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REVIEW

Metabolism-Related Adipokines and Metabolic Diseases: Their Role in Osteoarthritis

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Video abstract

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Abstract: Osteoarthritis (OA) affects several joints but tends to be more prevalent in those that are weight-bearing, such as the knees, which are the most heavily loaded joints in the body. The incidence and disability rates of OA have continued to increase and seriously jeopardise the quality of life of middle-aged and older adults. However, OA is more than just a wear and tear disease; its aetiology is complex, and its pathogenesis is poorly understood. Metabolic syndrome (MetS) has emerged as a critical driver of OA development. This condition contributes to the formation of a distinct phenotype, termed metabolic syndrome-associated osteoarthritis (MetS-OA), which differs from other metabolically related diseases by its unique pathophysiological mechanisms and clinical presentation. As key mediators of MetS, metabolic adipokines such as leptin, lipocalin, and resistin regulate inflammation and bone metabolism through distinct or synergistic signaling pathways. Their modulation of inflammatory responses and bone remodeling processes plays a critical role in the pathogenesis and progression of OA. Due to their central role in regulating inflammation and bone remodeling, metabolic adipokines not only deepen our understanding of MetS-OA pathogenesis but also represent promising targets for novel therapeutic strategies that could slow disease progression and improve clinical outcomes in affected patients.

Keywords: osteoarthritis, metabolic syndrome, adipokines

Introduction

OA is a chronic degenerative disease characterised by pain, joint stiffness, and swelling, mostly in the knee joint and hip joint.[1–4] There are gender differences in the prevalence and incidence of OA, with women generally being at higher risk than men, especially post-menopausal women around the age of 50; age is also an influencing factor in OA, with the incidence of OA of the knees and hips increasing with age for both men and women. Furthermore, the socio-economic level is an influencing factor in the incidence of OA, with poorer areas, such as rural areas, tending to have higher incidence rates than cities do.[5–9] The prevalence and burden of OA are growing exponentially and are expected to affect 78.4 million people by 2040.[10,11] As China gradually enters an ageing society, OA can seriously affect the quality of life of patients and impose a huge social and economic burden.[12] Current treatments for OA are largely limited to steroidal or non-steroidal anti-inflammatory drugs, which only relieve pain and inflammatory symptoms.[13] As a result, there is no effective treatment for the disease at this time.[14]

MetS is a multifaceted condition defined by a cluster of metabolic abnormalities, including obesity, hypertension, hyperglycemia, insulin resistance, and dyslipidemia.[15] While traditionally recognized as a major risk factor for cardiovascular diseases and diabetes, emerging evidence highlights its critical role in the pathogenesis and progression of OA.[15–17] MetS-related metabolic disturbances adversely affect multiple joint tissues, such as cartilage, bone, and synovium, through mechanisms that involve chronic low-grade inflammation, oxidative stress, and imbalances in adipokine regulation.[15–17]These interconnected processes collectively contribute to the initiation and exacerbation of

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OA, positioning MetS as a significant driver of disease development. The concept of metabolic syndrome-associated MetS-OA has recently been introduced, despite the high prevalence of MetS-OA, its underlying pathogenic mechanisms remain poorly understood.[16] Metabolic syndrome has been shown to promote the release of inflammatory cytokines, particularly adipokines, which play a pivotal role in establishing a chronic low-grade inflammatory state, driving cartilage degeneration, and disrupting the balance of the intra-articular environment.[16,18] These insights underscore the critical contribution of adipokines to the pathogenesis of MetS-OA.[16]

Adipokines, primarily secreted by white adipose tissue, are signaling molecules that regulate inflammation and metabolic processes, with dysregulation linked to various diseases, including OA.[19–21] In OA, they are central mediators of pathogenesis, contributing to chronic inflammation, cartilage degradation, and bone remodeling imbalances through shared inflammatory and metabolic pathways such as NF-κB, PI3K/Akt, and MAPK.[22,23] Recent clinical studies have highlighted their dual roles in OA progression, with some exacerbating the disease while others exhibit protective effects. This duality not only establishes adipokines as key contributors to OA pathophysiology but also underscores their potential as diagnostic biomarkers and therapeutic targets. Emerging targeted therapies for specific adipokines offer promising opportunities to modulate their activity, paving the way for personalized treatment strategies that address both inflammatory and metabolic components of OA and potentially transforming the management of this complex disease.

Further research is needed to confirm these relationships and investigate the role of adipose tissue in OA development. This review focuses on the impact and mechanisms of metabolic diseases and adipokines on OA onset and progression (Figure 1).

Metabolic Syndrome

MetS is a global health problem that is increasing globally and will account for approximately 1/3 of the world's population by 2022, making it a major public health problem.[24–26] It is usually made up of four components: hyperglycaemia, hypertension, dyslipidaemia, and obesity.[27–29] The relationship between MetS and OA has been extensively studied (Figure 2).Some studies argue that metabolism minimally impacts OA, with one study showing no significant effect of MetS on OA incidence after adjusting for body mass index (BMI).[30] Conversely, other research

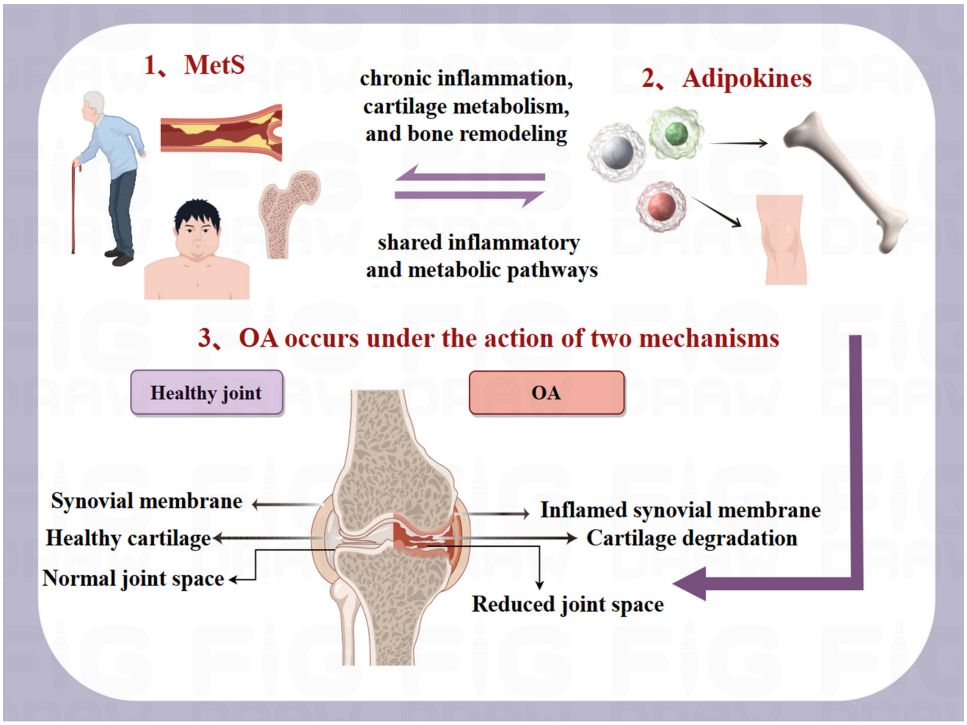

Figure 1 Metabolic diseases and adipokines influence the progression of OA through regulating inflammation and matrix degradation.

