significant role in the pathogenesis of OA [42]. Also, it seems that higher levels of HDL cholesterol appear to protect against early knee bone-marrow lesions [25].

In their meta-analysis, Baudart et al. [13] showed that the prevalence of dyslipidemia was statistically significantly higher among patients with OA (30%) compared to patients without OA (8%) and that people with OA had 1.98 times higher risk of developing dyslipidemia compared to people without OA. The heterogeneity of epidemiological studies may be due to the use of different definitions of OA and different definitions of dyslipidemia [13].

Conclusion

Holistic treatment of patients with osteoarthritis should be based on an individualized approach including identification and management of risk factors. In addition to symptomatic pain relief and support for weight reduction, it is necessary to treat metabolic disorders, which will eventually lead to an improved biomechanical and metabolic condition of the joint. It is necessary to raise the level of awareness about the importance of primary and secondary prevention of metabolic syndrome to slow down the epidemic of knee osteoarthritis. In the era of diseases related to age and obesity, combined preventive measures are necessary to prevent complications and reduce treatment costs.

References

1. Dickson BM, Roelofs AJ, Rochford JJ, Wilson HM, De Bari C. The burden of metabolic syndrome on osteoarthritic joints. Arthritis Res Ther. 2019;21(1):289.

2. Francisco V, Ruiz-Fernández C, Pino J, Mera A, González-Gay MA, Gómez R, et al. Adipokines: linking metabolic syndrome, the immune system, and arthritic diseases. Biochem Pharmacol. 2019;165:196-206.

3. de Munter W, van der Kraan PM, van den Berg WB, van Lent PL. High systemic levels of low-density lipoprotein cholesterol: fuel to the flames in inflammatory osteoarthritis? Rheumatology (Oxford). 2016;55(1):16-24.

4. Minaković I, Zvekić-Svorcan J, Krasnik R, Mikov J, Mikov I, Bošković K. Povezanost mineralne koštane gustine i osteoartroze kod žena u postmenopauzi. Balneoclimatologia. 2022;46(1):225-34.

5. Zvekić-Svorcan J, Filipović K, Janković T, Nenadov N, Vasić J, Kučević I. Osteoartroza šake - dijagnostički i terapijski pristup. MD Medical data. 2014;6(4):379-82.

6. Zvekić-Svorcan J, Mikov A, Filipović K, Janković T. Analiza bola i funkcionalnog statusa pacijenata sa osteoartrozom kolena nakon primene transkutane električne nervne stimulacije. PONS - medicinski časopis. 2013;10(2):50-4.

7. Zvekić-Svorcan J. Povezanost funkcijskog stanja šake u osteoartrozi i koštane mase merene centralnom dvostrukom apsorpciometrijom X-zraka kosti kod žena u postmenopauzi [dissertation]. Novi Sad: Univerzitet u Novom Sadu; 2019.

8. Zvekić-Svorcan J, Stamenković B, Minaković I, Krasnik R, Janković T, Mikov A. Risk factors for hand osteoarthritis. Med Pregl. 2020;73(3-4):81-7.

9. Lee BJ, Yang S, Kwon S, Choi KH, Kim W. Association between metabolic syndrome and knee osteoarthritis: a cross-sectional nationwide survey study. J Rehabil Med. 2019;51(6): 464-70.

10. Nur H, Sertkaya BS, Tuncer T. Determinants of physical functioning in women with knee osteoarthritis. Aging Clin Exp Res. 2018;30(4):299-306.

11. Liu SY, Zhu WT, Chen BW, Chen YH, Ni GX. Bidirectional association between metabolic syndrome and osteoarthritis: a meta-analysis of observational studies. Diabetol Metab Syndr. 2020;12(1):38.

12. Azzini GOM, Santos GS, Visoni SBC, Azzini VOM, Santos RGD, Huber SC, et al. Metabolic syndrome and subchondral bone alterations: the rise of osteoarthritis - a review. J Clin Orthop Trauma. 2020;11(Suppl 5):S849-55.

13. Baudart P, Louati K, Marcelli C, Berenbaum F, Sellam J. Association between osteoarthritis and dyslipidaemia: a systematic literature review and meta-analysis. RMD Open. 2017;3(2):e000442.

14. Flierl MA, Sobh AH, Culp BM, Baker EA, Sporer SM. Evaluation of the painful total knee arthroplasty. J Am Acad Orthop Surg. 2019;27(20):743-51.

15. Pejčić A, Radunović A, Vulović M. Analysis of inpatient costs in patients with knee osteoarthritis treated by implantation

of total condylar knee endoprosthesis. Vojnosanit Pregl. 2018;75(10):989-97.

16. Li H, George DM, Jaarsma RL, Mao X. Metabolic syndrome and components exacerbate osteoarthritis symptoms of pain, depression and reduced knee function. Ann Transl Med. 2016;4(7):133.

17. Georgiev T, Angelov AK. Modifiable risk factors in knee osteoarthritis: treatment implications. Rheumatol Int. 2019;39(7):1145-57.

18. Courties A, Berenbaum F, Sellam J. The phenotypic approach to osteoarthritis: a look at metabolic syndrome-associated osteoarthritis. Joint Bone Spine. 2019;86(6):725-30.

19. Zvekic-Svorcan J, Jankovic T, Aleksic J, Stamenkovic B, Krasnik R, Mikov A, et al. Can high BMI be considered a risk factor for hand osteoarthritis development? Osteoporos Int. 2020;31(Suppl 1):154.

