

Adipocytokines as Pathogenic Mediators and Therapeutic Targets in Metabolic Syndrome-Related Cardiocerebrovascular Events

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Abstract: Metabolic syndrome (MS), characterized by central obesity, hyperglycemia, hypertension, and dyslipidemia, substantially increases the risk of cardiovascular and cerebrovascular events. Adipose tissue is an active endocrine organ, and dysregulated adipokine secretion may contribute to the link between MS and vascular injury. In this narrative review, we synthesize evidence on adipokines implicated in MS-related cardiocerebrovascular disease and discuss their therapeutic potential. Adiponectin, fibroblast growth factor 21 (FGF21), and omentin are generally associated with improved insulin sensitivity, lipid handling, and endothelial homeostasis, whereas leptin, resistin, tumor necrosis factor- α , and interleukin-6 can promote inflammation and endothelial dysfunction through pathways including NF- κ B and JAK/STAT. However, these associations may be modified by obesity, insulin resistance, disease stage, and other confounding factors, and some adipokines, such as adipisin, show context-dependent effects. Current translational evidence is strongest for strategies targeting adiponectin/FGF21 signaling and IL-1/IL-6-related inflammatory pathways, while evidence for cerebrovascular outcomes remains limited. Adipokine-directed interventions therefore remain promising but require rigorous clinical validation and disease-specific stratification.

Keywords: metabolic disorders, adipokines, cardiovascular disease, cerebro-vascular disease

Introduction

Metabolic syndrome (MS) is a clinical syndrome characterized by central obesity, hyperglycemia, hypertension, and dyslipidemia.¹ In recent years, the global burden of this disease has continued to rise. Epidemiological data show that the prevalence of MS nearly doubled between 2000 and 2023; currently, approximately 154 million adults worldwide are affected by the disease, with a prevalence rate of 31.0% among women and 25.7% among men.² MS has become one of the major chronic diseases threatening public health. Numerous studies have confirmed that MS is closely associated with the onset and progression of various cardiovascular and cerebrovascular diseases, including atherosclerotic cardiovascular disease, coronary heart disease, heart failure, stroke, and cognitive impairment.³ MS not only significantly increases the risk of cardiovascular adverse events in individuals, but also increases the risk of all-cause mortality by approximately 1.5 times.⁴ Although metabolic disorders such as hypertension, hyperglycemia, dyslipidemia, and central obesity are considered major risk factors for cardiovascular and cerebrovascular diseases, the mechanisms underlying the development of these conditions in metabolic syndrome are highly complex, and their pathophysiology has not yet been fully elucidated.^{4–6} Therefore, a thorough investigation of the key mechanisms linking MS to cardiovascular and cerebrovascular diseases is of great significance for early intervention and precision treatment.

In recent years, as research into adipose tissue has deepened, scientists have gradually uncovered its biological characteristics as an important endocrine organ. Adipose tissue secretes a variety of bioactive molecules, collectively referred to as adipokines, including adiponectin, fibroblast growth factor 21 (FGF21), omentin, resistin, leptin, and

various inflammatory factors such as tumor necrosis factor- α (TNF- α) and interleukins.⁷ These factors contribute to the regulation of metabolic homeostasis, inflammatory responses, and vascular function. Further research indicates that different types of adipokines play distinct roles in MS and its associated cardiovascular and cerebrovascular diseases. Pro-inflammatory adipokines (such as resistin, interleukin-6, and TNF- α) promote the development of atherosclerosis and cardiovascular and cerebrovascular events by inducing chronic low-grade inflammation, impairing vascular endothelial function, and exacerbating insulin resistance.^{8,9} In contrast, anti-inflammatory adipokines (such as adiponectin, FGF21, and omentin) exert a protective effect on the cardiovascular and cerebrovascular systems through mechanisms such as suppressing inflammatory responses, improving insulin sensitivity, and maintaining vascular homeostasis.^{10–12} Therefore, dysregulated adipokine signaling may represent one pathophysiological mechanism linking metabolic disorders to cardiovascular and cerebrovascular damage.

Currently, intervention strategies for MS and related cardiovascular and cerebrovascular diseases continue to be based on lifestyle modifications, supplemented by symptomatic treatments such as blood pressure control, blood glucose control, and lipid-lowering therapy.¹ However, poor long-term adherence and difficulties in maintaining treatment efficacy remain major clinical challenges. Although new weight-loss medications have demonstrated some efficacy in the short term, issues such as weight regain after discontinuation limit their long-term benefits.¹³ As research continues to advance, the role of adipokines in the prevention and treatment of metabolic and cardiovascular diseases is attracting increasing attention and is gradually moving into the clinical translation phase.^{14–17} Adipokines contribute to the onset and progression of MS and may also serve as key bridging mediators linking MS to cardiovascular and cerebrovascular diseases. Therefore, a thorough analysis of their mechanisms of action may provide a new theoretical basis for early intervention in cardiovascular and cerebrovascular diseases and offer potential directions for the development of novel targeted therapeutic strategies.

Literature Search and Scope

This narrative review was informed by a structured search of PubMed from database inception through July 2026. The search combined Medical Subject Headings, where applicable, and free-text terms covering three principal domains: metabolic syndrome and its metabolic components; adipokines; and cardiovascular and cerebrovascular diseases. Terms related to metabolic disorders included “metabolic syndrome”, “MetS”, “central obesity”, “obesity”, “insulin resistance”, “hyperglycemia”, “hypertension”, and “dyslipidemia”. Adipokine-related terms included “adipokine”, “adipocytokine”, “adiponectin”, “fibroblast growth factor 21” or “FGF21”, “omentin” or “omentin-1”, “chemerin”, “retinoic acid receptor responder 2” or “RARRES2”, “resistin”, “leptin”, “tumor necrosis factor-alpha” or “TNF- α ”, “interleukin-1” or “IL-1”, “interleukin-6” or “IL-6”, “adipsin” or “complement factor D”, and “visfatin” or “nicotinamide phosphoribosyltransferase/NAMPT”. These terms were combined, as appropriate, with “cardiovascular disease”, “cerebrovascular disease”, “atherosclerosis”, “coronary artery disease”, “coronary heart disease”, “heart failure”, “stroke”, “ischemic stroke”, “vascular cognitive impairment”, “vascular dementia”, and “dementia”. Additional mechanism- and translation-related terms included “inflammation”, “endothelial dysfunction”, “oxidative stress”, “insulin resistance”, “biomarker”, “therapeutic target”, “agonist”, “antagonist”, “analogue”, and “clinical trial”. Boolean operators AND and OR were used to combine terms, and focused searches pairing individual adipokines with specific diseases, mechanisms, or therapeutic agents were performed when necessary.

Titles and abstracts were initially screened for relevance, followed by full-text assessment of potentially relevant publications. Articles were considered relevant if they addressed at least one of the following: (1) the relationship between adipokines and metabolic syndrome or its major components; (2) associations between adipokines and cardiovascular or cerebrovascular diseases; (3) molecular mechanisms involving inflammation, endothelial dysfunction, oxidative stress, or metabolic dysregulation; or (4) the biomarker or therapeutic potential of adipokine-related pathways. English-language original studies, randomized and non-randomized clinical studies, observational studies, experimental animal and cellular studies, systematic reviews, meta-analyses, and authoritative narrative reviews were considered. Priority was given to recent human studies, prospective cohorts, clinical trials, systematic reviews, and meta-analyses, while earlier landmark studies were retained when they provided essential mechanistic or historical evidence. Publications that were unrelated to the predefined scope, provided insufficient information, or substantially duplicated

evidence reported in more comprehensive or recent studies were not prioritized. Reference lists of relevant reviews and key primary studies were also manually screened to identify additional pertinent publications. Because this was a narrative review, study selection was relevance-based rather than exhaustive, and no formal risk-of-bias assessment or quantitative evidence synthesis was performed.

The Multiple Roles of Adipokines in Metabolic Syndrome

In MS, adipokines—important signaling molecules primarily secreted by adipose tissue—play a multifaceted role in regulating energy metabolism, immune responses, and inflammatory reactions.⁷ Adipokines can be divided into three major categories: first, anti-inflammatory adipokines (adiponectin, FGF21, omentin, etc); second, pro-inflammatory adipokines (leptin, resistin, angiotensin II, TNF- α , and interleukins, etc); and third, adipokines that can act both as anti-inflammatory and pro-inflammatory agents (adipsin, visfatin).^{18–21} These factors are involved in lipid metabolism and have also been associated with the development and progression of cardiovascular disease. This paper primarily focuses on adipokines, which are closely associated with MS and cardiovascular complications, as shown in Figure 1.

Anti-Inflammatory Adipokines

Adiponectin

Adiponectin is a secreted protein containing a signal peptide, a collagen-like domain (Gly-X-Y repeats), and a globular domain; structurally, it bears significant similarity to proteins such as complement C1q and collagen $\alpha 1(X)$.²² It exerts its biological functions through signaling pathways mediated by the AdipoR1, AdipoR2, and T-cadherin receptors.^{23,24} As an anti-inflammatory and metabolic regulator secreted by fat cells, adiponectin is attracting increasing attention for its role in MS.²⁵ Low plasma adiponectin levels at baseline and a decline in adiponectin levels during follow-up were both independently associated with an increased risk of developing MS.²⁶ Adiponectin has a wide range of biological effects. It primarily acts by binding to AdipoR1 and AdipoR2, thereby activating signaling pathways such as AMPK and PPAR- α , promoting fatty acid oxidation and glucose metabolism, and consequently improving insulin sensitivity.²⁷ In addition, through its anti-inflammatory effects, adiponectin inhibits the NF- κ B signaling pathway, reduces the expression of pro-inflammatory cytokines (such as TNF- α and IL-6), and alleviates systemic inflammatory responses, thereby potentially contributing to the pathophysiology of MS.²⁸

In animal models, ACRP30 knockout mice exhibit metabolic disorders resulting from the absence of adiponectin/ACRP30. Specifically, the absence of adiponectin leads to severe insulin resistance by elevating TNF- α levels, inhibiting the expression of FATP-1 mRNA in muscle, and reducing IRS-1-mediated insulin signaling.²⁹ In contrast, in another study, researchers successfully increased adiponectin levels in mice by delivering the adiponectin gene via muscle-specific electroporation.¹⁰ This treatment significantly slowed weight gain and fat accumulation in mice induced by a high-fat, high-sugar diet, improved insulin sensitivity, and effectively improved glucose metabolism by enhancing hepatic insulin signaling and suppressing hepatic gluconeogenesis. In clinical studies, low plasma adiponectin levels have been closely associated with various core indicators of MS (such as hypertension, dyslipidemia, obesity, and diabetes). A case-control study involving 923 patients with severe obesity and liver disease found that lower plasma adiponectin levels were associated with the development of dyslipidemia, hypertension, and diabetes, and that this association was not influenced by gender.³⁰ Furthermore, prospective studies have shown that individuals with higher plasma adiponectin levels have a significantly lower risk of developing type 2 diabetes, further highlighting the potential preventive role of adiponectin in MS.³¹