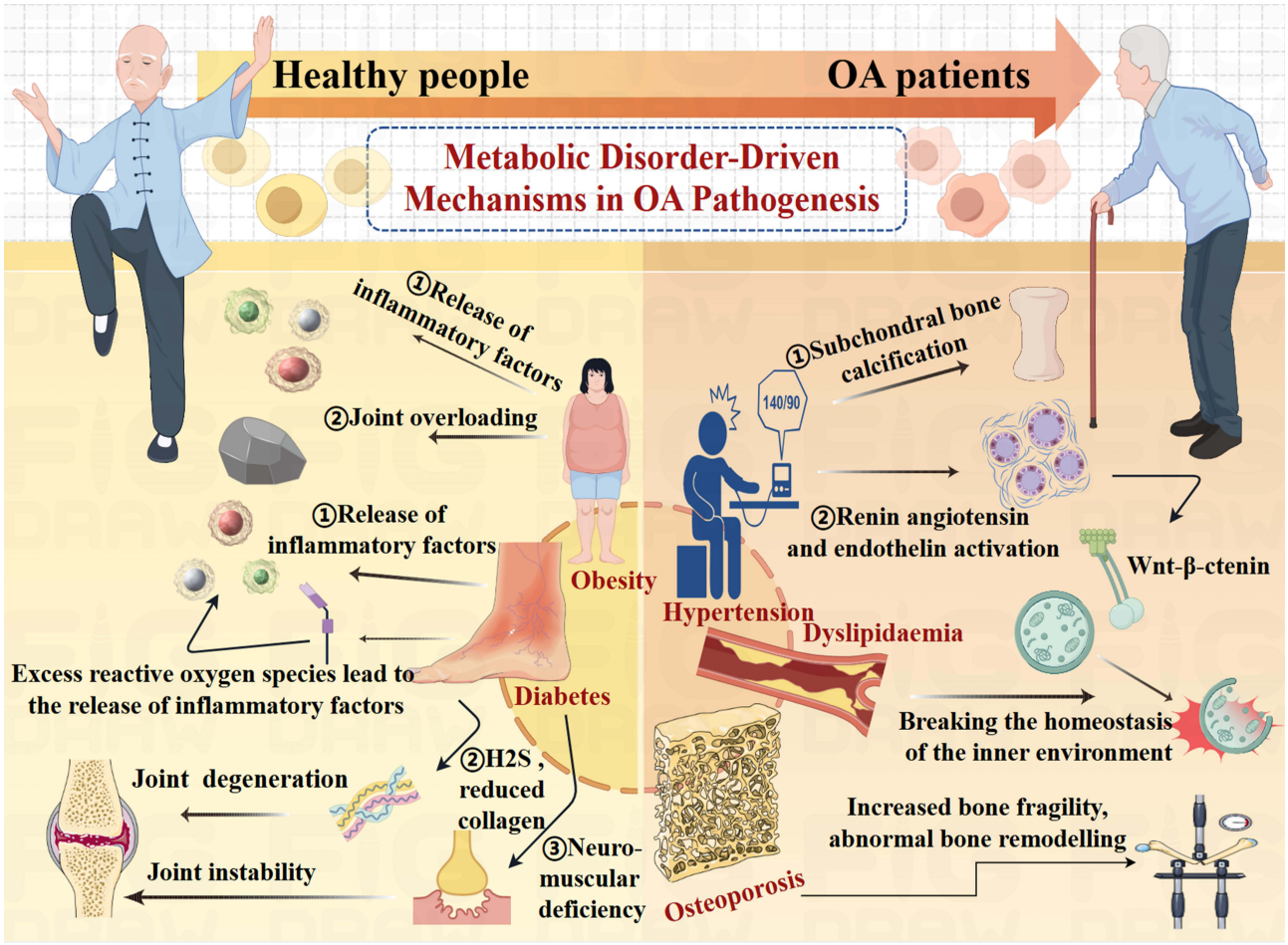

Figure 2 A Comprehensive Overview of OA Pathophysiology Linked to Metabolic Diseases: Mechanisms of Onset. This figure illustrates the mechanisms by which MetS contributes to OA development through shared pathways of inflammation, oxidative stress, and metabolic dysregulation: Obesity: Drives cartilage degradation and joint instability via pro-inflammatory cytokines (IL-6, TNF-α), ROS, and increased joint loading. DM: Amplifies oxidative stress and inflammation through AGEs and ROS while reduced H2S levels and impaired collagen synthesis exacerbate cartilage degeneration and joint instability. HT: Activates renin-angiotensin, endothelin, and Wnt-β-catenin pathways, leading to subchondral bone calcification and remodeling imbalance. DL: Induces chronic inflammation and oxidative stress, disrupting cartilage homeostasis and accelerating OA progression. OP: Weakens subchondral bone, resulting in cartilage calcification, biomechanical imbalance, and rapid OA progression.

suggests that MetS contributes to OA by increasing systemic inflammatory mediators from adiposity.[31] Moreover, in patients aged 18–78 years with OA, those with MetS develop OA earlier, have more extensive pathology, increased inflammation, and increased joint pain than do those without it.[32,33] MetS manifests in a variety of ways, depending on the components that make up the syndrome,[34] making its early recognition particularly important. In the context of economic development and improved living standards, the number of patients with MetS has increased dramatically worldwide.[35,36] Therefore, there is a need to explore the links and mechanisms between MetS and OA to facilitate better prevention and treatment of OA.

Relationship Between Obesity and OA

Obesity, a hallmark of MetS, is characterized by excessive fat accumulation. Over the past 50 years, its prevalence has risen steadily worldwide, with more than 2 billion individuals expected to be affected in the near future.[37,38] As a major global health challenge, obesity has emerged as a significant risk factor for OA progression through adipose tissue-dependent inflammation.[39–43] BMI, the primary clinical and research metric for measuring obesity, is positively correlated with OA risk. Specifically, individuals with a BMI greater than 30 face a two-thirds lifetime risk of OA and a doubled risk of asymptomatic OA.[44,45] While mechanical joint overload caused by a high BMI has long been considered a primary driver of OA,[46–49] it fails to fully explain the high prevalence of OA in non-weight-bearing joints, such as the hands.[45] Recent evidence highlights

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the critical role of obesity-associated systemic inflammation and metabolic dysregulation in OA pathogenesis.[50] In obesity, adipose tissue undergoes inflammatory remodeling, marked by a significant increase in pro-inflammatory macrophage infiltration. These macrophages release cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), disrupting chondrocyte homeostasis and accelerating cartilage degradation.[51–55] Concurrently, elevated leptin levels in synovial fluid enhance the interaction between chondrocytes and synovial fibroblasts, further amplifying IL-6 production and exacerbating local inflammatory responses.[56,57] This adipose tissue-driven inflammatory cascade links systemic metabolic disturbances to localized joint pathology, establishing a critical connection between obesity and OA.

By elucidating the interplay between systemic inflammation, local joint damage, and metabolic dysregulation, this framework underscores the central role of adipose tissue-dependent inflammation in OA. These insights deepen our understanding of obesity-induced OA and provide a robust foundation for developing targeted interventions that address both the inflammatory and metabolic components of this complex disease.

Relationship Between Diabetes Mellitus and OA

Diabetes mellitus (DM) is a prevalent non-communicable disease characterized by systemic metabolic dysregulation caused by an imbalance between risk and protective factors.[58,59] Studies have demonstrated a strong association between DM and the onset and progression of OA.[58] Compared to non-diabetic OA patients, those with DM typically exhibit greater pain intensity and poorer physical and mental health.[60] While numerous studies have identified a significant link between DM and OA—such as an increased risk of joint replacement surgery—the exact mechanisms underlying this relationship remain unclear and controversial.[61,62]

Emerging evidence indicates that DM exacerbates OA progression through three primary mechanisms: chronic inflammation, joint structure degeneration, and joint instability.[63] Elevated levels of IL-6 and Progranulin(PGRN) in OA joint tissues of DM patients suggest that cartilage in these individuals is more susceptible to pro-inflammatory stress, leading to heightened inflammatory responses.[64] Furthermore, increased reactive oxygen species (ROS) in DM-associated OA not only stimulate the production of inflammatory mediators such as IL-1β but also inhibit collagen synthesis in cartilage, accelerating cartilage degradation.[65–67] This oxidative stress further disrupts cartilage homeostasis, potentially due to decreased levels of protective factors such as hydrogen sulfide (H2S) and nuclear factor erythroid 2-related factor 2 (Nrf-2).[68] DM also contributes to neuromuscular deficits, which exacerbate joint instability and increase cartilage friction, thereby further advancing OA progression.[68] These DM-induced structural changes amplify joint instability, accelerating disease development. However, some studies dispute the direct relationship between DM and OA, arguing that DM is not an independent risk factor for OA. Such discrepancies may arise from differences in study design, patient populations, and the multifactorial etiologies of both diseases.[69–71]

To resolve these controversies, future research should clarify the molecular mechanisms linking DM to OA, particularly through inflammatory and oxidative stress pathways. Studies should examine how DM differentially affects weight-bearing and non-weight-bearing joints and explore variations in OA progression across DM types. Addressing these gaps will enhance our understanding of the DM-OA relationship and facilitate the development of targeted therapies addressing shared metabolic and inflammatory pathways.

Relationship Between Hypertension and OA

Hypertension (HT) affects more than 1 billion adults worldwide, and its prevalence is on the rise.[72] HT has been found to be significantly associated with the development of OA, and OA prevalence in patients with hypertension is approximately 40%.[73,74] Gender is an influential factor in the relationship between HT and OA, with Lawrence suggesting that HT is associated with OA in women.[75] Yang et al concluded that HT is linked to an increased OA risk in men, potentially due to joint structural degeneration and biochemical pathways.[76] Increased subchondral bone calcification was found in hypertensive OA animals compared to normal OA animals,[77] and a meta-analysis reported a stronger correlation between hypertension and knee OA on imaging, suggesting that hypertension is strongly associated with structural damage to the OA.[78] Furthermore, HT activates the renin-angiotensin and endothelin systems, affecting the Wnt-β-catenin signalling pathway and potentially influencing joint disease.[76] The causal link between OA and HT is unclear, and future research should clarify how HT impacts OA joints.

Relationship Between Dyslipidaemias and OA

Dyslipidaemias (DLs) are typically characterised by abnormal levels of serum cholesterol, triglycerides, or both, as well as abnormal levels of associated lipoprotein species.[79] The link between DL and OA is debated. Several studies indicate DL may elevate OA risk,[80–83] likely due to its impact on body homeostasis and association with chronic inflammation and oxidative stress.[84,85] Conversely, Inoue found no significant of DL on hand OA risk.[86]

Relationship Between Osteoporosis and OA

Osteoporosis (OP) is a systemic skeletal disease increasingly prevalent with aging, marked by reduced bone strength and microarchitectural deterioration.[87] Both OP and OA are complex, multifactorial disorders lacking a complete cure, significantly contributing to pain and socio-economic burdens worldwide. It is imperative to explore their interrelation and devise new therapeutic strategies.[88–90] Recent studies highlight OA's susceptibility to subchondral fragility, potentially leading to the emergent concept of OP-OA, meriting further attention.[91] Although a negative correlation between OP and subsequent OA development is suggested by most research, including a two-sample MR analysis indicating that OP may lower OA incidence, this relationship remains debated.[92,93] Further findings indicate that OP-OA patients experience faster OA progression due to abnormal subchondral bone remodelling, increased cartilage calcification and damage, and biomechanical deterioration.[94–96] However, the exact mechanisms linking these conditions require more investigation.

