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DISCUSSION ON THE RELATIONSHIP BETWEEN METABOLIC SYNDROME AND OSTEOARTHRITIS

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Abstract: Osteoarthritis (OA) is a multifactorial degenerative joint disease, mainly involving changes in articular cartilage, subchondral bone, ligaments, joint capsule, synovium and periarticular structures. Its pathogenesis remains unclear. As my country's population ages, the incidence of OA is gradually increasing. At the same time, most elderly patients are accompanied by basic metabolic diseases such as hypertension and diabetes. Metabolic osteoarthritis has now been identified as a new subtype of OA. In addition to surgical treatment, palliative treatment is the first choice, but its effect is limited. Therefore, metabolic osteoarthritis imposes a heavy burden on society and individuals, especially elderly patients. This article mainly introduces the current research status of the relationship between metabolic syndrome and osteoarthritis, and provides reference for the exploration of related targeted therapies.
Keywords: Osteoarthritis; Metabolic syndrome; Adipocytokines; Macrophages; Intestinal flora

1OSTEOARTHRITIS OVERVIEW OF OSTEOARTHRITIS (OA) AND METABOLIC SYNDROME

The main symptom of OA is pain. It is estimated that the number of patients worldwide exceeds 250 million, and the annual medical expenditure for this disease exceeds US$185 billion [1]. It is more common in middle-aged and elderly people. The most common site of disease is the knee joint, followed by the hand and hip joint. The incidence rate is higher in women than in men [2]. Wallace et al.[3] studied a large number of American adult remains and found that the incidence of OA has increased more than 2 times since the mid-20th century. However, there is evidence that increased life span may not be the only reason for the increase in the incidence of OA, as it is related to most diseases. Similarly, the pathogenesis of OA involves the interaction between genes and the environment. To some extent, OA also conforms to the concept of what biologists call "mismatch disease", such as the improvement of people's quality of life and the The prevalence of obesity caused by changes in modern lifestyles is a recognized risk factor for OA. It is also worth noting that elderly patients often have one or more comorbidities. A foreign study shows that more than half of elderly OA patients suffer from hypertension, followed by cardiovascular disease (20%), blood lipids Abnormalities (19%), diabetes (14%), etc.[4-5].

Metabolic syndrome is a disease caused by the interaction of environmental factors and genetic defects. The core of the disease is insulin resistance [4]. This new non-communicable disease has become a major health threat in modern society. The definition of metabolic syndrome varies slightly between regions and organizations. The most popular one used for investigation and medical care is the 1999 WHO definition of metabolic syndrome. Symptoms are: insulin resistance combined with at least 2 of obesity, elevated triglyceride levels, reduced high-density lipoprotein levels, or hypertension. Based on the characteristics of the Chinese population, the 2017 version of China’s Type 2 Diabetes Prevention and Treatment Guidelines stipulates that at least three of the following are required to diagnose metabolic syndrome: (1) Abdominal obesity (ie, central obesity): waist circumference ≥ 90 cm for men and ≥ 85 cm for women; (2) Hyperglycemia: Fasting blood glucose ≥ 6.l mmol/L or 2 hours after glucose load blood glucose ≥ 7.8 mmol/L and/or those who have been diagnosed and treated for diabetes; (3) Hypertension: blood pressure ≥ 130/85 mm Hg (1 mm Hg = 0.133 kPa) and/or those with confirmed and treated hypertension; (4) Fasting triglyceride ≥ 1.70 mmol/L; (5) Fasting high-density lipoprotein < 1.04 mmol/L. Metabolism has an important influence on cartilage and synovial joint function. Under adverse microenvironmental conditions, the cellular metabolism of mammalian cells undergoes a transition from a resting regulatory state to a hypermetabolic activation state to maintain energy homeostasis. This phenomenon also leads to an increase in metabolic intermediates in the biosynthesis of inflammatory and degradable proteins, which in turn activates key transcription factors and inflammatory signaling pathways involved in catabolic processes, and perpetuates the driving factors of pathogenesis [6-7]. Foreign studies have suggested that abnormal immune metabolism is an important feature of the pathogenesis of OA, and have proposed that metabolic OA may be a new subtype of OA [8].