FGF21

Fibroblast Growth Factor 21 (FGF21) is a secreted protein primarily produced by the liver and belongs to the endocrine fibroblast growth factor family.³² In humans, the mature protein consists of 209 amino acid residues and features a characteristic β -trefoil core structure, with extended loop structures at both the N-terminus and C-terminus; these features distinguish FGF21 from other members of the FGF family in terms of sequence and function.^{32–34} FGF21 exerts its effects in multiple target tissues by binding to the FGF receptor and its co-receptor β -Klotho, thereby activating downstream signaling pathways such as ERK1/2 and Akt.³⁵ Its target organs include adipose tissue, the liver, and the central nervous system, where FGF21 regulates physiological processes such as energy metabolism, lipid homeostasis, and insulin resistance.^{36,37}

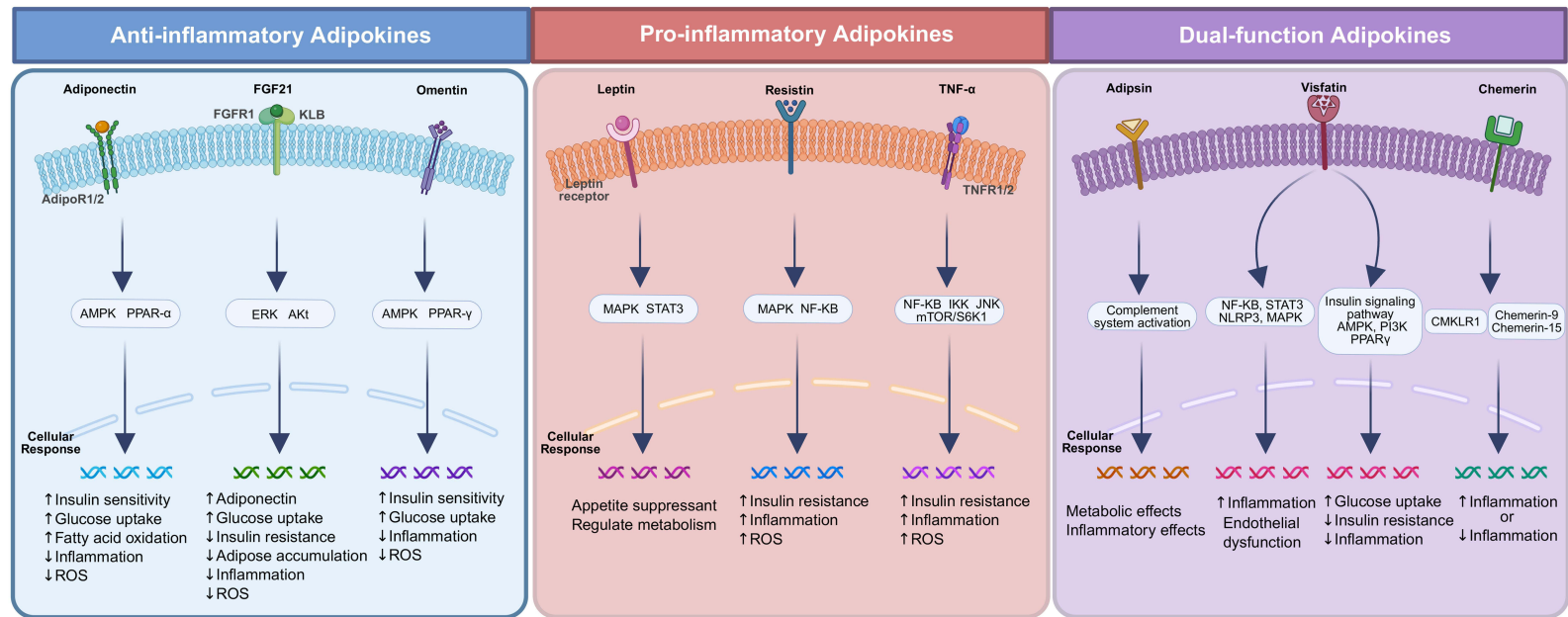


Figure I Adipocytokines closely related to metabolic syndrome and cardiovascular disease complications.

Note: “↑” indicates increased levels and “↓” indicates decreased levels.

In recent years, clinical research has focused on the potential of FGF21 and its analogues in the treatment of metabolic diseases. The FGF21 analog LY2405319 has demonstrated significant efficacy in patients with type 2 diabetes and obesity, improving lipid levels: LDL-C decreased by 20.2% to 29.5%, triglycerides decreased by 44.6% to 46.2%, and body weight decreased by 1.49 kg to 1.75 kg, while insulin levels were significantly reduced.¹¹ Another randomized, double-blind, placebo-controlled study demonstrated that AKR-001, a long-acting Fc-FGF21 analog, consistently improved insulin sensitivity and lipid metabolism in patients with type 2 diabetes and was well tolerated.³⁸ Interestingly, existing GLP-1-based antidiabetic drugs also work by stimulating the liver to secrete FGF21, thereby inhibiting hepatic glucose output and significantly improving blood glucose control in people with diabetes.³⁹ In addition, a study involving participants from four major ethnic groups (a total of 5783 participants) found a positive correlation between high levels of FGF21 and MS.⁴⁰ This phenomenon may be due to a compensatory increase in FGF21 caused by metabolic stress, or it may be related to a mechanism of FGF21 resistance, whereby supraphysiological levels of FGF21 are required to maintain its normal physiological function.

Omentin

Omentin is an adipokine secreted by adipose tissue; it belongs to the adipokine family and is primarily produced by stromal vascular cells in visceral adipose tissue.⁴¹ Omentin is a protein composed of 313 amino acids with a molecular weight of approximately 34 kDa; it contains a secretory signal sequence and a fibrinogen-related domain.⁴¹ Omentin primarily exists in two isoforms: Omentin-1 and Omentin-2, with Omentin-1 being the predominant form in serum and having been extensively studied in relation to metabolic diseases.^{42,43} Omentin-1 has been proposed to contribute to the regulation of insulin sensitivity and glucose and lipid metabolism. Specifically, Omentin-1 can improve insulin sensitivity by enhancing insulin-dependent glucose uptake, thereby counteracting insulin resistance; it has demonstrated potential therapeutic benefits, particularly in patients with obesity and type 2 diabetes.^{43–45}

In clinical studies of MS, Omentin-1 levels are typically lower than those in healthy control groups and are negatively correlated with obesity, insulin resistance, blood glucose levels, blood lipids, and inflammatory markers. For example, in patients with MS, plasma and subcutaneous adipose tissue levels of omentin-1 are significantly lower than those in the general population, and this difference remains significant even after adjusting for obesity.¹² Further studies have also shown that omentin-1 levels are significantly reduced in individuals with prediabetes and type 2 diabetes, and are negatively correlated with BMI, the homeostatic model assessment of insulin resistance, and inflammatory cytokines such as TNF- α and IL-6.⁴⁶ These findings support the use of omentin-1 as a potential biomarker for MS.

Pro-Inflammatory Adipokines

Resistin

Resistin is a 114-amino acid peptide containing 11 cysteine residues that is secreted as a disulfide-linked dimer.⁴⁷ It primarily causes metabolic disorders through inflammatory responses and insulin resistance. Studies have shown that resistin promotes systemic inflammatory responses by activating signaling pathways such as NF- κ B, MAPK, and PI3K, thereby enhancing the expression of pro-inflammatory cytokines such as TNF- α , IL-6, and IL-12.⁴⁸ Further research has shown that these inflammatory responses can lead to endothelial dysfunction and promote the development of atherosclerosis.⁴⁹ Consistent with this, its concentration in the bloodstream is positively correlated with type 2 diabetes and coronary atherosclerosis.⁵⁰ However, the role of resistin in insulin resistance remains controversial. Although most studies support the view that resistin plays a significant role in the development of insulin resistance,^{51,52} some studies have proposed alternative perspectives. For example, Lee et al found that circulating resistin levels are not associated with obesity or insulin resistance in humans and are not modulated by fasting or leptin administration.⁵³ Recent studies have further revealed that resistin, by inducing insulin resistance, suppresses the stem cell properties and metabolic characteristics of human adipose-derived mesenchymal stem cells.⁵⁴ In terms of clinical associations, the SIRCA study suggests that resistin levels are significantly higher in patients with MS than in those without it.⁸ These findings are consistent with those of Ding et al, whose study demonstrated that serum resistin levels are positively correlated with key components of MS—triglycerides (TG) and fasting blood glucose—suggesting that disturbances in glucose and lipid metabolism may interact with elevated resistin levels and jointly contribute to the pathophysiological processes underlying MS.⁵⁵

Leptin

Leptin is a peptide hormone encoded by the *ob/Lep* gene located on chromosome 7.⁵⁶ It has a molecular weight of approximately 16 kDa and consists of 167 amino acids; it is primarily synthesized in white adipose tissue.⁵⁶ Leptin primarily regulates appetite, energy balance, and metabolic processes by binding to its receptor, LEPR.⁵⁷ The proper functioning of these physiological processes depends on maintaining leptin concentrations in the bloodstream at effective levels. Leptin levels in the peripheral blood of obese patients are often significantly elevated, suggesting that obesity is not caused by insufficient leptin secretion, but rather by a decreased responsiveness to leptin, ie, leptin resistance.⁵⁸ Leptin levels are also generally elevated in patients with MS; particularly in female patients, leptin concentrations are positively correlated with markers of insulin resistance (such as the HOMA index), suggesting that leptin may play a role in the onset and progression of insulin resistance and related metabolic disorders.⁵⁹ In patients with type 2 diabetes, elevated levels of soluble leptin receptors in serum are positively correlated with abnormal glucose metabolism and changes in proteolysis.⁶⁰ In obese individuals, molecular and cellular mediators such as SOCS3, PTP1B, endoplasmic reticulum stress, and inflammation play a key role in the development of leptin resistance by directly inhibiting the LEPR-B signaling pathway.⁶¹ In addition, the mechanisms underlying leptin resistance include a reduction in the number of leptin receptors, impaired receptor function, reduced transport of leptin across the blood-brain barrier, and the suppression of leptin function by circulating inhibitory factors.⁶² In summary, leptin resistance is considered an important pathological feature of obesity and MS. This condition disrupts the negative feedback mechanism regulating energy balance, leading to increased food intake and further weight gain, thereby creating a persistent vicious cycle.

