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REVIEW

Revisiting the Subtle Relationship Between Metabolic Syndrome and Osteoarthritis

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Background: Osteoarthritis (OA) is a common disabling joint disorder traditionally attributed to mechanical wear. Emerging evidence shows that metabolic syndrome (MetS) and its components—obesity, hypertension, hyperglycemia, and dyslipidemia—are closely associated with OA onset and progression, suggesting that OA also has a metabolic-inflammatory nature.

Main Text: This review highlights mechanisms linking each MetS component to OA. Obesity contributes not only by increasing joint load but also through adipokines such as leptin, resistin, and visfatin, which activate inflammatory pathways and promote cartilage degradation and synovitis. Hypertension may worsen OA via joint ischemia, oxidative stress, and renin–angiotensin system activation. Hyperglycemia damages cartilage and ligaments by promoting advanced glycation end product accumulation and oxidative stress. Dyslipidemia influences OA through cholesterol deposition and inflammatory responses. Metabolic inflammation and immunometabolic reprogramming further drive OA progression.

Conclusion: MetS and OA are interconnected through mechanical stress, adipokine activity, inflammatory signaling, and metabolic dysregulation. Future studies should clarify how MetS affects pain, subchondral bone remodeling, and other OA phenotypes, aiding the development of individualized, metabolism-targeted strategies for early intervention and comprehensive OA management.

Keywords: inflammatory factors, metabolic syndrome, metabolomics, osteoarthritis

Review Criteria

Using the keywords "osteoarthritis", together with "metabolic abnormalities", "metabolic syndrome", "obesity", "hypertension", "hyperglycemia", "diabetes", "insulin resistance", "dyslipidemia", "inflammatory factors", and "immunometabolism", we conducted independent searches in the PubMed database. We focused on research evidence published within the past five years and restricted the search to studies written in English. Duplicate records, studies with low relevance or poor quality, articles with unclear viewpoints, and literature that was not accessible for full-text download were excluded.

Background

Osteoarthritis (OA) is the most common form of arthritis and is characterized as a chronic degenerative disease affecting the joints. Its primary clinical manifestation is joint pain, which ultimately leads to structural abnormalities and loss of joint function, making OA a major cause of disability.[1] Pathological changes typically include partial or full-thickness loss of articular cartilage, synovial inflammation, osteophyte formation, meniscal extrusion and tearing, bone marrow lesions, and narrowing of the joint space (Figure 1).[2,3] As there are currently no effective therapies capable of halting OA progression, patients with end-stage disease often require joint replacement surgery, imposing a substantial global medical and economic burden.[4] As of 2024, OA remains the most prevalent musculoskeletal disorder, with its global burden continuing to rise; approximately 7.6% of the world's population is affected, and this figure is projected to increase by 60–100% by 2050. Notably, among all disabling conditions in individuals aged over 70 years, OA ranks

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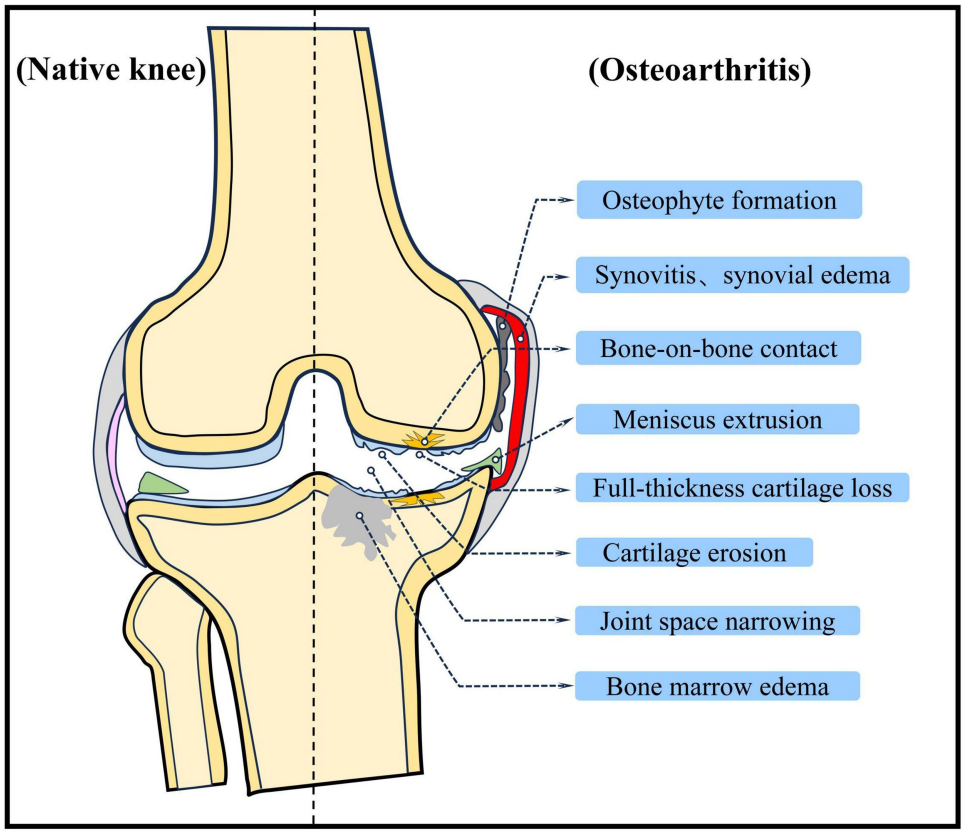