The study of metabolic diseases associated with OA has transformed our understanding of its pathogenesis. It is now recognized that OA extends beyond mere joint "wear and tear" due to overloading; it is a chronic inflammatory condition influenced by systemic metabolism, inflicting both physical and psychological stress on patients, and imposing a significant economic burden on society. Consequently, exploring the link between metabolic diseases and OA to identify novel treatment strategies is a promising approach. The various roles of metabolic diseases in the context of OA have been discussed in Table 1.

Metabolic Diseases and OA Pathogenesis

Obesity, DM, HT, DL, and OP collectively drive the onset and progression of OA through convergent mechanisms involving inflammation, oxidative stress, and metabolic dysregulation. Together, these MetS not only contribute to structural joint damage but also reveal the intricate, multifaceted complexity of OA pathogenesis.

Pro-inflammatory factors associated with obesity, such as IL-6, TNF-α, and leptin, aggravate cartilage degradation and local inflammation through the activation of NF-κB and PI3K/Akt signaling pathways.[51–55] In DM, the accumulation of advanced glycation end-products (AGEs) and elevated levels of ROS amplify oxidative stress in cartilage while suppressing protective mechanisms mediated by nuclear factor Nrf-2 and H2S.[68] This interplay accelerates cartilage deterioration and exacerbates joint instability. Hypertension contributes to OA-related structural damage by activating the Wnt-β-catenin pathway, which promotes subchondral bone calcification and remodeling imbalances.[76,77] Although the precise role of dyslipidemia remains contested, chronic inflammation and oxidative stress likely mediate its contribution to OA progression.[84,85] Osteoporosis introduces the concept of "OP-OA", emphasizing how subchondral bone fragility exacerbates cartilage calcification and biomechanical imbalances, further driving OA advancement.[93,95]

Future research should focus on the differential effects of shared inflammatory and metabolic pathways in various joints and the synergistic impact of MetS components like obesity, DM, and HT. Targeting common molecular mechanisms through precision medicine approaches based on inflammatory and metabolic biomarkers can improve clinical outcomes and reduce OA's socioeconomic burden.

Relationship Between Metabolism-Related Adipokines and OA and Their Pathways of Action

Adipokines

Adipokines are bioactive molecules secreted primarily by adipose tissue, particularly white adipose tissue, and include hormones, cytokines, and chemokines.[19] These molecules function through autocrine, paracrine, and endocrine pathways

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Table 1 Major Epidemiological Studies of Metabolic Diseases Associated with OA

Metabolic Disease	Major Findings			Reference
	Mechanism	Signaling Pathway	Related Effectors	
Obesity				
	Abnormal mechanical loading	NF-κB,Wnt TGF-β,miRNA	IL-1β,TNF-α	[49]
	Systemic inflammatory response and Metabolic dysregulation	Wnt/β-catenin	IL-1β,TNF-α, NF-κB,Wnt TGF-β	[51]
	Metabolic dysfunction and accumulation of apoptotic cells	GAS6/Axl	TNF-α,IL-1β, IL-6 and Axl	[52]
	Metabolic dysregulation and immune cell infiltration and polarization.	Inflammatory pathway, adipokine pathway, and immune cell infiltration and polarization	IL-6,TNF-α,adiponectin,visfatin, adipsin, macrophages, and T cells.	[53,54]
	Local synovial inflammation	Inflammatory pathway, macrophage polarization, chondrocyte dysfunction.	IFN-γ and IL-1β, CD68, iNOS and Arg1, MMP13 and ADAMTS5	[55]
	The inflammatory interaction between synovial fibroblasts	Inflammatory pathway and cellular cross-talk mechanism	IL-6, IL-8, leptin	[56]
	Carbon stress	Carbon stress pathway and Sirt5 pathway	SCK, MAK and Sirt5	[57]
Diabetes				
	Metabolic dysregulation and local synovial inflammation	Wnt/β-catenin	IL-6,TNF-α,IL-1β,Adiponectin, Visfatin,Adipsin,CD68, iNOS,Arg1, MMP13,ADAMTS5 and Sirt5	[64]
	Abnormal cellular metabolism and increased oxidative stress	Glucose metabolic pathway	IL-6,PGE2,ROS,NO and GLUT-1	[66]
	Accelerated degradation of the cartilage matrix	Diabetes-induced systemic inflammatory pathways Collagen matrix changes in high glucose environments	AGEs	[67]
	Disorder of chondrocyte metabolism	Nrf-2/HO-1	H2S,Nrf-2,HO-1,COX-2 and IL-6	[68]
Hypertensive				
	Mechanical wear and cartilage remodelling	RAS, Wnt-β-catenin	VEGF,MMPs,ET1,RUNX2, RANKLand TGF-β	[76]
	Autonomic nervous system disorder	Autonomic nervous system dysregulation pathways and bone remodelling pathway	Angiotensin II receptor and ET1	[77]
Dyslipidemia				
	Chronic inflammatory response and abnormal lipid metabolism	NF-κB,MAPK	TNF-α,IL-6,HDL-C,LDL-C,ApoE,PPARγ and LXR	[84]
	Degeneration of articular cartilage and increased inflammatory response	NF-κB	IL-1β,TNF-α,HDL and 8-isoprostanesOsteoporosis	[85]
Osteoporosis				
	Inflammatory response and abnormal angiogenesis	NF-κB and mTORC1	FABP4	[93]
	Degeneration and damage to articular cartilage		MMP-13	[95]

to regulate a range of physiological and pathological processes, including energy metabolism, inflammatory responses, immune regulation, and insulin sensitivity.[20] Beyond their critical role in maintaining metabolic homeostasis, adipokines are deeply involved in the pathogenesis of various diseases, such as metabolic syndrome, cardiovascular diseases, and OA.[21] Adipokines play a central role in the pathogenesis of OA by modulating chronic inflammation, disrupting cartilage metabolic balance, and impairing bone remodeling.[21] These interconnected mechanisms not only accelerate joint degeneration but also underscore the pivotal role of metabolic disturbances in driving OA progression.[97–100] Furthermore, the unique contributions of adipokines, independent of mechanical loading, in obesity- and metabolic syndrome-associated OA highlight their potential as key targets for elucidating OA pathophysiology and developing innovative therapeutic strategies.[101,102] This understanding offers a comprehensive perspective on the multifaceted roles of adipokines in OA and provides a robust foundation for future research focused on personalized interventions targeting adipokines and their associated signaling pathways.

Adipokines in Osteoarthritis: Clinical Evidence and Therapeutic Implications

Recent clinical studies have demonstrated that adipokines play a pivotal role in the onset and progression of OA, particularly in the regulation of inflammation, cartilage degradation, and metabolic dysregulation. Leptin levels are significantly associated with the severity of joint pain in OA patients, likely by exacerbating inflammation-induced pain.[103,104] In contrast, adiponectin levels are reduced in late-stage OA and are inversely correlated with the severity of pain in OA patients, highlighting its potential protective role in joint health.[103] Furthermore, leptin concentrations in synovial fluid are strongly correlated with BMI and waist circumference, suggesting that obesity and metabolic syndrome accelerate OA progression through leptin-mediated mechanisms.[105] LCN2, a pro-catabolic adipokine, is markedly elevated in the synovial fluid and cartilage of OA patients. It enhances the activity of MMPs, promoting cartilage matrix degradation and intensifying inflammatory responses.[106] Similarly, visfatin levels in serum and synovial fluid are strongly associated with inflammation severity and disease progression in OA, further exacerbating joint tissue damage.[103] Resistin levels are significantly increased in the synovial fluid and serum of OA patients, accelerating OA pathogenesis by promoting extracellular matrix degradation and the release of pro-inflammatory cytokines.[103,107] Additionally, adipsin levels are significantly associated with lateral cartilage volume loss in the knee, suggesting its role in structural joint damage.[108] OPN levels in serum are strongly correlated with OA severity, particularly in the early stages of the disease, highlighting its potential as a biomarker for early diagnosis and intervention.[104] RBP4 is highly expressed in the serum and synovial fluid of OA patients, with levels significantly associated with matrix metalloproteinase (MMP) activity and pro-inflammatory cytokines, underscoring its critical role in cartilage degradation and inflammation.[109] Omentin-1 levels are significantly reduced in the plasma and synovial fluid of OA patients. This reduction is closely linked to joint pain, stiffness, and advanced radiographic severity, indicating a potential protective role for omentin-1 in joint health.[110] Metrnl levels are notably lower in late-stage OA patients compared to those in earlier stages, with higher Metrnl levels in synovial fluid inversely correlated with MMP-13, a key marker of cartilage degradation.[111] These findings suggest that Metrnl may protect cartilage and mitigate inflammation. Conversely, nesfatin-1 levels are significantly elevated in the serum of OA patients, and its synovial fluid concentrations are positively correlated with pro-inflammatory cytokine IL-18, further supporting its role as a pro-inflammatory mediator.[112]

These findings collectively underscore that adipokines are not only critical regulators of inflammation and metabolic processes in OA progression but also represent promising diagnostic and therapeutic targets. This evidence provides a robust foundation for developing personalized treatment strategies based on adipokine levels, offering new avenues for precision medicine in OA management.

