



Adiponectin, May Be a Potential Protective Factor for Obesity-Related Osteoarthritis

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Abstract: Osteoarthritis (OA) is the most common joint disease in elderly individuals and seriously affects quality of life. OA has often been thought to be caused by body weight load, but studies have increasingly shown that OA is an inflammation-mediated metabolic disease. The current existing evidence suggests that OA is associated with obesity-related chronic inflammation as well as abnormal lipid metabolism in obesity, such as fatty acids (FA) and triglycerides. Adiponectin, a cytokine secreted by adipose tissue, can affect the progression of OA by regulating obesity-related inflammatory factors. However, the specific molecular mechanism has not been fully elucidated. According to previous research, adiponectin can promote the metabolism of FA and triglycerides, which indicates that it is a potential protective factor for OA through many mechanisms. This article aims to review the mechanisms of chronic inflammation, FA and triglycerides in OA, as well as the potential mechanisms of adiponectin in regulating chronic inflammation and promoting FA and triglyceride metabolism. Therefore, adiponectin may have a protective effect on obesity-related OA, which could provide new insight into adiponectin and the related mechanisms in OA.

Keywords: adiponectin, obesity, osteoarthritis, inflammation, fatty acid, triglyceride

Introduction

Osteoarthritis (OA) is the most common degenerative joint disease characterized by joint pain, swelling and dysfunction. According to its causes, OA can be divided into primary and secondary forms.¹ Although the detailed pathogenesis pathways of primary OA are still unclear, most scholars agree that biomechanical, inflammatory, and metabolic factors (obesity) are main risk factors in the occurrence and development of the disease. In addition, aging, endocrine (estrogen deficiency) and muscle reduction factor has also been proposed.² According to these different risk factors, Herero-Beaumont³ proposed the existence of four clinical phenotypes-biomechanical OA, osteoporotic OA, metabolic OA (obesity-related OA), and inflammatory OA. In the obese population, the occurrence of OA is related to joint overload as well as chronic inflammation and abnormal lipid metabolism (Figure 1).⁴⁻⁶ In obesity-related OA, there are many M1 macrophages in adipose tissue and high levels of inflammatory factors such as interleukin-1 (IL-1), IL-6 and tumor necrosis factor- α (TNF- α) produced by adipose tissue-derived M1 macrophages.⁷ These cytokines are considered to be the main causes of chondrocyte damage and cartilage matrix degeneration.⁸ According to the researches, high levels of fatty acids (FA) and triglycerides were found to be related to the occurrence and development of OA.^{9,10} FA can be divided into saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs) according to the length of the carbon chain and the number of double chains. PUFAs can be divided into omega-3 (n-3) and omega-6 (n-6) PUFAs according to the double bond position.¹¹ Although n-3 PUFAs can help reduce inflammation and protect joints,¹² SFAs and n-6 PUFAs have strong proinflammatory effects, and they play an important role in promoting the secretion of inflammatory factors in chondrocytes and structural damage.^{13,14} Epidemiological studies have shown that triglycerides can increase the risk of OA in the hand joints.⁶ Vitro experiments have found that

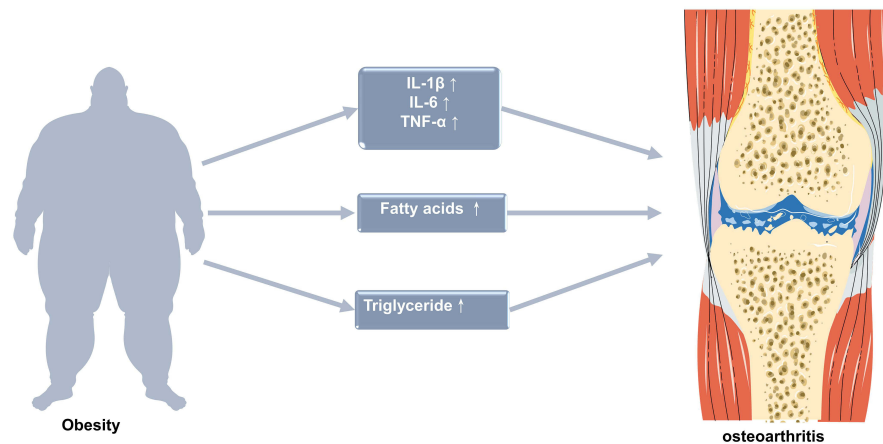


Figure 1 Possible mechanisms of obesity leading to osteoarthritis. IL-1 β , interleukin 1 β . TNF- α , tumor necrosis factor- α .

triglycerides can promote the release of chondrocyte inflammation markers and the breakdown of extracellular matrix (ECM).¹⁵ Therefore, FA and triglycerides may play an important role in the progression of OA.

Adiponectin is a protein hormone derived from adipose tissue. Previous studies have found that adiponectin and its receptor are of great significance for the treatment of obesity-related diseases such as atherosclerosis and type 2 diabetes. Adiponectin can significantly improve insulin sensitivity and has anti-inflammatory properties on endothelial cells and macrophages.^{16,17} Meanwhile, adiponectin inhibits inflammation by regulating the proliferation and function of M1 and M2 macrophages, and also promotes FA metabolism in liver and skeletal muscle by activating amp-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor- α (PPAR- α).¹⁸ On the one hand, adiponectin can increase the activity and expression of enzymes that promote triglyceride hydrolysis, such as lipoprotein lipase (LPL), hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL); on the other hand, adiponectin can promote FA decomposition to reduce the materials for synthesizing triglycerides.^{18–20} Therefore, adiponectin can regulate lipid metabolism in obese people and reduce the circulating levels of FA as well as triglycerides. Therefore, adiponectin can reduce the risk factors for obesity-related OA.