Figure 1 Native knees and osteoarthritic knees exhibit significant structural and functional differences.

seventh worldwide and predominantly affects the knee joint.[5] In traditional concepts, the etiology of OA was primarily attributed to mechanical wear and other external forces, with obesity considered the major contributing factor. However, the most recent perspectives regard OA as a highly complex mechanical–inflammatory disease characterized by heterogeneity, multifactorial influences, multidimensional interactions, and multiple sources and origins. Accordingly, OA can be classified into several distinct phenotypes and endotypes, among which metabolic OA represents an important subtype.[6,7] Moreover, studies have shown that hand joints, as non–weight-bearing regions, can still develop hand osteoarthritis (HOA). After excluding the direct confounding mechanical effects of obesity, HOA was found to be significantly associated with metabolic syndrome (MetS).[8–10] These findings highlight the critical role of metabolic abnormalities in the onset and progression of OA.

Table 1 summarizes the commonly used definitions of MetS in recent years.[11–13] MetS is regarded as a clinical syndrome comprising multiple metabolic abnormalities, including central obesity, hypertension, hyperglycemia, and dysregulated lipid metabolism.[14] It is also considered a major risk factor for cardiovascular diseases.[15] In clinical practice, we frequently observe that many patients with OA requiring surgical intervention present with comorbid

Table 1 Definitions of Metabolic Syndrome[#]

	NCEP ATP III (2005)[4]	IDF (2005)[5]	IDF and AHA/NHLBI (2009)[6]
Diagnostic premise	Any three of the five	Obesity plus two of the four others	Any three of the five
Obesity	Waist circumference: ≥94cm (men) ≥80cm (women)	Waist circumference: ≥94cm (men) ≥80cm (women)	Population- and country-specific definitions*
Elevated blood pressure	≥130mmHg systolic or ≥85mmHg diastolic	≥130mmHg systolic or ≥85mmHg diastolic	≥130mmHg systolic or ≥85mmHg diastolic

(*Continued*)

Table 1 (Continued).

	NCEP ATP III (2005)[4]	IDF (2005)[5]	IDF and AHA/NHLBI (2009)[6]
Elevated fasting glucose	Fasting glucose ≥5.6mmol/L	Fasting glucose ≥5.6mmol/L	Fasting glucose ≥5.6mmol/L
Elevated triglycerides	TG ≥1.7mmol/L	TG ≥1.7mmol/L	TG ≥1.7mmol/L
Reduced HDL-C	<1.03mmol/L (men) <1.29mmol/L (women)	<1.03mmol/L (men) <1.29mmol/L (women)	<1.00mmol/L (men) <1.30mmol/L (women)

Notes: # All values were derived in the absence of pharmacological intervention. Abbreviations: NCEP ATP III-the US National Cholesterol Education Program Adult Treatment Panel III; IDF-International Diabetes Federation; AHA/NHLBI-the American Heart Association/National Heart, Lung, and Blood Institute. * Refer to the cited literature for specific numerical values.

MetS. Joint pain is the predominant symptom of OA, and current evidence suggests that OA-related pain mainly originates from synovitis, bone marrow lesions, osteophyte formation, meniscal degeneration or tears, and the infrapatellar fat pad (IFP).[16–18] Moreover, OA is often accompanied by hyperalgesia.[19] The systemic and local inflammatory state induced by MetS is closely intertwined with these pain-generating mechanisms in OA.[20,21] Furthermore, the presence of MetS is associated with an earlier onset of OA and more severe symptoms. Therefore, elucidating the relationship between MetS and OA holds substantial clinical and scientific significance.

In this review, we primarily discuss the relationships between various metabolic abnormalities within MetS and the pathological changes observed in different joint tissues affected by OA. In addition, we address the interactions between inflammatory and immune factors and the development of OA.

Obesity and Osteoarthritis

Obesity—particularly abdominal obesity—plays a critical role in the onset and progression of OA[22] and is widely recognized as a major risk factor. Obesity directly increases the mechanical load on weight-bearing joints, exacerbating mechanical wear and thereby promoting the development and progression of OA.[23] For example, a high body mass index (BMI) is significantly positively correlated with the incidence of OA in weight-bearing joints such as the hip and knee, and is also associated with increased pain severity.[1] At the same time, obesity reflects an expansion of adipose tissue volume. Numerous studies have demonstrated that adipokines released by adipose tissue contribute to OA progression[24,25] and exert detrimental effects on the synovium, bone, and other joint tissues.[26] In the following sections, we discuss the relationship between obesity and OA from both mechanical and biological perspectives.