Therapeutic Potential of Adipokines in OA Treatment

Adipokines have recently emerged as promising therapeutic targets for OA, offering innovative strategies to mitigate disease progression by modulating inflammation, cartilage degradation, and metabolic dysregulation. Leptin, a pro-inflammatory adipokine, has been targeted through therapeutic approaches such as leptin receptor antagonists (eg, Allo-aca) and leptin analogs (eg, Metreleptin), which have shown potential in alleviating inflammation and addressing metabolic disorders by modulating leptin signaling pathways.[113,114] In contrast, adiponectin exhibits anti-inflammatory

and chondroprotective properties. Its receptor agonist, AdipoRon, demonstrated efficacy in preclinical models by significantly reducing inflammation and preserving cartilage integrity.[115] Similarly, visfatin, another pro-inflammatory mediator associated with OA, has been targeted using the specific inhibitor FK866, which has shown promise in suppressing inflammatory responses and represents a potential therapeutic target.[116] Additionally, RBP4 exacerbates metabolic dysregulation in OA. The RBP4 inhibitor Fenretinide has demonstrated efficacy in mitigating metabolic disturbances, highlighting its potential as a viable treatment option for OA.[117]

These findings underscore the pivotal role of adipokines in OA pathophysiology and highlight their targeted therapeutic potential. Future research should prioritize validating these therapeutic strategies through rigorous clinical trials and evaluating their integration into precision medicine frameworks.

Leptin's Role in OA

Leptin was first identified as a product of the ob gene in 1994;[118] it is one of the most intensively studied adipokines, exhibiting pleiotropic properties and being mainly involved in both pro-inflammatory and bone metabolism in the pathomechanisms of OA.[119–121] Inflammatory factors play an important role in the developmental process of inflammation in OA, and IL-1, IL-6, TNFα, and IL-17 are the major cytokines involved in the pathogenesis of OA.[122] Furthermore, some studies have found that the levels of IL-6, IL-18, and leptin are significantly correlated with the severity of post-traumatic osteoarthritis (PTOA), with the combination of IL-6 and leptin being the most discriminatory biomarker of PTOA.[123] IL-1β is the factor most correlated with leptin and has been extensively studied, with reports indicating that levels of both leptin and IL-1β correlate with OA.[124] Both leptin and IL-6 significantly contribute to the development of OA through the JAK-STAT pathway, a crucial element in OA pathogenesis.[125] Both molecules operate via the JAK-STAT3 pathway and play roles in OA-associated regulatory mechanisms; notably, leptin not only activates the OBRl receptor, which subsequently activates the IRS-1, PI3K, Akt, and AP-1 pathways enhancing IL-6 expression.[126] Specifically, in fibroblasts of the temporomandibular joint (TMJ-SFs), leptin engages the JAK2/STAT3 or p38 MAPK or PI3K/Akt signalling pathway and binds to the leptin-specific receptor (Ob-Rb) in the TMJ-SFs to regulate IL-6 production in vitro.[127] Furthermore, leptin, in synergy with IL-1β, prompts chondrocytes to secrete pro-inflammatory agents such as IL-6, IL-8, nitric oxide, and cyclooxygenase-2 and modulates IL-6 and IL-8 production through CD4+ T cells.[128–130] Furthermore, leptin regulates bone metabolism,[125,131] in correlation with the extent of cartilage destruction;[132] bone metabolism is also partially affected. Inflammatory factors such as TNF-α, IL-1, and IL-6 notably induce MMP and prostaglandin production and inhibit proteoglycan and type II collagen synthesis, therefore, they play a key role in cartilage matrix degradation and bone resorption in OA.[133] Leptin and its downstream factors influence bone metabolism via multiple pathways, these include the induction of human ADAMTS-4 in chondrocytes through the mitogen-activated protein kinase and NF-kB signalling pathways; similarly, leptin promotes the expression of ADAMTS-4 and ADAMTS-5 in human chondrocytes, which are implicated in joint damage and the onset of OA.[134] Furthermore, leptin induces cellular senescence in OA chondrocytes by activating the mTOR pathway. Additionally, a high level of Ob-Rb expression accelerates chondrocyte senescence through the leptin pathways in OA.[135] Moreover, leptin enhances VCAM-1 expression in cartilage cells via the kinase kinases JAK2, PI3K, and AMPK, leading to accelerated cartilage degradation by promoting leukocyte and monocyte infiltration in inflamed joints.[136] Leptin increases MMP production via the JAK2 signal transducer and activator of STAT3 signalling pathway, which has a catabolic effect on OA cartilage and promotes apoptosis.[137] Finally, leptin acts through the JAK2/STAT3 signalling pathway to inhibit chondrogenicity and prevent chondrocyte apoptosis.[138] Factors downstream of leptin also play a partial role in bone metabolism, with DUSP19 downstream inhibiting chondrocyte apoptosis by dephosphorylating JNK.[139] Furthermore, LOXL3, downstream of leptin, stimulates chondrocyte apoptosis and inhibits chondrocyte autophagy.[137] Taken together, the evidence increasingly supports the potential role of leptin in OA.[122,140,141] Leptin and its receptors are critical targets for intervention in OA.[142]

Lipocalin's Role in OA

Lipocalin is a metabolism-related adipokine that regulates lipid metabolism, bone metabolism, and glucose homeostasis.[16,143] It has been found that in joints, joint adipose tissue and synovium in patients with inflammatory

joint diseases are important sources of lipocalin.[144,145] Current research highlights the significant relationship between lipocalin, adipose tissue, and synovium in patients with inflammatory joint diseases. The association between lipocalin and OA remains a subject of debate, with various studies indicating that lipocalin levels are positively correlated with the development of OA and associated with OA joint pain.[16,142,146,147] However, the underlying mechanisms by which lipocalin contributes to OA are still not fully understood and warrant further investigation.[148] Notably, lipocalin has been shown to correlate positively with IL-6 levels and enhance IL-6 production in synovial fibroblasts via the AdipoR1 receptor/AMPK/p38/IKK alpha beta and NF-κB signalling pathways.[149] This process is crucial for the pathogenesis of OA.[150] Lipocalin has also been found to increase VCAM-1 expression in chondrocytes through kinases such as JAK2, PI3K, and AMPK, accelerating chondrocyte degradation by inducing infiltration of leukocytes and monocytes in the inflamed joints.[136] However, other studies have indicated that lipocalin levels are negatively correlated with the severity of OA and exhibit an anti-inflammatory role in its development. Notably, lipocalin levels were observed to decrease significantly with the increasing severity of Kellgren-Lawrence OA; furthermore, the concentrations of lipocalin in blood and synovial fluid were significantly and negatively correlated with the grading of OA, leading researchers to suggest that lipocalin may serve a protective role in OA.[151] Feng et al reviewed the protective mechanisms of lipocalin in OA in terms of both apoptosis and autophagy.[143] Liu et al found that lipocalcin activated the AdipoR1/AMPK/PKC pathway to reduce endoplasmic reticulum stress-induced apoptosis and reduced apoptosis by regulating anti-apoptotic proteins, such as Bcl-2, in mouse adipose tissues, thereby reducing the severity of OA.[152] He and Duan discovered that LipocalinRon induces autophagy to mitigate cartilage calcification in OA, where He demonstrated that lipocalcin activates autophagy by mediating the AMPK-mTOR signalling pathway.[27] It has been proposed that lipocalcin levels do not correlate with OA development.[50] Lipofuscin-2 (Lipofectin) also plays a critical role in OA development. Lipocalin-2 (LCN2), also known as neutrophil gelatinase-associated lipocalin, is identified as a novel adipokine with catabolic functions in OA.[153,154] Most studies indicate that LCN2 serves as a biomarker for cartilage degradation in OA, and complexes comprising LCN2 and MMP9 are prevalent in synovial fluid from patients with OA, contributing to matrix degradation and OA exacerbation.[155,156] However, other research has shown that while LCN2 expression is elevated in OA chondrocytes and cartilage, its overexpression does not change the expression levels of metabolic enzymes involved in matrix degradation, such as catabolic MMP3 or anabolic chondrogenic matrix molecules; thus, its increased levels are neither sufficient nor necessary for cartilage destruction in mouse OA.[157] These conflicting findings indicate that lipocalin and LCN2 have dual or complex roles in OA, highlighting the uncertainty of their impact on OA and underscoring the need for further investigations.