This review summarizes the role of chronic inflammation, FA and triglycerides in the progression of OA in obese people, as well as the potential mechanism by which adiponectin reduces chronic inflammation and promotes FA and triglyceride metabolism (Figure 2).

Obesity-Related Biological Processes and OA

Chronic Inflammation and OA

Osteoarthritis (OA)²¹ is one of the most common chronic joint diseases. Advances in epidemiology and basic medicine have given us a new definition of OA, metabolic OA, which is closely related to obesity.²² In addition to mechanical load, an increasing number of experiments have shown that inflammatory factors produced by adipose tissue play an increasingly important role in the occurrence of OA.²³ As an endocrine organ, adipose tissue contains a variety of immune cells, including macrophages, T cells, B cells and neutrophils, and it is an important source of proinflammatory factors such as IL-1 β , IL-6, and TNF- α .²⁴ Macrophages are functionally classified into classically activated M1 macrophages and alternatively activated M2 macrophage.²⁵ Pro-inflammatory M1 macrophages can secrete many inflammatory factors, such as IL-1 β , IL-6, TNF- α , IL-8, IL-12 and IL-23,²⁶ and the function of these cytokines in OA has been well established. Although anti-inflammatory M2 macrophages generate anti-inflammatory cytokines and anabolic factors, such as IL-4, IL-10, IGF-1 and transforming growth factor- β (TGF- β),^{27,28} these anti-inflammatory cytokines are insufficient to counteract the catabolic inflammatory response, particularly during the

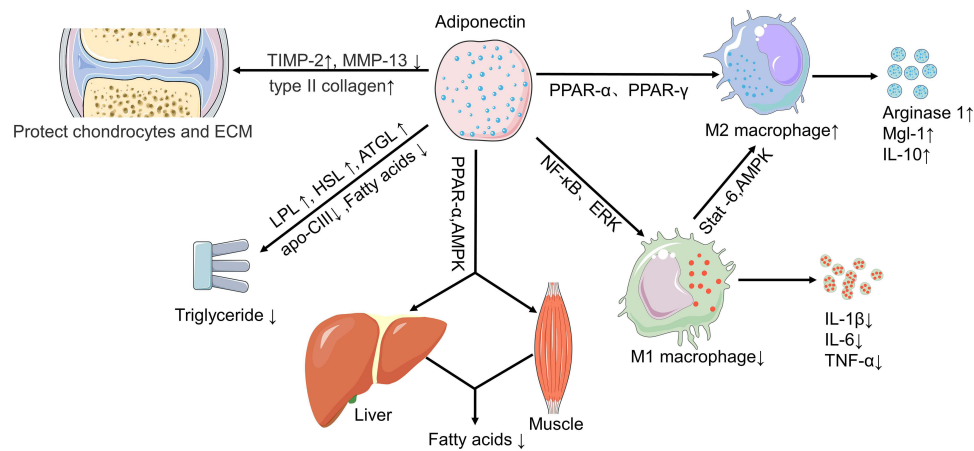


Figure 2 Possible mechanisms by which adiponectin regulates risk factors for OA in obese patients.

Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; PPAR, peroxisome proliferator-activated receptor; NF-κB, nuclear factor kappa-B; Mgl-1, macrophage galactose N-acetyl-galactosamine specific lectin-1; ERK, extracellular regulated protein kinases; LPL, lipoprotein lipase; HSL, hormone-sensitive lipase; ATGL, adipose triglyceride lipase; Apo-CIII, apolipoprotein-CIII; TIMP-2, tissue inhibitor of matrix metalloproteinases-2; MMP-13, matrix metalloproteinase.

imbalance of a high pro-inflammatory (M1-like) to anti-inflammatory (M2-like) ratio.^{29,30} In obese tissues, anti-inflammatory M2 macrophages are converted into pro-inflammatory M1 macrophages.^{27,28} In a rat model of obesity-related OA, infiltrating macrophages in the synovium and bone marrow-derived macrophages in synovial fluid are of the M1 phenotype,²⁹ and inducing the polarization of M2-phenotype macrophages contributes to reducing the progression of OA.³¹ Therefore, we have reasons to believe that M1 macrophages are the main causes of chronic inflammation in obese people.

Among the inflammatory factors released by fat cells and infiltrating macrophages, IL-1 β , TNF- α and IL-6 are the key mediators involved in the progression of joint tissues in OA patients, although others also play very important roles, such as IL-15, IL-17, and IL-18.⁸ IL-1 β and TNF- α can induce ECM degradation of chondrocytes and upregulate the expression of other factors such as iNOS, NO, COX-2, PGE₂, MMPs and ADAMTS.⁸ These cytokines can regulate the anabolic activities of chondrocytes and destroy the cartilage structure. Studies have shown that increased concentrations of IL-1 and TNF- α can be observed in various anatomical structures of joints, such as synovial fluid, synovium, cartilage and subchondral bone layer.³² After treatment with IL-1 β and TNF- α , the secretion of MMPs are significantly increased in chondrocytes, which have a key regulatory role in cartilage destruction.³³ In articular cartilage, Type II collagen in cartilage and type I collagen in adjacent tendons and bones sustain joint structure strength. MMPs mediate the degradation of almost all collagen proteins.³⁴ PGE₂ can stimulate the expression and production of MMP-13 and ADAMTS-5 in human chondrocytes. This result is related to the signaling pathway mediated by EP4, which is a PGE₂ receptor.³⁵ In addition, PGE₂ upregulates the expression of IL-6 mRNA and protein of T/C-28a2 chondrocytes through the cyclic adenosine monophosphate (cAMP) signaling pathway, and the level is time- and dose-dependent.³⁶ Experimental results have shown that IL-1 β and TNF- α can promote the expression of ADAMTS family members, such as ADAMTS-4 and ADAMTS-5.³⁷ The ADAMTS family of enzymes can effectively cleave the aggregated proteins in the extracellular matrix of chondrocytes.³⁶ In animal experiments, after deletion of the catalytic domains of ADAMTS4 and ADAMTS5, the destruction of mouse chondrocytes was significantly reduced.^{38,39} Studies have shown that IL-1 and TNF- α can promote iNOS activity, leading to over expression of NO in chondrocytes.^{40,41} On the one hand, NO can promote chondrocyte MMP expression and increase the sensitivity of chondrocytes to oxidants. On the other hand, NO indirectly participates in the production of inflammatory factors by promoting the production of TNF- α in synovial cells.⁴² In addition, TNF- α can recruit osteoclasts to promote bone destruction. Lam J reported that although TNF- α alone cannot induce the differentiation of macrophages into osteoclasts, TNF- α and RANKL, which are nuclear factor kappa-B (NF-κB) receptor activator ligands, can significantly enhance the activity of NF-κB and stress-activated protein kinase/c-Jun N-terminal kinase.⁴³ These two signaling pathways are critical to the formation of osteoclasts. Therefore, TNF- α can promote macrophages with permissive levels of RANKL to generate osteoclasts.