Mechanical Factors

Studies have shown that moderate mechanical stress—such as jogging or swimming—can stimulate chondrocytes to secrete collagen, thereby prolonging joint longevity. In contrast, excessive mechanical loading in individuals with obesity generates high-intensity stress that promotes chondrocyte catabolism and induces a senescence-associated secretory phenotype (SASP).[27,28] Moreover, excessive mechanical stress can directly cause cartilage injury.[29,30] Recent evidence further demonstrates that in both in vivo and in vitro settings, mechanical overload leads to downregulation of FBXW7 (a ubiquitin ligase) in chondrocytes, which subsequently promotes chondrocyte senescence and apoptosis through the MKK7–JNK signaling pathway.[30] However, the mechanisms underlying the FBXW7 downregulation induced by excessive mechanical stimulation remain unclear.

In addition, an increasing number of studies have identified numerous mechanosensitive ion channels on the chondrocyte surface that respond to external mechanical stress and help maintain the stability of their physiological structure.[31–33] Consequently, mechanical stimulation can influence the metabolic microenvironment of chondrocytes. For example, excessive mechanical loading has been shown to induce GPX4-downregulation–related ferroptosis in chondrocytes. Mechanical overload activates the mechanosensitive Piezo1 channel on the chondrocyte membrane, leading to increased Ca^{2+} influx and accelerated ferroptosis. It can also activate the NF-κB signaling pathway, promoting the

senescence of human nucleus pulposus cells (hNPCs) and contributing to spinal degeneration. Interestingly, supplementing overloaded chondrocytes with ferroptosis-regulating factors such as Fsp1 and CoQ10 can rescue cells from ferroptosis and oxidative damage.[34,35] For example, excessive mechanical loading reduces the expression of PDZK1 (a PDZ domain–containing protein that functions as a mechanosensitive Na^+/H^+ exchange channel) on the surface of chondrocytes. This reduction directly impairs the mitochondrial oxidative respiratory chain, leading to mitochondrial dysfunction, accumulation of reactive oxygen species (ROS), and subsequent cellular senescence. Notably, overexpression of PDZK1, exogenous supplementation with the mitochondria-targeted coenzyme Q analogue (MitoQ), or treatment with β-hydroxybutyrate (BHB) can alleviate OA symptoms.[36] These findings indicate that excessive mechanical stress negatively affects chondrocyte metabolism through mechanogated channels. Age-related degeneration of articular cartilage leads to joint space narrowing and alterations in limb alignment, followed by the formation of periarticular osteophytes. Excessive osteophyte growth can further trigger synovitis and meniscal damage, thereby exacerbating knee pain.[18,37] In addition, hypertrophic osteophytes in the intercondylar notch may exert a cutting effect on the anterior cruciate ligament (ACL), resulting in knee instability.[38,39] Figure 2 summarizes these mechanistic processes.

Biological Factors

In addition to increasing the mechanical load on weight-bearing joints, obesity is characterized most prominently by an overall expansion of adipose tissue mass. The role of adipose tissue in OA was previously underappreciated; however, with advances in clinical research, it has become clear that adipose tissue produces numerous adipokines—such as leptin, resistin, visfatin, and adiponectin.[40–42] These adipokines contribute to systemic or local inflammatory states and play a crucial role in the initiation and progression of OA.[43–46] Adipose tissue is now widely regarded as a specialized endocrine organ.[47] Within human joints, articular cartilage consists of chondrocytes and the extracellular matrix (ECM). Early degenerative changes in OA are characterized by the degradation of collagen and proteoglycans within the ECM, and adipokines are key triggers of this matrix breakdown.[2,43] In addition, the IFP is an important contributor to knee pain in patients with OA. Thrombospondin-4 (TSP-4), released by the IFP, is closely associated with synovitis and synovial fibrosis.[48–50] Both clinical studies and animal experiments have demonstrated that partial resection of the IFP can significantly reduce joint inflammation and pain, while