OA and metabolic syndrome have a close co-morbidity relationship. Statistics on 7714 cases show that metabolic syndrome is prevalent in 59% of OA patients and 23% of people without OA. The study also found that people without obesity and other metabolic-related problems The risk of knee OA in the general population is only 9.6%, while the risk of obese people, especially women, is as high as 23.8% [6].

Obesity is an important risk factor for OA. It has long caused the loss of cartilage and the generation of osteophytes. It is also considered to be the protective role of bone and the reaction process to stabilize joints. However, surveys have found that such patients have problems with non-weight-bearing parts such as hands. The incidence of OA has also

increased significantly [9]. Clinical and animal findings suggest that this link is more likely to be related to increases in metabolic and immune-related systemic and local inflammation. Engstrδm et al [10] conducted a cohort study of 5171 cases from 1991 to 1994, suggesting that obese patients with metabolic syndrome have an increased risk and severity of knee and hand OA. The above studies have shown that metabolic syndrome is closely related to the occurrence of OA. In addition to the additional mechanical stress caused by overweight, metabolic syndrome can also affect the occurrence of OA through various other pathways. Metabolic syndrome has also been identified as an important contributor to the increased prevalence of metabolic syndrome by affecting adipokines levels, inducing macrophage polarization, and altering intestinal obesity-related chronic low-grade inflammation [9]. Adipocytes are the main component of adipose tissue and can secrete physiologically active molecules and inflammatory cytokines. These secreted products are called adipokines. Adipokine plays an important physiological role in metabolic activities. Taking the knee joint as an example, the infrapatellar fat pad is the main source of adipokine in the synovial fluid of the knee joint. Adipocytes will also increase in the process of aging and obesity. Accumulated in bone marrow, its adipokines can be used as the relationship and mechanism between microbial flora composition and OA.

2ADIPOKINE AND OA

People have gradually recognized that OA is a disease in which joints are in a state of persistent low-grade inflammation. Obesity, especially the expansion of visceral fat, can lead to chronic low-grade inflammation throughout the body [11-12], which is also a senescence associated secretory phenotype factor (SASPs) [13] and adipokines involved in chondrocyte aging. It participates in the regulation of systemic and local joint-related autoimmune and/or inflammatory processes. Therefore, the dysregulation of pro-inflammatory adipokines secreted by metabolic syndrome is an important trigger factor in mediating joint lesions.

1. Adiponectin is a hormone secreted by adipocytes, also known as Acrp30 (30 kDa adipose complement-related protein), apM1 (the most abundant gene transcript in adipose tissue), GBP28 (28 kDa gelatin-binding protein) or AdipoQ (highly pure recombinant protein) [14]. Adiponectin mainly works through two receptors, namely AdipoR1, which exists in skeletal muscle, and AdipoR2, which mainly exists in the liver. When adiponectin binds to its receptor, it will cause adenylate-activated protein kinase (AMPK). , PPAR-C and PPAR-γ and other signaling pathways [15]. Adiponectin plays an important role in fighting atherosclerosis and diabetes, and is closely related to metabolic syndrome. It is found in patients with pathological obesity, metabolic syndrome, and animal models of insulin resistance [16]. The level is significantly reduced. Adiponectin may have anti-inflammatory effects on chondrocytes, thus protecting cartilage from degeneration. Studies have shown that primary chondrocytes treated with adiponectin up-regulate tissue inhibitor of metalloproteinase-2 and down-regulate IL-1β-mediated human matrix metalloproteinase-13 (MMP13) gene expression. Adiponectin-treated rat articular cartilage Cells induce autophagy through AMPK/m-TOR and attenuate H2O2-induced apoptosis [17]. Landgraeber et al [18] used immunohistochemical methods to detect adiponectin levels, receptors and cell apoptosis in patients with aseptic loosening and non-loosening patients after joint replacement. In addition, they also established adiponectin gene knockout mice. Murine models demonstrated that adiponectin plays an important role in particle-induced osteolysis. Current evidence suggests that high levels of adiponectin play a protective role in the occurrence of metabolic syndrome and prosthetic loosening after OA joint replacement.

