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Inflammatory mechanisms underlying metabolic syndrome-associated and potential treatments

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ABSTRACT

Objectives: Osteoarthritis (OA), a debilitating disease, has been recognized as a heterogenous disease, with metabolic syndrome-associated osteoarthritis (MetS-OA) emerging as a significant area of interest. Currently, the understanding of MOA remains limited, with a prevailing consensus attributing its etiology to the core components of metabolic syndrome: obesity, hyperglycemia, dyslipidemia, and hypertension. The aim of this review is to summarize the current understanding of the complex relationship between metabolic syndrome and OA from the perspectives of epidemiology and molecular biology, and to explore potential targeting strategies for metabolic syndrome in MetS-OA management.
Methods: This narrative review evaluated literature (2010–2024) from PubMed, examining clinical and mechanistic evidence linking metabolic syndrome to OA, including therapeutic studies targeting MetS-OA.
Results: Metabolic syndrome aggravate the cartilage injury in MetS-OA through metabolic biomarkers (adipokines, advanced glycation end-products and oxidized LDL), metabolic responses (oxidative stress, insulin resistance and ischemic hypoxic injuries), and abnormally activated cells (adipocytes and macrophages). It ultimately lead to the aggravation of synovitis in MetS-OA through inflammatory mediators.
Conclusions: The exploration of the relationship between metabolic syndrome and OA could benefit the development of targeting strategies for MetS-OA, including currently FDA-approved drugs for the treatment of metabolic syndrome and potential drugs targeting metabolic factors, which might provide a novel avenue for the future management of MetS-OA.

1. Introduction

Osteoarthritis (OA) is a joint disease that affects approximately 654 million people worldwide, with rates of knee OA (KOA) doubling since the mid-20th century due to an ageing population and increased obesity [1]. However, OA is not solely age- or obesity-related but rather a complex, multifactorial disease. Therefore, research into the phenotypes of OA, based on various risk factors, has become a focus to develop more targeted treatments. Due to the close relationship between metabolism and inflammation, the phenotype of OA associated with metabolic syndrome (MetS), referred to as MetS-OA, has garnered significant interests.

MetS, defined by the co-occurrence of at least three of five components (central obesity, hypertension, dyslipidemia, insulin resistance, and hyperglycemia), has emerged as a key driver of metabolic syndrome-associated osteoarthritis (MetS-OA) pathogenesis through systemic metabolic disorders [2]. The Rotterdam Study (n = 3563) revealed that MetS patients exhibited 3.2-fold higher odds of developing symptomatic OA compared to metabolically healthy individuals [3]. Importantly, this relationship persisted in non-weight-bearing joints, with hand OA (HOA)

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prevalence being 2–3 times higher in obese individuals even after adjusting for BMI, confirming the metabolic contributions independent of mechanical loading [4]. Furthermore, this metabolic disorders induced chronic low-grade inflammation correlated strongly with OA progression, as evidenced by reduced joint replacement risk in MetS patients receiving IL-1β inhibitors [5]. Indeed, in obesity and hyperlipidemia, excessive secretion of adipokines, such as leptin, adiponectin, and visfatin, contribute to the inflammatory response process of OA as pro-inflammatory factors [6,7]. These results suggest that metabolic disorders are associated with systemic low-grade inflammation in the pathogenesis of MetS-OA (Fig. 1).

Despite the increasing recognition of MetS-OA, current diagnostic and therapeutic strategies tend to emphasize universal approaches while overlooking the complexity of MetS-OA development. Actually, certain FDA-approved drugs for the treatment of metabolic diseases have been shown to significantly relieve MetS-OA symptoms. Notably, metformin (MET) has the potential to enhance cartilage degradation and modulate the inflammatory response as an adjunctive therapy for obese OA patients [8]. In addition, semaglutide was shown to alleviate pain related to KOA among obese persons in a recently randomized, double-blind, placebo--controlled trial [9]. These findings demonstrate that improving metabolic parameters can alleviate MetS-OA symptoms, while elucidating the inflammatory mechanisms triggered by metabolic dysregulation may identify novel therapeutic targets for this distinct OA phenotype.

Therefore, in this review, we discussed the underlying inflammatory mechanisms and potential therapeutics options for MetS-OA.

2. Inflammatory mechanism of MetS-OA

2.1. Obesity and OA

Obesity is widely regarded as a significant modifiable risk factor influencing the occurrence and progression of OA. It was reported that obesity increases the incidence of weight-bearing joint OA, such as in the knees and hips. Notably, a positive correlation between obesity and OA was reported in non-weight-bearing joints, such as the hand joints. Results from a meta-analysis demonstrated that for every 5-unit increase in BMI, the risk of radiographic development of HOA increased by 6 % [4]. These studies suggest that the metabolic effects of obesity are one of the major factors contributing to the high prevalence of OA in obese individuals. Indeed, within the metabolic processes of obese individuals, adipose tissue, together with the adipokines it secretes, may act as pro-inflammatory factors in the inflammatory response associated with OA. Therefore, in addition to the direct stress damage caused by mechanical loading, it is likely that the progression of MetS-OA in obesity is driven by obesity-related metabolic inflammation.