TNF- α and Interleukin

TNF- α is a cytokine secreted by cells such as adipocytes and macrophages, and its relationship with MS has been extensively studied.⁶³ Studies have shown that TNF- α promotes the development of insulin resistance by inhibiting insulin signaling pathways, thereby exacerbating the pathological progression of MS.⁶⁴ Specifically, TNF- α promotes insulin resistance by influencing free fatty acid levels, Glut4 protein expression, and insulin receptor signaling.⁶⁵ Related studies have shown that mice lacking TNF- α exhibit significantly improved insulin sensitivity, further supporting a contributory role in metabolic disorders.⁶⁵

The interleukin family, including IL-6 and IL-1 β , also plays an important role in MS. IL-6 has both pro-inflammatory and anti-inflammatory effects. Its anti-inflammatory effects are primarily mediated through classical signaling pathways, whereas its pro-inflammatory effects are exerted through trans-signaling mechanisms.⁶⁶ Research has shown that IL-6 signaling helps regulate inflammation and metabolism through T cells during the early stages of obesity.⁶⁷ However, over time, IL-6 enhances its pro-inflammatory effects through the soluble IL-6 receptor, thereby exacerbating late-stage inflammatory responses and insulin resistance.⁶⁷ In addition, IL-6 promotes the development of hypertension through various mechanisms, including impairing endothelial function, activating the renin-angiotensin-aldosterone system (RAAS), stimulating sympathetic nerve activity, and directly acting on renal sodium channels.⁶⁸ The role of IL-1 β in obesity-related chronic inflammation has also attracted significant attention. Studies have shown that IL-1 β enhances the interaction between insulin resistance and inflammatory responses by activating the NLRP3 inflammasome, thereby further exacerbating MS.⁶⁹ IL-1 β is also closely associated with lipid metabolism, fatty acid oxidation, and hepatic fat accumulation, further exacerbating the phenotype of MS.⁷⁰ In addition, IL-1 β interacts with pro-inflammatory factors such as TNF- α and IL-6 to form a complex cytokine network, which collectively drives the development of insulin resistance and chronic low-grade inflammation.⁷¹

Dual-Function Adipokines

Adipsin

Adipsin, also known as complement factor D, is an adipokine secreted by adipose tissue that contributes to metabolic homeostasis and inflammatory regulation.⁷² In the pathophysiological process of MS, adipsin has been associated with obesity, insulin resistance, and disturbances in glucose and lipid metabolism. However, its specific mechanisms of action and relationship with type 2 diabetes remain a subject of debate. Milek et al found that circulating levels of adipsin and its expression in adipose tissue were not associated with markers of impaired glucose or lipid metabolism in obese patients,

regardless of whether they had type 2 diabetes.⁷³ However, other studies have shown that Adipsin is independently associated with the risk of gestational diabetes, suggesting that it may play different roles in different types of diabetes.⁷⁴ The Framingham Heart Study found that higher plasma adipsin levels were associated with a more than 30% reduction in the risk of diabetes, but were also associated with a 68% increase in the risk of obesity, suggesting that adipsin may play different roles in different metabolic states.⁷⁵ On the other hand, research also suggests that increased fat mass partially mediates the development of MS by raising serum adipsin levels.⁷⁶ Adipsin may play a role in obesity-induced metabolic disorders through mechanisms such as promoting fat accumulation and adipocyte differentiation.⁷⁶ In type 2 diabetes, further evidence suggests that Adipsin effectively protects pancreatic β -cells in mice with type 2 diabetes by promoting C3a production and down-regulating DUSP26 expression.⁷⁵ This finding provides strong support for Adipsin as a potential therapeutic target for diabetes. Although the specific role of Adipsin in MS and diabetes is not yet fully understood, it may play diverse roles in various metabolic disorders and warrants further in-depth investigation.

Visfatin

Visfatin is a 52-kDa secreted protein, also known as nicotinamide phosphoribosyltransferase (NAMPT), which plays a crucial role in cellular metabolism by acting as the rate-limiting enzyme in the salvage pathway for NAD⁺ synthesis.⁷⁷ Visfatin primarily contributes to metabolic diseases by influencing oxidative stress responses, apoptosis, lipid and glucose metabolism, inflammation, and insulin resistance.⁷⁸ A high-fat diet and aging impair NAMPT-mediated NAD⁺ biosynthesis, thereby disrupting normal metabolic processes and promoting the development of type 2 diabetes.⁷⁹ Serum visfatin levels are often elevated in obese individuals or those with hyperglycemia, but they may decrease following weight loss.^{80–82} Intervention strategies targeting the NAMPT/NAD⁺ pathway have attracted significant attention. Supplementation with nicotinamide mononucleotide (NMN) promotes NAD⁺ production and improves glucose tolerance;⁷⁹ meanwhile, the compound P7C3, by activating NAMPT, has been shown to improve glucose metabolism, pancreatic β -cell function, and skeletal muscle function in T2DM model mice.⁸³ However, the relationship between visfatin and metabolic abnormalities remains controversial. For example, in Asian Indian populations, serum visfatin levels are significantly associated with obesity and visceral fat, but not with subcutaneous fat.⁸⁴ Although serum visfatin levels are elevated in patients with type 2 diabetes, this association is primarily mediated by obesity rather than by diabetes itself.⁸⁴ However, a study by Pagano et al showed that visfatin levels are significantly reduced in obese patients, and this reduction is not associated with insulin resistance.⁸⁵

Chemerin

Chemerin, encoded by the RARRES2 gene and also known as retinoic acid receptor responder protein 2, is an adipokine secreted predominantly by adipose tissue and the liver.⁸⁶ It is initially released as the precursor prochemerin and subsequently undergoes C-terminal proteolytic processing to generate molecular forms with distinct biological activities. Chemerin interacts primarily with three receptors: CMKLR1, GPR1, and CCRL2.^{87,88} Its biological effects are highly context-dependent and are jointly determined by its proteolytically processed form, receptor expression profile, target cell type, and the local inflammatory microenvironment. Chemotactically active chemerin can promote the migration and recruitment of dendritic cells and macrophages through CMKLR1, thereby amplifying inflammatory responses.⁸⁷ Conversely, chemerin and its C-terminal-derived peptides may also exert anti-inflammatory effects under specific conditions. For example, C15 has been shown in murine models to attenuate neutrophilic inflammation, suppress the release of pro-inflammatory mediators, and enhance macrophage clearance of microbial particles and apoptotic neutrophils.⁸⁷ Chemerin-9 can inhibit the expression of endothelial adhesion molecules and pro-inflammatory mediators, reduce monocyte adhesion, and attenuate macrophage inflammatory responses.⁸⁹ In addition, it suppresses foam cell formation by downregulating CD36 and upregulating ABCA1, while limiting vascular smooth muscle cell migration and proliferation, suggesting potential anti-inflammatory and anti-atherosclerotic effects.⁸⁹

In MS, chemerin may contribute to metabolic dysregulation by modulating adipogenesis and lipid metabolism, enhancing inflammatory responses, disrupting insulin signaling, and promoting vascular constriction and remodeling.⁹⁰ Studies have shown that elevated circulating chemerin levels are associated with MS and its adverse metabolic components, with independent positive correlations with fasting blood glucose, blood pressure, and triglyceride levels,

and an independent inverse correlation with high-density lipoprotein cholesterol levels.⁹¹ Animal studies have further demonstrated that the CMKLR1 antagonist CCX832 can attenuate vascular oxidative stress and partially restore insulin-mediated vasodilation in diabetic obese mice.⁹² However, the available clinical evidence is not entirely consistent. A cross-sectional study involving 149 participants found no significant difference in total serum chemerin levels between individuals with and without MS, and chemerin was not significantly associated with major cardiometabolic risk factors within the MS group.⁹³ These findings suggest that the relationship between chemerin and MS may be influenced by factors such as its molecular isoforms, the characteristics of the study population, and the stage of disease.

The Pathogenic Association and Therapeutic Effects of Adipokines in Cardiovascular and Cerebrovascular Events

MS is characterized by an imbalance in adipokine secretion, manifested by decreased levels of protective factors (such as adiponectin and FGF21) and excessive secretion of pro-inflammatory factors (such as leptin and resistin). This imbalance may contribute to insulin resistance and chronic inflammation and thereby influence the onset and progression of cardiovascular disease. It is worth noting that different adipokines play distinct roles in cardiovascular and cerebrovascular diseases: on the one hand, certain factors (such as leptin and resistin) promote pathological processes by inducing inflammation and oxidative stress; on the other hand, protective factors (such as adiponectin and FGF21) have potential therapeutic effects by modulating inflammatory responses and improving endothelial function. For example, restoring adiponectin function or using FGF21 analogues has been proposed as a potential therapeutic strategy. However, the effects of these factors vary across different pathological contexts and may yield different outcomes in various cardiovascular and cerebrovascular diseases. This chapter will thoroughly explore the pathogenic mechanisms and therapeutic roles of various adipokines in cardiovascular and cerebrovascular diseases.