2. Leptin is mainly produced by adipocytes, and its level mainly depends on the quality of white adipose tissue. Some inflammatory factors can also regulate leptin levels [19]. Both leptin and its receptor (leptin receptor, Ob-R) can be detected in chondrocytes. Leptin is a powerful regulator of the immune system. In addition, it also affects food energy intake, bone and Cartilage metabolism and other functions [12,20]. Leptin is closely related to metabolic syndrome, and studies have found that hyperleptinemia has been observed in both male and female patients with metabolic syndrome [21]. As evidence accumulates, circulating leptin levels are considered an obesity-dependent predictor of the development of metabolic syndrome, which may be associated with the development of glucose intolerance and insulin resistance. Dumond et al [22] demonstrated elevated leptin levels in serum, infrapatellar fat pad, synovial tissue, and cartilage in OA patients compared with healthy controls. G6mez et al. [23] also recently discovered that leptin can also induce MMP13, IL-6, IL-8, nitric oxide (NO), nitric oxide synthase (NOS), prostaglandin E2 (PGE2) and Pro-inflammatory factors such as cyclooxygenase-2 (COX2) are expressed, thereby promoting cartilage degradation. This evidence strongly supports the link between leptin and OA.

3. Lipocalin-2 is a glycoprotein. Although there are fewer relevant studies on lipocalin-2 compared with adiponectin and leptin, it is also an adipokine with important immunomodulatory ability.. Lipocalin-2 plays an important role in metabolic syndrome. The concentration of lipocalin-2 is generally increased in obese patients and can be reduced after treatment with thiazolidinediones [23]. Circulating lipocalin-2 levels are positively correlated with obesity, hyperglycemia, insulin resistance, and hypertriglyceridemia, and negatively correlated with high-density lipoprotein levels [24]. In osteoblasts, lipocalin-2 is induced by tumor necrosis factor-C (TNF-C) and IL-17 in the absence of mechanical load, stimulating osteoclastic factors and activating nuclear factor kappa B (NF-κB). Signaling pathways and IL-6 promote bone metabolism. However, overexpression of lipocalin-2 in mouse cartilage did not induce the onset of OA, and knocking out lipocalin-2 did not affect cartilage destruction induced by medial meniscal instability in mice [25]. The relationship between lipocalin-2 and human OA still needs to be further elucidated.

