

Adiponectin as a potential biomarker of vascular disease

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Abstract: The increasing prevalence of diabetes and its complications heralds an alarming situation worldwide. Obesity-associated changes in circulating adiponectin concentrations have the capacity to predict insulin sensitivity and are a link between obesity and a number of vascular diseases. One obvious consequence of obesity is a decrease in circulating levels of adiponectin, which are associated with cardiovascular disorders and associated vascular comorbidities. Human and animal studies have demonstrated decreased adiponectin to be an independent risk factor for cardiovascular disease. However, in animal studies, increased circulating adiponectin alleviates obesity-induced endothelial dysfunction and hypertension, and also prevents atherosclerosis, myocardial infarction, and diabetic cardiac tissue disorders. Further, metabolism of a number of foods and medications are affected by induction of adiponectin. Adiponectin has beneficial effects on cardiovascular cells via its antidiabetic, anti-inflammatory, antioxidant, antiapoptotic, antiatherogenic, vasodilatory, and antithrombotic activity, and consequently has a favorable effect on cardiac and vascular health. Understanding the molecular mechanisms underlying the regulation of adiponectin secretion and signaling is critical for designing new therapeutic strategies. This review summarizes the recent evidence for the physiological role and clinical significance of adiponectin in vascular health, identification of the receptor and post-receptor signaling events related to the protective effects of the adiponectin system on vascular compartments, and its potential use as a target for therapeutic intervention in vascular disease.

Keywords: obesity, adiponectin, vascular disease

Introduction

The association between obesity and increased mortality rates is due to the increasing prevalence of a number of cardiovascular disorders, such as ischemic heart disease and stroke. Adipose tissue is a dynamic endocrine organ that secretes a variety of hormones known as adipokines. Adipokines secrete into the circulation and participate in regulation of a number of chronic diseases affecting insulin sensitivity, glucose, and lipid metabolism, as well as cardiovascular homeostasis.¹⁻⁴ In obesity, complicated metabolic status is created as a result of some inflammatory cells infiltration to adipose tissue especially activated macrophages. Under these conditions, adipose tissues produce proinflammatory adipokines such as tumor necrosis factor-alpha (TNF- α), leptin, interleukin (IL)-6, monocyte chemoattractant protein-1, lipocalin-2, resistin, adipocyte fatty acid binding protein, and plasminogen activator inhibitor-1, that encourage vascular disease.⁵ In these circumstances, production of adiponectin is markedly reduced. All of these changes have been shown to be key contributors to obesity-related vascular disease. Adiponectin is a protein hormone produced by adipose tissues, including white adipose tissue, and has

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vasoprotective properties.^{6,7} It is released into the blood stream at a concentration of around 0.01% of all plasma protein, ie, approximately 0.5–30 µg/mL, and the plasma concentration of adiponectin is 1,000-fold higher than that of most other hormones, including insulin.⁸ In vivo and in vitro studies in 1995–1996 identified adiponectin as a novel signaling protein in adipose tissue that was probably involved in the regulation of insulin.^{9–12} In recent studies, hypoadiponectinemia has also been shown to be associated with hypertension, dyslipidemia, and inflammation in both the general population and in diabetic patients.^{2,13,14} Adiponectin plays a role in the protection and inhibition of various metabolic disorders, including type 2 diabetes,¹⁵ obesity, and atherosclerosis, and in particular has a vasoprotective effect.¹⁶ Here, we summarize and review the studies reported from 1991 to 2014 on the role of adiponectin in vascular disease. We focus on recent evidence for the physiological role and clinical significance of adiponectin in vascular health, identification of the receptor and post-receptor signaling events related to the protective effects of the adiponectin system on vascular compartments, and its potential use as a target for therapeutic intervention in vascular disease.

Biology and structure

Adiponectin is a hormone with a protein structure and is synthesized exclusively by adipocytes.¹¹ It is also known as Acrp30, GBP28, adipoQ, or apM1, and has been mapped to chromosome 3q27, which has also been linked to type 2 diabetes. Secreted by glands in white fat, adiponectin contains 244 amino acids and four distinct domains, a short signal sequence that

targets hormone secretion from outside the cell, a short region that differs between species, and a globular domain with 65 amino acids that is similar to collagenous protein. A collagen domain is located at the N-terminus and a globular domain at the C-terminus.¹⁷ Adiponectin circulates in plasma in three forms: as a low molecular weight trimer, as a trimer-dimer or middle molecular weight hexamer, and as a high molecular weight (HMW) 12–18 mer form.^{18,19} Its domain structure is similar to that of complement protein C1q.¹¹

In humans, adiponectin circulates mainly as a low molecular weight (180 kDa) hexamer and an HMW multimer (about 360 kDa). In human plasma, the globular form of adiponectin, a full-length protein or a proteolytic cleavage product of adiponectin, which leaves only the globular head domain intact, circulates at very low levels (Figure 1).²⁰ The crystal structure of the globular domain of adiponectin bears a marked similarity to the structure of TNF-α.¹⁷ The octameric structure of HMW adiponectin has been detected by sedimentation, equilibrium centrifugation, and gel electrophoresis.²¹

Studies in mice report that the half-life of circulating adiponectin is 75 minutes and that its clearance is mediated by the liver. Despite its rapid turnover, plasma clearance is slower for HMW adiponectin and its levels remain fairly constant in the circulation.²²

The treatment with thiazolidinedione, sensitized vital hepatic function of insulin with enhancing serum levels of HMW adiponectin.^{23,24} HMW adiponectin is the most active oligomeric form of adiponectin and is clearly associated with a number of metabolic disorders. It is thought that adiponectin has enhanced biological activity, including insulin action