Cardiovascular Diseases

Atherosclerosis and Coronary Artery Disease

Atherosclerosis is the pathological basis of coronary heart disease.⁹⁴ It is the pathological basis of coronary heart disease. Resistin, leptin, TNF- α , and IL-6 play important roles in the development and progression of atherosclerosis and coronary heart disease. In animal models of atherosclerosis, local overexpression of resistin accelerates plaque formation and leads to plaque instability.⁹⁵ Leptin accelerates the progression of atherosclerosis by regulating the adhesion of endothelial cells, increasing the uptake of oxidized low-density lipoprotein (oxLDL), and promoting the proliferation of vascular smooth muscle cells.⁹⁶ Salvianolic acid B can suppress TNF- α -induced inflammatory responses and inhibit the activated NF- κ B/NLRP3 signaling pathway, thereby slowing the progression of atherosclerosis.⁹⁷ IL-6 further promotes endothelial inflammation and vascular remodeling by enhancing immune responses and platelet aggregation, thereby exacerbating the severity of atherosclerosis.⁹⁸

Adiponectin levels are negatively correlated with BMI, waist-to-hip ratio, and triglycerides, and positively correlated with HDL and insulin sensitivity, highlighting its potential anti-atherosclerotic effects.⁹⁹ Treatment with the FGF21 analog pegozafermin significantly reduces levels of atherosclerosis-associated lipoproteins, including non-HDL-C, ApoB, and ApoC3, suggesting that it combats atherosclerosis by reducing the production of triglyceride-rich lipoproteins and improving their clearance.¹⁰⁰ Omentin-1 has a preventive effect on atherosclerosis.¹⁰¹ Among 264 patients with chronic limb-threatening ischemia due to diabetes who underwent endovascular revascularization, low levels of omentin-1 were associated with an increased risk of major adverse cardiac events and major adverse limb events.¹⁰² The role of Adipsin in atherosclerosis remains controversial. One study suggests that it inhibits foam cell formation;¹⁰³ another study found that higher levels of adipsin increase mortality following acute myocardial infarction.¹⁰⁴ Although Visfatin plays a dual role in MS, it primarily acts as a contributing factor in atherosclerosis. Treatment with the Visfatin antagonist FK866 inhibits NF- κ B activation, thereby reducing the expression of inflammatory mediators (such as IL-6 and IL-8) in human coronary endothelial cells.¹⁰⁵ Elevated circulating chemerin levels have been associated with the presence of coronary artery disease (CAD) and greater disease burden in patients with MS. A cross-sectional study involving 112 patients with MS showed that serum chemerin levels were significantly higher in those with CAD than in those without

CAD.¹⁰⁶ After adjustment for relevant confounding factors, chemerin levels remained independently associated with the presence of CAD.¹⁰⁶ Further studies demonstrated that elevated serum chemerin levels were independently associated with a higher risk of CAD, a greater number of diseased coronary vessels, and increased Gensini scores, and were also correlated with metabolic abnormalities, including elevated triglyceride and total cholesterol levels, insulin resistance, and MS.¹⁰⁷ Figure 2 illustrates the roles of adipokines in atherosclerosis and coronary artery disease.

Heart Failure

MS—particularly obesity, insulin resistance, and hypertension—is a major risk factor for HF. It increases the burden on the heart and promotes inflammatory responses, thereby accelerating the onset of HF.¹⁰⁸ Pro-inflammatory factors such as resistin, leptin, TNF- α , and interleukin often trigger the onset of HF. Studies have shown that higher levels of resistin are associated with greater baseline insulin resistance and higher C-reactive protein levels, and these markers have been shown to predict the incidence of HF.¹⁰⁹ High leptin levels (>18.9 ng/mL) were significantly associated with the risk of hospitalization for HF; after adjusting for potential confounding factors, the risk nearly doubled, suggesting that high leptin levels may be an independent predictor of hospitalization for HF.¹¹⁰ In patients with HF, TNF- α levels are often elevated, and high levels of TNF- α are closely associated with structural and functional changes in the heart.¹¹¹ Patients with psoriasis who receive anti-TNF- α biologics have a significantly reduced risk of cardiovascular disease.¹¹¹ During HF, pro-inflammatory mediators (IL-6, IL-1 β) promote pathological changes such as cardiomyocyte hypertrophy and fibrosis.¹¹² In patients with HFpEF, elevated IL-6 levels are closely associated with greater body fat accumulation, a significant decline in exercise capacity, and poorer health status.¹¹³ These pro-inflammatory factors are associated with disease severity, poor prognosis, high hospitalization rates, and increased mortality.

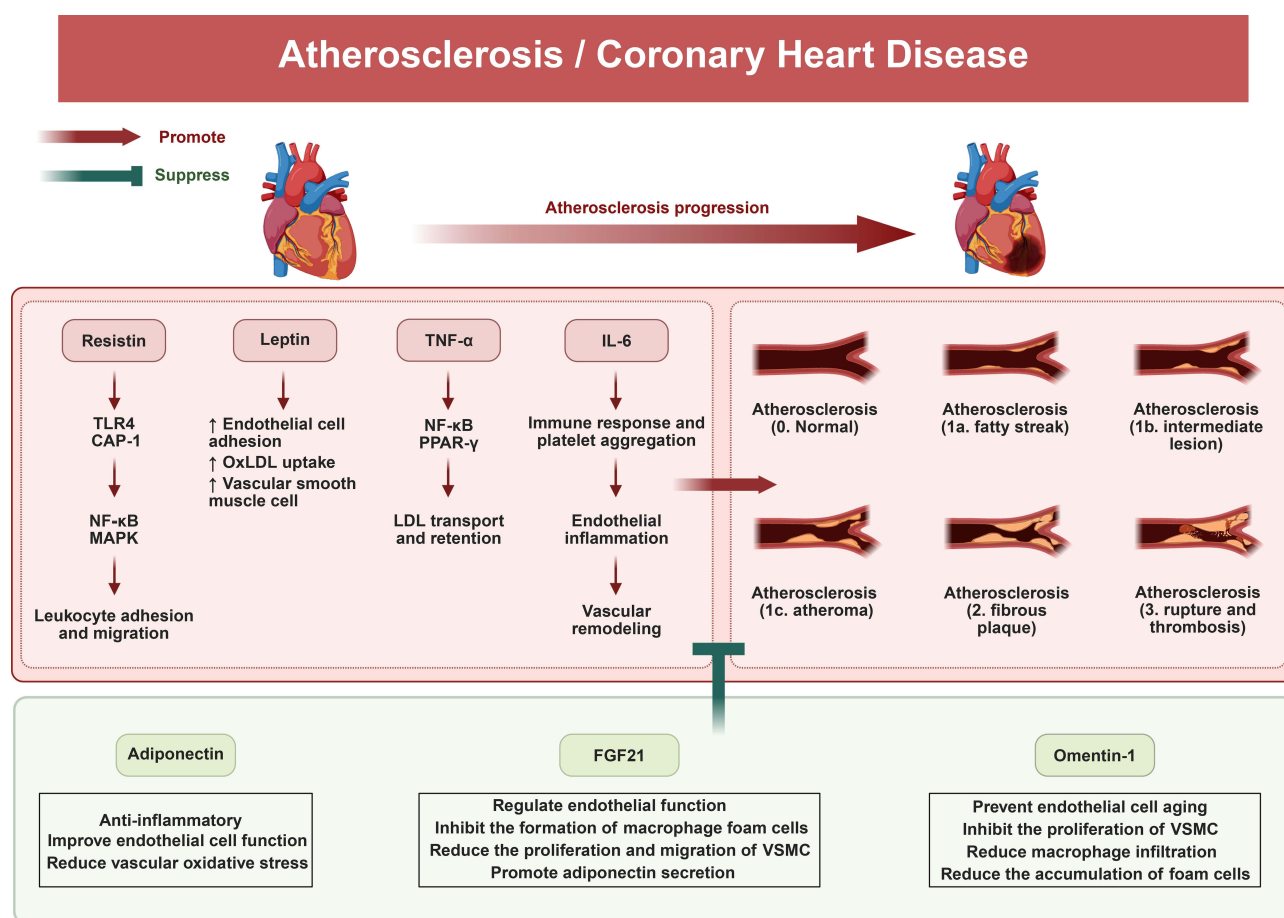


Figure 2 The roles of adipokines in atherosclerosis and coronary artery disease.

Note: “↑” indicates increased levels; green flat-headed arrows indicate inhibition; and red arrows indicate promotion.

ALY688, an adiponectin receptor agonist, significantly improved cardiac function by alleviating stress-induced cardiac hypertrophy, fibrosis, inflammatory responses, and metabolic disorders, suggesting its potential clinical value in the treatment of HF with reduced ejection fraction (HFrEF).¹¹⁴ FGF21 exerts a protective effect in heart failure with preserved ejection fraction and slows the progression of cardiac hypertrophy.^{115,116} Omentin-1 can improve mitochondrial biosynthetic function via the WNT5A/ Ca^{2+} signaling pathway, thereby mitigating myocardial ischemia-induced damage and slowing the progression of HF.¹¹⁷ Lower serum levels of omentin-1 are significantly associated with the occurrence of adverse cardiac events in patients with HF.¹¹⁸ In the prospective EPIC-Potsdam cohort study, higher circulating chemerin levels were significantly associated with an increased risk of incident heart failure.¹¹⁹ After comprehensive adjustment for obesity, metabolic abnormalities, coronary heart disease, lipid parameters, and inflammatory markers, participants in the highest quartile of chemerin levels still had a 4.23-fold higher risk of heart failure than those in the lowest quartile.¹¹⁹ In rat models of diabetic cardiomyopathy and H9c2 cardiomyocytes, activation of the chemerin/CMKLR1 axis promoted myocardial inflammation, pyroptosis, hypertrophy, and fibrosis and aggravated cardiac dysfunction by activating the NLRP3 inflammasome and its downstream caspase-1/IL-1 β signaling pathway, whereas CMKLR1 silencing partially reversed these pathological changes.¹²⁰ Research on Adipsin and Visfatin in HF remains limited, and further investigation is urgently needed. Figure 3 illustrates the roles of adipokines in heart failure.