3 METABOLIC SYNDROME INDUCES MACROPHAGE POLARIZATION

1. Macrophages are the key effector cells of OA. They are cells with significant plasticity and mainly have two activation types: M1 type induced by pro-inflammatory factors and M2 type with anti-inflammatory protective effect. Synovial membrane And the tilt of macrophages in adipose tissue toward a pro-inflammatory M1 phenotype is thought to play a role in the pathogenesis of OA [26]. Early evidence comes from the collagenase-induced mouse OA model. When macrophages are ablated before induction of the OA model, osteophyte formation can be reduced by 84% [27]. Recently, Kraus et al. [28] also confirmed this through SPECT-CT. Activated macrophages are directly involved in the development of synovitis in human OA. The proliferation, plasticity and polarization of macrophages are also affected by metabolic syndrome. Metabolic syndrome can promote macrophages to change from M2 phenotype to M1 phenotype through various molecular mechanisms such as cellular metabolism disorders and changes in adipokine levels. This change can be observed in metabolic tissues such as fat, liver, and muscle.
2. The activation and infiltration of macrophages into the synovium is caused by initial damage to the joint, releasing a large number of damage-associated molecular patterns (DAMPs), which are recognized by pattern recognition receptors expressed by macrophages and subsequently activated. The NF-κB signaling pathway produces inflammatory mediators such as TNF, IL-6, IL-1β, etc., and the released inflammatory mediators further lead to the activation of fibroblast-like synoviocytes, producing matrix metalloproteinases (MMPs) and type I platelets. adisintegrin and metalloprotease with thrombospondin 1 repeats, ADAMTS) thus leading to cartilage degradation [29]. At the same time, activated macrophages and fibroblasts can release chemotactic proteins to recruit circulating monocytes to infiltrate into the synovium, and these monocytes differentiate into macrophages [30], and so on, OA patients The vast majority of macrophages in joints ultimately skew towards the pro-inflammatory M1 phenotype. Macrophages can also sense the level of metabolic disorders through AMPK and mammalian target of rapamycin-1 (mTORC1). A large number of studies have shown that the presence of metabolic syndrome reduces the level of AMPK [17], and macrophages also increase cellular anaerobic glycolysis through hypoxia-inducible factor-1 (HIF-1), increasing the production of reactive oxygen species. The NF-κB signaling pathway is activated, ultimately leading to the polarization of macrophages toward the M1 phenotype and accelerating the progression of OA. Protein kinase B (AKt) is a protein kinase that plays a key role in cell survival and apoptosis. It can upregulate genes such as Ym1, Arg, and Fizz1 that are extremely important for macrophage M2 phenotype polarization. It can also downregulate PRR and Toll-like receptors-4 (TLR4) produces the necessary Forkhead transcription factor 1 (FOXO1) to inhibit macrophage M1 phenotype polarization, while obesity and overnutrition promote the overactivation of mTORC1, thereby inhibiting The expression of AKt [31] ultimately leads to the M2 phenotype polarization defect of macrophages, promotes the expression of OA-related genes, and ultimately induces the formation of OA.
3. In addition to affecting key nutritional sensors, multiple studies have also shown that metabolic syndrome can directly affect advanced glycation end products (AGEs) [32] and free fatty acids [33] to affect macrophages. function. AGEs are responsible for changing biochemical properties in normal cartilage tissue. Under the influence of high blood sugar, the self-changing ability of AGEs is reduced. The AGEs receptors on macrophages recognize AGEs, activate the NF-κB signaling pathway, and promote the increase in TNF and IL-1β transcription. , ultimately causing macrophages to polarize toward the M1 phenotype. Free fatty acids are also in a similar situation. When the body has excess nutrition, healthy fat cells expand excessively, and the fat cells cannot safely store lipids. Excess lipids exist in the form of free fatty acids. Free fatty acids combine with TLR4 to cause a large amount of Pro-inflammatory factors are released and the macrophage M1/M2 phenotype ratio increases. It can be seen that the imbalance of macrophage polarization is also an important common mechanism between metabolic syndrome and OA.

4 INTESTINAL MICROBIOTA AND OA

1. The human digestive tract is a huge ecosystem rich in nutrients and containing countless microorganisms. The total area of the digestive tract can reach 250 to 400 m2. A large number of bacteria live in the vast intestinal tract. Environmental stability plays an important role [34]. Imbalance of intestinal microflora mainly refers to: reduction of beneficial bacteria, increase of pathogenic bacteria or reduction of overall biodiversity. Changes in the balance mechanism of the microbiome in the body caused by overnutrition, use of microbial agents or immune dysfunction are the basis for many diseases.. Many studies have confirmed that intestinal microorganisms are related to the pathogenesis of OA. Guss et al. [35] used continuous weight-bearing to induce cartilage damage in mice. The cartilage damage of mice treated with antibiotics for a long time was much lower than that of mice in other groups. This shows that treatment of intestinal flora is effective in alleviating cartilage damage in OA. Boer et al. [36] found that the abundance of Streptococcus in the intestine was positively correlated with joint pain scores, and was positively correlated with the degree of local inflammation in the joint (assessment of fluid effusion volume), suggesting that Streptococcus may aggravate pain by increasing local inflammation. It can be inferred that intestinal microbiota may be related to the onset and clinical manifestations of OA.
2. Dietary fiber governs the metabolism of the intestinal microbiota and protects against diseases such as diabetes and coronary heart disease. There are also data suggesting that the gut microbiota may determine adipose tissue physiological characteristics through lipopolysaccharide-endocannabinoid system regulatory loops and may play a key role in adipose tissue plasticity during obesity [37]. Wang et al. [38] also found that metabolic-related diseases in obese