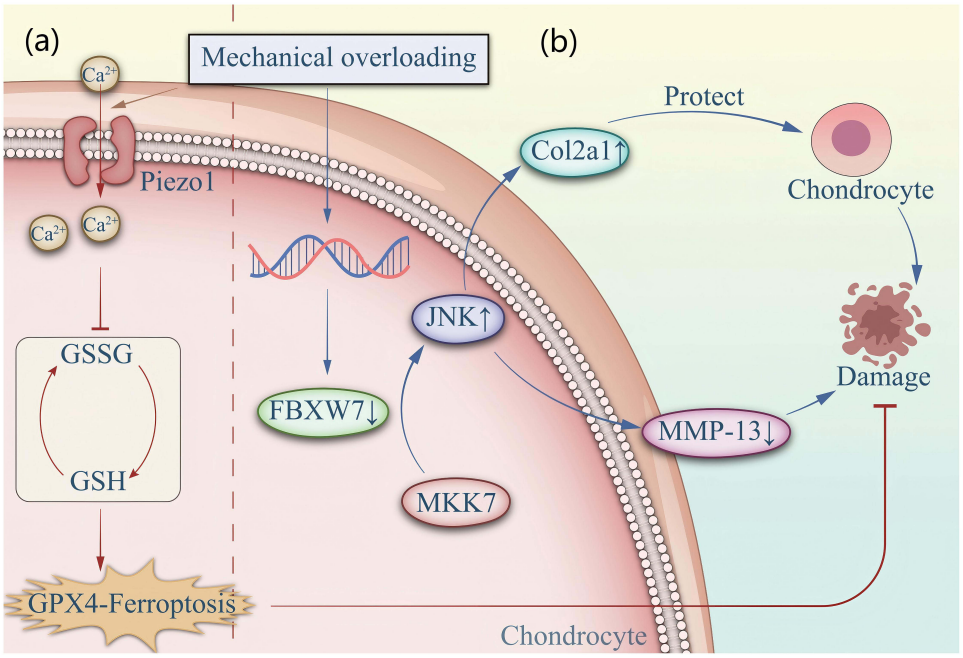

Figure 2 (**a**) Mechanical overloading stimulates an increase in intracellular Ca^{2+} influx, leading to a decrease in intracellular GSH content and a concurrent reduction in GPX4 levels, which induces ferroptosis. (**b**) Under normal conditions, FBXW7 inhibits the activation of the MKK7-JNK signaling pathway, thereby protecting chondrocytes. However, mechanical overloading downregulates FBXW7 in chondrocytes, leading to cellular senescence.

also exerting protective effects on joint stability and cartilage longevity.[51,52] The following sections will discuss in detail the relationships between adipokines and various joint tissues involved in OA.

Leptin

Leptin is primarily produced by adipose tissue,[53] and its overall circulating level is largely associated with the amount of white adipose tissue (WAT).[54] Generally, women exhibit higher leptin levels than men;[55] however, intra-articular leptin is mainly derived from the IFP.[56] Numerous studies have demonstrated that leptin can act synergistically with various chemokines to accelerate the degradation of the ECM in chondrocytes. For example, in primary human articular chondrocytes (HACs), leptin binds to its receptor and activates signaling pathways such as JAK–STAT, MAPK, and PI3K–Akt to promote the synthesis of MMP-1 and MMP-13. It can also act in synergy with IL-1 to further enhance ECM breakdown in cartilage tissue.[57,58] Additionally, leptin promotes the expression of histone deacetylases (HDAC3/4), thereby activating the TGF-β/Smad pathway and enhancing the production of MMP-1, MMP-13, and ADAMTS-4.[59] Based on these characteristics of leptin, Koskinen-Kolasa et al identified a potential therapeutic opportunity for OA: suppressor of cytokine signaling-3 (SOCS-3) can inhibit these signaling pathways and counteract leptin-induced protease release, ultimately alleviating OA-related symptoms.[60] Furthermore, MRI findings in OA patients show that serum leptin levels are positively correlated with osteophyte size, infrapatellar synovitis, and joint effusion.[61]

Resistin

Resistin is a dimeric protein that can induce insulin resistance in both humans and mice.[62–64] In contrast to leptin, the concentration of resistin in serum is much higher than in synovial fluid, and its levels are significantly elevated in patients with OA.[65] Compared with articular cartilage, resistin exhibits a stronger catabolic effect on the meniscus, and among these adipokines, it exerts the most detrimental influence on meniscal tissue by depleting sulfated glycosaminoglycans (sGAG).[66] In articular cartilage, resistin promotes matrix degradation by upregulating pro-inflammatory cytokines and chemokines, thereby activating signaling pathways such as cAMP/PKA, p38-MAPK, C/EBP-β, and NF-κB, leading to enhanced release of matrix metalloproteinases and subsequent cartilage destruction.[67] However, in human OA synovial fibroblasts (OASFs), resistin can activate the MEK and ERK pathways to suppress the levels of inflammatory mediators such as TNF-α and IL-1β, suggesting that resistin may exert certain protective effects on the synovium.[68]

Visfatin

Visfatin was initially identified in the liver, skeletal muscle, and bone marrow, and was previously known as pre-B colony–enhancing factor (PBEF). It exerts pro-inflammatory and catabolic effects on cartilage.[69] Studies have shown that visfatin increases the expression of intercellular adhesion molecule-1 (ICAM-1) in synovial cells. In OA synovial tissue, local infiltration of monocytes into the periarticular synovium is considered an important contributor to synovial pathology, and this process is mediated through ICAM-1–dependent chemotaxis. Therefore, visfatin facilitates monocyte infiltration in OA synovium.[70] Furthermore, visfatin promotes OA progression by stimulating human chondrocytes to produce PGE2, MMP-3, and MMP-13, thereby inducing a pro-degradative and pro-inflammatory chondrocyte phenotype.[71–73] The therapeutic potential of targeting visfatin in OA has now been widely recognized.