Cerebrovascular Diseases

Stroke

Adipokines are implicated in metabolic diseases, and a growing body of research suggests that they may also influence the onset, progression, and prognosis of ischemic stroke. The study found that elevated resistin levels are significantly associated with the risk of in-hospital mortality in patients with acute ischemic stroke, suggesting that resistin may serve as a promising prognostic biomarker.¹²¹ High levels of resistin in the bloodstream are closely associated with an increased risk of ischemic stroke, and this association is independent of obesity and other cardiovascular risk

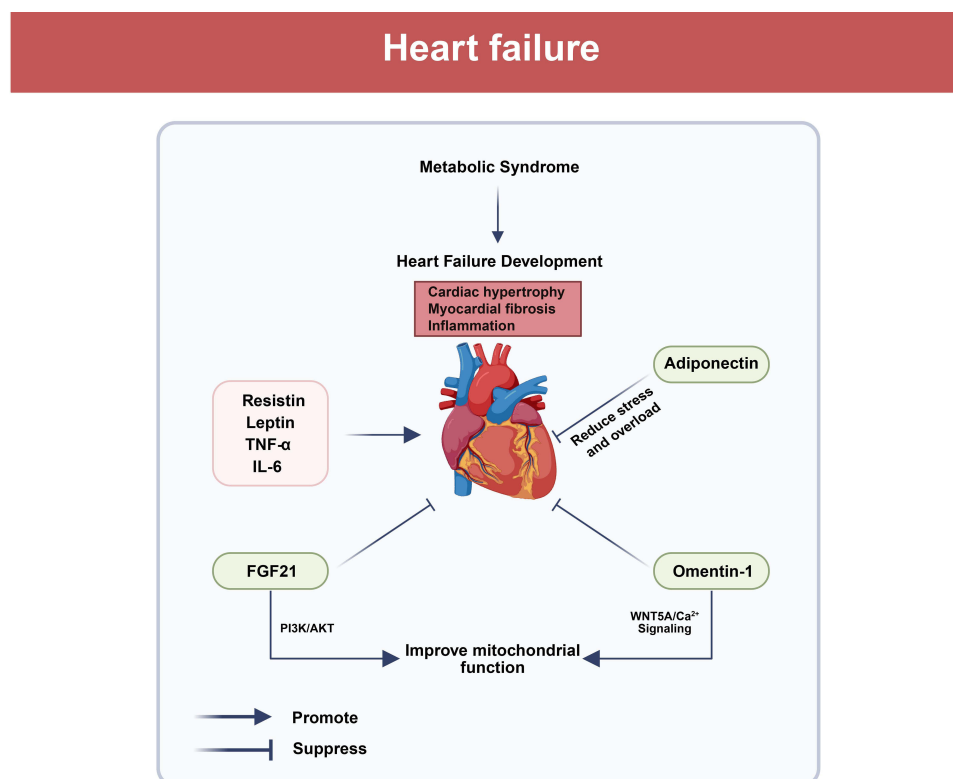


Figure 3 The roles of adipokines in heart failure.

Note: The pointed arrows indicate promotion and the flat-headed arrows indicate inhibition.

factors.¹²² Leptin, another adipokine, has attracted significant attention for its role in ischemic stroke. A study by Zhang et al indicates that leptin exerts significant neuroprotective effects by activating the ERK 1/2 signaling pathway and the CREB transcription factor, thereby effectively alleviating ischemic brain injury.¹²³ It is worth noting that even when administered late after ischemic brain injury, leptin still demonstrates potential therapeutic value; therefore, leptin holds promise as a candidate drug for the treatment of ischemic stroke.¹²³ In addition to resistin and leptin, IL-6 and TNF- α —inflammatory cytokines whose levels are elevated in patients with acute ischemic stroke—are also closely associated with stroke severity and long-term functional recovery.¹²⁴ Therefore, early monitoring of these inflammatory biomarkers may provide important insights for assessing patient prognosis.

Although adiponectin is generally considered to have a protective effect in cardiovascular disease, recent studies have shown that elevated serum levels of adiponectin are associated with an increased risk of ischemic stroke.¹²⁵ This finding contradicts a previous meta-analysis, which had indicated that there was no significant association between adiponectin and the risk of stroke.¹²⁶ However, recent prospective cohort studies have found that higher serum adiponectin levels are associated with stroke severity, functional outcomes, and mortality risk in patients with ischemic stroke.¹²⁷ Specifically, for every 1 $\mu\text{g/ml}$ increase in adiponectin, the risk of an adverse clinical outcome increases by 24%.¹²⁷ This discrepancy may be closely related to factors such as an individual's metabolic status and inflammatory response, suggesting that, in certain circumstances, elevated adiponectin levels may actually serve as an indicator of poor prognosis. Therefore, although adiponectin has a protective effect in certain situations, its role in specific pathological conditions requires further in-depth study. Recombinant human FGF21 has also shown promise in studies on ischemic stroke. FGF21 inhibits the secretion of pro-inflammatory cytokines (such as IL-1 β , TNF- α , and IL-6) and promotes the secretion of anti-inflammatory cytokines (such as IL-10 and TGF- β), thereby significantly reducing infarct volume (from 17.16% to 9.66%) and improving neurological function in a mouse model of ischemic stroke, demonstrating its potential as an anti-inflammatory therapeutic strategy for stroke.¹²⁸ In the PRIME study, elevated plasma levels of adiponectin were independently associated with a 10-year risk of ischemic stroke.¹²⁹ The study found that for every one-standard-deviation increase in plasma adiponectin levels, the risk of ischemic stroke increases by approximately 2.01-fold, providing new evidence that adiponectin may serve as a potential prognostic biomarker.¹²⁹ In addition, exogenous visfatin exerts a neuroprotective effect in ischemic stroke through its NAMPT enzymatic activity. Under ischemic conditions, plasma visfatin concentrations increase significantly.¹³⁰ Further studies have shown that in spontaneously hypertensive rats prone to stroke, plasma visfatin levels at 6 months of age were significantly lower than those in age-matched Wistar-Kyoto rats, and this difference was associated with increased stroke susceptibility.¹³⁰ Visfatin enhances autophagy via astrocyte-derived exosomes (OGD/R-ADEXs) through the AMPK/mTOR signaling pathway, thereby reducing neuronal death and improving neurological function in acute ischemic stroke.¹³¹ Observational studies have shown that elevated circulating chemerin levels are associated with the occurrence of acute ischemic stroke, ischemic cerebrovascular disease, and more severe neurological deficits.^{132–134} However, experimental evidence suggests that the chemerin/ChemR23 axis may exert protective effects in ischemic brain injury that differ from those associated with total circulating chemerin. In mouse models of permanent middle cerebral artery occlusion and SH-SY5Y cell models subjected to oxygen–glucose deprivation, activation of ChemR23 by RvE1 or chemerin-9 attenuated ischemic brain injury by suppressing NLRP3 inflammatory activation and GSDMD-mediated neuronal pyroptosis.¹³⁵ Conversely, genetic deletion or pharmacological inhibition of ChemR23 aggravated these pathological changes.¹³⁵ In addition, chemerin-15 enhanced microglial phagocytic activity through the ChemR23/p38 MAPK pathway, thereby alleviating cerebral ischemia–reperfusion injury. Collectively, these findings suggest that the effects of chemerin in stroke may depend on the specific ligand form, tissue context, and stage of disease.¹³⁶ Figure 4 illustrates the roles of adipokines in stroke.

Vascular Cognitive Impairment and Dementia

Vascular cognitive impairment (VCI) is one of the most common types of dementia in older adults. Its clinical symptoms typically worsen gradually over time and may eventually progress to vascular dementia.¹³⁷ Studies have shown that pro-inflammatory cytokines (such as TNF- α , IL-1 β , and IL-6) have been implicated in VCI caused by chronic cerebral hypoperfusion.¹³⁸ These cytokines accelerate cognitive decline by triggering inflammatory cascades, disrupting the blood-brain barrier, and promoting nerve damage.

Stroke

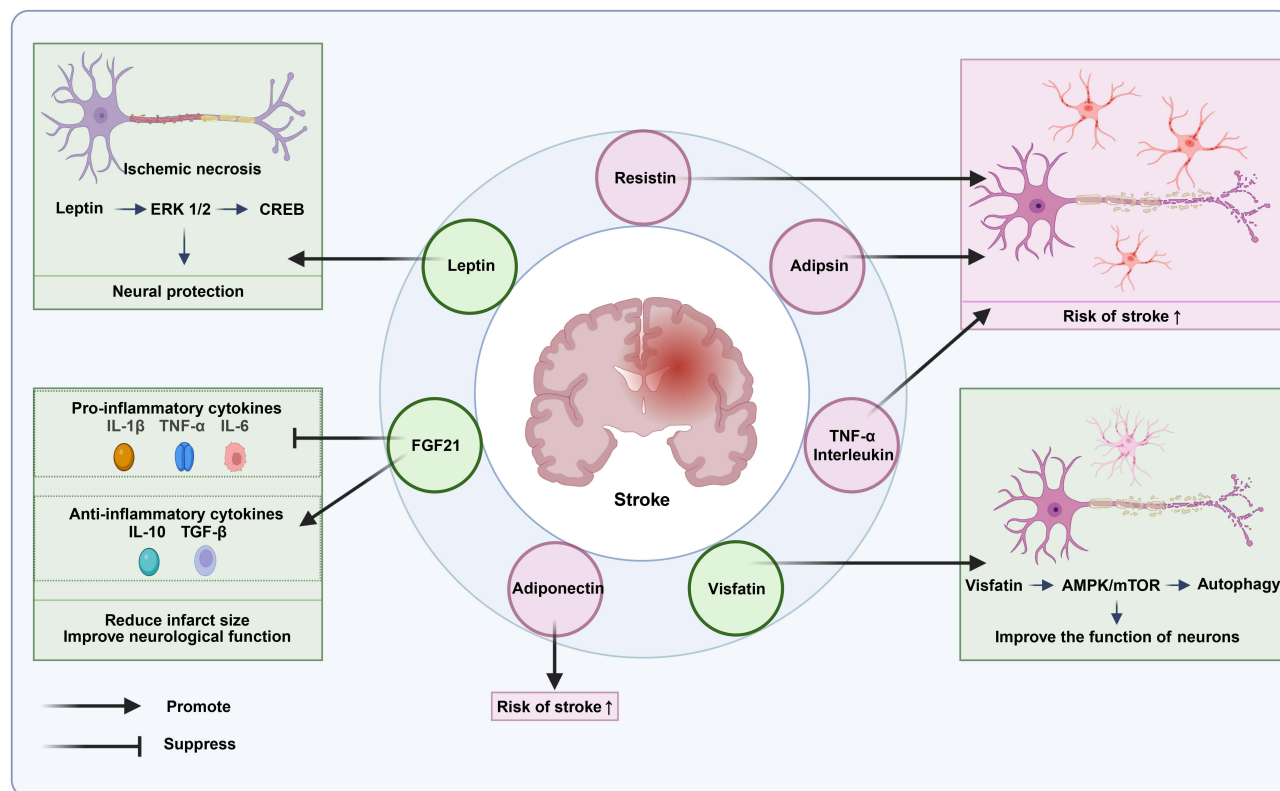


Figure 4 The roles of adipokines in stroke.

Note: The black pointed arrows indicate promotion, flat-headed arrows indicate inhibition, blue arrows indicate process progression, and upward arrow increased levels.