High levels of IL-6 are detected in knee synovial fluid and surrounding tissues during the early stages of OA.⁴⁴ Stannus et al reported that circulating levels of IL-6 were associated with JSN and cartilage loss in older adults.⁴⁵ Latourte et al confirmed that IL-6 increases the production of the main proteases involved in OA pathogenesis, such as MMP-3, MMP-13, ADAMTS-4 and ADAMTS-5, which are induced by Stat3 and ERK1/2 signaling pathway in chondrocytes. Blocking the effect of IL-6 with receptor blockers can reduce OA cartilage damage, osteophyte formation, and the degree of synovial inflammation.⁴⁶ In addition, IL-6 is related to metabolic disorders of subchondral bone tissue. Peruzzi has reported that IL-6 inhibits the differentiation of osteoblasts into osteocytes through the SHP2/MEK2, SHP2/AKT2 and IGFBP5 signaling pathways. In addition, after treating primary mouse osteoblasts with IL-6, the expression of Runx2, collagen 1A2, and osteocalcin was reduced, which can be reversed by anti-IL-6 antibodies.^{47,48} RANKL and osteoprotegerin (OPG) are key regulators of osteoclast formation. Semi-quantitative RT-PCR analysis showed that the mRNA expressions of RANKL and OPG increased after 24 h incubation with human soluble IL-6 plus human soluble IL-6R (both 100ng/mL).⁴⁹ This biological process involves the STAT3 signaling pathway.⁵⁰

In addition to the above mentioned proinflammatory factors, the pathological mechanism of OA also involves several other chemokines, such as IL-15, IL-17, and IL-18. The level of IL-15 in joint fluids increases in early-stage OA patients, and IL-15 significantly increases the levels of MMP-1 (mean \pm SEM MMP-1 release: 843% \pm 222 of control) and MMP-3 (mean MMP-3: 206% \pm 42 of control) secreted by articular cartilage. Moreover, IL-15 receptor α gene (IL15RA) has been associated with the development of neuropathic pain-like symptoms after nerve injury.⁵¹ In the serum and synovial fluid of OA patients, IL-17 levels are elevated and positively correlated with OA severity. Na et al reported that IL-17 stimulates chondrocytes and fibroblasts to secrete proinflammatory factors such as IL-1 β , IL-6 and TNF- α , which further promote cartilage destruction.⁵² Bao et al reported that treating chondrocytes with different concentrations of IL-18 (0, 1, 10, 100 ng/mL) for 24 h, the mRNA expressions of Collagen II, Sox9 and Aggrecan were downregulated in a dose-dependent manner. They also find that IL-18 promotes the proapoptotic effect of rat chondrocytes by activating the PI3K/Akt/mTOR signaling pathway (Table 1).⁵³

FAs and OA

In addition to low levels of systemic inflammation, another characteristic of obese patients is increased plasma levels of free FAs.⁵⁴ Based on the above classification, FAs can be further classified (Figure 3). For example, SFAs include

Table 1 Inflammatory Factor Involved in the Pathophysiology of OA

Inflammatory Factor	Activities in OA
TNF- α and IL-1	Be observed synovial fluid, synovium, cartilage and subchondral bone layer. ³² Increases MMPs. ³³ Promotes the expression of ADAMTS. ³⁷ Promotes iNOS activity. Leading to overexpression of NO in chondrocytes. ^{40,41}
TNF- α	Enhances the activity of NF- κ B and stress-activated protein kinase/c-Jun N-terminal kinase. ⁴³
IL-6	Detected in knee synovial fluid and surrounding tissues. ⁴⁴ Associated with JSN and cartilage loss. ⁴⁵ Increases MMP-3, MMP-13, ADAMTS-4 and ADAMTS-5. ⁴⁶ Blocking the effect of IL-6 to reduce OA cartilage damage, osteophyte formation, and synovial inflammation. ⁴⁶ Inhibits the differentiation of osteoblasts into osteocytes. ⁴⁸ Reduces the expression of Runx2, collagen 1A2, and osteocalcin. ⁴⁷ Increases the mRNA expressions of RANKL and OPG. ⁴⁹
IL-15	Increased in joint fluids is increased in early-stage OA. ⁵¹ Increases the levels of MMP-1 and MMP-3. ⁵¹ Associated with the development of neuropathic pain-like symptoms. ⁵¹
IL-17	IL-17 levels are elevated and positively correlated with OA severity. ⁵² Stimulates the production of IL-1 β , IL-6 and TNF- α . ⁵²
IL-18	Downregulated the mRNA expressions of Collagen II, Sox9 and Aggrecan. ⁵³ Promotes the proapoptotic effect of chondrocytes. ⁵³
MMPs	Mediates the degradation of collagen proteins. ³⁴
PGE ₂	Stimulate the expression of MMP-13 and ADAMTS-5. ³⁵ Upregulates the expression of IL-6 mRNA. ³⁶
ADAMTS	Cleave the aggregated proteins. ³⁶
NO	Promote chondrocytes MMP expression, increase the sensitivity to oxidants. ⁴² Promoting the production of TNF- α in synovial cells. ⁴²