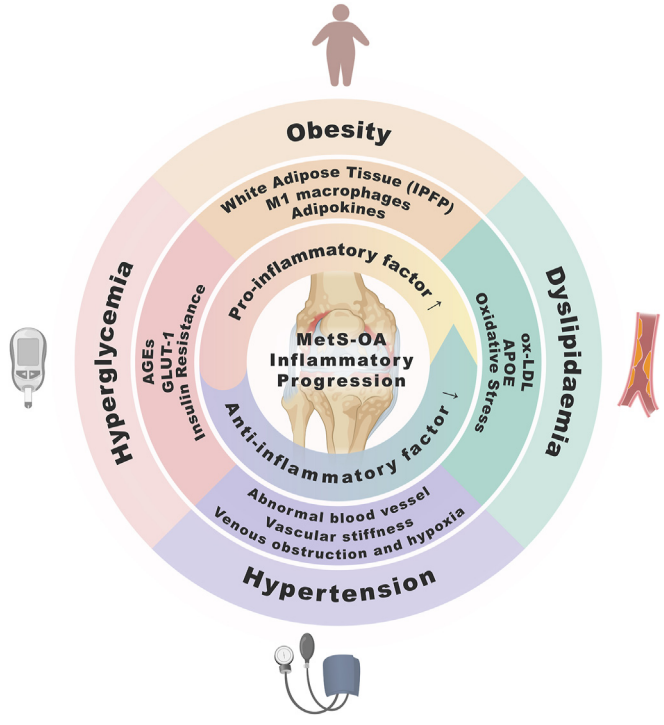

Fig. 1. Effects of MetS on the inflammatory progression of OA. The effects of metabolic disorders of metabolic syndrome (e.g., obesity, dyslipidaemia, diabetes, hypertension) on the progression of OA inflammation are illustrated. Different metabolic disorders can produce related molecules or reactions that cause the upregulation of pro-inflammatory factors and the downregulation of anti-inflammatory factors in OA, which both promote the inflammatory progression of MetS-OA.

2.1.1. Adipose tissue

Obesity can induce inflammation and fibrosis in white adipose tissue, leading to local and systemic metabolic dysfunction. Collins et al. proposed that mice with adipose tissue atrophy were protected from spontaneous or traumatic OA inflammation induced by a high-fat diet, and that susceptibility to OA inflammation could be increased by implanting adipose tissue [10]. This suggests that obesity-induced MetS-OA may be caused by pro-inflammatory mechanisms related to adipose tissue.

Subcutaneous abdominal adipose tissue (SAAT) is a type of systemic adipose tissue that plays a role in metabolic inflammation associated with obesity. Excess SAAT explants promoted the production of pro-inflammatory cytokines in OA, indicating that SAAT may contribute to the inflammatory pathogenesis of KOA. Furthermore, local adipose tissue such as the infrapatellar fat pad (IPFP), located beneath the knee joint and serving as a white adipose tissue within the joint capsule and outside the synovium, could interact with adjacent tissues, potentially influencing joint homeostasis and the progression of OA. Fat-derived mediators from IPFP could activate the p38MAPK and ERK1/2 pathways, thereby inducing inflammation [11]. Despite some studies suggesting that obesity has little impact on IPFP tissue, many studies have reported the pro-inflammatory nature of this tissue, such as increased release of TNF-α and fatty acids from the IPFP in patients with OA and obesity [12]. In addition, mice on a high-fat diet show increased secretion of inflammatory cytokines and adipokines in the IPFP compared to mice on a normal diet [13].

2.1.2. Macrophages in the joint cavity

With increasing obesity, adipose tissue macrophages switch from M2 macrophages, which produce anti-inflammatory or synthetic metabolic molecules, to M1 macrophages, which produce high levels of pro-inflammatory cytokines. The dynamic balance between M1 and M2 macrophages is particularly crucial for the inflammatory progression of OA. In patients with obesity, the synovium shows marked fibrosis and a notable rise in macrophage infiltration. In addition, the presence of $CD45^{+}$ and $CD14^{+}$ macrophages was increased in IPFP and synovium of obese patients with OA [14]. These observations strongly buttress the theory positing that inflammation is a key driver in the development of OA within this high-risk patient group. Consequently, obesity can promote macrophage infiltration in OA and lead to the accumulation of pro-inflammatory M1 macrophages, causing elevated synovial inflammation and promoting the progression of OA [15] (see Table 1).

2.1.3. Adipokines

Adipose tissue can also increase susceptibility to MetS-OA induced by a high-fat diet through paracrine signals [10]. A series of metabolic factors, especially adipokines (such as leptin, resistin, and adiponectin), secreted by adipocytes, influence the metabolism of articular cartilage and the inflammation of synovial tissue. Several studies have compared the levels of adipokines in joint fluid or blood between osteoarthritic and non-osteoarthritic patients, revealing that higher levels of adipokines are present in both joint fluid and serum of osteoarthritic patients, and these levels are associated with the severity of OA [16]. In this article, we focus

Table 1
The list of abbreviation and its full name from the document, presented alphabetically in English.