20. Jiang L, Xie X, Wang Y, Wang Y, Lu Y, Tian T, et al. Body mass index and hand osteoarthritis susceptibility: an updated meta-analysis. Int J Rheum Dis. 2016;19(12):1244-54.

21. Consensus statements. 2006 [updated 2020 Jul 29; cited 2021 Sep 11]. Available from: https://www.idf.org/e-library/consensus-statements/60-idfconsensus-worldwide-definitionof-the-metabolic-syndrome.html

22. Li S, Felson DT. What is the evidence to support the association between metabolic syndrome and osteoarthritis? A systematic review. Arthritis Care Res (Hoboken). 2019;71(7):875-84.

23. Niu J, Clancy M, Aliabadi P, Vasan R, Felson DT. Metabolic syndrome, its components, and knee osteoarthritis: the Framingham Osteoarthritis Study. Arthritis Rheumatol. 2017; 69(6):1194-203.

24. Xie DX, Wei J, Zeng C, Yang T, Li H, Wang YL, et al. Association between metabolic syndrome and knee osteoarthritis: a cross-sectional study. BMC Musculoskelet Disord. 2017; 18(1):533.

25. Courties A, Sellam J, Berenbaum F. Metabolic syndrome-associated osteoarthritis. Curr Opin Rheumatol. 2017;29(2):214-22.

26. Chang J, Liao Z, Lu M, Meng T, Han W, Ding C. Systemic and local adipose tissue in knee osteoarthritis. Osteoarthritis Cartilage. 2018;26(7):864-71.

27. Gratal P, Lamuedra A, Medina JP, Bermejo-Álvarez I, Largo R, Herrero-Beaumont G, et al. Purinergic system signaling in metainflammation-associated osteoarthritis. Front Med (Lausanne). 2020;7:506.

28. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science. 1993;259(5091):87-91.

29. Zhang YM, Wang J, Liu XG. Association between hypertension and risk of knee osteoarthritis: a meta-analysis of observational studies. Medicine (Baltimore). 2017;96(32):e7584.

30. Calvet J, Orellana C, Gratacós J, Berenguer-Llergo A, Caixàs A, Chillarón JJ, et al. Synovial fluid adipokines are associated with clinical severity in knee osteoarthritis: a cross-sectional study in female patients with joint effusion. Arthritis Res Ther. 2016;18(1):207.

31. Louati K, Vidal C, Berenbaum F, Sellam J. Association between diabetes mellitus and osteoarthritis: systematic literature review and meta-analysis. RMD Open. 2015;1(1):e000077.

32. Williams MF, London DA, Husni EM, Navaneethan S, Kashyap SR. Type 2 diabetes and osteoarthritis: a systematic review and meta-analysis. J Diabetes Complications. 2016;30 (5):944-50.

33. Veronese N, Cooper C, Reginster JY, Hochberg M, Branco J, Bruyère O, et al. Type 2 diabetes mellitus and osteoarthritis. Semin Arthritis Rheum. 2019;49(1):9-19.

34. Neumann J, Hofmann FC, Heilmeier U, Ashmeik W, Tang K, Gersing AS, et al. Type 2 diabetes patients have accelerated cartilage matrix degeneration compared to diabetes free controls: data from the Osteoarthritis Initiative. Osteoarthritis Cartilage. 2018;26(6):751-61.

35. Li Q, Wen Y, Wang L, Chen B, Chen J, Wang H, et al. Hyperglycemia-induced accumulation of advanced glycosylation end products in fibroblast-like synoviocytes promotes knee osteoarthritis. Exp Mol Med. 2021;53(11):1735-47.

36. Ashmeik W, Joseph GB, Nevitt MC, Lane NE, McCulloch CE, Link TM. Association of blood pressure with knee cartilage composition and structural knee abnormalities: data from the Osteoarthritis Initiative. Skeletal Radiol. 2020;49 (9):1359-68.

37. Ma H, Sun G, Wang W, Zhou Y, Liu D, Tong Y, et al. Association between interleukin-6 -572 C>G and -174 G>C polymorphisms and hypertension: a meta-analysis of case-control studies. Medicine (Baltimore). 2016;95(2):e2416.

38. Qu XQ, Wang WJ, Tang SS, Liu Y, Wang JL. Correlation between interleukin-6 expression in articular cartilage bone and osteoarthritis. Genet Mol Res. 2015;14(4):14189-95.

39. Angeli F, Trapasso M, Signorotti S, Verdecchia P, Reboldi G. Amlodipine and celecoxib for treatment of hypertension and osteoarthritis pain. Expert Rev Clin Pharmacol. 2018; 11(11):1073-84.

40. Veronese N, Stubbs B, Solmi M, Smith TO, Noale M, Schofield P, et al. Knee osteoarthritis and risk of hypertension: a longitudinal cohort study. Rejuvenation Res. 2018;21(1):15-21.

41. Lo K, Au M, Ni J, Wen C. Association between hypertension and osteoarthritis: a systematic review and meta-analysis of observational studies. J Orthop Translat. 2022;32:12-20.

42. Xiong J, Long J, Chen X, Li Y, Song H. Dyslipidemia might be associated with an increased risk of osteoarthritis. Biomed Res Int. 2020;2020:3105248.

43. Hashimoto K, Akagi M. The role of oxidation of low-density lipids in pathogenesis of osteoarthritis: a narrative review. J Int Med Res. 2020;48(6):300060520931609.

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