Adiponectin

Adiponectin is also primarily produced by white adipose tissue. In the circulation, native adiponectin mainly exists in two forms—globular adiponectin and full-length adiponectin[74] and exerts its biological functions through two different receptors. AdipoR1 is predominantly expressed in skeletal muscle and cartilage, whereas AdipoR2 is mainly found in the liver.[75] The role of adiponectin in the pathogenesis and progression of OA remains controversial, with evidence supporting both protective and deleterious effects.[76] Some studies have reported that globular adiponectin (gAPN) protects rat chondrocytes from H_2O_2-induced apoptosis via the AMPK/mTOR signaling pathway. Low concentrations of gAPN antagonize H_2O_2-induced cytotoxicity in a dose-dependent manner; however, at higher concentrations, gAPN exhibits cytotoxic effects.[74] Consistent with these findings, a meta-analysis has also indicated a positive association between adiponectin levels and the incidence of OA.[77] The adiponectin receptor agonist AdipoRon has been shown to

activate the AMPK/mTOR signaling pathway to regulate autophagy and protect chondrocytes from calcification,[78] and it can also slow intervertebral disc (IVD) degeneration.[79] In addition, adiponectin promotes the osteogenic differentiation of human bone marrow–derived stromal cells (hBMSC) in vitro by suppressing the expression of phosphatase and tensin (PTEN) homolog deleted on chromosome ten.[80]

Hypertension and OA

Hypertension is a common comorbidity of OA, yet its association with OA has only gained increasing attention in recent years. An analysis of nearly two decades of nationally representative data from the U.S. National Health and Nutrition Examination Survey (NHANES) confirmed a significant relationship between hypertension and arthritis. Notably, this association remained statistically significant even after adjusting for sex, race, age, socioeconomic factors, excessive sodium intake, physical activity, obesity, smoking history, diabetes, and other comorbidities. In addition, elevations in systolic blood pressure and pulse pressure have been correlated with an increased incidence of radiographic osteoarthritis (ROA).[81]

Hypertension can exert varying degrees of influence on intra-articular tissues, particularly being closely associated with cartilage degeneration and synovitis, with this association appearing more pronounced in female OA populations.[82] This phenomenon may be attributed to multifaceted physiological mechanisms. Primarily, the decline in estrogen levels following menopause diminishes its protective effects on both the cardiovascular system and joint tissues, rendering females more susceptible to hypertension-induced systemic low-grade inflammation, characterized by elevated levels of IL-6 and TNF-α. Furthermore, evidence suggests that hypertension-related microcirculatory disturbances in multiple joints are more prevalent in women, which exacerbates subchondral ischemia and subsequent cartilage degradation. Recently, a large-scale cohort study demonstrated that hypertensive women exhibit significantly higher expression levels of synovial inflammatory markers compared to their male counterparts, suggesting that hypertension may accelerate the progression of synovitis through sex-specific inflammatory pathways.[83–85] During OA progression, hypertension may lead to subchondral ischemia, thereby damaging cartilage tissue, which is currently a widely accepted mechanism.[86–88] Chronic hypertension impairs the microcirculation within the subchondral bone, reducing the delivery of essential nutrients and oxygen to the overlying articular cartilage, thus accelerating its degeneration. In recent years, however, chronic low-grade inflammation has emerged as another important factor mediating OA development in hypertensive patients. Elevated circulating inflammatory mediators such as IL-6, TNF-α, and CRP have been observed in individuals with hypertension;[89] these factors can enter the joint cavity through the bloodstream, activating synovial macrophages to release inflammatory mediators and subsequently inducing synovial inflammation and cartilage destruction.[30,90] Animal studies have demonstrated that hypertension is associated with OA progression in rats. Activation of the renin–angiotensin system (RAS) exacerbates cartilage damage in hypertensive mice, primarily via stimulation of angiotensin type 1 receptors (AT1R) on chondrocytes. This suggests that modulation of the RAS pathway may represent a potential therapeutic target for OA patients with hypertension.[82,91] Furthermore, hypertension-related endothelial dysfunction can result in localized ischemia–reperfusion injury, further triggering oxidative stress and inflammatory cascades within the joint.[92] Antihypertensive medications may mitigate OA progression; for instance, traditional medicine–derived agents such as lyophilized methanolic extract from flowering buds of Capparis spinosa (LECS) have shown cartilage-protective effects. Experimental evidence also indicates that calcium channel blockers can reduce chondrocyte apoptosis by inhibiting calcium influx.[93,94] Nevertheless, current research on the relationship between hypertension and OA-related meniscal injury, infrapatellar fat pad inflammation, and osteophyte formation remains limited, despite these being important contributors to OA-associated pain and restricted joint mobility.

Hyperglycemia and OA

In recent years, the association between hyperglycemia and OA has become a research hotspot. However, regarding the study outcomes, there is still no definitive evidence that hyperglycemia is an independent risk factor for OA. Some studies have suggested that there is no significant association between diabetes and OA, which may be attributed to the confounding effect of BMI, as BMI significantly increases the risk of diabetes.[95–97] Recent Mendelian randomization studies and large-scale cohort analyses have further demonstrated that after rigorous adjustment for BMI, the direct

causal link between type 2 diabetes and OA development is considerably attenuated, highlighting the pivotal role of adiposity in this relationship. Many previous studies did not adequately adjust for obesity, which may act as a bridge linking diabetes mellitus (DM) and OA, or indicate that diabetes itself is not a risk factor for OA.[98,99] Nevertheless, from the perspective of OA pathogenesis, recent studies have provided several important insights into hyperglycemia-induced OA. Diabetes and chronic hyperglycemia have been shown to promote OA development, and this association appears to be independent of BMI and age. In a prospective study involving 10,730 participants without knee OA, HbA1c >7.7% and fasting blood glucose >10.3 mmol/L were significantly positively associated with the risk of knee OA. Hyperglycemia was also found to reduce quadriceps muscle strength, leading to joint instability and contributing to symptomatic OA.[100] Mechanistically, hyperglycemia-induced oxidative stress, accumulation of inflammatory mediators, and increased advanced glycation end products (AGEs) can negatively affect key joint tissues, including articular cartilage, bone, synovium, and ligaments.[101–103]