Among the factors associated with dementia, the two adipokines resistin and leptin have shown a strong association in distinct studies. Higher levels of resistin and leptin are associated with a lower risk of dementia, particularly among individuals with a higher body mass index and those carrying the APOE $\epsilon 4$ genotype, suggesting that these two adipokines may play a protective role in the pathophysiology of dementia.¹³⁹ Specifically, in Alzheimer's disease, plasma leptin may have a certain protective effect against the pathological progression of AD.¹⁴⁰ In addition, the adiponectin/PPAR γ signaling pathway helps alleviate cognitive deficits in VCI by modulating microglial function. It has been found that a deficiency in adiponectin exacerbates inflammatory responses and nerve damage, whereas adiponectin receptor agonists suppress inflammatory responses and improve cognitive symptoms by increasing PPAR γ expression.¹⁴¹ Therefore, the adiponectin pathway holds potential therapeutic value in the treatment of VCI. VCI is primarily caused by vascular risk factors and cerebrovascular disease.¹⁴² In this process, FGF21 plays an important protective role. The study found that mice lacking FGF21 exhibited larger areas of cerebral infarction (1.8-fold increase) following ischemic brain injury, as well as more severe neurological deficits, accompanied by enhanced glial reactivity and inflammatory responses.¹⁴³ This suggests that FGF21 protects the brain from damage by regulating inflammatory and neurotrophic pathways. Although there are few studies on adipsin and VCI, existing research suggests that adipsin may play a role in mild cognitive impairment (MCI) among patients with type 2 diabetes. Among Chinese patients with type 2 diabetes, elevated plasma adipsin levels are significantly associated with the onset of MCI, suggesting that adipsin may be associated with early cognitive decline in this population.¹⁴⁴ In a model of chronic cerebral hypoperfusion, activation of the chemerin receptor ChemR23 attenuated brain tissue injury and improved cognitive function by suppressing NLRP3 inflammasome-mediated neuronal pyroptosis through the PI3K/AKT/Nrf2 signaling pathway.¹⁴⁵ These findings

Vascular cognitive impairment and dementia

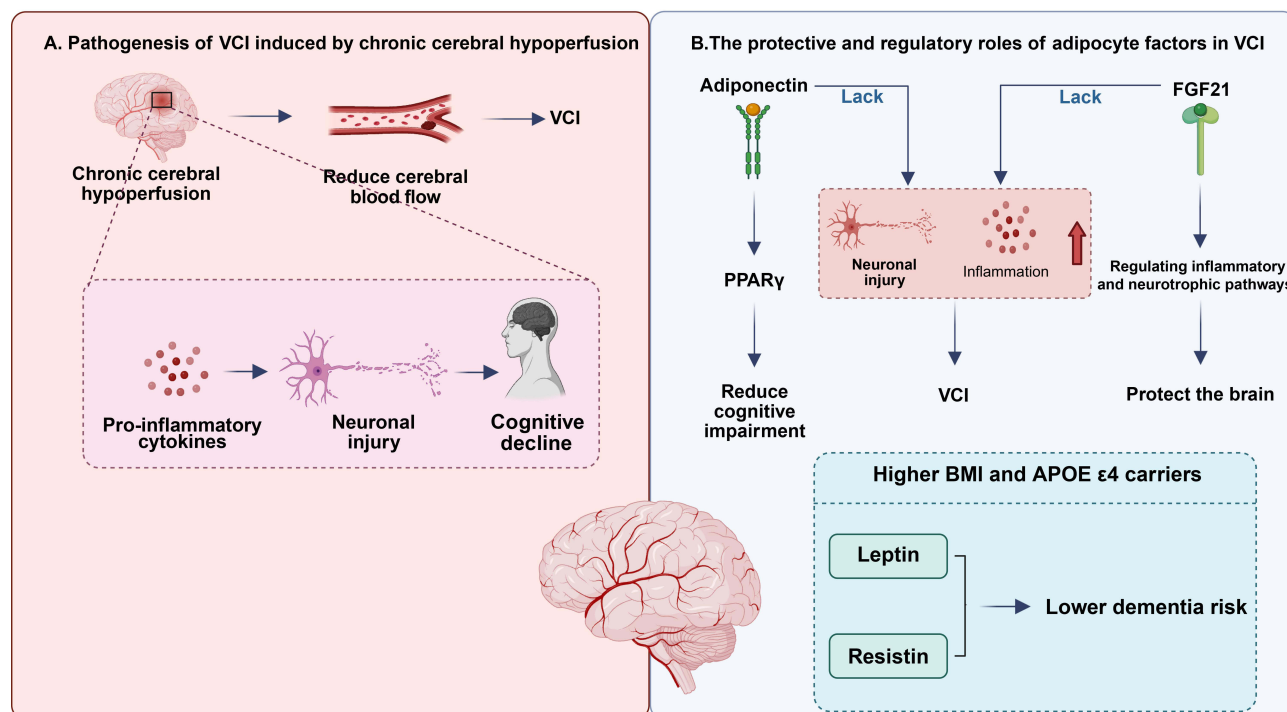


Figure 5 The roles of adipokines in vascular cognitive impairment and dementia.

Notes: (A) Pathogenesis of vascular cognitive impairment induced by chronic cerebral hypoperfusion. Chronic cerebral hypoperfusion reduces cerebral blood flow and promotes the release of pro-inflammatory cytokines, neuronal injury, cognitive decline, and ultimately the development of vascular cognitive impairment. (B) Protective and regulatory roles of adipocyte factors in vascular cognitive impairment. Adiponectin may alleviate cognitive impairment through the PPAR γ signaling pathway, whereas adiponectin deficiency may exacerbate neuronal injury and promote inflammation. FGF21 may protect the brain by regulating inflammatory and neurotrophic pathways, whereas FGF21 deficiency may aggravate neuronal injury and inflammation. Among individuals with a higher BMI and those carrying the APOE ϵ 4 allele, higher leptin and resistin levels are associated with a lower risk of dementia.

suggest that the chemerin/ChemR23 axis may represent a potential therapeutic target for vascular cognitive impairment. Figure 5 illustrates the roles of adipokines in vascular cognitive impairment and dementia.

The Pathogenic Mechanism of Adipokines in Cardiovascular and Cerebrovascular Diseases

Inflammatory Response

Adipokines may contribute to the onset and progression of cardiovascular and cerebrovascular diseases. By modulating the function of immune cells, causing endothelial damage, and promoting vascular remodeling, they induce a chronic, low-grade inflammatory response, thereby accelerating the progression of cardiovascular and cerebrovascular diseases. Adipokines (such as resistin, leptin, TNF- α , and IL-6) participate in inflammatory responses through various small-molecule mechanisms.

Resistin enhances inflammatory responses by activating pro-inflammatory signaling pathways such as NF- κ B, JAK/STAT, and MAPK, leading to vascular endothelial damage and impaired vascular homeostasis, which in turn exacerbates atherosclerosis. By acting on macrophages and monocytes, it promotes the secretion of inflammatory factors such as TNF- α and IL-6, thereby further exacerbating the inflammatory response in the blood vessel walls.⁸ At the same time, it promotes the formation of foam cells by enhancing the uptake of oxLDL by macrophages, and by altering fatty acid metabolism, it increases the availability of non-esterified fatty acids within cells, thereby driving the progression of atherosclerosis and cardiovascular disease.¹⁴⁶ In addition, resistin binds to the TLR4 receptor, activates the MyD88-

dependent pathway, and enhances the NF- κ B pathway, leading to the production of pro-inflammatory cytokines.¹⁴⁷ Resistin can also further impair vascular endothelial function by enhancing oxidative stress, thereby providing a pathological basis for cardiovascular and cerebrovascular diseases.¹⁴⁸ Leptin activates the JAK2/STAT3 signaling pathway through its receptor, LepR, promoting the secretion of pro-inflammatory factors such as TNF- α and IL-6, thereby facilitating the activation of immune cells and causing damage to endothelial cells.^{149,150} In obese individuals, leptin also partially activates the Toll-like receptor signaling pathway, thereby activating the NF- κ B pathway, promoting the development of chronic inflammation and insulin resistance, and further contributing to the onset and progression of cardiovascular and cerebrovascular diseases.¹⁵¹

TNF- α binds to the tumor necrosis factor receptor, thereby activating the NF- κ B, MAPK, and AP-1 signaling pathways, enhancing inflammatory responses in endothelial cells and vascular smooth muscle cells, increasing vascular endothelial permeability, and promoting leukocyte aggregation.^{152,153} TNF- α also contributes to angiotensin II-induced hypertension and cardiac hypertrophy by upregulating AT1 receptor expression and activating the NF- κ B signaling pathway, thereby providing a potential mechanism for the onset of MS and the progression of cardiovascular and cerebrovascular diseases.¹⁵⁴ IL-6 and IL-1 β are important mediators of the inflammatory response. IL-6 binds to the IL-6 receptor, activates the JAK/STAT signaling pathway, promotes the synthesis of acute-phase reactants (such as CRP), and regulates lipid metabolism, thereby further contributing to the development of atherosclerosis.⁹⁸ IL-1 β triggers a cytokine storm by activating the NLRP3 inflammasome, exacerbating the systemic inflammatory response, which in turn leads to damage to the vascular endothelium and thickening of the arterial walls, thereby promoting the development of cardiovascular and cerebrovascular diseases.¹⁵⁵

Endothelial Dysfunction

Impaired endothelial cell function is an important feature in cardiovascular and cerebrovascular diseases such as atherosclerosis and hypertension. Adipokines promote the onset and progression of cardiovascular and cerebrovascular diseases by regulating NO synthesis in endothelial cells, inhibiting vasodilation, and inducing apoptosis, thereby leading to vasoconstriction and impaired blood flow.