Abbreviations	Full name
AGEs	Advanced glycation end-products
APOE	Apolipoprotein E
BMP	Bone morphogenetic protein
BMI	Body Mass index
$CD14^+$	CD14 positive cells
$CD45^+$	CD45 positive cells
cPLA2	Cytosolic phospholipase A2
DMM	Destabilization of the medial meniscus (OA mouse model)
DPP-4	Dipeptidyl Peptidase-4
ERK1/2	Extracellular signal-regulated kinase 1/2
FDA	Food and drug administration
GLP-1	Glucagon-like Peptide-1
GLP-1RA	Glucagon-like Peptide-1 receptor agonist
GLUT-1/3/9	Glucose transporter 1/3/9
HIF-1α	Hypoxia-inducible factor 1-alpha
IL-1β/6/8	Interleukin-1β/6/8
JNK	c-Jun N-terminal kinase
LDL-C	Low-density lipoprotein cholesterol
LOX-1	Lectin-like ox-LDL Receptor-1
M1/M2	Macrophage type 1/Type 2
MAPK	Mitogen-activated protein kinase
MMP-2/3/13	Matrix metalloproteinase-2/3/13
NF-κB	Nuclear factor-kappa B
NOS	Nitric oxide synthase
p38MAPK	p38 mitogen-activated protein kinase
PPAR-α	Peroxisome proliferator-activated receptor α
RAGE	Receptor for advanced glycation end-products
ROS	Reactive oxygen species
TKR	Total knee replacement
THR	Total hip replacement
TNF-α	Tumor necrosis factor-alpha
VEGF	Vascular endothelial growth factor

on discussing the impact of adipokines on the inflammatory progression of MetS-OA (Table 2).

Among them, leptin is the first discovered adipokine. Numerous reports have suggested that leptin has an impact on OA cartilage, indicating a significant role in the progression of MetS-OA. Studies have found that mice with impaired leptin signaling can reduce susceptibility to OA induced by a high-fat diet [17]. Leptin secreted from adipocytes can promote the proliferation of effector T cells and regulate the expression of pro-inflammatory factors such as IL-6, IL-8, and CCL3 in $CD4^+$ T cells of OA patients [18]. It can also induce the expression of NO and IL-6 in mouse chondrocytes through the AMPK-PI3K pathway, thereby exerting a pro-inflammatory effect [19].

Plasma adiponectin levels are significantly higher in OA patients and are associated with progression in HOA patients [20]. Similarly, adiponectin can promote the expression of IL-6 and NOS2 and other pro-inflammatory factors in OA patients [19]. Philp et al. reported that chondrocytes in obese OA could induce the expression of VXAM-1 and MMP-2 by expressing higher levels of adiponectin receptor 1 antibodies, thereby enhancing the pro-inflammatory signals of OA [21]. Resistin exacerbates OA severity by promoting pro-inflammatory cytokine release in chondrocytes, a finding supported by clinical correlations between resistin levels and joint degeneration [22]. Similarly, visfatin drives OA progression via IL-6, PGE2, and CCL20 secretion, perpetuating synovial inflammation [23].

Among other adipokines, clusterin amplifies synovitis and cartilage degradation through NF-κB-driven IL-8 overproduction, directly disrupting ECM homeostasis [24]. Chemerin activates AKT/MEK/MAPK pathways in chondrocytes, promoting TNF-α, IL-6, and IL-8 release, which accelerates cartilage catabolism [25]. Nesfatin-1 links systemic metabolic dysfunction to joint pathology by enhancing IL-18/NF-κB signaling, inducing oxidative stress (via ROS), suppressing autophagy, and upregulating MMP-3/13 through MAPK/ERK activation. Oxidized low-density lipoprotein (LDL) (ox-LDL), elevated in obesity and hyperlipidemia, aggravates MetS-OA via lipid-driven inflammation [26]. Its specific role in lipid-driven joint degeneration will be detailed in the hyperlipidemia section as a key mediator of metabolic-inflammatory crosstalk. In contrast to pro-inflammatory adipokines, adropin may mitigate inflammation in MetS-OA by suppressing TNF-α and MMP-13 activity, though its precise mechanistic role in disease progression remains incompletely defined [27].

2.2. Hyperglycemia and OA

With the increasing coexistence of OA and type 2 diabetes (T2D), various meta-analyses have confirmed the epidemiological relationship between T2D and OA, indicating that diabetic patients have a greater risk of developing OA. Louati et al.'s meta-analysis of 49 studies (N = 1,192,518) revealed a significant association between OA and T2D, demonstrating a 29.5 ± 1.2 % prevalence of OA in diabetic patients and 14.4 ± 0.1 % diabetes mellitus prevalence in OA patients, with increased

Table 2
Roles of adipokines in the inflammatory progression of OA.

Adipokine	Role in inflammatory progression of OA	Expression in OA	Reference
Leptin	Induces the expression of NO and IL-6 in murine chondrogenic cells mediated through AMPK-PI3K pathway	Upregulated (OA)	[19]
	Regulates the production of pro-inflammatory factors such as IL-6, IL-8, and CCL3 expression in $CD4^+$ T cells from OA patients	Downregulated in serum with weight loss (OA)	[20]
Adiponectin/ AdipoQ	Promotes the expression of IL-6 and NOS2 and other pro-inflammatory factors in OA patients	Upregulated (OA)	[21]
Resistin	With a role identified for resistin in enhancing the pro-inflammatory milieu by release of pro-inflammatory cytokines in chondrocytes	Upregulated (MOA)	[83]
Adropin	Inhibition of pro-inflammatory cytokines (TNF-α)	Downregulated (OA)	[27]
Visfatin	Exert a pro-inflammatory effect by inducing the production of IL-1β, IL-6, and TNF-α in lymphocytes	Upregulated (OA)	[30]
Clusterin	Pain, synovitis inflammation (IL-6,8, NF-κB) and cartilage degeneration	Upregulated (OA)	[24]
Chemerin	Endothelial & synovial inflammation (cytokine release from synovial fibroblasts); Promote articular cartilage catabolism and inflammatory signaling	Upregulated (OA)	[25]
Nesfatin-1	Chondrocyte expression levels of nesfatin-1 in OA subjects were found to be positively correlated with IL-18 levels	Upregulated (OA)	[26]
ox-LDL	Binds chondrocyte LOX—oxidative stress, cartilage degeneration and inflammation; Binding of ox-LDL to its scavenger receptor—LOX-—reduces cell viability and PG synthesis in cartilage matrix, and increases intracellular ROS production leading to activation of NF-κB	Upregulated (OA)	[44,84]