Abbreviations: MMPs, matrix metalloproteinase; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; iNOS, Inducible nitric oxide synthase; JSN, joint space narrow; IL-1, interleukin 1; RANKL, receptor activator of NF- κ B ligand; OPG, osteoprotegerin; TNF, tumor necrosis factor; PGE₂, prostaglandin E2.

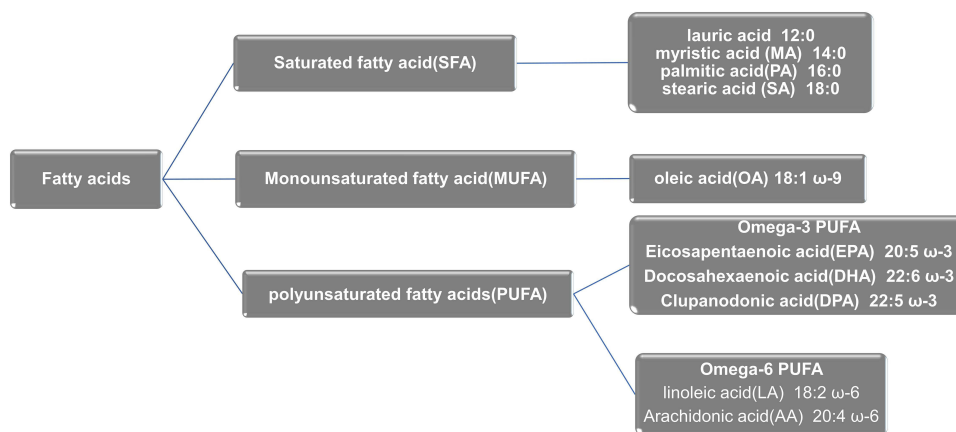


Figure 3 Fatty acids subtype.

palmitic acid (PA) and stearic acid (SA), MUFAs include oleic acid (OL) and palmitoleic acid (POA), n-3 PUFAs include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and n-6 PUFAs include linoleic acid (LA) and arachidonic acid (AA).⁵⁵ Recent studies have shown that FAs are involved in the pathogenesis of OA and different types of FAs have different effects on OA.⁵⁶

After measuring the deposited lipid composition in OA chondrocytes, it was found that the levels of FA, PA, SA, OL, LA and AA increased.^{13,57} In several vitro experiments, PA increased the levels of IL-1 β , IL-6, MMP-13, and ADAMTS and reduced the expression of the anti-inflammatory factor IL-10.^{58–60} Sekar et al found that after feeding rats PA- and SA-rich feed for 16 weeks, cartilage degeneration and OA-like changes in subchondral bone occurred in the knee joints, indicated by surface irregularity, disorganization of the articular cartilage and loss of proteoglycans.⁶¹ In further research, vitro data demonstrated an enhanced expression of the hypertrophic markers ADAMTS4 and ADAMTS5 and the cartilage degenerative marker MMP-13 as well as a declining expression of ACAN, COL2, and SOX9 in MA-, PA-, and SA-treated chondrocytes compared with LA treatment.⁶¹ Insulin-like growth factor-1 (IGF-1) plays an important role in chondrocytes survival and ECM synthesis. PA can induce CHOP expression in human chondrocytes, which leads to activation of the JNK signaling pathway and inhibits IGF-1 function.⁶² PA and SA activate the typical NF- κ B signaling pathway and promote autophagy in human chondrocytes.⁵⁸ Miao et al found that SA can activate a novel lactate-HIF1 α pathway to induce mice chondrocytes to express IL-1 β , IL-6 and TNF- α .⁶³ In a recent study, it was found that PA causes chondrocyte mitochondrial dysfunction and changes in glycolytic metabolism, and these effects can be partially reversed by MUFAs (such as OL).⁶⁴ In a study of the relation between diet and OA progression in 2092 OA patients, with increasing levels of SFA, joint space width decreases were 0.25 mm, 0.26 mm, 0.33 mm, and 0.37 mm at 12, 24, 36, 48 months, respectively.⁶⁵

Among MUFAs, the effect of OL on chondrocytes is controversial. On the one hand, OL can reduce the expression of COX-2 and MMP-1 in chondrocytes and inhibit the destruction of chondrocytes.⁶⁶ On the other hand, cocubation of OL and PA stimulate chondrocytes the production of ROS and RNS such as O₂⁻, H₂O₂, and NO, respectively, as well as the production of IL-6 and IL-8.⁶⁷