In endothelial cells, resistin promotes oxidative stress, thereby activating the reactive oxygen species(ROS)-dependent stress kinases p38 MAPK and JNK.¹⁵⁶ The activation of these kinases enhances the activity of c-Jun and other bZIP transcription factors, thereby inducing apoptosis in endothelial cells under conditions of severe stress.¹⁵⁶ At the same time, increased ROS levels exacerbate oxidative stress, directly damaging endothelial cells. Endothelial cell apoptosis reduces vascular repair capacity, increases vascular fragility, and leads to long-term endothelial dysfunction.¹⁵⁷ ROS reacts with NO to form peroxynitrite (ONOO⁻), which inhibits the biological activity of NO, further impairs endothelial vasodilation, and promotes the development of hypertension and atherosclerosis.¹⁵⁸ In addition, elevated levels of leptin promote vasoconstriction by increasing the expression of endothelin-1 in endothelial cells, leading to increased vascular tension and thereby raising the risk of hypertension.¹⁵⁹ Endothelin causes smooth muscle cell contraction via the ETA receptor and induces vasodilation in endothelial cells via the ETB receptor; the interaction between these two mechanisms may lead to dysregulation of vascular tone.¹⁶⁰ Although leptin increases the expression of endothelial NO synthase (eNOS), it reduces available NO by decreasing intracellular L-arginine levels, thereby decoupling eNOS activity.⁹ This change leads to the formation of harmful ONOO⁻, thereby exacerbating endothelial dysfunction.⁹

TNF- α promotes endothelial cell apoptosis by activating the Fas/FasL pathway, thereby reducing the number of endothelial cells, impairing vascular repair functions, and further exacerbating endothelial dysfunction.¹⁶¹ TNF- α also increases ROS production by activating NADPH oxidase(NOX); ROS reacts with NO to form peroxynitrite, which inhibits the biological activity of NO, reduces the vasodilatory function of endothelial cells, enhances vascular contractility, and contributes to the progression of cardiovascular and cerebrovascular diseases.¹⁶²

Excessive secretion of IL-6 not only increases oxidative stress levels in endothelial cells but also promotes the expression of endothelial cell adhesion molecules (such as ICAM-1 and VCAM-1), leading to increased leukocyte aggregation and further exacerbating endothelial damage.¹⁶³ IL-1, on the other hand, enhances the inflammatory response in endothelial cells by activating the NF- κ B pathway, increases vascular permeability, causing leukocytes and other

inflammatory cells to penetrate the vascular wall, and promotes the development of atherosclerosis.¹⁵² As a chemokine, IL-8 directs neutrophils to migrate to sites of endothelial damage, further increasing endothelial cell damage and exacerbating the inflammatory response in blood vessels, thereby worsening endothelial dysfunction.¹⁶⁴

Oxidative Stress

Oxidative stress is one mechanism through which adipokines may contribute to the pathogenesis of cardiovascular and cerebrovascular diseases. Resistin induces the production of ROS by binding to receptors on endothelial cells, thereby causing oxidative damage to the endothelial cells.¹⁵⁶ This process typically relies on the activation of the NOX system, which is an important source of oxidative stress responses by promoting the accumulation of ROS within cells.¹⁶⁵ Studies have shown that when NOX2 is activated in endothelial cells, it not only promotes the production of ROS but also influences vasodilation by regulating the activity of eNOS.¹⁶⁶ Resistin interacts with multiple signaling pathways, particularly the NF- κ B pathway, to activate the secretion of downstream pro-inflammatory cytokines (such as TNF- α and IL-6), thereby further exacerbating oxidative damage.⁸ Specifically, Resistin-induced oxidative stress activates the JNK (c-Jun N-terminal kinase) and p38 MAPK (mitogen-activated protein kinase) pathways; the activation of these pathways not only increases endothelial cell permeability but also promotes endothelial cell apoptosis, thereby exacerbating vascular damage.¹⁵⁶ Leptin regulates the accumulation of ROS through its receptor OB-R, activates NOX-dependent signaling pathways, and promotes the expression of inflammatory factors such as cPLA2 α and COX-2.¹⁶⁷ These reactions may exacerbate the onset and progression of cardiovascular and cerebrovascular diseases. TNF- α induces the production of ROS by activating mitochondria, NOX, and other enzymatic systems, and plays a regulatory role in signaling pathways such as NF- κ B, MAPK, and JNK, thereby triggering apoptosis or necrosis.¹⁶⁸ IL-6 enhances angiotensin II-induced oxidative stress by upregulating AT1 receptor expression, leading to the development of endothelial dysfunction.¹⁶⁹ IL-1 promotes oxidative stress by activating inflammatory responses and increasing the production of ROS, thereby accelerating the progression of atherosclerosis.¹⁷⁰ IL-4 enhances the expression of IL-6 in vascular endothelial cells via a NOX-mediated ROS production pathway, thereby further promoting vascular inflammation and the progression of atherosclerosis.¹⁷¹ The pathogenic mechanisms involving adipocytokines in cardiovascular and cerebrovascular diseases are summarized in Table 1.

Table 1 Major Adipocytokine-Related Mechanisms Implicated in Cardiovascular and Cerebrovascular Diseases

Pathogenic Mechanism	Adipocytokines	Representative Signaling Pathways or Molecular Changes	Principal Effects
Inflammatory response	Resistin Leptin TNF- α IL-6 and IL-1 β	Macrophage/monocyte activation; activation of NF- κ B, JAK/STAT, and MAPK signaling. Activation of JAK2/STAT3 signaling. Activation of NF- κ B, MAPK, and AP-1 signaling. Activation of JAK/STAT signaling.	Chronic low-grade inflammation and endothelial injury.
Endothelial dysfunction	Resistin and TNF- α Leptin TNF- α IL-6	Increased ROS generation and activation of p38 MAPK/JNK and c-Jun/bZIP signaling, contributing to endothelial cell apoptosis. Reaction of ROS with NO to form ONOO ⁻ reduces NO bioavailability and promotes vasoconstriction. Dysregulation of eNOS/L-arginine signaling, resulting in reduced eNOS activity and NO bioavailability; increased ET-1 production promotes vasoconstriction. Activation of Fas/FasL signaling. Upregulation of ICAM-1 and VCAM-1.	Endothelial cell apoptosis; reduced NO bioavailability; vasoconstriction; increased ET-1 production; upregulation of endothelial adhesion molecules; and endothelial injury.

(Continued)

Table 1 (Continued).

Pathogenic Mechanism	Adipocytokines	Representative Signaling Pathways or Molecular Changes	Principal Effects
Oxidative stress	Resistin, leptin, TNF- α , IL-6, and IL-1 β	Increased ROS generation.	ROS-mediated oxidative stress and vascular damage.

Therapeutic Prospects of Adipokines

There are variations in the drug development potential and the level of evidence for adipokines, and they are currently still in the transitional phase from basic mechanisms to clinical application. The development of therapies targeting adipokines primarily follows two approaches: first, enhancing the signaling of protective adipokines; and second, inhibiting pro-inflammatory adipokines and their downstream inflammatory pathways. It is important to note that, although the adipokine network involves numerous molecules, the targets that have actually entered a more systematic drug development phase are primarily concentrated on adiponectin, FGF21, and the IL-1/IL-6-related inflammatory pathways. The remaining targets are still in the stage of mechanism validation or early exploration.

Among anti-inflammatory adipokines, the adiponectin and FGF21 pathways currently hold the greatest potential for translation. Existing research has shown that various AdipoR agonists can improve cardiovascular function, myocardial pathology, lipid levels, and inflammatory responses in models of HF, atherosclerosis, type 2 diabetes, fatty liver disease, and liver fibrosis, while also improving metabolic and liver function.^{14,114,172–175} At the same time, FGF21 analogs and their receptor complex agonists have demonstrated consistent metabolic benefits in conditions such as atherosclerosis, obesity, type 2 diabetes, severe hypertriglyceridemia, and MASH/NASH, including weight loss, improved lipid profiles, reduced hepatic steatosis, and attenuated inflammatory responses.^{15,100,176–182} Compared to strategies that activate protective adipokines, therapeutic approaches targeting pro-inflammatory adipokines focus more on blocking the inflammatory networks they mediate, particularly the IL-1 and IL-6 pathways. Current clinical studies suggest that inhibiting these inflammatory pathways can improve microcirculation, reduce acute myocardial injury, and decrease the incidence of recurrent cardiovascular events, while also offering protection against the development of HF.^{16,17,183,184} However, there is no significant effect on stroke risk. Omentin, resistin, leptin, and TNF- α are associated with MS and cardiovascular and cerebrovascular events; however, due to the lack of robust evidence from interventions with clinical outcomes as endpoints, they remain potential therapeutic targets. Factors with dual effects, such as adiponectin and visfatin, present challenges for clinical translation and have limited practicality when used directly as therapeutic targets. For recent advances in understanding the roles and associations of adipokines in cardiovascular and cerebrovascular diseases, refer to [Table 2](#). For the role of adipokines in metabolic diseases and recent research advances, refer to [Table 3](#).

In addition to the adipokines discussed above, other adipokines, including fatty acid-binding protein 4 (FABP4), plasminogen activator inhibitor-1 (PAI-1), and asprosin, have also shown potential for translational application. FABP4 is expressed predominantly in adipocytes and macrophages and contributes to the integration of lipid metabolism and inflammatory responses.¹⁸⁶ In mouse models, its selective small-molecule inhibitor, BMS309403, has been reported to improve insulin sensitivity, attenuate adipose tissue inflammation, and substantially inhibit the development of atherosclerotic lesions.¹⁸⁶ In Western diet-fed LDL receptor-deficient mice, PAI-1 inhibition reduced obesity, adipose tissue inflammation, and hyperglycemia, while also decreasing cellular senescence and macrophage accumulation within atherosclerotic plaques.¹⁸⁷ Asprosin is a glucogenic protein hormone released primarily from white adipose tissue during fasting and promotes hepatic glucose output through activation of the G protein-cAMP-PKA pathway in hepatocytes.¹⁸⁸ Preclinical studies have shown that asprosin-neutralizing antibodies can reduce food intake, body weight, fat mass, and blood glucose levels in several mouse models of MS, suggesting that targeting asprosin may represent a potential therapeutic strategy for simultaneously modulating energy intake and impaired glucose metabolism.¹⁸⁹ Nevertheless, these targets remain largely at the preclinical stage, and their efficacy and safety in humans with MS and related cardiovascular and cerebrovascular diseases require further investigation.