Abbreviations: IGF-1, Insulin-like Growth Factor 1; TGF-β1, Transforming Growth Factor Beta 1; IL-1/6/8/18, Interleukin 1/6/8/18; IL-1β, Interleukin 1 Beta; TNF-α, Tumor Necrosis Factor Alpha; IFN-γ, Interferon Gamma; NO, Nitric Oxide; PI3K, Phosphoinositide 3-kinase; AMPK, AMP-Activated Protein Kinase; CCL3, Chemokine (C–C Motif) Ligand 3; $CD4^+$, CD4 Positive Cells; MMP-1/2/3/13, Matrix Metalloproteinase 1/2/3/13; ADAMTS-4, A Disintegrin And Metalloproteinase with Thrombospondin motifs 4; MetS-OA, Metabolic Syndrome-Osteoarthritis; PG, Prostaglandins; IL-17A, Interleukin 17A; NF-κB, Nuclear Factor kappa B; LOX, Lysyl Oxidase; LOX-1, Lectin-like Oxidized Low-Density Lipoprotein Receptor 1; oxLDL, Oxidized Low-Density Lipoprotein; ROS, Reactive Oxygen Species.

risks in both directions [28]. Some epidemiological studies have identified the connection between hyperglycemia, insulin resistance, and OA recently (Table 3).

While the detailed mechanisms between hyperglycemia and OA have not been fully revealed, some *in vitro* and *in vivo* studies link locally or systemically induced inflammation by high glucose concentrations to OA. It is mainly through three pathways that promote joint damage, including oxidative stress, the formation of advanced glycation end-products (AGEs) and insulin resistance.

Table 3
Clinical studies on hyperglycemia and OA in recent years.

Design	Population	Major findings	Comments	Reference
Longitudinal cohort study	Sample size: 852 (67.3 % female) Age: 59.5 ± 7.4 years BMI: 30.9 ± 6.5 kg/m^2 Diagnostic criteria: Radiographic Pain severity: N/A	People with DM were more likely to experience worsening pain; pain was assessed using the AUStralian CANadian OA hand index (AUSCAN).	The presence of comorbid CVD and DM affects the severity and progression of HOA.	[85]
Cohort study	Sample size: 60 (91 % female Age: 52.8 ± 8 years BMI: 39.2 ± 9 kg/m^2 Diagnostic criteria: Radiographic Pain severity: N/A	Hypertension (HTN) and DM (p = 0.009, 0.002 respectively) than MetS patients without OA.	There was a significant association of WOMAC score with DM in linear regression analysis.	[86]
Cohort study	Sample size: 2481 (61 % female) Age: 65 years BMI: 31.6 kg/m^2 Diagnostic criteria: Radiographic Pain severity: N/T	Individuals with DM had worse KOOS pain (β = −4.72; 95 % CI = −7.22-2.23) and worse NRS pain (β = 0.42; 95 % CI = 0.04–0.80) independent of BMI, OA severity, age, and sex. The negative influence of DM was also apparent for SF-12 PCS (β = −3.49; 95 % CI = −4.73 to −2.25), SF-12 MCS (β = −1.42; 95 % CI = −2.57 to −0.26]), and CES-D (β = 1.08; 95 % CI = 0.08–2.08).	Individuals with DM had worse KOOS pain, and worse NRS pain independent of BMI, OA severity, age, and sex.	[87]
Cohort study	Sample size: 819 (54.3 % female) Age: 65.08 ± 9.77 years BMI: 37.7 ± 0.5 kg/m^2 Diagnostic criteria: OA initiative Pain severity: 5.3	Increased HbA_{1c} value was significantly associated with higher pain severity (B = 0.36; 95 % CI = 0.036–0.67, p = 0.029) after controlling for age, gender, BMI.	HbA_{1c} value was significantly associated with increased joint pain severity after adjustments for age, gender, BMI, OA location, and pain medication.	[88]
Cohort study	Sample size: 1319 (56.5 % female) Age:61.2 ± 9.04 years BMI: 30.1 ± 4.9 kg/m^2 Diagnostic criteria: OA initiative Pain severity: 5.4	Participants with KOA and DM had 2.45 (95 % CI = 1.07–5.61) to 2.55 (95 % CI = 1.12–5.79) times higher likelihood of having unilateral and bilateral knee pain than those without DM and without knee pain.	DM is significantly associated with increased knee pain severity over 7 days and 30 days after adjustment for age, gender, race, depression symptoms, composite OA score, use of medication, and knee injection.	[89]
Cross-sectional analysis	Age ≥40 years and known diabetes status (n = 109,218)	Diabetes was associated with back/lower back pain (OR = 1.2; 95 % CI = 1.1–1.2; $p < 0.001$), pain in the limbs (1.4 (1.3–1.4), $p < 0.001$), shoulder/neck pain (1.2 (1.1–1.3), $p < 0.001$), OA (1.3 (1.2–1.4), $p < 0.001$), osteoporosis (1.2 (1.1–1.4), $p = 0.010$), and rheumatoid arthritis (1.6 (1.4–1.7), $p < 0.001$).	Diabetes was associated with elevated odds of having OA, osteoporosis, and rheumatoid arthritis. The most frequent disease in individuals with diabetes was OA.	[90]
Cross-sectional analysis	A total of 37,353 T1DM (1584 KOA + 35,769 non-KOA + 15 obese + 1569 non-obese) and 1,218,254 T2D (41,325 KOA + 1,176,929 non-KOA + 667 obese + 40,658 non-obese) persons were included	The associations between KOA and T1D (OR = 1.40; 95 % CI = 1.33–1.47; p < 0.0001) and T2D (OR = 2.75; 95 % CI = 2.72–2.78; p < 0.0001) were significant. The association between T1D and KOA among the obese (OR: 0.99 (0.54–1.67), p = 0.0477) was insignificant compared to the non-obese (OR: 1.40 (1.33–1.48), p < 0.0001). Interestingly, a higher association between T2D and KOA among non-obese persons (OR: 2.75, (2.72–2.79), p < 0.0001) compared to the obese (OR: 1.71 (1.55–1.89), p < 0.0001) was noted.	DM is strongly associated with KOA, and obesity may not be a confounding factor.	[91]
Prospective cohort study	Aged ≥45 years (n = 10730)	KOA was related to DM (HR = 1.29; 95 % CI = 1.02–1.78), bad glycemic regulation in DM patients (HR = 1.41; 95 % CI = 1.05–2.09), and long-term DM (≥5 versus <5 years; HR = 1.49; 95 % CI = 1.02–2.17).	DM, bad glycemic management, and long-term DM are potential risk factors of symptomatic KOA independent of age and body mass index. Targeting blood glucose, in addition to bodyweight, may be an important avenue for prevention of KOA.	[92]
Cross-sectional analysis	A population cohort aged ≥55 years recruited from 1996 to 1998 (n = 16,362)	Hip/knee joints with OA and incident diabetes: HR for two vs no osteoarthritic hips 1.25 (95 % CI 1.08, 1.44); HR for two vs no osteoarthritic knees 1.16 (95 % CI 1.04, 1.29).	In a large population cohort aged ≥55 years who were free of diabetes at baseline, and after controlling for confounders, the presence and burden of hip/knee OA was a significant independent predictor of incident diabetes.	[93]
Cross-sectional analysis	Radiographic KOA (Kellgren-Lawrence grade ≥2) (n = 698)	DM was associated with an increased risk of worsening KOA-related symptoms (95 % CI 1.70, 1.18–2.46)	DM is associated with worsening KOA-related symptoms.	[94]