In recent years, the relationship between the plasma levels of N-3 PUFAs and N-6 PUFAs and the progression of OA has become a research hotspot. The most common N-6 PUFAs in the human diet are LA and AA, wherein LA is the precursor of AA, and AA is the precursor of PEG2 and leukotrienes.⁶⁸ After analyzing lipids in plasma and synovial fluid, Wu found that most N-6 PUFAs were positively correlated with the severity of osteoarthritis and synovitis.⁶⁹ Besides, in male patients with OA, plasma N-6 PUFA levels were positively correlated with joint effusion, knee joint structural damage,¹³ osteophyte formation, synovitis.⁷⁰ An vitro experiment proved that after culturing chondrocytes with LA, the production of PGE2, IL-6 and NO increased.^{14,66,71} In addition, AA can upregulate the expression of PEG, ADAMTS⁷² and COX-2⁷³ in animal chondrocytes. In contrast, research on n-3 PUFAs found that they may have a protective effect on OA. Sibille et al reported that OA patients with a high n-6/n-3 ratio had more severe pain symptoms

and functional limitations, while the levels of n-3 PUFAs were inversely correlated with the levels of inflammatory mediators and pain tolerance.⁷⁴ The reduction in the n-3/n-6 PUFA ratio in IFP may contribute to the inflammation and cartilage degradation of early OA.⁷⁵ Previous studies have shown that N-3 PUFAs significantly reduced the expression levels of ADAMTS-4, ADAMTS-5, MMP-3, MMP-13, TNF- α , IL1- β , IL-6, and COX-2. Among N-3 PUFAs, EPA is the most effective.⁷⁶⁻⁷⁸ Correspondingly, Dai et al reported that N-3 PUFAs can reduce the expression of Col-X and Runx2 to inhibit the hypertrophy and differentiation of chondrocytes.⁷⁹ Moreover, Kubo et al reported that the preoperative serum EPA + DHA levels and (EPA + DHA)/AA ratio were found to be negatively associated with the serum d-ROMs (a biomarker of oxidative stress resulting from IR injury) at 96 h after surgery and Δ d-ROMs (Table 2).⁸⁰

Triglycerides and OA

Epidemiological studies of abnormal blood lipid metabolism and OA have found that elevated serum triglycerides are risk factors for the progression of OA.⁸¹ Davies-Tuck et al reported that triglycerides are associated with the prevalence of BMLs in asymptomatic middle-aged women for more than two years. The results of this study provide a basis for the hypothesis that vascular pathological changes are involved in the progression of OA.⁸² In another study, it was reported that triglycerides increased the risk of hand OA.⁶ Abourazzak et al found that hypertriglyceridemia was associated with a higher pain visual analogue scale and Lequesne index.⁸³ Pan et al divided the pain into three groups according to the pain trajectory: minimal pain, mild pain, and moderate pain. After adjusting for potential confounding factors, it was found that hypertriglyceridemia was associated with moderate pain.⁸⁴ Pan et al found that hypertriglyceridemia was independently associated with volume loss of the medial tibial cartilage on MRI. Moreover, triglycerides significantly increased the size of the BML in the medial compartment BML.⁸⁵ Some studies have provided evidence for this link between hypertriglyceridemia and OA. High ECM catabolism and excessive chondrocyte death are the two main pathological features of OA.^{86,87} Research by Xie showed that triglycerides can promote NF- κ B nuclear translation by inducing endoplasmic reticulum stress, which leads to the release of proinflammatory factors such as collagen-II and MMP-3, thereby enhancing the catabolism of the ECM.^{15,88}

Table 2 FAs Involved in the Pathophysiology of OA

FAs		Activities in OA
SFA	FA, PA, SA, OL, LA and AA PA and SA	Increases in OA chondrocytes. ^{13,57} Increases the levels of IL-1 β , IL-6, MMP-13, and ADAMTS and reduced the expression of the IL-10. ⁵⁸⁻⁶⁰ Cartilage degeneration and OA-like changes appear. ⁶¹ Promotes chondrocytes autophagy. ⁵⁸
	MA, PA and SA	Enhances expression of the hypertrophic markers ADAMTS4, ADAMTS5 and MMP-13. Declines the expression of ACAN, COL2, and SOX9. ⁶¹
	PA	Induces CHOP expression. ⁶² Causes chondrocyte mitochondrial dysfunction and changes in glycolytic metabolism. ⁶⁴
	SA	Induces the expression of IL-1 β , IL-6 and TNF- α . ⁶³
MUFAs	SFA	Decreases joint space width. ⁶⁵
	OL	Reduces the expression of COX-2 and MMP-1. ⁶⁶
N-6 PUFAs	OL and PA	Stimulates the production of ROS and RNS such as O ₂ ⁻ , H ₂ O ₂ , NO, IL-6 and IL-8. ⁶⁷
	N-6 PUFAs	Positively correlated with the severity of osteoarthritis and synovitis. ⁶⁹ Positively correlated with joint effusion, knee joint structural damage, ¹³ osteophyte formation, synovitis. ⁷⁰
n-3 PUFAs	LA	The production of PGE ₂ , IL-6 and NO increased. ^{14,66,71}
	AA	Upregulate the expression of PEG, ADAMTS ⁷² and COX-2. ⁷³
	n-3 PUFAs	Inversely correlated with the levels of inflammatory mediators and pain tolerance. ⁷⁴ Reduces the expression levels of ADAMTS-4, ADAMTS-5, MMP3, MMP-13, TNF- α , IL1- β , IL-6, and COX-2. ⁷⁶⁻⁷⁸ Reduces the expression of Col-X and Runx2. ⁷⁹
	EPA + DHA	Negatively associated with the serum d-ROMs. ⁸⁰

Abbreviations: MMPs, matrix metalloproteinase; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; IL-1, interleukin 1; TNF: tumor necrosis factor; ACAN, aggrecan; COL2, collagen type II; SOX9, SRY-related HMG box-containing 9; CHOP, a protein marker for ER stress; COX-2, cyclooxygenase-2; ROS, reactive oxygen species; RNS, reactive nitrogen species; PGE₂, prostaglandin E₂; Col-X, type X collagen; Runx2, Runt-related transcription factor 2.