Resistin's Role in OA

The primary source of resistin is white adipose tissue, which can be produced by macrophages as well as by cartilage itself.[96,157] Resistin plays an important role in synovial inflammation and cartilage degradation.[158] It is a highly potent pro-inflammatory cytokine that elevates the production of various inflammatory factors, including IL-1, TNF, and other inflammatory factors.[159,160] It has been observed that resistin facilitates the release of pro-inflammatory factors through multiple pathways.[159] It suppresses the expression of miR-149 and boosts the expression of TNF-α and IL-1β via MEK and ERK signalling.[161] Nirupama et al discovered that the enhanced secretion of pro-inflammatory cytokines could also be mediated by NF-κB;[162] resistin can further activate the p38-MAPK and NF-κB signalling pathways in human OA chondrocytes by binding to CAP1, fostering the expression of pro-inflammatory cytokines (CCL3, CCL4) and matrix-degrading enzymes (MMP-13, ADAMTS-4), and the release of these substances disrupts intra-articular homeostasis, leading to synovitis in knee joints and cartilage degeneration.[163] Moreover, resistin induces the expression of pro-inflammatory cytokines as well as miR-34a and miR-146a, which mediate mucin-induced oxidative stress in OA through the NF-κB pathway.[159] Chen et al also noted that resistin inhibits the synthesis of miR-381 via the PKCα, p38, and JNK signalling pathways, thereby influencing the expression of VCAM-1 and the adherence of monocytes to OASFs, in turn, impacts OA progression.[164] Some studies have found that resistin levels are positively associated with cartilage defects in OA,[165,166] promoting the generation of bone nodules.[167] Moreover, some researchers have found that resistin in OA bone fragments are mediated by p38 MAPK, which increases the release of pro-inflammatory mediators from osteoclasts and chondrocytes, aggravating the process of OA.[21] Additionally, resistin is known to be a key component in the

development and growth of bone mineralisation. Resistin inhibits cartilage synthesis by inducing the expression of pro-inflammatory factors such as degradative enzymes through the binding to Toll-like receptor 4 and adenylyl cyclase-associated protein 1 receptor;[168] moreover, resistin stimulates the significant overexpression of miR-34a, leading to apoptosis in OA chondrocytes and limiting proliferation.[169] Additionally, resistin promotes the expression of MMP-1 and MMP-13 in chondrocytes and increases Col2a1 mRNA, the primary collagen synthesized by these cells, thereby contributing to cartilage degradation.[169] Resistin has also been associated with OA and joint pain.[142,170,171] Notably, it has been found that garlic supplementation can reduce the severity of pain in women who are overweight or women with obesity suffering from OA, possibly through a reduction in resistin.[172] Therefore, resistin is a critical factor in the severity of OA and cartilage degeneration of the knee joint. Resistin, as a potential biomarker of knee OA disease severity and cartilage degeneration,[173,174] is closely related to the course of OA,[146,175,176] and further in-depth studies are needed to elucidate its effect on disease outcome.

Osteopontin's Role in OA

Osteopontin (OPN) is an extracellular matrix glycoprotein that plays an important role in the release of inflammatory factors and bone remodelling in OA.[177,178] The expression of OPN is regulated by the β-catenin/TCF-4 pathway and miRNA-127-5p.[179,180] Currently, several studies have concluded that OPN is significantly associated with the level of severity of OA.[104,181] OPN can promote the expression of metalloproteinase 13 (MMP13) in OA through the NF-kB signalling pathway,[182] and its deficiency induces the secretion of pro-inflammatory cytokines, such as COL10A1, IL-1β, IL-6, IL-8, and TNF- β, which exacerbate the progression of OA.[183,184] Recent studies have shown that OPN plays a crucial role in bone metabolism.[185] Moreover, the overexpression of many inflammatory factors also causes an imbalance in bone metabolism. Overexpression of MMP-1 degrades the main component of type II collagen of cartilage matrix proteins in mice;[186] the release of TNF-α, IL-6, and IL-1β induces apoptosis of chondrocytes.[187] Furthermore, IL-1β, OPN, p53 upregulation, and COL1A1 and COL2A1 overexpression significantly inhibit chondrocyte viability and migration, enhance apoptosis, and induce cartilage damage.[188] Notably, OPN promotes NF-κB signalling, accelerates chondrocyte proliferation, and thus induces OA in rats.[189] Additionally, OPN-induced expression of VEGF in articular cartilage causes severe vascular invasion of cartilage and exacerbates the process of OA.[190]

Visfatin's Role in OA

Visfatin, an adipokine, is negatively correlated with the severity of OA.[169,191] It enhances inflammation in OA, as demonstrated by Yang, who reported increased levels of inflammatory markers such as MMP3 and MMP13 in chondrocytes.[192] Furthermore, Laiguillon observed that visfatin was implicated in pro-inflammatory activation between chondrocytes and osteoblasts, significantly inducing IL-6 release.[193] Moreover, Cheleschi noted that visfatin substantially upregulated the expression of inflammatory factors, including IL-1β, IL-6, TNF-α, MMP-1, and MMP-13.[159] In this regard, Han and other scholars have provided a more comprehensive summary of the role of visfatin in OA: visfatin affects the differentiation of mesenchymal stem cells (MSCs) to adipocytes or osteoblasts by increasing the production of MMPs and ADAMTS, leading to alterations in cartilage and bone tissue; induces the production of inflammatory factors, such as IL-6 and TNF-α, and promotes an inflammatory state; and inhibits the production of osteoblasts. Osteoclastogenesis, which may promote bone regrowth formation in the context of inflammatory diseases.[194]

Adipsin's Role in OA

Adipsin, discovered in 1987, is produced by adipocytes through activation of PPAR.[195–197] Notably, lipocalin deficiency protects joint tissues from the progression of OA.[198] Adipsin levels are significantly elevated in serum, SF, and cartilage in patients with OA.[199] However, the pathway of action between adipsin and OA remains unclear. Adipsin levels have been significantly associated with cartilage volume loss in the lateral compartment of the knee and correlated with the incidence of Total Knee Arthroplasty.[140,200]

Fatty Acid Binding Protein 4's Role in OA

Fatty acid binding protein 4 (FABP4), also known as adipocyte FABP, is involved in lipolysis and is secreted by macrophages and adipocytes.[93,201] In patients with OA, FABP4 levels negatively correlate with cartilage thickness and have been identified as playing a role in cartilage degradation.[202–205] Furthermore, FABP4 has been found to activate the NF-κB signalling pathway via PPARγ, enhancing IL-1β-induced inflammation, oxidative stress, apoptosis, and extracellular matrix degradation in chondrocytes;thus, FABP4 is implicated in promoting chondrocyte degeneration and plays a significant role in the progression of OA.[206,207]

Nesfatin-1's Role in OA

Nesfatin-1, an adipokine, is pivotal in OA development by modulating inflammatory mediators and chondrocytes, though its role in inflammation is debated. This adipokine notably enhances rat chondrocytes' collagen type II alpha-1 chain (Col2a1) expression and diminishes several inflammatory agents, such as MMPs, cyclooxygenase-2, nitric oxide, prostaglandin E2, and IL-6; additionally, reduces chondrocyte apoptosis, thus safeguarding against OA.[112,208] Conversely, most studies have demonstrated a significant positive correlation between nesfatin-1 levels and OA severity.[209,210] Furthermore, Lee reported that nesfatin-1 contributes to the production of inflammatory cytokines, particularly promoting IL-1β production in osteoarthritic synovial fibroblasts by suppressing miR-204-5p synthesis through the AP-1 and NF-κB pathway.[211] In contrast, some studies suggest that Nesfatin-1, by blocking the activation of the RhoA/ROCK pathway, prevents excessive autophagy in OA cartilage and enhances chondrocyte cytoskeletal integrity.[212] Thus, Nesfatin-1 is pivotal in OA progression, yet its interactions with inflammatory factors are underexplored, warranting further investigation as a potential therapeutic target for OA.

Serpin Peptidase Inhibitor, Clade E, Member 2's Role in OA

Serpin peptidase inhibitor, clade E, member 2 (Serpin E2) exhibits beneficial effects on the progression of OA, offering chondroprotective benefits, inhibiting cartilage degradation, and preventing joint destruction in rabbits.[213,214] Crucially, the efficacy of Serpin E2 hinges on its interaction with MMPs.[215,216] Among these, MMP-13 emerges as a critical collagenase involved in cartilage catabolism in OA. Santoro et al demonstrated that Serpin E2 obstructs IL-1-induced MMP-13 expression in chondrocytes via pathways involving ERK, NF-κB, and AP-1, thereby mitigating cartilage catabolism.[215]

Progranulin's Role in OA

PGRN is an adipokine with multifaceted functions, contributing to chondrogenesis and anti-inflammation in OA and preventing further OA deterioration.[217,218] Atsttrin, a derivative of PGRN, protects against early OA.[219] Autophagy serves as a protective mechanism for normal cartilage,[220] and its loss is linked to pathological changes in OA.[221] PGRN regulates chondrocyte autophagy by modulating the interaction with the ATG5-ATG12 complex, thus providing a protective effect on cartilage.[222] Furthermore, PGRN interacts with the inositol-requiring enzyme 1α, an inositol-requiring enzyme, enhancing the expression of collagen type 2 and maintaining collagen homeostasis to protect cartilage.[223] As an antagonist of TNF-α signalling, PGRN plays a crucial role in the pathogenesis of inflammatory arthritis in mice, antagonizes TNF-α, and protects against cartilage destruction in OA.[224,225] Additionally, PGRN restores chondrocyte metabolic homeostasis by activating the ERK1/2 signalling pathway and elevating anabolic biomarkers, including collagen type 2 and Aggrecan.[226]

Chemerin's Role in OA

Chemerin exhibits a pro-inflammatory effect, and in vitro studies suggest its role in inflammatory lesions and cartilage degeneration in OA.[17,227,228] This protein is pro-inflammatory in OA; notably, chemerin induces the release of inflammatory mediators such as IL-6, TNF-a, and metalloproteinases from macrophages and chondrocytes.[229] Furthermore, chemerin elevates TLR4 expression and triggers CCL2 release from synovial fibroblasts, enhancing leukocyte migration to inflammation sites and amplifying inflammatory signalling in chondrocytes.[155] Moreover, chemerin intensifies

inflammatory signals in macrophages and chondrocytes,[230] influences chondrocyte metabolism by boosting AKT/ERK phosphorylation, and decreases chondrocyte proliferation, worsening OA symptoms.[231] Therefore, while chemerin's role in OA development is acknowledged, its precise pathways and mechanisms warrant further study.