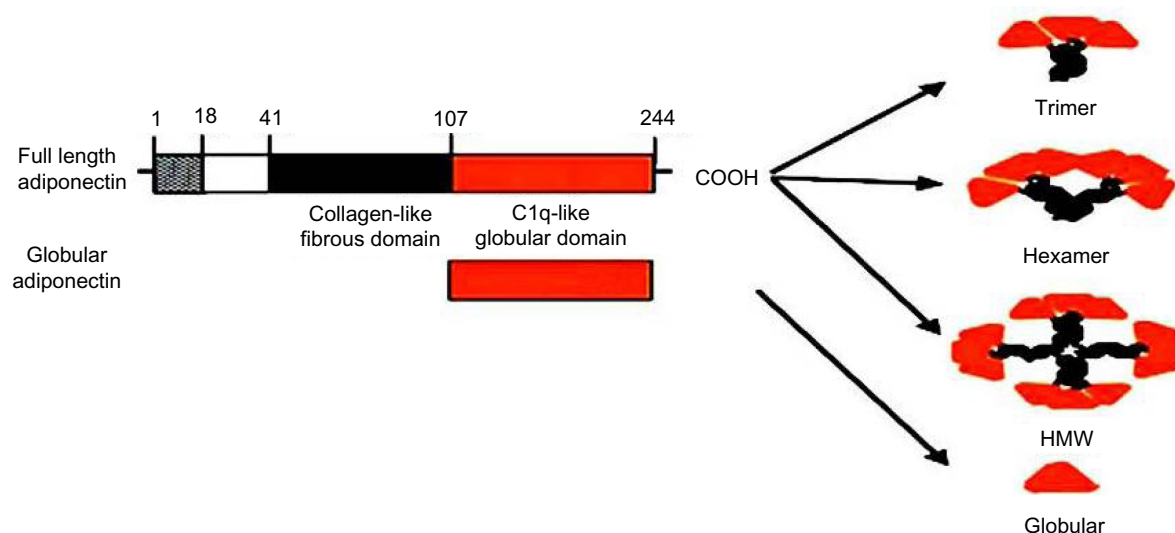


Figure 1 Domains and structure of adiponectin.
Abbreviation: HMW, high molecular weight.

and apoptosis suppression in cultured endothelial cells and activation of muscle AMP-activated protein kinase (AMP kinase).^{24,25} HMW adiponectin can serve as a precursor pool of the hormone that is activated with low molecular weight adiponectin and is responsible for the impact of adiponectin on the activity of AMP kinase. In contrast with this, reduced serum concentrations of total adiponectin (not only HMW) have been reported in obesity,²⁶ type 2 diabetes,²⁷ and cardiovascular disease (CVD),²⁸ and there is some evidence indicating a correlation between circulating levels of total/HMW adiponectin and coronary heart disease, ischemic stroke, and peripheral arterial disease.^{29–31} There is also evidence of a proinflammatory effect of reduced concentrations of total adiponectin in human rheumatoid arthritis synovial fibroblasts, lymphocytes, and endothelial cells, which may predispose to CVD.³² Dessein et al demonstrated that total circulating adiponectin had a paradoxical effect on the risk of CVD in patients with rheumatoid arthritis.³³ Thus, there are some controversies on different biological activities among various adiponectin isoforms that are partly due to difficulty in circulating isoforms determinations.^{34–36}

Adiponectin receptors

The vascular actions of adiponectin are mediated by three receptors, ie, AdipoR1, AdipoR2, and T-cadherin. AdipoR1 and AdipoR2 are located integrally in the cell membrane with seven transmembrane domains, and the N terminus is located within the cell with inverted membrane topology. In AdipoR1, the short C terminus (with about 25 amino acids) is located externally in the cell membrane like G-protein coupled receptors, but is structurally and functionally distinct from classical G-protein coupled receptors. AdipoR1 is expressed in most cells, but its major expression is in skeletal muscle where it is associated with activation of AMP kinase pathways. AdipoR2 is abundantly expressed in the liver, where it is linked to activation of peroxisome proliferator-activated receptor (PPAR)- α pathways.^{37,38} Activated AdipoR1 and AdipoR2 increase mitochondrial biogenesis, improve oxidation of fatty acids in the liver and skeletal muscle, enhance glucose uptake in cells, reduce hepatic gluconeogenesis, increase lactate production in skeletal muscle, and inhibit inflammation and oxidative stress, which are important metabolic risk factors for cardiovascular disease.^{39,40}

APPL1, an adaptor protein consisting of a PH pleckstrin homology domain, a phosphotyrosine binding domain, and a leucine zipper motif, interacts directly with AdipoR1 and AdipoR2.^{41,42} One of the important functions of APPL1 appears to be coupling of adiponectin receptors with their

downstream signaling cascades, although the precise molecular mechanisms involved are not yet known. The intracellular portion of the adiponectin receptor interacts with the phosphotyrosine binding domain of APPL1, which results in mediation of downstream adiponectin signaling cascades and metabolic effects by APPL1. APPL1 has a key role in mediation of the adiponectin-dependent, insulin-signaling pathway in skeletal muscle and contributes to the anti-inflammatory and protective effect of adiponectin in endothelial cells. APPL1 acts as a signaling pathway mediator in cross-talk with adiponectin and insulin, interacts directly with membrane receptors and signaling proteins, and plays critical roles in cell proliferation, apoptosis, and survival, endosomal trafficking, and chromatin remodeling. Impaired adiponectin-stimulated AMP kinase and PPAR- α signaling are, respectively, the result of targeted disordered AdipoR1 and AdipoR2. In contrast, destruction of AdipoR1 and AdipoR2 causes insulin resistance and glucose intolerance because of impaired adiponectin connection to these receptors and its performance.³⁸

AdipoR1 and AdipoR2 have been suggested to have opposing effects on the pathways for glucose and lipid metabolism. In a study by Bjursell et al, AdipoR1-null mice showed a diet-induced increase of fat and glucose intolerance.⁴³ This result is the opposite with lean AdipoR2-null mice.⁴³ In this study, deletion of AdipoR2 reduced the dyslipidemia and insulin resistance induced by a high-fat diet but promoted type 2 diabetes.⁴⁴ The precise physiological roles of these two receptors need further clarification in future studies.

The T-cadherin-glycosyl phosphatidyl-inol-linked cell surface molecule was initially identified 2 decades ago as an axon guidance molecule and a modulator of neural crest cell migration.⁴⁵ It is now appreciated that T-cadherin has functions that extend beyond the typical behavior of cadherin during cell-to-cell adhesion. T-cadherin is a hexameric HMW adiponectin receptor and is expressed on a number of cell types, including vascular endothelial cells, smooth muscle cells (SMCs), and pericytes.⁴⁶ Its expression mainly increases in atherosclerotic region. The activated form of T-cadherin protects vascular endothelial cells against apoptosis resulting from oxidative stress.^{47,48} Expression of T-cadherin is critical for the revascularization activity of adiponectin *in vitro* and *in vivo*;⁴⁹ however, the functional relevance of binding between adiponectin and T-cadherin is not understood (Figure 2).

