

Endocrine Functions of Adipose Tissue: Focus on Adiponectin

JAMES R. SOWERS, MD

University of Missouri–Columbia School of Medicine
Departments of Medicine, Pharmacology, and Physiology
Diabetes and Cardiovascular Center of Excellence
Harry S. Truman VA Medical Center
Columbia, Missouri

Accumulating evidence indicates that obesity and overweight are associated with, and contribute to, the development of type 2 diabetes mellitus (DM), cardiovascular disease (CVD), and chronic kidney disease (CKD). The adipocyte-derived cytokine, adiponectin, has been shown to improve insulin sensitivity, increase rates of fatty acid oxidation, decrease muscle lipid content, and reduce inflammation and vascular injury. However, adiponectin levels have been found to be reduced in persons with obesity and type 2 DM. Furthermore, adiponectin levels are inversely associated with those of tumor necrosis factor- α and C-reactive protein—markers of endothelial dysfunction and systemic inflammation. The 2 receptors for adiponectin—Adipo R₁ and Adipo R₂, which are expressed in muscle and liver tissue and in human fat cells—are hormonally regulated, with increased insulin levels causing a reduction in their abundance. The hyperinsulinemia observed in obesity, therefore, may be partially responsible for the reduction in the numbers of adiponectin receptors. Adiponectin aggregates range from a hexamer of low molecular weight to larger multimeric structures of high molecular weight. A smaller proteolytic fragment—the globular head domain of adiponectin, or gAd—interacts specifically with skeletal muscle. The relation of circulating adiponectin to its biologic actions is more complex than originally believed; therefore, it is the multimeric forms of the adiponectin molecule that need to be measured and evaluated in relation to associated metabolic, cardiovascular, and renal functions. Furthermore, strategies to measure the numbers of adiponectin receptors on available tissue need to be developed to fully assess the clinical role of adiponectin in type 2 DM, CVD, and CKD. (*Clinical Cornerstone*. 2008;9[1]:32–40) © 2008 Elsevier. All rights reserved.

Obesity and overweight are increasing dramatically not only in the United States but also in much of the world. There is accumulating evidence that these metabolic conditions are associated with, and contribute to, the development of type 2 diabetes mellitus (DM), cardiovascular disease (CVD), and chronic kidney disease (CKD).^{1–10} Adipocyte-derived cytokines (adipokines) appear to act as a nexus between accumulated adipose tissue, insulin sensitivity, glucose metabolism, systemic inflammation, and oxidative stress on the one hand and the propensity to develop type 2 DM, CVD, nonalcoholic fatty liver disease (NAFLD), and CKD on the other.^{3–13} One of these adipokines—adiponectin—has unique beneficial qualities. Its multimeric forms, particularly full-length adiponectin, improve insulin sensitivity, increase rates

of fatty acid oxidation, decrease muscle lipid content, and reduce inflammation and vascular injury.^{14–39} Whereas adiponectin levels, especially the active full-length form, are reduced in persons with obesity and type 2 DM,^{18–20} they can be increased with weight reduction as well as pharmacotherapy with thiazolidinediones (TZDs) and the investigational CB₁ receptor blocker, rimonabant.^{40–44} Increases in adiponectin, resulting from weight reduction and pharmacotherapy, may play an important role in reducing the burden of type 2 DM, CVD, and CKD.^{38,39}

In this review, adiponectin is examined with regard to its normal biologic function, its various circulating molecular forms, and its alterations in association with obesity and type 2 DM. Finally, both nonpharmacologic

and pharmacologic strategies to increase inappropriately low levels of adiponectin are discussed.

DELETERIOUS EFFECTS OF OVERWEIGHT AND OBESITY

Overweight and obesity are associated with insulin resistance, hypertension, and increased risk for CVD and CKD.^{1–6} Prospective cohort studies^{7,8} have reported that moderate increases in body mass index (BMI) are associated with an increased risk of death from CVD and other causes. However, measures of abdominal, or visceral, adiposity, including waist:hip ratio and waist circumference, may predict risk of mortality better than does BMI.⁹ Obesity, hypertension, systemic inflammation, and oxidative stress—components of the cardiometabolic syndrome (CMS)—are also risk factors for NAFLD, and NAFLD is an increasingly common cause of cirrhosis and end-stage liver disease.^{9,10} Excess adipose tissue appears to create an inflammatory milieu, characterized by high levels of C-reactive protein (CRP) and other inflammatory biomarkers, and increased oxidative stress, which, in turn, predispose to CVD, CKD, and certain malignancies.^{3,5,9}

KEY POINT

Moderate increases in BMI are associated with an increased risk of death from CVD and other causes. However, waist:hip ratio and waist circumference may predict risk of mortality better than does BMI.