Wnt-1-Induced Signalling Pathway Protein 2's Role in OA

Emerging adipokines, such as Wnt-1-induced signalling pathway protein 2 (WISP-2) or CCN5, have been linked to OA progression. Found in the chondrocytes and synovial membranes of OA patients, WISP-2 significantly influences OA pathogenesis.[232–234] Studies indicate that WISP-2 counters the effects of IL-1β on MMP-13 and ADAMTS-5, and decreases IL-6 and IL-8 levels in OA chondrocytes through the WNT/β-catenin pathway, thus potentially slowing OA progression.[235]

Visceral Adipose Tissue-Derived Serpin's Role in OA

Visceral adipose tissue-derived Serpin (vaspin), which is expressed at multiple sites and possesses pleiotropic properties, has also emerged.[236] Serum vaspin levels are lower in OA patients than in healthy controls.[237] Vaspin may inhibit the release of pro-inflammatory factors and certain adipokines such as leptin and resistin,[238] influencing the inflammatory process in OA and promoting the development of bone mesenchymal stem cells through activation of the PI3K/AKT pathway.[239,240] Reduced expression of vaspin inhibits cholesterol synthesis via the miR155/LXRα efflux pathway, contributing to the accumulation of cholesterol in the cartilage and the development of OA.[241]

Serum Amyloid A's Role in OA

Serum Amyloid A (SAA) is a newly discovered adipokine; studies have shown that the level of SAA in serum and synovial fluid (SF) of OA patients was higher than normal, and its expression level was positively correlated with the severity of OA.[242,243] Furthermore, it was found that SAA induces the release of pro-inflammatory cytokines,[244,245] which plays a key role in the inflammatory process of OA and induces the secretion of MMPs by chondrocytes under the control of TGF-b, exacerbating the progression of OA.[246]

Omentin-1's Role in OA

Omentin-1 (also known as Intelectin-1) is a newly discovered adipokine, and multiple studies have found that its level is negatively correlated with OA severity.[247,248] Omentin-1 displays anti-inflammatory effects in OA, with both omentin-1 and IL-4 levels significantly reduced in OA patients relative to controls. Studies have shown that omentin-1 triggers IL-4-dependent anti-inflammatory responses and M2 macrophage polarization in OA synovial fibroblasts via PI3K, ERK, and AMPK pathways, thereby preventing cartilage degradation and bone erosion.[249] Additionally, omentin-1 has been described as a pleiotropic protective adipokine that offers a repair mechanism for chondrocytes in joint tissue. This is done by attenuating IL-1β-induced G1-phase cell cycle block and inhibiting IL-1-induced cellular senescence, thus protecting chondrocytes from senescence.[250]

Metrnl's Role in OA

Metrnl, a newly discovered adipokine, has been linked to the pathogenesis of OA. Studies have shown that higher levels of Metrnl correlate with a reduced likelihood of developing OA.[251–253] It has also been shown that Metrnl can regulate IL-4 and IL-13 expression levels to exert anti-inflammatory effects;Liu has noted that its anti-inflammatory effects are mediated by inhibiting the PI3K/Akt/NF-κB pathway.[254,255]

Adipokines as Key Mediators in the Pathogenesis of OA

Adipokines play a pivotal role in the pathogenesis of OA through complex interactions within shared inflammatory and metabolic signaling pathways, including NF-κB, PI3K/Akt, MAPK, and others. These molecules influence critical processes such as chronic inflammation, cartilage metabolism, and bone remodeling, contributing to the progression of OA.

Firstly, Chronic Inflammation Driven by NF-κB and JAK/STAT Pathways: Adipokines such as leptin, resistin, and lipocalin establish a positive feedback loop by co-activating NF-κB and JAK/STAT signaling pathways.[21,113,146] This significantly amplifies the release of pro-inflammatory cytokines (eg, IL-6, TNF-α), maintaining a chronic low-grade inflammatory microenvironment in the joint.[21,113,146] Such sustained inflammation exacerbates cartilage degradation, synovial inflammation, and overall OA progression. Secondly, Cartilage Metabolic Imbalance via PI3K/Akt and MAPK Pathways: Leptin, Visfatin, and Nesfatin-1 also converge on the PI3K/Akt and MAPK pathways to regulate chondrocyte metabolic activity.[104,112,194,197] This disrupts the balance between cartilage matrix synthesis and degradation, accelerating cartilage degeneration and further driving OA progression.

Thirdly, Bone Remodeling Imbalance via ERK and mTOR Pathways: adipokines such as leptin and osteopontin modulate osteoclast and osteoblast activity through ERK and mTOR signaling pathways.[118,119,177] This results in increased bone resorption, inhibited bone formation, and progressive structural deterioration of bone tissue, destabilizing joint integrity and worsening OA outcomes. Lastly, Insufficient Anti-Inflammatory Protection via PPARγPathways: anti-inflammatory adipokines, including metrnl, and FABP4, exhibit protective effects by mitigating inflammation and preserving joint structures through Wnt/β-catenin and PPARγ pathways.[116,239] However, these protective mechanisms are often insufficient to counteract the strong pro-inflammatory signals driven by other adipokines, limiting their ability to effectively slow OA progression.

Chronic low-grade inflammation and bone destruction, mediated by key adipokines, are fundamental to OA pathogenesis within the framework of MetS. Pro-inflammatory adipokines, including leptin, resistin, and osteopontin, exacerbate cartilage degradation and synovial inflammation by activating signaling pathways such as NF-κB, PI3K/Akt, and WNT/β-catenin, leading to chondrocyte catabolism and inflammatory cascades.[21,128,183,256] Conversely, protective adipokines like Serpin E2, PGRN, and WISP-2 counteract these processes by suppressing cartilage degradation and enhancing anti-inflammatory mechanisms, promoting tissue homeostasis.[213,215,217] Notably, adipokines such as lipocalin, adipsin, and nesfatin-1 exhibit context-dependent dual roles, either promoting inflammation or supporting cartilage stability, reflecting their complex contributions to OA progression.[112,152,200] Understanding these diverse functional phenotypes and underlying molecular mechanisms is critical for identifying therapeutic targets and advancing treatments for metabolic OA. Epidemiological studies strongly reinforce the link between adipokines and OA, underscoring their pivotal roles in disease initiation and progression. Tables 2 and 3, along with Figure 3,

Table 2 The Role of Different Adipokines in the Pathogenesis of OA

Adipokine	Major Findings			Reference
	Mechanism	Signaling Pathway	Related Effectors	
Leptin	Release of inflammatory factors	IRS-1/PI3K/Akt,AP-1	IL-6,c-Jun	[126]
	Release of inflammatory factors and cartilage degradation	JAK2/STAT3, PI3K/Akt and p38 MAPK	IL-6 and Ob-Rb receptor	[127]
	Inflammatory response, cartilage degradation, apoptosis and phenotype loss	JAK2/STAT3,MAPK,PI3K/Akt and NF-κB	MMPs,ADAMTS enzymes, iNOS and COX-2	[128]
	Inflammation response, extracellular matrix and cartilage degradation		IL-1β,MMPs,ADAMTS and miR-27	[129]
	Interaction of metabolism and inflammation, bone remodeling		IL-1β, interferon-γ, IL-6, TNF-α, MMPs and NO	[130]
	Pro-inflammatory effects and bone metabolic imbalance	JAK-STAT,NF-κB and MAPK/ERK	IL-1β, TNF-α and IFN-γ, MMPs	[134]
	Cellular senescence, inhibition of autophagy	Leptin-Ob-Rb, mTOR signaling pathway	ob-Rb,mTOR,p53 and p21	[135]
	Pro-inflammatory response and Cellular senescence and autophagy	JAK2/PI3K/AMPK, mTOR and p53/p21	VCAM-1,MMPs and iNOS	[136]

(*Continued*)

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Table 2 (Continued).