Anatomic location of adipose tissue

Sectional adipose tissues due to its several metabolic factors have some considerable cardiometabolic effects, so, fat depots are separated based on their location and

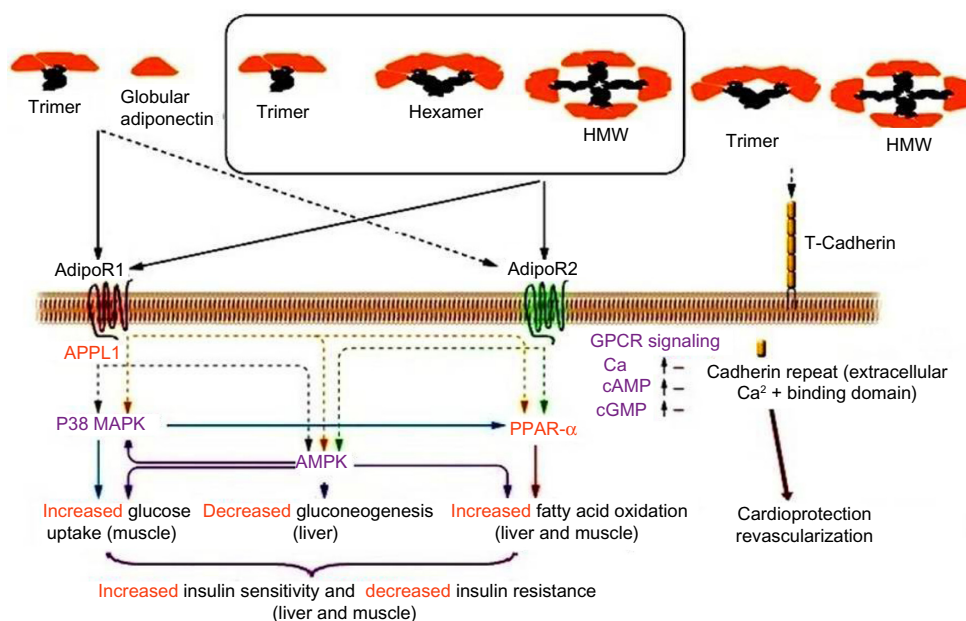


Figure 2 Adiponectin-mediated intracellular cardioprotective signaling pathways via adiponectin receptors.

Abbreviation: HMW, high molecular weight.

their association with local or systemic effects. The two major types of white adipose tissue are visceral fat (located in the mediastinum and abdominal cavity) and subcutaneous fat (located in the hypodermis). In visceral obesity, infiltration of macrophages and other types of

inflammatory cells causes inflammation and production of more inflammatory cytokines that increase the risk of obesity-related metabolic disorders, such as insulin resistance, plasma lipid disorders, and CVD (Figure 3). In contrast, subcutaneous fat is a major source of adiponectin

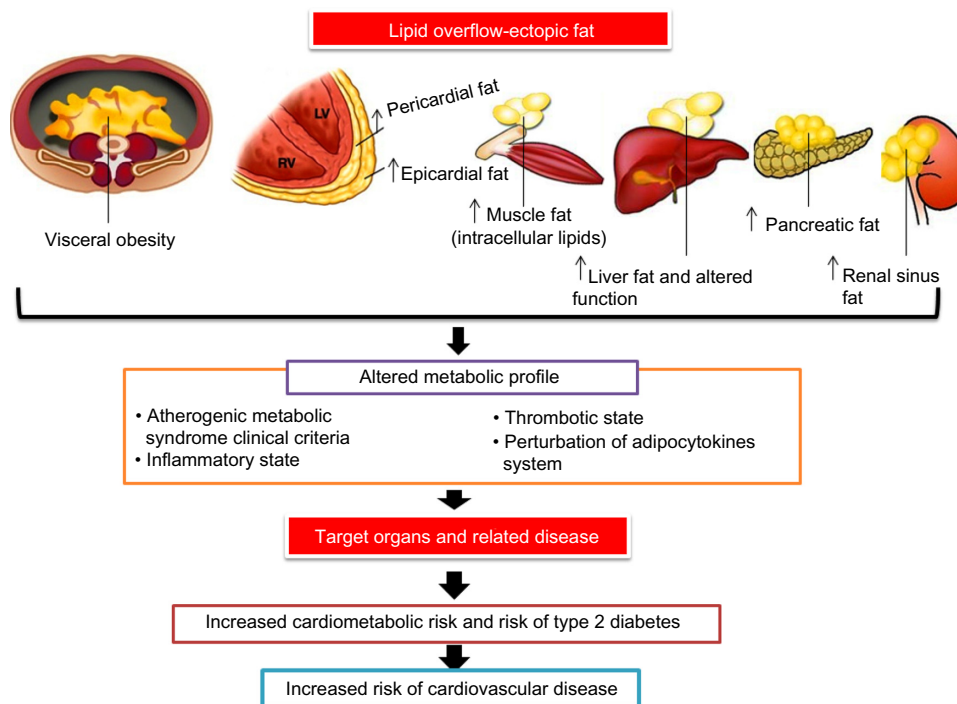


Figure 3 Working model showing how excess ectopic adiposity is associated with increased cardiovascular risk.

Abbreviations: LV, left ventricle; RV, right ventricle.

and leptin. The increase in subcutaneous fat is related to plasma lipid profiles.⁵⁰

Because of the existence of adipose tissue between skeletal muscle cells, including intramyocellular and intermuscular fat, the percentage of skeletal muscle fat can be a risk factor for the development of insulin resistance and increased risk of CVD.⁵¹ Also, two anatomically distinct fat depots (epicardial and pericardial) cover the heart. Epicardial fat is located between the myocardium as intermuscular fat, and the visceral pericardium and pericardial adipose tissue located in the external layer of the pericardium (Figure 3). Epicardial adipose tissue provides the fuel used for skeletal and cardiac muscle work and contraction.⁵¹ In humans, epicardial adipose tissue makes up about 20% of total ventricular weight. It is located in the atrioventricular and interventricular grooves of both ventricles, and extends to the ventricular apex and the coronary arteries.⁵² Approximately 80% of the heart is covered by pericardial adipose tissue. This type of fat constitutes about 20%–50% of the weight of the human heart.⁵⁰

In general, deposition of triglyceride droplets in non-adipose tissue is known as ectopic fat storage. Ectopic fat consists of peripheral tissues fat storage, ie, epicardial and pericardial fats, and is linked to tissue-specific insulin resistance, both in overweight individuals and those with normal weight.^{53,54} Adipocytes in epicardial fat are smaller than those in peritoneal and subcutaneous fat. In normal situations, epicardial and pericardial adipose fats are a vital local energy source for maintaining cardiac contractility by lipolysis of fats and release of fatty acids (Figure 3). Adipocyte size, in both epicardial and subcutaneous fat, is positively associated with insulin resistance and obesity-related cardiac dysfunction, and has a negative association with local adiponectin gene expression. Gene expression for adiponectin is decreased in subjects with coronary artery disease.^{55,56} The morphology and function of adipose tissue is influenced by sex and anatomic location. Adipocytes in both subcutaneous and visceral depots are larger in size in obese males than in females. These fat storages are significantly correlated with proinflammatory cytokine expression.⁵⁷