Biological Actions of Adiponectin on Obesity-Induced OA

Adiponectin

Adiponectin, also known as AdipoQ, Acrp30, ApM1, or GBP28, is a protein hormone produced exclusively by adipocytes that was first reported in 1995.⁸⁹⁻⁹¹ This cytokine is a 28–30 kDa collagen-like protein composed of 244 amino acids. The interaction between the disulfide bonds at the amino terminus of adiponectin can form polymers of different molecular weights, including low-molecular-weight adiponectin (trimer), medium-molecular-weight adiponectin (hexamer) and high-molecular-weight adiponectin (HMW).⁹² Yamauchi T first confirmed AdipoR1 and AdipoR2 as adiponectin receptors in 2003.¹⁶ AdipoR1 is mainly expressed in skeletal muscle, while AdipoR2 is abundant in the liver. Adiponectin can activate AMPK, PPAR- α , PPAR- γ and other signaling pathways through these two receptors to participate in metabolic regulation.¹⁸

Adiponectin and Chronic Inflammation

Adiponectin, as a typical anti-inflammatory and antioxidant stress active substance, has been proven to have a protective effect on diabetes and atherosclerosis. However, the role of adiponectin in osteoarthritis has not been well studied.⁹³ Recently, numerous animal and human studies have shown that adiponectin delays the progression of OA through anti-inflammatory factors. Honsawek et al⁹⁴ reported that the concentration of adiponectin in blood and synovial fluid was significantly negatively correlated with the grade of OA by KL grading criteria, which suggested that it might have a potentially protective effect. Zheng and Chen et al^{94,95} found that plasma adiponectin levels were positively correlated with synovial fluid levels and that plasma adiponectin levels were significantly higher than synovial adiponectin levels. These results indicate that the main source of adiponectin in synovial fluid is blood. Moreover, Yusuf et al⁹⁶ reported that patients with higher serum adiponectin triplets had a 70% reduced risk of developing hand OA compared with patients with the lowest serum adiponectin triplets over 6 years.

Many studies have shown that adiponectin can regulate the proliferation and function of M1 and M2 macrophages to exert its anti-inflammatory properties.⁹⁷⁻⁹⁹ In vitro, adiponectin promotes the production of IL-10 and IL-1 receptor antagonist in monocytes, monocyte derived macrophages and dendritic cells.¹⁰⁰ Yokota et al reported that adiponectin inhibits the proliferation of bone marrow monocyte progenitor cells by inducing apoptosis and inhibits the functions of mature macrophages, including phagocytosis and the release of TNF- α .⁹⁷ Wulster-Radcliffe et al found that adiponectin can inhibit the production of IL-6 and TNF- α in pig-derived adipocytes and macrophages. This biological effect is partly mediated by inhibiting the NF- κ B signaling pathway and ERK1/2 activity.^{101,102} In adiponectin knockout mice, M1 markers, including TNF- α , IL-6 and MCP-1, were increased. Conversely, M2 markers, such as arginase-1, macrophage galactose N-acetyl-galactosamine specific lectin-1 and IL-10, were remarkably reduced.⁹⁹ In addition, Wang et al previously reported that adiponectin inhibits proinflammatory cytokines, including IL-1, IL-6 and TNF- α in alveolar macrophages through the TLR2/4 signaling pathway and inhibits macrophage polarization through the COX-2/PGE2 signaling pathway.¹⁰³ In subcutaneous white adipose tissue, adiponectin can promote the proliferation of M2 macrophages by activating AKT.⁹⁸ Full-length adiponectin promotes the transformation of the M1 to M2 state through the AdipoR2 \rightarrow IL-4 \rightarrow STAT-6-dependent signaling pathway and AdipoR2 \rightarrow AMPK signaling pathway.¹⁰⁴ In addition to the AMP-activated protein kinase and peroxisome proliferator activated receptor (PPAR)- γ , adiponectin also mediates the differentiation of monocyte macrophages into M2 macrophages through PPAR- α . Adiponectin can reduce macrophage markers in adiponectin knockout mice through these two signaling pathways.¹⁰⁵ Therefore, adiponectin suppresses the activation of M1 subtype macrophages and enhances the proliferation of anti-inflammatory M2 subtype macrophages. However, the mechanism needs further exploration.

Chen et al reported that adiponectin can upregulate tissue inhibitor of matrix metalloproteinases-2 (TIMP-2) and downregulate IL-1 β -induced MMP-13 in human chondrocyte.⁹⁵ TIMP-2 has good inhibitory properties on the activity of MMPs and ADAMTS.¹⁰⁶ After treating ATDC5 mouse chondrocytes with 0.5 μ g/mL adiponectin, increases in chondrocyte proliferation, proteoglycan synthesis and matrix mineralization were observed, which as reflected by the upregulation of type II collagen, aggrecan, Runx2 and type X collagen in chondrocytes. The underlying mechanism may be that adiponectin upregulated the expression of cartilage signaling molecules, such as IHH, PTHrP, Ptc1, FGF18,

BMP7, IGF1 and P21.¹⁰⁷ HU reported that subsequent to 6 h of H₂O₂ treatment, significant reduction in rat chondrocyte viability was demonstrated in the treated groups. However, the percentage of H₂O₂ induced apoptotic significantly reduced in chondrocytes pretreated with 0.5 µg/mL global adiponectin for 24 h by activating AMPK/ mTOR Signaling pathway.¹⁰⁸ As mentioned above, adiponectin may have a protective effect on OA by reducing the inflammatory level in obese people and resisting the degradation of cartilage extracellular matrix.