Adipokine	Major Findings			Reference
	Mechanism	**Signaling Pathway**	**Related Effectors**	
Lipocalin	Proinflammatory effects and cartilage matrix degradation	JAK/STAT,PI3K/AKT and MAPK/ERK	OB-Rb,MMPs,IL-1, TNF-α and other pro-inflammatory factors	[138]
	Pro-inflammatory and inhibits apoptosis protective factor	JAK/STAT,MAPK/JNK	DUSP19,JNK,IL-1β,TNF-α and other pro-inflammatory factors	[139]
	Oxidative stress, apoptosis, pyroptosis, and autophagy	Adiponectin-AMPK-mTOR, Adiponectin-AMP K-ULK1, Adiponectin-NLRP3	Adiponectin, AMPK, mTOR and NLRP3 inflammatory bodies	[143]
	Pro-inflammatory	AMPK/Mtor	IL-6,TNF-α1 and NLRP3	[149]
	Pro-inflammatory, apoptosis and dysregulation of lipid metabolism	AMPK/PKC, PPARα/ ATF2	PPARα and IL-6,TNF-α	[152]
	Regulates autophagy and inhibits calcification	AMPK-mTOR	AMPK,mTOR,LC3 and Beclin-1	[153]
Resistin	Exacerbates the degradation of cartilage	NF-κB	MMP-9, IL-1β	[156,159]
	Promotes chondrocyte proliferation and differentiation	NF-κB,JAK/STAT and MAPK	ROS,MMPs and IL-8	[21]
	Pro-inflammatory effects, degradation of cartilage matrix, interference of oxidative stress and autophagy	NF-κB, MAPK and JAK/STAT	MMPs,IL-6 and TNF-α	[156]
	Pro-inflammatory, matrix degradation and inhibits matrix synthesis	NF-κB and JAK/STAT	MMPs,IL-1,IL-6,TNF-α	[158]
	Inflammatory response, oxidative stress, apoptosis and cartilage degradation	NF-κB and ERK/p38/MAPK	MMPs, IL-1β,IL-6,IL-17A	[159]
	Pro-inflammatory	MEK/ERK,	TNF-α, IL-1β and miR-149	[160]
	Pro-inflammatory, inhibits cartilage matrix proteins	NF-κB, C/EBPβ	CCL3 and CCL4	[161]
	Inflammatory response and matrix degradation	p38-MAPK and NF-κB	CCL3,CCL4,MMP13 and ADAMTS-4	[163]
Osteopontin	Cartilage degradation	NF-κB	MMP-1, MMP-13 and miRNA	[169]
	Cartilage degradation	NF-κB	MMP13, NF-κB	[182]
	Promotes inflammatory response and matrix degradation	NF-κB,MAPK	MMPs, TNF-α and IL-1β	[183]
	Promotes sclerosis of subchondral bone and enhances breakdown of cartilage matrix	FAK/PI3K/Akt,TGF-β	MMPs, Integrin Receptors IL-1β,TNF-α	[256]
	Cartilage erosion and abnormal bone metabolism	TGFβ-Smad2/3	Alkaline phosphatase, osteocalcin	[184]
	Cartilage degeneration	NF-κB	Cyclin D1, Caspase-3	[189]
Visfatin	Degeneration and inflammation of joints	PI3K/AKT and ERK1/2	VEGF, MMPs	[190]
	Pro-inflammatory and oxidative stress	NF-κB	IL-1β,IL-6, MMP-1 SOD-2, CAT, NRF2	[159]
	Accelerated cartilage degradation		HIF-2α, MMPs and IL-6	[191]

(*Continued*)

Table 2 (Continued).

Adipokine	Major Findings			Reference
	Mechanism	**Signaling Pathway**	**Related Effectors**	
	Pro-inflammatory effect		IL-6,MCP-1 and keratinocyte Chemokine	[192]
	Pro-inflammatory, promotes degradation of cartilage matrix	IL-6/STAT-3/HIF-2α,PI3K/Akt/MAPK	ADAMTS-5	[194]
		β1 integrin/ERK/p38 MAPK/NF-κB pathway	IL-1β,IL-6,TNF-α, ADAMTS-4	
Adipsin				
	Promotes cartilage volume loss	PPAR activation	TNF-α,IL-1β	[140]
	Loss of cartilage volume		Monocyte chemotactic protein-1 and C-reactive protein	[200]
FABP4				
	Pro-inflammatory effects, lipid metabolism and cartilage degradation	NF-κB	MMP-13,ADAMTS4,IL-6	[205]
	Pro-inflammatory, oxidative stress and apoptosis	PPARγ/NF-κB	MMPs,IL-6,TNF-α, Bax and Bcl-2	[206]
	Chondrocyte degeneration	NF-κB	PGE2,IL-6,MMP3 and MMP13	
Nesfatin-1				
	Inhibition of the inflammatory response, reduction of chondrocyte apoptosis and protection of the cartilage matrix	NF-κB,MAPK	MMPs,ADAMTS5,Bax and Bcl-2	[207]
	Pro-inflammatory effect	NF-κB,MAPK	IL-6,MIP-1α,COX-2	[208]
	Pro-inflammatory effect	PI3K/Akt,AP-1 and NF-κB	IL-1β and miR-204-5p	[211]
	Inhibition of chondrocyte autophagy and improvement of cytoskeletal integrity	RhoA/ROCK	Autophagy-related proteins, f-actin and G-actin	[212]
Serpin E2				
	Inhibition of the expression of MMPs and inflammatory factors	ERK,NF-κB and AP-1	MMP-13,IL-1β and TNF-α	[213]
	Regulation of chondrocyte apoptosis and matrix degradation	CircSERPINE2-miR-1271-ERG	MMPs,miR-1271 and ERG	[214]
	Reduced degradation of cartilage matrix	ERK 1/2, NF-κB and AP-1	MMP-13 and ERK 1/2	[215]
Progranulin				
	Inhibits the production of inflammatory mediators and reduces matrix-degrading enzymes	PGRN-TNFR1/TNFR2 and PGRN-ADAMTS	TNF-α,TNFR1,TNFR2 and ADAMTS-7 and ADAMTS-12	[217]
	Regulates autophagy	ATG5-ATG12	PGRN, ATG5, ATG12 and LC3	[222]
	Maintain cartilage matrix homeostasis	IRE1α-XBP1	PGRN,IRE1α and XBP1s	[223]
	Regulates inflammation and bone repair	PGRN-TNFR1/2	PGRN,TNF-α,TNFR1 and TNFR2	[224,225]
	Prevents osteophyte formation and cartilage damage	PGRN-TNFR	PGRN,TNF-α,TNFR and β-Catenin	[226]
Chemerin				
	Promotes inflammatory response and cartilage degradation	ChemR23	IL-6,IL-1β,TNF-α and MMPS	[229]
	Exacerbates inflammation and cartilage degradation	TLR4	TLR4 and CCL2	[230]

(*Continued*)

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Table 2 (Continued).

Adipokine	Major Findings			Reference
	Mechanism	**Signaling Pathway**	**Related Effectors**	
	Exacerbates inflammation and	ChemR23-AKT/ERK	MMP-1,MMP-3,MMP-13	[231]
	Regulates cartilage degradation	Wnt/β-catenin	MMP-13,ADAMTS-5	[235]
WISP-2				
Vaspin				
	Anti-inflammatory, reduces degradation of cartilage matrix	NF-κB	TNF-α,IL-6 and MMPs	[238]
	Regulates cholesterol metabolism and reduces the expression of inflammatory factors	MiR155-LXRα	MiR155,LXRα,ABCA1, ABCG1 and SR-B1	[241]
Serum Amyloid A				
	Inhibits the production of inflammatory	PGRN-TNFR1/TNFR2 and PGRN-ADAMTS	TNF-α,TNFR1,TNFR2 and	[217]
	Exacerbates articular cartilage damage and inflammatory responses	SAA-TLR4	TLR4,IL-6,IL-8,GRO-α, and MCP-1 and MMPS	[246]
Omentin-1	Reduces inflammation and protects cartilage	NF-κB	TNF-α, COX-2, IL-6, and IL-1β	[247]
	Reducing inflammation and inhibiting cartilage degradation	AMPK	TNF-α and IL-6	[248]
	Promotes anti-inflammatory responses by inducing IL-4 expression; facilitates	PI3K, ERK and AMPK	IL-4, IL-10, IL-13, IL-1β,IL-6, IL-8, TNF-α.	[249]
	M2 macrophage polarization protects chondrocytes; inhibiting IL-1β-induced senescence.	SIRT1-p53	P21, PAI-1 and Caveolin-1	[250]
Metrnl				
	Reduces inflammation-induced cartilage degradation	Metrnl-PPARγ	IL-4/IL-13,IL-1β and TNF-α	[254]
	Anti-inflammatory and anti-pyroptosis inflammatory effects	PI3K/Akt/NF-κB, Metrnl-NLRP3 /caspase-1/GSDMD	Caspase-1,IL-1β,MMP-13 and ADAMTS-5	[255]

Table 3 Adipokines in Osteoarthritis: Multifaceted Roles, Mechanistic Pathways, and Clinical Implications

Adipokine	Functional Phenotype	Pathways	Clinical Impact	Reference
Leptin	Promotes inflammation, cartilage degradation and bone metabolism imbalance	NF-κB, JAK/STAT, PI3K/Akt, mTOR	Potential therapeutic target for inflammation and cartilage degeneration	[126–131,133–139]
Lipocalin	Dual role in inflammation, promotes VCAM-1 expression and autophagy	AdipoR1/AMPK, NF-κB, AMPK-mTOR	Controversial roles in OA, needs further investigation	[143–145,147–156,257]
Resistin	Induces pro-inflammatory cytokines, cartilage degradation, and apoptosis	NF-κB, p38 MAPK, PKCα	Critical biomarker for OA severity and cartilage degeneration	[157–169]
Osteopontin	Enhances inflammation, promotes vascular invasion and bone remodeling	NF-κB, ERK1/2	Key player in vascular invasion and cartilage damage	[182–190,256]

(*Continued*)

Table 3 (Continued).