Ability of adiponectin to protect against vascular disease

Over the past several years, clinical findings generally support an etiological role of adiponectin deficiency in the development of various vascular complications in humans.^{58,59} Hypoadiponectinemia was found to be a significant predictor of endothelial dysfunction in both the peripheral and coronary arteries independent of insulin resistance index,

body mass index, and dyslipidemia.^{60–62} Consistent with the clinical observations described above, it has been shown that adiponectin-deficient animal models are more susceptible to developing vascular disorders, neointimal hyperplasia after acute vascular injury,^{63,64} impaired endothelium-dependent vasodilation,⁶⁵ and high blood pressure.⁶⁶ Both adenovirus-mediated overexpression of full-length adiponectin⁶⁷ and transgenic overexpression of globular adiponectin⁶⁴ resulted in marked alleviation of atherosclerotic lesions in apolipoprotein (apo)E-deficient mice, which showed a major improvement in endothelial dysfunction and hypertension.^{65,66} Treatment with adiponectin resulted in a significant reduction of atherosclerotic plaque area on the abdominal aorta in a rabbit model. Adiponectin-mediated attenuation of atherosclerosis in this model was associated with decreased expression of adhesion molecules, including vascular cell adhesion molecule-1 and intercellular adhesion molecule-1.⁶⁶ Therefore, adiponectin, in addition to having beneficial effects on insulin sensitivity and lipid metabolism, exerts multiple vasoprotective effects via its action on the vascular system, including endothelial cells, monocytes, macrophages, leukocytes, platelets, and SMCs, plaque formation, and development of thrombosis.

Anti-inflammatory properties of adiponectin

The anti-inflammatory properties of adiponectin are likely to be the major component of its beneficial effects in vascular disease. Many benefits of adipokine products in the cardiovascular system are attributable to adiponectin. Inflammatory conditions like obesity, insulin resistance, and ultimately diabetes mellitus are intertwined and closely associated with the development of vascular disease.^{68–70} This observation may explain the close link between obesity and atherosclerosis; however, the exact mechanism involved in the relationship between low-grade inflammation and fat remains unclear. C-reactive protein (CRP) is an inflammatory cytokine product and an independent risk predictor of vascular disorders like coronary heart disease.^{71,72} High CRP levels have been suggested to be a useful biomarker for chronic obesity-related inflammation.⁷³ The biosynthesis of CRP takes place in the liver, but also occurs under inflammatory stress in other types of cells, including macrophages, SMCs, and endothelial cells in atherosclerotic lesions.^{74,75} Some inflammatory cytokines, eg, TNF- α and NF κ B, are induced by the direct proinflammatory action of CRP.⁷⁴ Adiponectin activates AMP kinase and NF κ B activity in human aortic endothelial cells under hyperglycemic conditions. This adipokine decreases CRP

messenger RNA and CRP protein,⁷⁶ and inhibits stimulation of NF κ B signaling and TNF- α secretion from macrophages.⁶⁸ Adiponectin suppresses TNF- α -induced monocyte adhesion to human aortic endothelial cells and the expression of certain other adhesion molecules.⁷⁷ Consistent with these studies, adiponectin reduces expression of cell adhesion molecules and activation of IL-8 and NF κ B by decreasing TNF- α in endothelial cells.^{76,78}

Some of the insulin-sensitizing and cardioprotective actions of adiponectin have been shown to be mediated by AMP kinase signaling in various cells, including hepatocytes, myocytes, and endothelial cells.^{40,79,80} Consistent with these findings, activation of AMP kinase by 5-aminoimidazole-4-carboxamide-1-beta-D-ribofuranoside inhibits fatty acid-induced NF κ B activation in endothelial cells.⁸¹ Adiponectin modulates macrophage function and phenotype.⁸² Adiponectin inhibits the expression and activity of the class A macrophage scavenger receptor and suppresses transformation of macrophages to foam cells.⁸³

It is revealed the decrease in expression of anti-inflammatory M2-type markers and reactive oxygen species (ROS) generation and increase in the expression of pro-inflammatory M1-type markers of peritoneal macrophages and stromal vascular fraction cells in adiponectin-deficient mice. It may be because of the stimulation of the arginase-1 expression in these special cells and stimulation of them with recombinant adiponectin.⁸⁴

The promotion of phagocytosis by macrophages has been performed by including options to form a bridge between dead cells and macrophages by adiponectin like other members of the collectin family of proteins.⁸⁵ This activity is mediated by binding of adiponectin to calreticulin and CD91 on the surface of the macrophage and recognition motifs referred to as apoptotic cell-associated molecular patterns on the dead cell surface. Therefore, abnormally low levels of adiponectin could considerably impair the clearance of cell apoptosis. Especially, none of the adiponectin receptors (AdipoR1, AdipoR2, and T-cadherin), are demanded for the phagocytotic activities of adiponectin.⁸⁵ The lower adiponectin receptors have been manifested in monocytes of overweight/obese subjects with type 2 diabetes⁸⁶ and CVD patients.⁸⁷

Stimulation of IL-10 and IL-1 receptor antagonists is one of the anti-inflammatory actions of adiponectin in human monocytes, monocyte-derived macrophages, and dendritic cells.⁸⁸ Decreased surface expression of adiponectin receptors in peripheral monocytes, together with reduced adiponectin-induced IL-10 secretion from macrophages, has been reported in patients with coronary artery disease.⁸⁷ Via

induction of IL-10, adiponectin selectively increases tissue inhibitor of metalloproteinases-1 (TIMP-1) expression in human monocyte-derived macrophages,⁸⁹ and adiponectin has a negative relationship with the matrix metalloproteinase (MMP)-9/TIMP-1 ratio in patients with acute coronary syndrome.⁹⁰ It has been confirmed that, with induction of IL-10, adiponectin selectively increases expression of TIMP-1 in human monocyte-derived macrophages.⁸⁹ TIMP-1 levels and the MMP-9/TIMP-1 ratio are independent predictors of the stability of atherosclerotic plaque and the severity of coronary atherosclerosis. Plasma adiponectin also has a negative relationship with other markers of inflammation and atherosclerosis, including adipocyte fatty-acid-binding protein⁹¹ and lipocalin-2.⁹² Adiponectin in macrophages can alter multiple pathways of lipid metabolism in macrophages, including downregulation of sterol O-acyltransferase 1, which catalyzes the formation of cholesterol esters in cultured human monocyte-derived macrophages⁹³ and reduces lipid accumulation in human THP-1 macrophage foam cells.