CMS comprises a constellation of cardiovascular, metabolic, and renal abnormalities that are associated with increased risk for type 2 DM, CVD, and CKD.^{5–10} Emerging evidence indicates that this syndrome is, in part, the result of increased inflammation and oxidative stress in various affected tissues. Data from the Insulin Resistance Atherosclerosis Study (IRAS),¹¹ a population-based study of 1008 relatively healthy, nondiabetic persons, indicate that systemic inflammation, as determined by elevated CRP, fibrinogen, and plasminogen activator inhibitor-1 levels, is associated with known metabolic

components of CMS. These components include elevated levels of hepatocellular enzymes as biomarkers for NAFLD and risk for type 2 DM.¹² During the 12.7-year period of observation in the longitudinal San Antonio Heart Study,¹³ persons with CMS, but not type 2 DM, had a 2-fold risk for CVD, similar to the risk conferred by hypertension or smoking. In the same study, the presence of CMS increased the incidence of type 2 DM 4-fold, leading to a 7-year absolute risk of 15%. These results have led to the suggestion that the presence of CMS be used for risk stratification for development of type 2 DM and CVD.⁹ These findings suggest the need to better understand the role of biomarkers present in CMS that predispose to the development of type 2 DM, CVD, and CKD.

KEY POINT

In the San Antonio Heart Study, persons with CMS, but not type 2 DM, had a 2-fold risk for CVD, similar to the risk conferred by hypertension or smoking. In the same study, the presence of CMS increased the incidence of type 2 DM 4-fold.

Persons with CMS often display a phenotype characterized by altered partitioning of abdominal and muscle lipids and a dysfunctional adipose tissue microenvironment that is associated with enhanced production of inflammatory adipokines, such as interleukin-6 and tumor necrosis factor (TNF)- α .³ In parallel with the overproduction of these inflammatory adipokines is the underproduction of adiponectin.^{3,9,14–16}

THE ROLE OF ADIPONECTIN

Circulating levels of adiponectin have been observed in different population cohorts to be inversely associated with those of TNF- α and CRP—markers of endothelial dysfunction and systemic inflammation (**Table**).^{3,9,16–19} Adiponectin has been shown to circulate in serum in at least 3 forms: low molecular weight, middle molecular weight, and high molecular weight,^{14–16} the most biologically active form being high molecular weight.^{19–22} Two receptors for adiponectin also have been identified—

TABLE. PUTATIVE BENEFICIAL EFFECTS OF ADIPONECTIN.^{3,9,16-19}

Metabolic	Systemic	Vascular
↑ Insulin signaling through AMP-activated protein kinase	↓ CRP	↓ Adhesion molecule expression in EC
↑ Fatty acid oxidation	↓ IL-6	↓ EC apoptosis
↓ Intramyocellular lipid content	↓ TNF- α	↓ Neointimal formation
↓ Liver lipid content	↓ Fibrinogen	↓ Proliferation and migration of VSMC
↓ Hepatic glucose production	↓ PAI-1	↑ EC nitric oxide production
↓ Serum triglyceride and ↑ HDL-C	↓ ICAM, VCAM, and P-selectin	↓ EC nitric oxide destruction
↓ Apo B	↓ Lp(a)	↓ Transformation of macrophages to foam cells
↓ Lp(a)		↑ Tissue PA

AMP = adenosine monophosphate; HDL-C = high-density lipoprotein cholesterol; Apo B = apolipoprotein B; LP(a) = lipoprotein a; CRP = C-reactive protein; IL-6 = interleukin-6; TNF- α = tumor necrosis factor-alpha; PAI-1 = plasminogen activator inhibitor-1; ICAM = intracellular adhesion molecule; VCAM = vascular cell adhesion molecule; EC = endothelial cells; VSMC = vascular smooth muscle cells; PA = plasminogen activator.

Adipo R₁ and Adipo R₂—which are expressed in muscle and liver tissue²³ and in human fat cells.^{24,25} The expression of these receptors is hormonally regulated, with increased insulin levels causing a reduction in their abundance.²⁶ Thus, the hyperinsulinemia observed in obesity and CMS may be partially responsible for the reduction in the numbers of adiponectin receptors. Given the various effects of metabolic factors on adiponectin receptors, it is becoming increasingly clear that changes in the numbers of tissue receptors as well as the function of these receptors must be evaluated in concert with levels of circulating adiponectin to appropriately evaluate the role of this adipokine in various metabolic, cardiovascular, and renal abnormalities.

KEY POINT

Circulating levels of adiponectin have been observed in different population cohorts to be inversely associated with those of TNF- α and CRP—markers of endothelial dysfunction and systemic inflammation.