For the knee joint, the synovium plays a crucial role in cartilage metabolism. Immunohistochemical comparisons between synovia from diabetic OA patients and non-diabetic OA patients revealed that levels of MMP-13, ADAMTS-5, and inflammatory mediators were significantly elevated in the diabetic OA group. This suggests that hyperglycemia can disrupt normal cartilage structure by stimulating synovial cells to release proteases and inflammatory factors. In addition, animal studies have shown that hyperglycemia can activate the HIF-1α/GLUT1 pathway in synovial cells, promoting the accumulation of AGEs and thereby damaging cartilage.[104] Prolonged glucose overload allows glucose to infiltrate the joint cavity, altering the cartilage microenvironment and impairing the optimal morphology of chondrocytes. This is manifested as tissue loosening, including reduced chondrocyte volume and increased intercellular space, along with decreased ECM density. Consequently, the cartilage's tolerance to mechanical load diminishes, potentially serving as a trigger for OA development.[105] At the microscopic level, hyperglycemia excessively activates the p38-MAPK signaling pathway, leading to elevated proteases and inflammatory mediators and resulting in ECM degradation of chondrocytes. This also indicates that the p38-MAPK pathway may serve as a potential target for disease intervention.[106]

Moreover, a high-glucose environment reduces the expression of peroxisome proliferator-activated receptor γ (PPARγ) and type II collagen in chondrocytes, both of which represent potential pathogenic mechanisms in hyperglycemic OA. Therefore, pioglitazone, a PPARγ agonist, can not only lower blood glucose but also mitigate the deleterious effects of hyperglycemia on chondrocytes.[107] Oleanolic acid (OLA) exerts a similar but slightly different effect by activating the PPARγ/SOD2 signaling pathway, thereby protecting mitochondrial function in chondrocytes, reducing inflammatory mediator levels, and promoting type II collagen production.[108]

Hyperglycemia also adversely affects ligaments. In OA, ligament contracture and tears are common, particularly ACL injuries, which contribute to knee instability. Animal experiments have confirmed that a hyperglycemic environment promotes fibrosis of the medial collateral ligament (MCL), reducing its elasticity and hindering self-repair of injured ligaments. Interestingly, melatonin can counteract the detrimental effects of hyperglycemia on ligaments;[109] however, whether melatonin provides similar benefits for human joint ligaments requires further investigation.

Dyslipidemia and OA

Currently, most evidence, including recent meta-analyses and mechanistic explorations, indicates a significant association between lipid metabolism disorders (especially hypercholesterolemia) and OA.[110,111] However, a few studies using Mendelian randomization have presented equivocal findings regarding the direct causal links, suggesting a more complex interplay.[112,113] The lipid abnormalities commonly referred to include elevated total cholesterol (TCHO), decreased high-density lipoprotein cholesterol (HDL), and increased low-density lipoprotein cholesterol (LDL).[114]

Multiple studies have indicated that elevated cholesterol levels are closely associated with the onset and progression of OA.[115–118] The key protein responsible for cholesterol efflux in OA chondrocytes—apolipoprotein A1 binding protein (A1BP)—is significantly downregulated, leading to markedly increased intracellular cholesterol levels, which in turn results in cholesterol accumulation and inhibition of ECM synthesis. Upregulation of A1BP can reverse these effects.[119,120] Animal studies have further confirmed that intracellular cholesterol accumulation in chondrocytes markedly reduces the expression of cholesterol metabolism–related genes, such as low-density lipoprotein receptor–related protein

3 (LRP3), thereby promoting protease production and damaging the chondrocyte ECM. This mechanism has been referred to as the cholesterol–LRP3–SDC4 metabolic axis.[121] Given the role of cholesterol in OA, several therapeutic strategies have been proposed. For instance, cholesterol-lowering therapy combined with IL-1β inhibitors can reduce synovial hyperplasia and cartilage degeneration in mice.[122] Adenoviral-mediated upregulation of circRNA, specifically circARPC1B, significantly delays OA progression induced by a high-cholesterol diet, as circRNAs play a critical role in maintaining ECM homeostasis.[123] In addition, lipid-lowering drugs such as atorvastatin and simvastatin can ameliorate the metabolic impact of cholesterol on chondrocytes and slow OA progression,[124,125] representing a potential breakthrough for symptom intervention in OA patients with hyperlipidemia.