Finally, macrophages converted with the adiponectin gene demonstrate reduced oxidized low-density lipoprotein (LDL) uptake and elevated high-density lipoprotein-mediated cholesterol efflux.⁹⁴ A gradual decrease in Toll-like receptor (TLR)4 signaling, attenuation of inflammatory activation, and an interaction between cardiac and immune cells account for the protective function of adiponectin against inflammation and injury in autoimmune myocarditis. These findings suggest that adiponectin has a protective effect against systemic inflammation.⁹⁵

Adiponectin in regulation of endothelial function

Clinical observations indicate that there is a close relationship between hypoadiponectinemia and peripheral arterial dysfunction.^{65,66,96} The first and essential event in the development, progression, and appearance of hidden macroangiopathy involves endothelial dysfunction.⁹⁷ Circulating levels of total adiponectin are inversely related to the risk of myocardial infarction.^{96,98} A comparison of adiponectin knockout mice and their wild-type littermates showed significantly increased neointimal hyperplasia,^{63,64} disordered endothelium-dependent vasodilation, and increased blood pressure.⁶⁵ Flow-mediated dilation of the brachial artery has a significant relationship with plasma HMW adiponectin levels in young healthy men and could be used for assessment of endothelial function. In this way, assessment of HMW adiponectin could be a more useful indicator than assessment of total adiponectin for evaluation

of endothelial dysfunction before any overt vascular disease is apparent.⁶¹

The vasodilation activity of adiponectin affects endothelial function by inhibition of ROS production as well as monocyte adhesion. Activation of AMP kinase that leads to an increase in endothelial nitric oxide (NO) synthase (eNOS) activity and NO production is mediated by the action of adiponectin. Biosynthesis of NO is performed by AMP kinase and is mediated via phosphorylation of eNOS at Ser1177⁷⁶ and Ser633⁹⁹ by both the full-length and globular domains of adiponectin. The vascular system is protected by endothelial-derived NO, which enhances vasodilation and inhibits platelet aggregation, monocyte adhesion, and SMC proliferation.¹⁰⁰ Regulation of adiponectin-induced phosphorylation of AMP kinase at Thr172 and eNOS at Ser1177 has recently been demonstrated.¹⁰¹ Adiponectin also determines formation of the complex between heat shock protein 90 and eNOS that is required for enzyme activation.^{101–103} The signaling events linking AdipoRs and activation of AMP kinase/eNOS are not clear, but it is believed that the key mediator molecule may be APPL1.⁴¹

An impaired vasodilator response of the small mesenteric vessels to adiponectin has been shown in relation to APPL1 expression in both Zucker diabetic fatty rats and *db/db* obese mice.^{41,104} This finding suggests a key role of APPL1 as a signaling relay point that mediates the adiponectin-induced cellular signaling cascade leading to production of NO. However, overexpression of an active AMP kinase can increase activation of eNOS and production of NO, even in conditions of suppressed APPL1 expression,⁴¹ suggesting that AMP kinase acts downstream of APPL1 and is directly responsible for both phosphorylation of eNOS at Ser and its interaction with heat shock protein 90. There is some evidence suggesting involvement of phosphoinositide 3-kinase in adiponectin-induced production of endothelial NO, possibly via activation of AMP kinase.^{99,103,105} The key feature of oxidative stress is the increased production of vascular ROS, resulting in the quenching of NO and activation of proinflammatory signaling pathways such as protein kinase C and NFκB.¹⁰⁶ Adiponectin improves the redox state in human vessels by restoring eNOS coupling, indicating a novel role of vascular oxidative stress in the regulation of adiponectin expression in human perivascular fat.¹⁰⁷

Production of ROS is inhibited by adiponectin, and this metabolic function is possibly induced by high glucose concentration,¹⁰⁸ basal and oxidized LDL,^{109,110} and palmitate¹¹¹ in endothelial cells. This activity is produced

by suppression of nicotinamide adenine dinucleotide phosphate oxidase.

The antioxidant activity of adiponectin is mediated by the cyclic AMP/protein kinase A pathway¹⁰⁸ and AMP kinase.¹¹¹ Aortic rings in adiponectin knockout mice show higher superoxide anion and peroxynitrite concentrations, which can be reversed when these mice are treated with recombinant adiponectin.¹¹²

In Wistar rats, augmentation of adiponectin was able to improve left ventricular dysfunction induced by chronic intermittent hypoxia and associated myocardial apoptosis by inhibition of ROS-dependent endoplasmic reticulum stress.¹¹³ The first step in this inflammatory reaction during development of atherosclerosis involves activation of endothelial cells and is characterized by increased expression of adhesion molecules (including intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin) and monocyte attachment.⁷⁸

Adiponectin inhibits the interaction between leukocytes and endothelial cells by reducing the expression of E-selectin and vascular cell adhesion molecule-1 and by increasing endothelial NO.¹⁰⁸ This adiponectin-related decrease in expression of adhesion molecules has been demonstrated in an animal model of atherosclerosis.¹¹⁴ Adiponectin inhibits this step by suppressing the expression of adhesion molecules after induction by TNF-α, resistin and IL-8, which, in turn, results in attenuation of monocyte attachment to endothelial cells.⁷⁸

The inhibitory effect of adiponectin on leukocyte adhesion and expression of adhesion molecules can be reversed by inhibition of eNOS, suggesting a need for eNOS/NO signaling for the anti-inflammatory actions of adiponectin in endothelial cells. Further, adenovirus-mediated expression of adiponectin in the aortic tissue of apoE-deficient mice and atherosclerotic rabbits inhibits expression of adhesion molecules.^{67,105} This anti-inflammatory activity of adiponectin is regulated in endothelial cells by protein kinase A-dependent inhibition of NFκB via AMP kinase-dependent and AMP kinase-independent mechanisms.^{76,115} However, acute treatment of endothelial cells with globular adiponectin activates NFκB and enhances the expression of adhesion molecules and monocyte chemoattractant protein-1 via activation of the sphingosine kinase signaling pathway.¹¹⁶ These inconsistencies may be attributed to the different forms of adiponectin or different incubation times used in different studies. Indeed, there is evidence that different oligomeric forms of adiponectin may have opposite functions with regard to modulating NFκB activity in C2C12 myotubes.¹¹⁷ Adiponectin inhibits

high glucose-induced I κ B phosphorylation, NF κ B binding activity, and production of CRP in human aortic endothelial cells.¹¹⁸