In contrast, some studies have found that adiponectin has proinflammatory effects on OA. On the one hand, Korkmaz et al confirmed the positive correlation between adiponectin level and OA severity in Ahlback classification.¹⁰⁹ On the other hand, Honsawek et al suggested that plasma adiponectin levels are negatively correlated with OA severity.⁹⁴ Tang et al reported that treatment of osteoarthritis synovial fibroblast (OASF) with adiponectin (0.1–30µg/mL) for 24 h, the production of IL-6 is in a concentration-dependent manner and time-dependent manner. Further, mRNA levels of IL-6 and AdipoR1 subtype receptor were evidently increased after 12 h of adiponectin (3µg/mL) treatment. These results suggest that AdipoR1 may be involved in adiponectin-induced expression and release of IL-6 in OASF.¹¹⁰ Zuo et al showed that AdipoR1 may mediate adiponectin to induce synovial fibroblasts to produce PGE2 in a concentration-dependent manner.¹¹¹ Tong et al reported that qPCR analysis showed that the expression of MMP-3 mRNA was significantly increased after the chondrocytes were incubated with adiponectin (30 ng/mL) for 24 h.¹¹² Chen suggested that adiponectin up-regulates the production of Intercellular adhesion molecule-1 (ICAM-1) in human OASF via the LKB1/CaMKII, AMPK, c-Jun, and AP-1 signaling pathway.¹¹³ Besides, adiponectin could elicit perpetuate cartilage-degrading processes by inducing expression of vascular cell adhesion molecules-1 (VCAM-1) in chondrocytes, which is responsible for infiltration of leukocyte and monocyte into OA joints.¹¹⁴ These conflicting findings, showing protective and damaging properties, may also suggest a dual or more complex role for adiponectin in OA. Consequently, current evidence indicates that the role of adiponectin in the pathogenesis of OA has not been completely elucidated.

Adiponectin and FAs

As a candidate for the treatment of obesity-related metabolic syndrome, adiponectin can reduce plasma free FA levels after meals,¹¹⁵ increase plasma lipid clearance,¹¹⁶ and promote FA oxidation in the liver and muscle.¹¹⁷ Adiponectin can increase the activity of carnitine palmitoyl transferase I to enhance the oxidation of FAs in the liver, and it can also reduce the activities of two key enzymes involved in FA synthesis, including acetyl-CoA carboxylase (ACC) and FA synthase (FAS).¹¹⁸ Studies have found that full-length adiponectin can increase the level of AMPK in isolated liver cells and promote ACC phosphorylation and FA oxidation.¹¹⁹ Correspondingly, the production of malonyl-coenzyme A is reduced, which relieves the inhibition of carnitine palmitoyl transferase-1 (CPT-1) activity and enhances the entry of FA into the mitochondria for β oxidation.¹²⁰ Schindler et al reported that adiponectin upregulated the mRNA levels of the FA transporters CD36, FATP4, FABP4 and HSL through the AMPK signaling pathway.¹²¹ The inhibition of FAS is due to adiponectin decreasing the expression of FA genes in the liver.¹¹⁸ CPT-1 is a potential regulator of FA β oxidation and can promote lipid inflow to the mitochondria for oxidation.¹²² Awazawa et al found that adiponectin inhibits the expression of sterol regulatory element binding protein (SREBP1c), which is the main regulator of enzymes related to FA synthesis in hepatocytes.¹²³ They also found that adiponectin can inhibit SREBP1c through AdipoR1. For example, deleting LKB1, an upstream kinase of AMPK, can eliminate the negative effects of adiponectin on SREBP1c expression. These data indicate that adiponectin inhibits SREBP1c through the AdipoR1/LKB1/AMPK pathway, which suggests that adiponectin may inhibit the synthesis of FAs in the liver.^{123,124} In addition, adiponectin promotes FA oxidation by participating in the activation of peroxisome proliferator-activated receptor (PPAR-α).^{125,126} Adiponectin activates PPAR-α through AdipoR2 to promote triglyceride decomposition, intracellular FA transport, and mitochondrial FA β -oxidation.^{127,128} Blocking AdipoR1 and R2 leads to increased tissue triglyceride content, inflammation and oxidative stress.¹⁸ Fruebis et al reported that globular adiponectin can improve the systemic metabolic environment by promoting the oxidation of skeletal muscle FAs.^{116,117} Yamauchi et al reported that after treating C2C12 cardiomyocytes with adiponectin, the phosphorylation levels of FA oxidation, AMPK and ACC increased.¹¹⁹ Yoon et al reported that adiponectin promotes FA oxidation in muscle cells by sequentially activating AMPK, p38 MAPK and PPAR-α.¹²⁵ Besides, adiponectin can increase the expression of PPAR-α target genes in C2C12 myotubes, such as ACO, CPT1 and FABP3.^{125,129,130} Overexpression of adiponectin can significantly upregulate the expression of genes involved in

intracellular mitochondrial FA transport (LPL, CD36, CPT1B) and lipolysis (HSL, ATGL).²⁰ Rice found that AdipoR1 overexpression in retinal pigment epithelial cells enhanced DHA uptake (Table 3).¹³¹ Since adiponectin can reduce the levels of local and circulating adiponectin by promoting FA oxidation, they are able to reduce the progression of OA. Future research may focus on revealing the relationship between adiponectin and various subtypes of FAs.