mice improved after probiotics were used to improve the composition of intestinal microflora. Based on this, multiple studies have used prebiotic supplements to modulate the intestinal microbiota to confirm its causal relationship with systemic inflammation, metabolic dysregulation, and host disease [39]. The main component of prebiotics is cellulose, which plays an important role in the activation and growth of bacteria. For example, indigestible fiber fructose oligosaccharides are not metabolized or absorbed before entering the colon. Instead, they pass through the gastrointestinal tract and are fermented by different species of resident microbial communities in the colon. It follows that the host effects of fructooligosaccharides and other similar prebiotics are dependent on the biological effects exerted by the gut microbiota. Because of their ability to predictably alter the gut microbiota without direct effects on the host, prebiotics have become important research reagents that shed light on the relationship between gut microbes and the host. In this context, Schott et al. [40] found that mice fed a high-fat diet lost a large number of bifidobacteria after treatment with fructooligosaccharides, and this change in intestinal microbiota can directly affect intestinal epithelial permeability. The integrity of intestinal microbiota and barrier function resulted in a decrease in the circulating levels of pro-inflammatory cytokines including KC, MIP-IB, M-CSF, Tnf and IL-12 in mice. This finding strongly demonstrates the impact of intestinal microbiota on systemic or Local inflammatory responses have far-reaching consequences

3. Steves et al [41] found that intestinal flora can change the inflammatory state of an individual by affecting the host's metabolic potential and its innate and adaptive immune systems. It is reported that vitamins, magnesium, and especially amino acids in the daily diet have a significant impact on the intestinal microflora, especially the ratio of Firmicutes/Bacteroidetes, and are also related to the onset of OA. This is precisely because the intestinal Changes in the abundance of intestinal microbiota can lead to increased translocation of microbe-associated molecular patterns (MAMPs) on the intestinal endothelium into the systemic circulation. Microbial polysaccharides, including lipopolysaccharides, peptidoglycan and bacterial DNA and other factors, can stimulate changes in bacterial abundance in the resident flora of bone, cartilage and synovium and the deposition of synthetic immune complexes in the synovium [42]. The intestinal microbiota and the innate immune system can function as a complex whole. The innate immune system can shape the intestinal microbiota, and the intestinal microbiota also has the function of immune activation. Ulici et al. [43] and Cheng et al. [44] found Genetic modification of NLRP3 inflammasome or TLR5 can lead to impaired glucose metabolism, which is closely related to changes in the structure of the intestinal microbiota, which further validates the above view. At the same time, changes in the structure of the intestinal microbiota, increased levels of TLR ligands, and overexpression of TLRs have also been observed in mice and humans with obesity or metabolic disorders [44]. Therefore, the intestinal microbiota has been confirmed to be an important cause of immune triggering in the pathogenesis of OA. Recently, Huang et al. [45] transplanted feces from Met-OA patients into germ-free mice. Through 16S rRNA gene sequencing and gene set enrichment analysis, they found that the changing trend of intestinal microbiota abundance is related to the histological severity of OA and inflammatory organisms. The markers are closely related, proving the important role that intestinal microbiota plays in the occurrence of OA.

5 SUMMARY

The previous understanding of the pathogenesis of OA only focused on "wear and tear". With the accumulation of a large amount of new evidence, the importance of systemic and local "chronic low-grade inflammation" in OA has begun to receive attention. Although in several recent reviews In recent studies, metabolic syndrome and its specific components (hypertension, hypertensive The correlation between sugar, hyperlipidemia) and OA is still controversial [46-47], but many Metabolic syndrome can affect adipokine levels and macrophage polarity. ation, providing a permissive inflammatory environment for the pathophysiology of OA, and also It can activate the host's natural immunity by changing the composition of intestinal microflora. Provides a unifying mechanism for the link between OA and metabolic inflammation. do For clinicians, through understanding the relationship between metabolic syndrome and OA, It will help to carry out better early diagnosis and prevention work for such patients in the future, Improve the patient's prognosis and effectively improve the patient's quality of life.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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