Since overexpression of AdipoRs increases the inhibitory effect of adiponectin on endothelial expression of adhesion molecules, AdipoRs can be assumed to have an important role in regulating the anti-inflammatory effect of adiponectin in the endothelium.⁵ In atherosclerotic lesions, local apoptosis of endothelial cells increases their turnover rate and is involved in atherosclerosis. These lesions can be induced by high glucose, angiotensin II, palmitate, and oxidized LDL.¹¹¹ HMW adiponectin inhibits caspase 3 activity in human umbilical vein endothelial cells via activation of the AMP kinase signaling pathway.¹¹⁹ In human umbilical vein endothelial cells, the globular domain of adiponectin inhibited angiotensin II-induced apoptosis in a dose-dependent manner, possibly through activation of eNOS and the interaction between eNOS and heat shock protein 90.⁵ By synthesis of NO through the phosphoinositide 3-kinase/AKT and AMP kinase signaling pathways, globular adiponectin reduces irregular high glucose-induced apoptosis and oxidative stress in human umbilical vein endothelial cells.¹²⁰ The effects of adiponectin in terms of vascular endothelial damage and apoptosis via AMP kinase activation are dependent on binding of adiponectin to AdipoR1 on the cell surface.^{121,122} Activation of AMP kinase via the endosomal adaptor protein (consisting of phosphotyrosine binding, pleckstrin homology domains, and leucine zipper motif) regulates the protective effects of adiponectin against angiotensin II cytotoxicity on vascular cells.¹²²

Adiponectin and adaptive immunity

In obesity, low-grade inflammation normally occurs in adipose tissue as a result of chronic activation of the innate immune system. This can explain the relationship between this anthropometric status of a person and the production of atherosclerosis.⁶⁹ Adiponectin, with its anti-inflammatory property that was mentioned in “Anti-inflammatory properties of adiponectin”, inhibits T-lymphocyte recruitment and accumulation in macrophages. In human monocyte-derived macrophages stimulated with lipopolysaccharide, adiponectin suppresses the expression of a range of chemokines, including the T-lymphocyte chemoattractants interferon gamma-inducible protein (IP)-10 (CXCL10), IFN-inducible T-cell α chemoattractant (CXCL11), and Mig (CXCL9). These chemokines together with their receptor CXCR3, are expressed by various types of cells in human atheroma, including macrophages, endothelial cells, and smooth muscle

cells.¹²³ These chemokines potentially induce T-lymphocyte chemotaxis and recruit activated T lymphocytes during atherogenesis.¹²⁴

The TLR4 signaling pathway is involved in the development of atherosclerosis and insulin resistance. TLRs recognize specific microbial components and activate innate immunity pathways, so interact with proinflammatory pathways by activation of endogenous inflammatory ligands.¹²⁵ Adiponectin is selectively involved in prevention of atherosclerosis and insulin resistance by its interaction with the TLR4 pathway.^{125–127} Activation of transcription factor 2 and NF κ B, which are involved in the MyD88-dependent pathway, is reduced by adiponectin. This effect of adiponectin on NF κ B is in agreement with previously published results using lipopolysaccharide-stimulated macrophages and TNF- α -stimulated human aortic endothelial cells.^{76,78,128} Therefore, in nonobese subjects, higher levels of adiponectin may efficiently reduce the proinflammatory functions of these chemokines. Accompanying in vitro findings, in vivo evidence showed raised plasma levels of interferon gamma-inducible protein-10, increased accumulation of T lymphocytes within lesions, and accelerated the development of atherosclerosis in E-null mice with lack of adiponectin.²⁶

Adding adiponectin to polyclonal activated CD4+ T lymphocytes induced messenger RNA expression and secretion of protein for interferon-gamma and IL-6, enhanced phosphorylation of p38 mitogen-activated protein kinase, and STAT 4, a transcription factor belonging to the signal transducer and activator of transcription protein family, and increased T-bet expression without any effect on cell proliferation. Therefore, adiponectin enhances Th1 differentiation via activation of the p38-STAT4-T-bet axis. This suggests that adiponectin can have a proinflammatory role in isolated macrophages and T-cells, confirming that adiponectin induces a limited spectrum of inflammatory activation, probably to make these cells less sensitive or reactive to more proinflammatory stimuli.¹²⁹

Inhibition of smooth muscle proliferation

Rapid multiplication and migration of vascular SMCs toward the intima during development and progression of vascular lesions contribute to intimal thickening of the arteries and development of atherosclerosis. Such proliferation and migration in human aortic SMCs is inhibited by adiponectin. Adiponectin blocks this by inhibiting several atherogenic growth factors, including platelet-derived growth factor-BB, basic fibroblast growth factor, and heparin-binding epidermal

growth factor.^{130,131} Oligomerization of adiponectin, which is reliant on interaction with these growth factors, can block binding to their respective cell membrane receptors.¹³⁰ The clear findings by adiponectin-deficient mice, as compared with wild-type controls, showed an increased proliferation of vascular SMCs and neointimal thickening after mechanical injury.¹³² It was concluded that adiponectin can be detected by immunohistochemistry only in the walls of the injured vessels,¹³³ suggesting a role in protection against the development of atherogenic vascular changes.

Adenovirus-mediated expression of adiponectin in mechanical balloon-injured arteries of adiponectin-deficient mice decreased the degree of neointimal proliferation,⁶³ suggesting that therapeutically increasing plasma adiponectin might be beneficial for prevention of vascular restenosis after angioplasty.

Endothelial construction and angiogenesis

Impaired endothelial repair is a feature of vascular disease and heralds the start of atherosclerotic progression. Endothelial progenitor cells (EPCs) contribute critically to endothelial repair next to vascular injury.¹³⁴ Dysfunction and/or low numbers of EPCs are associated with impaired endothelial function.¹³⁵ Clinical and animal studies in subjects with coronary heart disease report a positive correlation between circulating levels of adiponectin and numbers of EPCs.⁷⁹ Adiponectin increases the number and function of EPCs and promotes endothelial repair and angiogenesis.^{136,137}

The angiogenic repair of ischemic hind limb, as estimated by laser Doppler flow method, and impaired capillary density analysis, was impaired in adiponectin-knockout mice. These were reversed by adenovirus-mediated addition of adiponectin.⁷⁹ Almost all steps in endothelial repair of EPCs are modulated by adiponectin; these steps consist of mobilization of EPCs progenitors from the bone marrow or spleen into the blood circulation, recruitment and adhesion of EPCs to the injured endothelium, their differentiation to EPCs, and creation of EPCs tube-like structure.^{136,137}

In diabetic mice, treatment with cobalt protoporphyrin, an inducer of heme oxygenase-1 (an antioxidant), leads to accelerated vascular repair by improving the function of EPCs as a result of upregulation of adiponectin.¹³⁸ This evidence highlights the importance of adiponectin in the prevention of atherosclerotic progression by endothelial renovation and angiogenesis.