Abbreviations: T2D, Type 2 Diabetes; SF, Synovial Fluid; COMP levels, Cartilage Oligomeric Matrix Protein levels; DM, Diabetes Mellitus; CVD, Cardiovascular Disease; MetS, Metabolic Syndrome; WOMAC score, Western Ontario and McMaster Universities Osteoarthritis Index score; KOOS pain, Knee injury and Osteoarthritis Outcome Score pain; NRS pain, Numeric Rating Scale for pain; SF-12 MCS, Short Form 12 Mental Component Summary; CES-D, Center for Epidemiologic Studies Depression Scale; HbA1c, Hemoglobin A1c; T1D, Type 1 Diabetes; TUG test time, Timed Up and Go test time; MVPA time, Moderate to Vigorous Physical Activity time.

2.2.1. Oxidative stress

Chondrocytes rely on high-level glycolysis to maintain their physiological functions in a low-oxygen environment primarily, which causes oxidative stress and excessive pro-inflammatory cytokines in joints. They can sense and adapt to changes in glucose levels through the expression of GLUT-1, GLUT-3, and GLUT-9 [29]. However, when joints are chronically exposed to high glucose levels, OA chondrocytes are unable to downregulate GLUT-1, leading to the generation of more reactive ROS [30]. This situation explains the heightened response of OA chondrocytes to inflammatory stress in T2D patients. Similarly, in a high-glucose environment, the Nrf-2/HO-1 signaling axis, critical for intracellular antioxidant properties, was inhibited, thereby promoting the secretion of potent pro-inflammatory mediators [31]. Hyperglycemia has been shown to promote increased oxidative stress and activate synovial neovascularization, leading to the recruitment of local pro-inflammatory cells and ultimately promoting synovitis. Li et al. confirmed that under high-glucose conditions, the GLUT1 pathway promoted the increase of inflammatory factors in rat fibroblast-like synoviocytes [32].

2.2.2. AGEs

Hyperglycemia is associated with the formation of AGEs through the AGE/RAGE axis, which may contribute to inflammation and cytokine expression via RAGE activation, potentially leading to chondrocyte damage. Experimental studies suggest that AGEs can stimulate inducible iNOS expression and nitric oxide release in various cell lines [33]. Like the excess ROS produced by GLUT-1 dysregulation, AGEs may also promote ROS generation via the NADPH oxidase system. For instance, Zhang et al. reported that AGEs promoted the reduction of mitochondrial membrane potential and induced the enhancement of the NADPH oxidase subunit NOX-4 in human chondrocytes [34]. Furthermore, AGEs trigger a cascade of signaling events, including phosphorylation of p38-MAPK, JNK, and ERK-MAPK, and increase the expression of inflammatory factors such as IL-6 and IL-8 by activating RAGE in OA [35]. In Li et al.'s study, the excessive accumulation of AGEs in fibroblast-like synoviocytes tissue induced by high blood sugar increased the release of inflammatory factors in FLS, ultimately inducing chondrocyte degradation and promoting the progression of OA [32].