Table 2 The Role and Correlation of Adipokines in Cardiovascular and Cerebrovascular Diseases: Research Progress

Adipokines	Drug Name	Drug Class	Disease	Experiment Model	Duration of Intervention	Effects of Cardiovascular and Cerebrovascular Diseases	Reference
Adiponectin	AdipoRon	Adiponectin receptor agonist	HFpEF	Mice	4 weeks	↑Diastolic function ↑Exercise capacity and glucose tolerance ↓Cardiac hypertrophy ↓BNP levels ↓Pulmonary congestion/pulmonary edema ↓Myocardial lipid deposition ↓Myocardial fibrosis	[172]
Adiponectin	ADP355	Adiponectin receptor agonist	Atherosclerosis	ApoE ^{-/-} mice	12 weeks	↓HDL cholesterol levels ↓The area of the lesional region in the diseased aortic segment and in the aortic root sinuses ↓CD68 expression ↓LDL cholesterol levels	[14]
Adiponectin	ALY688	Adiponectin receptor agonist	HFrEF	C57BL/6 mice	5 weeks	↓Hypertrophic remodeling ↓Fibrosis ↓Inflammation markers	[114]
FGF2I	LY2405319	FGF2I analogue	Atherosclerosis	C57BL/6J ApoE ^{-/-} mice	5 weeks	↑Adiponectin levels ↑HDL-cholesterol levels ↓Triglycerides and LDL/VLDL cholesterol ↓Atherosclerotic plaque area ↓Fasting insulin levels and HOMA-IR ↓Inflammatory biomarkers (hs-CRP, fibrinogen, SAA, and lipoprotein(a))	[15]
IL-6	Zlivelkimab	IL-6 inhibition	Stage 3–5 chronic kidney disease with elevated hs-CRP and high atherosclerotic cardiovascular risk	Human clinical trials	12 weeks	↓Inflammatory biomarkers (hs-CRP, fibrinogen, SAA, and lipoprotein(a))	[16]
IL-6	Tocilizumab	Interleukin-6 receptor inhibitor	Acute STEMI	Human clinical trials	Single-dose administration	↑Myocardial salvage ↓Microvascular obstruction ↓CRP ↓Final infarct size trend Improved acute STEMI-related injury	[183]
IL-1	Canakinumab	IL-1 inhibitor	Atherosclerosis	Human clinical trials	Subcutaneous injection every 3 months; median follow-up 3.7 years	↓Recurrent cardiovascular events ↓Myocardial infarction risk ↓Coronary revascularization Stroke risk showed no significant change	[17]
IL-1	Anakinra	IL-1 receptor antagonist	STEMI	Human clinical trials	2 weeks	↓hsCRP ↓Incidence of heart failure hospitalization and new onset/worsening heart failure	[184]

Notes: “↑” indicates increased levels and “↓” indicates decreased levels.

Table 3 The Role of Adipokines in Metabolic Diseases and Related Research Progress

Adipokines	Drug Name	Drug Class	Disease	Experiment Model	Duration of Intervention	Effects of Diseases	Reference
Adiponectin	PEG-BHD1028	Adiponectin receptor agonist	T2DM	C57BLKS/J db/dB mice	① Daily administration for 21 days (1–200 µg/Kg SC); ② Single injection (50–200 µg/Kg SC) for OGTT	↑Lipid metabolism and mitochondrial biogenesis ↓Insulin resistance	[173]
Adiponectin	JT003	Adiponectin receptor agonist	NAFLD/NASH	C57BL/6J mice	4 weeks	↓Mice weight, liver sizes and ALT ↓Fasting blood glucose, fasting serum insulin levels and insulin resistance ↓Lipid accumulation, steatosis ↓Inflammation area	[174]
Adiponectin	JT003	Adiponectin receptor agonist	Liver fibrosis	C57BL/6J mice	3 weeks	↓Inflammation, necrosis and fibrosis area ↓The activation of HSC ↓ER stress and mitochondrial dysfunction	[174]
Adiponectin	AdipoRaMab	Adiponectin receptor agonist	NASH	C57BL/6J Ham Slc-ob/ob mice	4 weeks	↓Insulin resistance ↓Inflammation	[175]
FGF2I	PF-05231023	FGF2I analogue	Obesity	Cynomolgus monkeys	4 weeks	↑Adiponectin levels ↑HDL cholesterol levels ↓Body weight and food intake ↓TG, TC, and LDL	[176]
FGF2I	PF-05231023	FGF2I analogue	T2DM	Human clinical trials	4 weeks	↑HDL cholesterol levels ↓Triglycerides and VLDL cholesterol ↓Weight	[176]
FGF2I	pegbelfermin (BMS-986036)	FGF2I analogue	NASH	Human clinical trials	16 weeks	↑Adiponectin levels ↑HDL-cholesterol levels ↓LDL cholesterol levels and Fasting triglyceride levels ↓ALT and AST ↓Liver stiffness ↓PRO-C3 levels	[177]
FGF2I	pegozafermin	FGF2I analogue	Severe hypertriglyceridemia	Human clinical trials	8 weeks	↑HDL-C levels (significant in the 27 mg QW group) ↓Non-HDL-C, ApoB and ApoC3 levels ↓Liver steatosis ↓ALT and AST (significant in the 27 mg QW group) ↓hs-CRP	[100]

FGF2I	pegozafermin	FGF2I analogue	NASH	Human clinical trials	24 weeks	↑Adiponectin levels ↑HDL-cholesterol levels ↓Triglycerides ↓Liver fat content, liver enzymes, iron-corrected TI, liver stiffness, Pro-C3, liver volume, and spleen volume	[178]
FGF2I	Efruxifermin	FGF2I analogue	MASH	Human clinical trials	96 weeks	↑MASH remission ↓Liver fibrosis	[179]
FGF2I	Efimosfermin alfa (BOS-580)	FGF2I analogue	MASH	Human clinical trials	24 weeks	↑NAS ↑HDL-cholesterol levels ↓HFF ↓Pro-C3 ↓ALT and AST ↓TG ↓HbA1c (In diabetic participants) ↑HMW adiponectin levels↑Spry4/Dusp4 expression ↓Weight,fat mass and food intake	[180]
FGF2I	BFKB8488A	Bispecific anti-FGFR1/KLB agonist antibody	Obesity	Cynomolgus monkeys	Single-dose administration	↑Adiponectin levels ↑HDL-cholesterol levels ↓weight (transient) ↓TG and LDL-C ↓Fasting insulin ↓Sweet preference and carbohydrate intake Improved obesity-related metabolic dysfunction	[181]
FGF2I	BFKB8488A	Bispecific FGFR1c/β-Klotho agonist antibody	Overweight/obesity	Human clinical trials	Single-dose administration	↑Adiponectin levels ↑HDL-cholesterol levels ↓weight (transient) ↓TG and LDL-C ↓Fasting insulin ↓Sweet preference and carbohydrate intake Improved obesity-related metabolic dysfunction	[181]
FGF2I	MK-3655	β-Klotho/FGFR1c receptor-complex agonist monoclonal antibody	Pre-cirrhotic MASH	Human clinical trials	52 weeks	↑MASH resolution ↓liver fat content ↓Fibrosis improvement	[182]
Chemerin	α-NETA	CMKLR1 small molecule antagonist	Diabetic nephropathy	C57BL/6J mice	4 weeks	↑Creatinine clearance ↓Fasting blood glucose, serum creatinine, urinary total protein and urinary albumin ↓Glomerulosclerosis and renal inflammation	[185]

Notes: “↑” indicates increased levels and “↓” indicates decreased levels.

Overall, adipokines show some therapeutic potential, but the evidence is primarily focused on atherosclerosis, STEMI, HF, and metabolic diseases; research on cerebrovascular conditions remains limited. Future research should involve large-scale, long-term follow-up studies with a clear focus on clinical outcomes to evaluate benefits, safety, and the appropriate patient population, thereby facilitating the transition from mechanistic targets to verifiable treatment strategies.

Conclusion and Prospects

Adipokines may serve as important regulatory mediators linking MS with cardiovascular and cerebrovascular diseases. Their dysregulation may contribute to disease onset and progression through multiple pathways, including metabolic disturbances, chronic inflammation, endothelial dysfunction, and oxidative stress. Different adipokines may exert protective, pro-inflammatory, or context-dependent effects, highlighting the complexity and heterogeneity of their regulatory networks. Current evidence has provided an important basis for understanding the roles of adipokines in MS and related cardiovascular and cerebrovascular diseases; however, much of the available evidence is still derived from basic research, animal studies, and observational investigations. The bidirectional effects and causal relationships of certain adipokines remain incompletely understood, while evidence regarding long-term clinical outcomes and the safety of adipokine-targeted interventions is still limited.

Future research should focus on several key areas: (1) conducting large-scale, multicenter prospective studies with long-term follow-up and randomized controlled trials to clarify the causal relationships between adipokines and cardiovascular and cerebrovascular outcomes and to assess their predictive value; (2) integrating multi-omics approaches and single-cell technologies to further elucidate adipokine regulatory networks and their differential effects across distinct metabolic states; (3) establishing standardized detection methods and evaluation frameworks, together with stratified analyses according to sex, age, metabolic phenotype, and disease stage; and (4) exploring precision intervention strategies targeting protective and pro-inflammatory adipokines after rigorous evaluation of their efficacy and safety. Overall, adipokines show promise as potential biomarkers and therapeutic targets for MS and its cardiovascular and cerebrovascular complications; however, their clinical application will require more rigorous mechanistic investigation and validation through high-quality clinical evidence.

Abbreviations

MS, Metabolic syndrome; IL-6, Interleukin-6; IL-8, Interleukin-8; IL-10, Interleukin-10; IL-1 β , Interleukin-1 β ; TGF- β , Transforming growth factor-beta; TNF- α , Tumor necrosis factor- α ; ROS, Reactive oxygen species; TG, Triglycerides; TC, Total cholesterol; LDL, Low-density lipoprotein; VLDL, Very low-density lipoprotein; HDL, High-density lipoprotein; RAAS, Renin-angiotensin-aldosterone system; NAMPT, Nicotinamide phosphoribosyltransferase; NMN, Nicotinamide mononucleotide; NF- κ B, Nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK, Mitogen-activated protein kinase; oxLDL, Oxidized low-density lipoprotein; NO, Nitric oxide; AMI, Acute myocardial infarction; HF, Heart failure; HFpEF, Heart failure with preserved ejection fraction; HFrEF, Heart failure with reduced ejection fraction; VCI, Vascular cognitive impairment; MCI, Mild cognitive impairment; CRP, C-reactive protein; ONOO⁻, Peroxynitrite; eNOS, Endothelial nitric oxide synthase; NOX, NADPH oxidase; FGFR1, Fibroblast growth factor receptor 1; FGF21, Fibroblast growth factor 21; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; PRO-C3, Procollagen III N-terminal peptide; HMW, High-molecular-weight; MASH, Metabolic dysfunction-associated steatohepatitis; NASH, Non-alcoholic steatohepatitis; BNP, B-type natriuretic peptide; HOMA-IR, Homeostasis model assessment of insulin resistance.

Data Sharing Statement

No datasets were generated or analysed during the current study.

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Author Contributions

Yue Wu: Conceptualization, Methodology, Writing - original draft. Jialin Zhong: Conceptualization, Methodology, Writing - original draft. Xiaodan Yan: Validation, Writing – review and editing. Lin Jin: Visualization, Writing - review and editing. Yunjiao Yang: Visualization, Writing - review and editing. Qiu Chen: Conceptualization, Methodology, Project administration, Supervision, Writing-review and editing. All authors 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 report no conflicts of interest in this work.

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