In *db/db* diabetic mice without adiponectin, rosiglitazone (a PPAR- γ agonist from the thiazolidinedione class

of antidiabetic drugs) increased circulating EPC numbers and endothelial repair. More rapid impairment of re-endothelialization has been reported after wire-induced carotid denudation in animal models of diabetes with insufficient adiponectin.¹³⁹ Adiponectin prevents the impact of high glucose levels on stimulation of senescence in EPCs by decreasing the expression of p16 INK4A, a senescence marker that serves as a key mediator of the aging process in stem cells, in human peripheral blood, and in mouse bone marrow.¹⁴⁰ Another reported importance of adiponectin is marked reduction of intracellular ROS accumulation and activation of p38 mitogen-activated protein kinase.¹³⁹

The activity of adiponectin in vascular recruitment of EPCs requires activation of AMP kinase.^{80,133} Involvement of the endothelial phosphoinositide 3-kinase/Akt and AMP kinase pathways is thought to interfere with adiponectin-induced angiogenesis.⁸⁰ Clinical and animal studies have demonstrated the antioxidant properties of adiponectin.^{108,141–143} Circulating adiponectin in humans is in inverse association with certain markers of oxidative stress, including 8-epi-prostaglandin F2 α .¹⁴¹

Adiponectin decreases accumulation of intracellular ROS in conditions caused by high glucose, such as diabetes. In this way, adiponectin can deal with diabetes-induced damage of EPC function through activation of AMP kinase, inhibiting p38 MAP kinase, and decreasing expression of p16INK4A (a senescence marker).¹³⁷ Because of eNOS' promoting effect on EPCs recruitment, adiponectin is necessary to repair endothelial cells. Adiponectin protects against EPC dysfunction in diabetic patients by enhancing eNOS production and signaling.¹⁴⁴

Globular adiponectin significantly increased endothelial cell proliferation, in vitro migration, and angiogenesis by the AMP kinase/Akt pathways through increased expression of MMP-2, MMP-9 and vascular endothelial growth factor.¹⁴⁵ The effect of globular adiponectin on vascular endothelial growth factor appears to be mediated by AdipoR1, while the effect on MMP-2 and MMP-9 is mediated by AdipoR1 and AdipoR2. Further, globular adiponectin decreased glucose levels and CRP-induced angiogenesis in human microvascular endothelial cells, with a concomitant reduction in MMP-2, MMP-9, and vascular endothelial growth factor.¹⁴⁵

Antiatherosclerotic effects of adiponectin

Preclinical studies¹⁴⁶ and animal models have demonstrated the importance of adiponectin in inhibition of atherogenesis.^{40,67,114} High levels of plasma adiponectin

decrease atherosclerotic plaque formation in apoE-deficient mice.^{37,67} Without adiponectin, the inhibitory effects of PPAR- γ agonists on atherogenesis are lost.¹⁴⁷ In vitro studies have usually used high doses of adiponectin due to its low level of bioactivity and the impact of contaminants that could influence this activity; however, given the antiatherosclerotic actions of adiponectin on almost all types of vascular cells as discussed above, the role of adiponectin in human atherogenesis is still debated. Despite globular adiponectin appearing to be responsible for most of the biological effects of adiponectin and its frequent use in in vitro studies, there is still no evidence of the existence of this form of adiponectin in the peripheral circulation in humans. Inconsistent results have been reported from studies using adiponectin produced by *Escherichia coli*.¹⁴⁶

While genetic manipulation of adiponectin levels has yielded more reliable results, in a recent paper the Scherer's research group crossed adiponectin knockout mice (*Adn*^{-/-}) into the LDL receptor-null mice or mice with chronically hyperadiponectinemia into apoE-null mouse models. In this study, circulating adiponectin levels were not correlated with inhibition of atherogenesis. Regardless of the type of diet used in these animal models, circulating adiponectin levels had no effect on plaque size in the aortic root, cholesterol accumulation in the aorta, and plaque morphology.¹⁴⁸ These results are different from earlier reports obtained in an *ApoE*^{-/-} mouse model, which could be due to the use of different experimental paradigms, different forms of adiponectin, and different types of diet.¹⁴⁹ Lack of a phenotype in gain/loss-of-function studies in animal models suggests that adiponectin is not involved in the advanced stages of plaque progression.¹⁴⁸ These data indicate that adiponectin has complex and multifaceted actions in the cardiovascular system. Since mice are generally resistant to plaque rupture and myocardial infarction, there is still a need for more functional causation studies in humans.

Antithrombotic effect of adiponectin

Platelet activation plays a central role in the progression of atherosclerosis and plaque rupture. Inhibition of platelet aggregation has been suggested to prevent arterial thrombosis.¹⁵⁰ A clinical study has demonstrated that the plasma adiponectin level was negatively associated with platelet activation independent of other risk factors.¹⁵¹ Platelet aggregation and enhanced thrombus formation on a type I collagen-coated surface have been demonstrated in platelet cells harvested from adiponectin-deficient mice and

humans.¹⁵² Recombinant adiponectin repressed the enhanced platelet aggregation. Further, AdipoRs were found to be expressed in human platelets and in a megakaryocytic cell line.¹⁵³ While platelet counts or coagulation factors were not significantly different between wild-type and adiponectin knockout mice, adiponectin knockout mice showed accelerated thrombus formation upon carotid arterial injury with a He-Ne laser, and adenovirus-mediated expression of adiponectin reversed these changes.¹⁵² Consequently, adiponectin may serve as an endogenous antithrombotic factor.¹⁵² The inhibitory effect of adiponectin on thrombosis can be attributed to its ability to stimulate production of endothelial NO, as discussed above.

Therapeutic interventions and conclusion

As discussed here, a number of studies have reported an important role of adiponectin in the vasculature via various pathways. Therefore, therapeutic approaches that increase adiponectin levels or tissue sensitivity could lead to useful strategies for the prevention or treatment of adiponectin-related vascular disorders (Figure 4).