Regarding HOA, studies have indicated that hyperlipidemia may serve as an independent risk factor for HOA,[126] and lipid abnormalities are significantly associated with both the onset and progression of HOA, particularly elevated triglyceride levels.[127] Concerning HDL, experimental evidence has shown that direct HDL treatment can downregulate the expression of matrix metalloproteinases (MMP3/9/12/13) and ADAMTS4/5, thereby exerting a protective effect on OA cartilage.[120]

Metabolic Inflammation and OA

With the deepening investigation into the relationship between inflammatory factors and OA in recent years, OA is increasingly recognized not merely as a wear-and-tear disorder but as a complex, multifactorial, chronic degenerative disease mediated by inflammatory cytokines. Inflammatory mediators can damage multiple non–mechanically loaded joint tissues, such as the synovium and infrapatellar fat pad, initiating inflammatory cascades and exacerbating OA symptoms.[128,129] Moreover, low-grade systemic inflammation is consistently present in patients with OA. Locally within the joint, numerous studies have demonstrated that OA is frequently accompanied by infiltration of inflammatory cells within the synovium—including macrophages, T cells, mast cells, and B cells—whose secreted cytokines contribute substantially to OA onset and progression.[130–132] Synovial inflammation is also strongly associated with knee pain.[133,134]

Regarding systemic inflammation, there is no doubt that each component of MetS contributes to elevated levels of circulating inflammatory mediators, exerting detrimental effects on joint tissues. Metabolic dysregulation also disrupts the balance between M1 and M2 macrophage phenotypes, leading to chronic inflammation, which serves as an important driver of synovitis, cartilage degeneration, and osteophyte formation in OA.[129] Subsequently, as inflammatory cytokines induce joint-tissue damage, the accumulation of senescent cells further exacerbates oxidative stress,[135] creating a vicious cycle of persistent local inflammation.

Immunometabolism and OA

Immunometabolism is an emerging research field that focuses on metabolic pathway alterations within immune cells and their effects on the survival and function of surrounding cells. Although immunometabolism is not currently classified as a component of MetS, several elements of MetS—particularly obesity and hypertension—are closely associated with metabolic reprogramming in immune cells such as macrophages.[136,137] Dysregulation of immune-cell metabolism can lead to persistent inflammatory responses. Immunometabolism highlights the pivotal role of metabolic reprogramming within the immune system in the pathogenesis and progression of chronic inflammatory diseases.

To date, six major metabolic pathways have been identified as contributors to immunometabolism: glycolysis, the tricarboxylic acid (TCA) cycle, the pentose phosphate pathway (PPP), fatty acid oxidation, fatty acid synthesis, and amino acid metabolism.[138,139] Under adverse conditions, mammalian metabolism typically shifts from a low-level resting state to a highly active one. For instance, in the joints of patients with OA, the metabolic behavior of articular chondrocytes, subchondral bone cells, and synovial cells undergoes significant changes, and these cells interact with macrophages in the synovium and the immune system to influence disease progression.[140] A metabolic shift toward glycolysis is essential for activating inflammatory pathways during immune responses and in chronic inflammatory diseases such as OA and rheumatoid arthritis (RA).[141] Currently, research on immunometabolism in OA remains in its early stages, and more extensive and in-depth studies are needed.

Conclusion and Future Perspectives

In this review, we systematically examined recent studies concerning the relationship between MetS and OA, highlighting the complex and extensive connections between these two conditions. Although this review provides a detailed overview of the latest findings on the involvement of MetS in OA, many important questions remain to be explored. As a complex disorder involving the degeneration of multiple intraarticular tissues, OA must be viewed in its entirety. Cartilage aging and cartilage loss are indeed important components of disease progression, but they do not represent the whole picture. Notably, the primary symptom of OA, pain, is in most cases not caused by cartilage wear. Instead, it arises from synovial inflammation, subchondral bone remodeling, bone marrow lesions, osteophyte formation, and capsular contracture. However, current research places disproportionate emphasis on the roles of MetS in cartilage degeneration and synovitis, while studies investigating the effects of MetS on subchondral bone remodeling, bone marrow lesions, osteophyte formation, meniscal degeneration and tearing, and ligament injury are very limited. These factors are critical contributors to pain and functional impairment in patients with OA. Since the primary goal of all current OA treatments is still pain relief, it is clear that significant gaps remain in research focused on symptomatic OA. For patients with OA, pain is the predominant symptom and the problem they most urgently wish to resolve. Relief of pain is also one of the primary indicators for evaluating the effectiveness of OA treatments. In addition, many current theories regarding MetS-OA are derived from animal studies, particularly those conducted in rat models. Although the scientific value of animal research is undeniable, substantial and reliable clinical evidence is still lacking before these theories can be fully applied to human OA. For instance, whether pharmacologic interventions that alleviate metabolic abnormalities and improve OA symptoms in rodent models can be effectively translated to human patients remains uncertain, and many questions require further verification. Furthermore, although the signaling pathways through which individual components of MetS contribute to OA have been extensively studied, very few therapeutic agents have been developed to halt OA progression based on these pathways. This may be due to the fact that many of these molecular mechanisms have only been uncovered in recent years. With continued research, it is reasonable to anticipate that targeted interventions will gradually be developed and eventually integrated into clinical practice. Both MetS and OA are highly prevalent in older adults, and MetS is undoubtedly a major risk factor for the development of OA. However, whether OA itself may promote the onset of MetS has not yet been systematically investigated. Theoretically, OA-related knee pain can lead to reduced physical activity, which may in turn contribute to the development of MetS.