While these findings imply a potential role of AGEs in OA progression, the causal relationship between hyperglycemia-induced AGEs and OA pathogenesis remains unclear, requiring further studies to isolate their specific contributions from broader metabolic dysfunction.

2.2.3. Insulin resistance

Insulin resistance, as a primary metabolic abnormality in T2D patients, has been indicated to be associated with the accumulation of pro-inflammatory macrophages and inflammation. Mitsugu et al. used a mouse model combining genetically induced fat-specific insulin resistance and diet-induced obesity, reporting that insulin resistance led to the local accumulation of pro-inflammatory macrophages [36]. Mechanistically, insulin resistance may exacerbate macrophage activation and polarization toward the M1 pro-inflammatory phenotype, leading to elevated production of cytokines like TNF-α. Hamada et al. reported that TNF-α contributes to OA progression in T2D patients, with anti-TNF therapy showing greater efficacy in diabetic OA compared to non-diabetic cohorts [37]. These findings suggest a potential link between hyperglycemia-induced insulin resistance and OA inflammation via M1 macrophage activation.

However, the causal relationship between T2D, insulin resistance, and OA remains uncertain, as obesity, a common comorbidity in T2D, confounds these associations. For instance, while increased synovial macrophage infiltration has been observed in obese OA patients with T2D, it is unclear whether this phenomenon is driven by diabetic metabolic dysregulation or obesity-related adipose inflammation [37]. Further studies are needed to disentangle the independent effects of hyperglycemia and insulin resistance from those of obesity in OA pathogenesis.

2.3. Dyslipidaemia and OA

Dyslipidaemia is mainly manifested as hypercholesterolemia, low levels of high-density lipoprotein, high levels of LDL, or hypertriglyceridemia. Zhou et al. reported that for each unit increase in triglycerides, the clinical prevalence and the risk of clinical onset of KOA increased by 9 % and 5 %, respectively [38]. Moreover, Cho et al. indicated that the mild inflammation induced by hypercholesterolemia was an important factor influencing KOA pain [39]. In rodent studies, the use of $APOE^{-/-}$ mice, a low-cholesterol mouse model, and APOE*3Leiden.CETP mice, a hyperlipidemia model, both have demonstrated that hyperlipidemia can induce the occurrence and progression of OA [40,41]. Recently, we reported that intra-articular injection of anti-APOE neutralizing antibodies inhibited APOE signaling and reduced the progression of OA in mice [42]. These findings collectively indicate that a high lipid state may render joints more prone to a pro-inflammatory environment. This association might be linked to oxidative stress and ox-LDL production caused by dyslipidemia.

Under dyslipidemia, mitochondrial dysfunction can be induced by oxidative stress. In the primary culture of human articular chondrocytes stimulated by high cholesterol, mitochondrial dysfunction and increased ROS production were observed, as well as activation of p-ERK1/2 and p-JNK inflammatory pathways [40]. This suggests that high cholesterol can induce mitochondrial dysfunction in chondrocytes, promote the generation of reactive ROS from chondrocyte, and amplify chondrocyte inflammation.

Munter et al. established a mouse model of elevated systemic LDL cholesterol levels independent of body weight and found that elevated cholesterol levels significantly exacerbated the activation of synovial inflammation in OA [43]. While, in high-inflammation synovitis, endothelial cell activation and ROS release could promoted oxidize LDL, modifying it into ox-LDL.

Ox-LDL is increased in hyperlipidemia, which explains why apolipoprotein B, as a major component of ox-LDL, was accumulated in synovial tissue of high-cholesterol diet mice. Furthermore, ox-LDL is taken up by macrophages through various receptors, especially LOX-1. It can induce a phenotypic shift of macrophages toward a pro-inflammatory phenotype. This further activates the expression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), chemokines (IL-8, macrophage inflammatory protein-1b), enzymes (COX-2, iNOS, cPLA2), and adhesion molecules (intercellular adhesion molecule-1 and VCAM-1) [44]. Hashimoto et al. indicated that mice lacking LOX-1 showed resistance to age-related KOA, confirming the role of the LOX-1/oxLDL system in cartilage degradation [45].

2.4. Hypertension and OA

Hypertension, as an essential component of MetS, has been confirmed to be positively correlated with KOA in numerous epidemiological studies recently. A meta-analysis involving 9762 participants have revealed a significant association between hypertension and the risk of both radiographic and symptomatic KOA [46]. In addition, hypertension-induced OA rat models like the spontaneously hypertensive heart failure contribute to understanding the link between hypertension and OA [47]. Although fewer studies have focused on the primary mechanisms underlying the association of blood pressure with OA, current research has been primarily concentrated on the vascular pathology of ischemic hypoxic injuries in cartilage and subchondral bone.