Although direct use of exogenous adiponectin is successful in ameliorating CVD in animals, this becomes difficult in humans because of the high circulating levels needed, its multimeric conformations, and its moderately short half-life. Also, as medications undergo extensive posttranslational modification, therefore extensive posttranslational medicine wanted them for action. Therapeutic interventions to increase endogenous adiponectin levels are one potential option for safely treating cardiovascular pathophysiology. In some conditions, such as lipodystrophy in individuals with human immunodeficiency virus, hypoadiponectinemia is a metabolic marker of subclinical cardiac disease, hence interventions that increase adiponectin can be useful in the treatment or control of the associated damage.¹⁵⁴ Nutritional compounds, lifestyle changes, and several pharmacological drugs have been shown to enhance plasma adiponectin levels.⁶ Exercise (moderate aerobic training) and long-term weight loss by either gastric bypass surgery or calorie control increase plasma adiponectin levels in overweight/obese or diabetic subjects.^{155–157} Further, weight reduction selectively enhances blood levels of HMW oligomeric adiponectin.^{158–161} These results suggest that at least part of the benefits of lifestyle intervention for cardiovascular health is mediated by adiponectin. In animals and humans with or without diabetes, a large number of nutraceutical products have been demonstrated to have beneficial effects

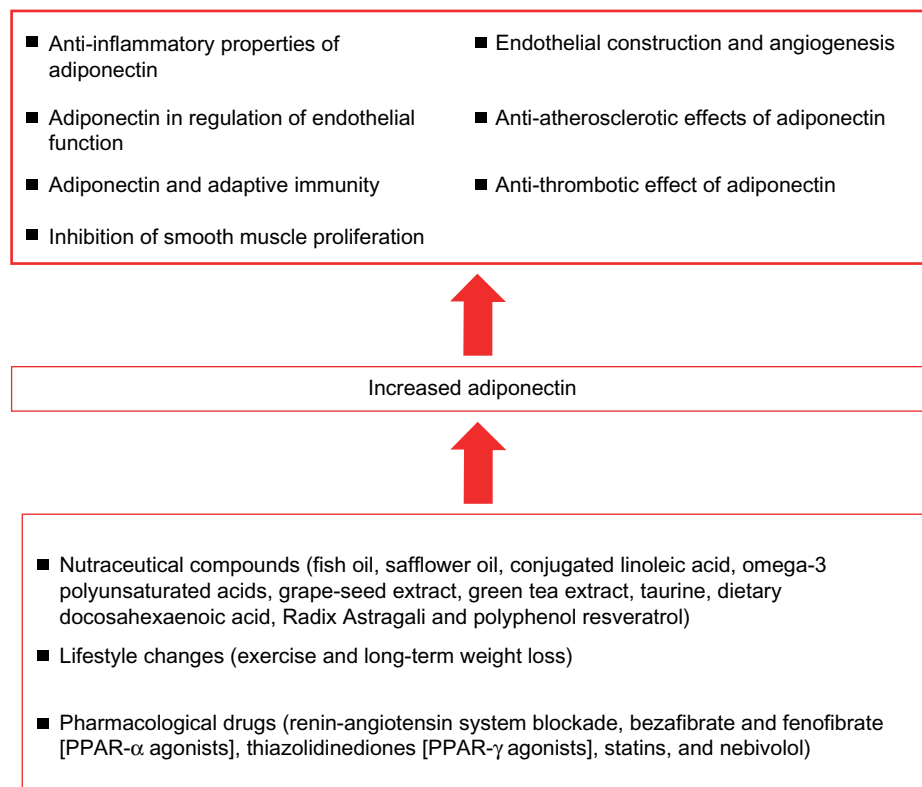


Figure 4 Summary of the cardioprotective effects and therapeutic interventions for enhancing adiponectin.

Abbreviation: PPAR, peroxisome proliferator-activated receptor.

on cardiovascular health by increasing the production of endogenous adiponectin. These including fish oil,¹⁶² safflower oil,¹⁶³ conjugated linoleic acid,¹⁶⁴ omega-3 polyunsaturated acids,¹⁶⁵ grape seed extract,¹⁶⁶ green tea extract,^{14,167} taurine,¹⁶⁸ dietary docosahexaenoic acid,¹⁶⁹ Radix Astragali,¹⁷⁰ aqueous humor, and the polyphenol resveratrol.¹⁷¹ Some pharmacological agents, including renin-angiotensin system blockers, PPAR-α agonists (bezafibrate and fenofibrate), PPAR-γ agonists (thiazolidinediones), statins, and nebivolol have all been shown to increase plasma adiponectin levels.

Thiazolidinediones (pioglitazone and rosiglitazone, both PPAR-γ agonists) elevate circulating adiponectin levels, especially HMW adiponectin, from adipocytes in both humans and rodents by increasing adiponectin gene expression.^{147,172–176} Due to some of the side effects of thiazolidinediones, including weight gain, fluid retention, and anemia,¹⁷⁷ using rosiglitazone poses a cardiac threat. A meta-analysis of controlled clinical trials reported that rosiglitazone, compared with placebo or standard drugs for diabetes, significantly increased the risk of myocardial infarction.¹⁷⁸ In contrast, adiponectin has cardioprotective activity. Therefore, using certain pharmacological agents, we can avoid these harmful effects of thiazolidinediones by selectively increasing plasma adiponectin levels.

The renin-angiotensin system is critical in the regulation of blood pressure. Enhanced angiotensin II in obesity is an important cause of insulin resistance, hypertension, and CVD. Circulating adiponectin can be increased by use of pharmacological inhibitors of the renin-angiotensin system, such as angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. These inhibitors are widely used in cardiology due to their ability to reduce blood pressure and protect the heart, as well as their antidiabetic activity.^{179,180} However, further studies are needed to determine whether or not some of these therapeutic effects are mediated by adiponectin.

There are some clinical data showing that losartan used alone or in combination with statins (in particular simvastatin) increases circulating adiponectin levels in hypertensive patients.¹⁸¹ However, some of the findings in these studies are inconsistent, indicating a need for further studies. Also, some recent findings show a change in the activity of adiponectin in relation to CVD risk factors in patients with rheumatoid arthritis, suggesting the importance of considering the health status of subjects before attempting adiponectin-enhancing interventions.³³ Because of extremely high circulating levels of adiponectin, it has been proposed that altering the ratio of circulating adiponectin to HMW forms would be a more advantageous

therapeutic approach than increasing total levels.^{182,183} Because circulating concentrations of globular adiponectin are very low, some investigators have suggested that the in vivo effects of globular adiponectin are not important. However, the current evidence shows that the bioactivity of globular adiponectin is greater than that of full-length adiponectin. Methods to enhance proteolytic cleavage of full-length adiponectin to globular adiponectin may serve as a potential therapeutic approach for enhancing the bioactivity of adiponectin.^{182,184} Additional research on the role of adiponectin as a therapeutic agent may lead to the development of an additional safe intervention to help decrease the epidemic of vascular disease.

Disclosure

The authors report no conflicts of interest in this work.

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