Adiponectin and Triglycerides

Most existing epidemiological studies have supported that circulating adiponectin is negatively correlated with serum triglycerides.^{132,133} Studies have shown that serum HMW adiponectin is negatively correlated with triglyceride-rich very low-density lipoprotein (VLDL) in univariate regression. Additionally, in multivariate regression analysis, adiponectin was the most significant predictor of plasma VLDL apolipoprotein B (apoB) concentration.¹³⁴ Lipoprotein lipase (LPL) is highly expressed in tissues that use and store triglycerides, such as heart, skeletal muscle and fat, and LPL is an important target of adiponectin to regulate triglyceride catabolism.¹³⁴ LPL can catalyze the hydrolysis of large amounts of triglycerides in VLDL.¹³⁵ Studies have found that there is a positive correlation between LPL and adiponectin in normal subjects, patients with metabolic syndrome and T2DM.¹³⁶ After treatment of mice with globular adiponectin, LPL activity released by heparin was significantly increased. Additionally, the activity of LPL in epididymal white adipose tissue and heart also increased.¹³⁷ Another study found that adiponectin can promote LPL and VLDL receptor (VLDLr) mRNA levels in mouse skeletal muscle, and the activity of LPL in mouse skeletal muscle was significantly increased by 41%.¹⁹ These results indicate that adiponectin promotes the catabolism of VLDL to reduce plasma triglyceride levels. The reduction of serum apo-CIII, a well-known LPL inhibitor, induced by adiponectin may be another mechanism by which adiponectin promotes triglyceride degradation. According to reports, there is a negative correlation between circulating adiponectin and serum apo-CIII.^{138,139} Moreover, after adiponectin treatment of human HepG2 hepatocytes, apo-CIII mRNA levels were downregulated.¹⁹ Lopez et al found that in vitro model, adiponectin can upregulate the mRNA levels of HSL and ATGL, which can promote the catabolism of triglycerides and release free FAs.²⁰ Yamauchi et al reported that adiponectin stimulates FA oxidation through the AMPK and PPAR- α pathways, which may be a potential mechanism for adiponectin to reduce triglycerides.¹⁸ The mechanism is as described above.

Table 3 Adiponectin and FAs

	Author	Activities on FAs
Liver	Berg AH, Fruebis J and Yamauchi T	Adiponectin can reduce plasma free FA levels after meals. ¹¹⁵ Increases plasma lipid clearance, ¹¹⁶ and promotes FA oxidation in the liver and muscle. ¹¹⁷
	Xu A and Yamauchi T	Increases the activity of carnitine palmitoyl transferase I and Reduces the activities of ACC and FAS. ^{118,119}
	Schindler M	Adiponectin upregulates the mRNA levels of the FA transporters. ¹²¹
	Xu A	Decreases the expression of FA genes. ¹¹⁸
	Awazawa M	Adiponectin inhibits the expression of SREBP1c. ¹²³
Muscle	Pawlak M and Ishtiaq SM	Promotes triglyceride decomposition, intracellular FA transport, and mitochondrial FA β -oxidation. ^{127,128}
	Yamauchi T	Blocking AdipoR1 and R2 leads to increased tissue triglyceride content, inflammation and oxidative stress. ¹⁸
	Fruebis J and Yamauchi T	Adiponectin promotes the oxidation of skeletal muscle FAs. ^{116,117}
	Yamauchi T	Adiponectin increases the phosphorylation levels of FA oxidation, AMPK and ACC. ¹¹⁹
	Yoon MJ	Adiponectin promotes FA oxidation by activating AMPK, p38 MAPK and PPAR- α . ¹²⁵
	Yoon MJ, Shabani P and Nakamura MT	Adiponectin can increase PPAR- α target genes such as ACO, CPT1 and FABP3. ^{125,129,130}
	Lopez-Yus M	Adiponectin can upregulate the expression of genes involved in intracellular mitochondrial FA transport (LPL, CD36, CPT1B) and lipolysis (HSL, ATGL). ²⁰

Abbreviations: FA, fatty acids; ACC, acetyl CoA carboxylase; FAS, fatty acid synthase; SREBP1c, sterol regulatory element-binding protein 1c; AMPK, AMP-activated protein kinase; PPAR- α , peroxisome proliferator activated receptor alpha; ACO, acetyl CoA carboxylase oxidase; CPT1, carnitine palmitoyl transferase 1; FABP3, fatty acid binding protein 3; LPL, lipoprotein lipase; CPT1B, carnitine palmitoyl transferase 1B; HSL, hormone-sensitive lipase; ATGL, adipose triglyceride lipase.

Conclusion

In vivo and in vitro research continues to provide scientific evidence for the relationship between obesity and OA. The levels of inflammatory factors, FAs and triglycerides in obese people are higher than those in healthy people. Many M1 macrophages present in adipose tissue will replace M2 macrophages and release inflammatory factors, leading to cartilage cell destruction and matrix degradation. In addition, recent studies have shown that FAs and triglycerides play important roles in the progression of OA through different mechanisms. Adiponectin is a classic anti-inflammatory and antioxidant cytokine. On the one hand, adiponectin can reduce the level of inflammation in the body by regulating the proliferation and function of macrophages. On the other hand, adiponectin inhibits the secretion and function of MMPs after IL-1 β treatment of chondrocytes. However, studies have shown that adiponectin is involved in the inflammation of synovial membrane and chondrocytes. Therefore, the relationship between adiponectin and OA is controversial. Moreover, adiponectin can promote the decomposition of FAs in the liver and skeletal muscle and can also promote the decomposition of triglycerides by regulating the metabolism of VLDL, a lipoprotein that contains the most triglycerides. Although the role of adiponectin in OA has not been elucidated, it has been indicated to be effective in decreasing inflammatory factors and promoting the metabolism of FA and triglyceride. Therefore, adiponectin may be one of the important factors involved in the molecular events that prevent the development of OA. Future studies need to explicitly study the anti-inflammatory activity of adiponectin in different clinical OA subtypes and levels. Investigating the clinical significance of adiponectin in the normal and pathological process of OA may provide a potential therapeutic target for disease treatment. In conclusion, adiponectin may have a protective effect on obesity-related OA.

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Disclosure

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