With continued advancements in understanding the etiology of OA, our knowledge of this disease has reached an unprecedented level. The strategies available to halt OA progression are now more diverse and effective than ever before. Future research should build upon the existing foundation and address the current gaps through targeted investigations. Inflammatory mediators serve as a central link between MetS and the progression of OA, and the relationships between metabolic abnormalities and damage to different joint tissues are intricate and highly complex (Figure 3). However, more

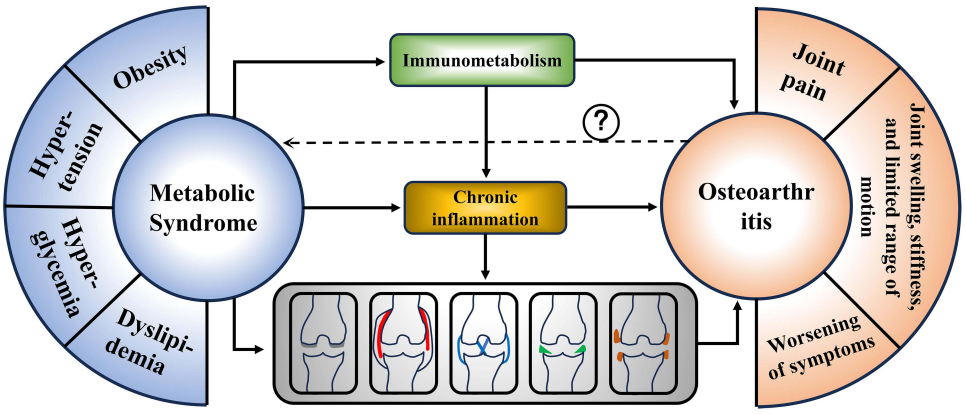

Figure 3 MetS is a heterogeneous condition characterized by obesity, hypertension, hyperglycemia, elevated triglycerides, and reduced high-density lipoprotein cholesterol; the presence of three or more of these components establishes the diagnosis. In OA, MetS is associated to varying degrees with aging-related degeneration across multiple intra-articular tissues, and low-grade chronic inflammation is a key driver of OA. Current evidence indicates that MetS is most strongly linked to OA-related cartilage and synovial pathology, whereas whether OA can in turn promote metabolic syndrome remains inconclusive (Dashed Arrow).

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systematic research in the future will undoubtedly clarify these mechanisms. It is conceivable that individualized treatment approaches based on specific metabolic abnormalities in patients with OA may eventually become possible, which would represent a transformative advance in the management of this disease.

Abbreviations

A1BP, A1 binding protein; ACL, anterior cruciate ligament; AGEs, advanced glycation end products; AT1R, angiotensin type 1 receptors; BHB, β-hydroxybutyrate; BMI, body mass index; DM, diabetes mellitus; ECM, extracellular matrix; gAPN, globular adiponectin; HACs, human articular chondrocytes; hBMSC, human bone marrow–derived stromal cells; HDAC, histone deacetylases; HDL, high-density lipoprotein cholesterol; hNPCs, human nucleus pulposus cells; HOA, hand osteoarthritis; ICAM-1, intercellular adhesion molecule-1; IFP, infrapatellar fat pad; IVD, intervertebral disc; LDL, low-density lipoprotein cholesterol; LECS, lyophilized methanolic extract from flowering buds of Capparis spinosa; LRP3, lipoprotein receptor–related protein 3; MCL, medial collateral ligament; MetS, Metabolic syndrome; MitoQ, mitochondria-targeted coenzyme Q analogue; NHANES, National Health and Nutrition Examination Survey; OA, osteoarthritis; OASFs, osteoarthritis synovial fibroblasts; OLA, Oleanolic acid; PBEF, pre-B colony–enhancing factor; PPARγ, peroxisome proliferator-activated receptor γ; PPP, pentose phosphate pathway; PTEN, phosphatase and tensin; RA, rheumatoid arthritis; RAS, renin–angiotensin system; ROA, radiographic osteoarthritis; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; sGAG, sulfated glycosaminoglycans; SOCS-3, suppressor of cytokine signaling-3; TCA, tricarboxylic acid; TCHO, total cholesterol; TSP-4, Thrombospondin-4; WAT, white adipose tissue.

Data Sharing Statement

No new data was generated for this article.

Author Contributions

Yuchen Wang is a co–first author of this article. Hongchen Ren; Conceptualization, Investigation, Writing – original draft. Yuchen Wang, Jingbo Cheng, Haicheng Tao and Hui Feng; Conceptualization, Data curation, Validation. Mingli Feng; Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology. All authors have made significant contributions to the work of the report and provided critical feedback on the revisions made to the article. Finally, all authors approved the upcoming version. They have reached an agreement on the journal to which the article will be submitted and have agreed to take responsibility for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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