Adipokine	Functional Phenotype	Pathways	Clinical Impact	Reference
Visfatin	Upregulates inflammatory markers, alters cartilage and bone metabolism	NF-κB,MAPK	Potential target for reducing cartilage and bone damage	[191–194]
Adipsin	Correlated with cartilage volume loss and OA progression	PPAR activation	Marker for cartilage volume loss, unclear pathway of action	[140,200]
FABP4	Promotes chondrocyte degeneration, oxidative stress, and ECM degradation	PPARγ, NF-κB	Therapeutic target for ECM preservation and chondrocyte health	
Nesfatin-1	Regulates inflammation and autophagy, with debated inflammatory roles	AP-1, NF-κB, RhoA/ROCK	Underexplored target for modulating inflammation and autophagy	[112,208–212]
Serpin E2	Inhibits cartilage degradation and prevents joint destruction	ERK, NF-κB, AP-1	Potential chondroprotective agent in OA management	[213–215]
Progranulin	Supports anti-inflammatory mechanisms and chondrocyte homeostasis	TNFR1/2, ATG5-ATG12	Supports cartilage preservation and metabolic balance	[217–226]
Chemerin	Induces inflammatory cytokines and cartilage degradation	TLR4, AKT/ERK	Pro-inflammatory role, potential target for inflammation control	[229–231]
WISP-2	Counters IL-1β effects, slows cartilage degradation via WNT/β-catenin	WNT/β-catenin	Novel target for cartilage preservation and OA progression control	[235]
Vaspin	Inhibits pro-inflammatory factors, promotes mesenchymal stem cells	NF-κB, miR155/ LXRα	Therapeutic potential in OA through MSC regulation	[238,241]
Serum Amyloid A	Induces pro-inflammatory cytokines, exacerbates cartilage degradation	TGF-β mediated MMP induction	Biomarker for OA progression and therapeutic target	[217,246]
Omentin-1	Triggers IL-4-dependent anti-inflammatory responses, prevents senescence	PI3K, ERK, AMPK	Anti-inflammatory potential in cartilage repair and senescence prevention	[247–250]
Metrnl	Inhibits NF-κB pathway, correlates with reduced OA likelihood	PI3K/Akt/ NF-κB	Promising therapeutic target to inhibit NF-κB pathway in OA	[254,255]

delineate the functional and clinical relevance of various adipokines, illustrating both shared and distinct mechanisms underlying OA pathophysiology. Pro-inflammatory adipokines, such as SAA and chemerin, amplify cytokine cascades, serving as critical markers of OA progression.[217,229] In contrast, anti-inflammatory adipokines like omentin-1 and Metrnl show promise in cartilage repair and symptom alleviation by inhibiting NF-κB signaling and promoting anti-inflammatory pathways.[247,255,]

Conclusion

OA is a complex degenerative joint disease significantly influenced by metabolic dysregulation, with metabolism-related adipokines playing a pivotal role in the pathogenesis of MetS-OA. While previous studies have highlighted the crucial roles of metabolic dysfunction and adipokines in OA progression, the precise mechanisms and interactions remain incompletely understood. The relationship between adipokines and OA is multifaceted, with these molecules exerting varying effects at different stages of the disease, from promoting inflammation and cartilage degradation to potentially modulating repair processes. This complexity underscores the importance of further investigating how adipokines influence OA progression and their roles in both early and advanced stages of the disease.

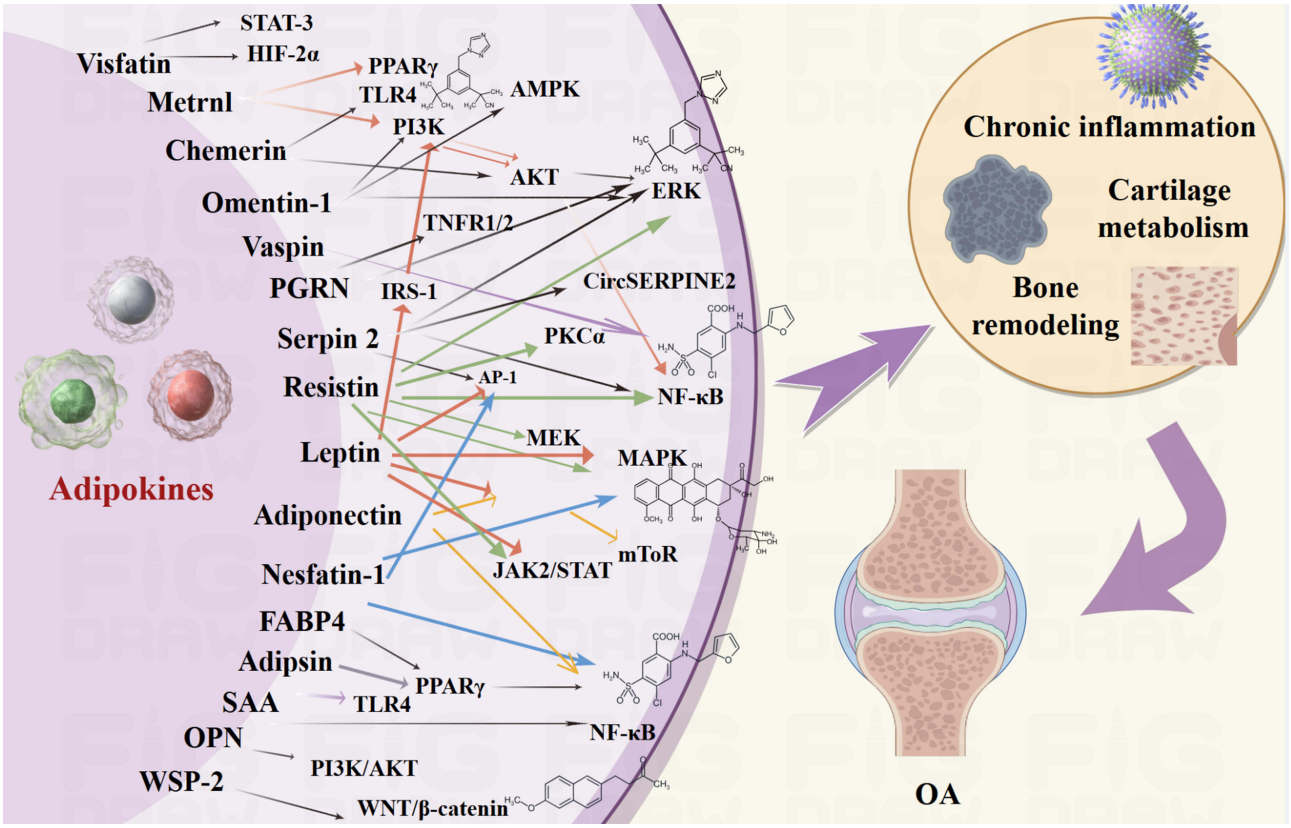

Figure 3 Pathways of action of multiple adipokines triggering OA.

Future research should focus on elucidating the diverse functions of adipokines at different stages of OA, particularly their dual roles in inflammation, metabolism, and tissue remodeling. A deeper understanding of the complex mechanisms underlying adipokine actions is essential for the development of targeted therapies. Targeting specific adipokines or their receptors could not only alleviate symptoms but also slow disease progression, providing long-term therapeutic benefits for OA patients. Moreover, combining adipokine-targeted treatments with other therapeutic approaches, such as cartilage repair or immune modulation, may offer a more comprehensive and effective disease management strategy.

Abbreviations

OA, Osteoarthritis; MetS, Metabolic syndrome; MetS-OA, Metabolic syndrome-associated osteoarthritis; BMI, Body mass index; IL-6, Interleukin-6; TNFα, Tumour necrosis factor alpha; DM, Diabetes mellitus; PGRN, Progranulin; ROS, reactive oxygen species; HT, Hypertension; DLs, Dyslipidaemias; OP, Osteoporosis ; Nrf-2, nuclear factor erythroid 2-related factor 2; AGEs, advanced glycation end-products; PTOA, post-traumatic osteoarthritis; TMJ-SFs, temporomandibular joint; Ob-Rb, leptin-specific receptor; MMP, metalloproteinase; LCN2, Lipocalin-2; OPN, Osteopontin; MMP13, Metalloproteinase 13; MSCs, Mesenchymal stem cells; FABP4, Fatty acid binding protein 4; Col2a1, Collagen type II alpha-1 chain; Serpin E2, Serpin peptidase inhibitor, clade E, member 2; WISP-2, Wnt-1-induced signalling pathway protein 2; Vaspin, Visceral adipose tissue-derived Serpin; SAA, Serum Amyloid A.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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