2.4.1. Venous obstruction and hypoxia

Under the influence of hypertension, the small blood vessels in the subchondral bone may undergo decreased blood flow due to vasoconstriction. It may lead to venous obstruction or the formation of microthrombi, narrowing the vessel lumen and causing subchondral ischemia, thereby affecting the nutritional status of the cartilage. Previous studies have indicated an association between hip joint OA and venous outflow obstruction, venous stasis, and reduced perfusion [48]. Similarly, in a

female rat model, induction of subchondral bone thrombosis in the temporomandibular joint promoted OA progression [49]. All of these indicate the role of vascularization in joint homeostasis, and it can be inferred that hypertension-induced vasoconstriction and venous stasis may promote the development of OA.

Ischemia in the subchondral bone can lead to significant changes, primarily characterized by hypoxia. Under hypoxia, osteoblasts respond by altering the expression of relevant cellular signaling pathways, leading to changes in the expression profile of cytokines, proteins and growth factors, thereby promoting cartilage degradation [50].

2.4.2. Vascular stiffness

The induction of high blood pressure in the circulation promotes vascular stiffness, which leads to vascular ageing and triggers inflammation around the blood vessels. We confirmed that high blood pressure and arterial stiffness were associated with lower tibial and femoral cartilage volumes, which may affect the progression of OA [51]. Mechanistically, bone morphogenetic protein (BMP) has been widely reported as a therapeutic target for vascular sclerosis in inflammatory vascular diseases such as atherosclerosis. Whether it can promote inflammation around subchondral blood vessels and affect the progression of OA has not been reported. Currently, most research on BMP is primarily focused on inducing hypertrophy of chondrocytes, but Jaswal et al. confirmed that blockade of the BMP signal can prevent the activation of inflammatory responses in OA [52]. Therefore, further investigation is still required to determine whether BMP signaling in hypertension-induced OA can induce inflammation around the subchondral bone vasculature by directly regulating the inflammatory pathway.

2.4.3. Abnormal blood vessel formation

The occurrence of abnormal vascular channels is indispensable for the infiltration of inflammatory mediators. Under normal circumstances, the calcified zone of cartilage and subchondral bone plate can block chemical and physical communication between bone and cartilage. However, under hypertensive conditions, HIF-1α and VEGF, as the main stimulatory factors for angiogenesis and vasculogenesis, can stimulate the generation of new blood vessels. This provides a pathway for the release of inflammatory factors by subchondral osteoblasts, promoting the progression of OA [53]. Although the increase in abnormal vascular channels in subchondral bone in OA has not been proven, we speculate that the subchondral bone ischemia and hypoxia induced by hypertension may potentially impact the progression of OA through this pathway.

3. Potential treatments for MetS-OA

3.1. Therapeutic measures for MetS-OA related to obesity

3.1.1. Metabolic modulators

MET has shown great potential for treating OA. By activating AMPK, MET suppresses pro-inflammatory cytokines from M1 macrophages and reduces leptin secretion in adipose tissue, mitigating cartilage degradation in obese mice [54]. Clinical evidence further supports its efficacy: a retrospective study of 862 obese KOA patients demonstrated that MET use was associated with a 74 % reduced risk of total knee arthroplasty and lower severity of knee joint pain [55].

In addition, semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist approved for weight management in obese individuals, was shown to alleviate pain related to KOA among obese persons in a recently randomized, double-blind, placebo-controlled trial [9]. Although this trial lacked an assessment of metabolic and inflammatory markers, its significant outcomes suggest the therapeutic potential of employing metabolic drugs for the treatment of MetS-OA. Exenatide, a hypoglycemic and anti-obesity drug targeting the GLP-1/GLP-1R axis, has positive effects on OA by protecting collagen and aggrecan and blocking the p38 pathways [56]. Liraglutide, another GLP-1RA and appetite suppressant, could reduce weight in obese OA patients, and its antioxidant and anti-inflammatory effects on OA have been confirmed experimentally despite controversial clinical trial results [57].

3.1.2. Macrophage polarization regulators

Targeting macrophage polarization offers a potential therapeutic avenue for obesity-induced MetS-OA. However, systemic macrophage depletion didn't consistently alleviate OA severity in obese mice, likely due to the complex roles of different macrophage subtypes [58]. Instead, more targeted approaches, such as selectively depleting M1 macrophages or promoting M2 anti-inflammatory polarization, may be more effective. Studies using clodronate-loaded liposomes to deplete synovial macrophages and resolvin D1 to reprogram macrophage polarization demonstrated significant reductions in synovitis and cartilage degradation in obese mice [59]. These findings underscore the need for precision strategies to reprogram macrophage phenotypes, balancing the suppression of pro-inflammatory responses while preserving anti-inflammatory mechanisms to mitigate obesity-related MetS-OA.

3.1.3. Adipokine-targeted therapies

The regulatory role of adipokines in MetS-OA suggests that neutralizing these factors may be an effective therapeutic strategy. For instance, leptin inhibitor promoted autophagy effects on chondrocytes, reducing mTORC1 activation and cartilage breakdown [60]. Visfatin inhibitors APO866 demonstrated potential as a novel treatment for MetS-OA by lowering the expression of pro-inflammatory cytokines [61].

3.2. Therapeutic measures for MetS-OA related to hyperglycemia

3.2.1. Targeting ROS and antioxidant pathways

As previously discussed, oxidative stress, a critical mechanism in hyperglycemia-induced OA progression, underscores the therapeutic potential of targeting ROS or antioxidant pathways.

In T1D rats, insulin administration prevented diabetes-induced OA by reducing biomarkers of inflammation and oxidative stress, while T2D patients receiving insulin treatment exhibited fewer knee osteophytes compared to non-users [62,63].

In addition, antioxidant compounds such as astaxanthin and bardoxolone methyl alleviated hyperglycemia-induced oxidative stress [64]. In OA, astaxanthin inhibited ROS generation and chondrocyte apoptosis via the SOD1 pathway, while bardoxolone methyl activated Nrf2 to enhance antioxidant enzyme activity [65,66]. Although these agents are currently limited to preclinical studies, their dual anti-OA and anti-hyperglycemic effects suggest promising therapeutic potential for hyperglycemia-induced OA.

3.2.2. Inhibiting AGEs formation and insulin resistance

Targeting AGEs and insulin resistance represents a promising strategy for alleviating hyperglycemia-induced OA.

For AGEs accumulation, thiazolidinediones, including rosiglitazone and pioglitazone, alleviated AGEs-induced inflammation and mitochondrial dysfunction, with pioglitazone shown to reduce AGEs-induced OA severity in animal models [67,68]. DPP-4 inhibitors like sitagliptin reduced AGEs by improving glucose metabolism and inhibiting the AGE-RAGE signaling pathway in OA [69]. Moreover, although not conventional antidiabetic agents, natural polyphenols like anthocyanins and resveratrol may hold therapeutic promise for hyperglycemia-induced OA through their AGE-inhibitory mechanisms in OA [70].

In addressing insulin resistance, antidiabetic drugs like GLP-1RA (e.g., liraglutide) and MET demonstrated significant improvements in insulin sensitivity, suppression of chondrocyte apoptosis, and reduction of inflammation [71]. MET, in particular, has shown significant clinical efficacy: a 12-year population-based cohort study found that MET users had a lower risk of total knee replacement or total hip replacement compared to non-users in diabetic patients [72]. Additionally, a retrospective study of 968 patients with both OA and T2D showed that combining MET with COX-2 inhibitors further reduced joint replacement rates [73].

3.3. Therapeutic measures for MetS-OA related to dyslipidemia

Dyslipidemia, common in obesity, can be treated through both anti-obesity medications (e.g., GLP-1RA) and lipid-lowering therapies (e.g., fibrates and statins).

Fibrates, represented by fenofibrate, demonstrated OA therapeutic potential by activating PPAR-α, which enhanced fatty acid oxidation and reduced triglyceride levels, thereby limiting lipid peroxidation and ox-LDL formation. In a small pilot study, Shirinsky et al. discovered fenofibrate treated erosive HOA by reducing circulating levels of IL-10 and improving systemic inflammation and lipid status [74].

Regarding statins, a large prospective cohort study suggested that statin drugs relieved KOA by reducing systemic low-grade inflammation and inhibiting cartilage degradation [75]. Among these, atorvastatin was shown to reduce LDL-C levels, limiting LDL oxidation substrates and potentially exerting anti-inflammatory, analgesic, and antioxidant effects [76]. In addition, preclinical data further indicated pravastatin has been shown to lower cholesterol levels, thereby reducing inflammation and chondrocyte apoptosis [77]. While statins demonstrated promising anti-inflammatory properties in OA pathogenesis, their clinical efficacy remained uncertain. A randomized placebo-controlled trial suggested limited therapeutic potential of atorvastatin for structural modification in OA [78]. This discrepancy between mechanistic insights and clinical outcomes highlights the importance of developing phenotype-specific treatment strategies, particularly for metabolic OA subtypes, to better realize statins' therapeutic potential through targeted patient stratification.

3.4. Treatment measures for MetS-OA related to hypertension

Current evidence suggests that certain antihypertensive medications demonstrate therapeutic potential for OA. In a prospective and sonographic-based study, low-dose spironolactone was a effective medical treatment for OA-related knee effusion [79]. Its use in the hypertensive model could reduce the development of inflammation and organ damage, which has good potential for the treatment of hypertension-induced MetS-OA [80]. Additionally, inhibitors of the renin-angiotensin system, such as losartan and captopril, have shown promising effects in the treatment of OA [81]. Moreover, calcium channel blockers, especially verapamil and amlodipine, could inhibit the activation of the NF-κB inflammatory pathway, reducing joint wear and tear, as well as joint damage caused by OA [82].

While current studies of antihypertensive drugs in OA have not specifically evaluated their effects under hypertensive or metabolic conditions, their dual mechanisms targeting both cardiovascular and joint pathologies suggest particular promise for hypertension-mediated OA. Building on our current understanding of the vascular pathophysiology in hypertension-mediated OA, future therapeutic strategies in MetS-OA may extend beyond traditional antihypertensives to include targeted interventions addressing these specific mechanisms.

4. Conclusions

Existing evidence supports that individuals with metabolic disorders are at a higher risk of developing OA. It is plausible to regard the systemic low-grade inflammation induced by metabolic disorders as a pivotal factor in the exacerbation of MetS-OA. Although there are still many potential drugs that lack clinical translation, they show great potential in the anti-inflammatory treatment of MetS-OA. Therefore, forthcoming therapeutic strategies should employ macroscopic approaches that target metabolic disorders to resolve local diseases, particularly those with multifactorial aetiologias such as OA.

Author contributions

All authors have made substantial contributions the conception and design of the study, data acquisition, revising the article and final approval.

Declaration of competing interest

No competing interests for any of the authors.

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