Adiponectin circulates in blood primarily as aggregates of the full-length form, ranging from a hexamer of

low molecular weight to larger multimeric structures of high molecular weight. About 1% of the total plasma adiponectin circulates as a smaller proteolytic fragment—the globular head domain of adiponectin, or gAd—in a trimeric form.²⁷ This gAd interacts specifically with skeletal muscle. The relation of circulating adiponectin to its biologic actions is more complex than originally believed. In fact, it appears that the level of circulating immunoreactive adiponectin is not the best indicator of insulin sensitivity and that impaired multimerization results in reduced interaction of adiponectin with its target tissues.^{20,28} Accordingly, it is increasingly being recognized that the multimeric forms of the adiponectin molecule need to be measured and evaluated in relation to associated metabolic, cardiovascular, and renal functions. Most reports on the relation of reduced adiponectin levels and metabolic disorders have not addressed this important issue. Furthermore, strategies to measure the numbers of adiponectin receptors on available tissue need to be developed to fully assess the clinical role of adiponectin in CMS, CVD, CKD, and type 2 DM.

In skeletal muscle, on binding to its receptor, adiponectin appears to produce signal transduction through phosphorylation and activation of adenosine monophosphate-activated protein kinase,²³ which modulates cholesterol synthesis, lipogenesis, lipid oxidation, and glucose transport and oxidation. Adiponectin enhances insulin sensitivity in both skeletal muscle and liver tissue, stimulating glucose uptake and fatty acid oxidation in skeletal mus-

cle and reducing gluconeogenesis in liver tissue. In addition to observational relations between reduced levels of circulating adiponectin and impaired insulin sensitivity, there is more definitive evidence that adiponectin is an insulin-sensitizing molecule. In lean rodents with normal glucose tolerance, the overexpression of adiponectin produced greater insulin sensitivity.²⁹ In type 2 diabetic rodent models (the db/db mouse), the administration of adiponectin was found to abrogate insulin resistance.³⁰ In the diabetic rodent models, the loss of peripheral stores of adipose tissue (ie, lipoatrophy) resulted in the deposition of excessive lipids in the skeletal muscle and liver tissue. The lipid abnormalities associated with lipoatrophy (ie, elevated levels of plasma lipids and lipid content in muscle and liver), as well as insulin resistance, are largely corrected by administration of gAd. Thus, inadequate amounts of well-differentiated, mature adipocytes may result in insufficient uptake and utilization of non-esterified free fatty acids, in part because of inadequate production of functional multimeric adiponectin. These abnormalities, therefore, result in ectopic deposition of triglycerides in the liver, heart, and skeletal muscle, and in perivascular and pericardial sites, all of which likely contribute to the development of NAFLD. The presence of ectopic fat also predisposes to insulin resistance, dyslipidemia, and other components of CMS.

KEY POINT

Adiponectin enhances insulin sensitivity in both skeletal muscle and liver tissue, stimulating glucose uptake and fatty acid oxidation in skeletal muscle and reducing gluconeogenesis in liver tissue.

CARDIOVASCULAR EFFECTS OF ADIPONECTIN

Adiponectin, especially high-molecular-weight adiponectin, appears to exert cardiovascular protection. It reduces endothelial cell apoptosis²² and exerts antiatherogenic effects, both directly and indirectly, through its efforts to increase high-density lipoprotein cholesterol (HDL-C) levels.^{22,28} It also reduces the numbers of low-

density lipoprotein particles.²⁵ In addition to its protective effects against endothelial cell apoptosis, adiponectin may reduce the risk for atherosclerosis by reducing vascular expression of adhesion molecules and foam cell formation³¹ and vascular smooth muscle cell proliferation.³²

KEY POINT

Adiponectin reduces endothelial cell apoptosis and may reduce the risk for atherosclerosis by reducing vascular expression of adhesion molecules and foam cell formation and vascular smooth muscle cell proliferation.

High-molecular-weight adiponectin levels are often very low in diabetic patients with atherosclerotic vascular disease.^{25,33} Low levels of adiponectin are associated with coronary artery disease^{31,33,34} and increased risk for future myocardial infarction.³⁵ Low levels of adiponectin are also associated with endothelial dysfunction, systemic inflammation, reduced levels of HDL-C, and other components of CMS.^{36–38} Furthermore, there are extant data suggesting that low levels of adiponectin may be one of the factors that link CKD with CVD.^{5,39} The relation between low levels of adiponectin and increased risk for CVD may start as early as childhood.³⁷

The precise mechanisms by which adiponectin reduces oxidative stress, inflammation, endothelial dysfunction, and early neointimal formation remain to be elucidated, and little is known about the mechanisms by which adiponectin reduces the development of glomerular injury and proteinuria. These remain areas for future research into the role of adiponectin in the development of CMS, CVD, CKD, and type 2 DM.

STRATEGIES TO INCREASE ADIPONECTIN LEVELS

Weight loss in obese and overweight persons has been found to increase adiponectin levels, including high-molecular-weight adiponectin.^{31,40,41} Therefore, this non-pharmacologic measure must be an integral component of any strategy to increase adiponectin levels. However,

pharmacologic strategies may also be required. Several studies^{42,43} have shown that treatment with TZDs increases adiponectin levels contemporaneously with improvement in insulin sensitivity and reduction in systemic markers of inflammation. For example, increases in adiponectin levels associated with pioglitazone therapy may contribute significantly to improvements in insulin sensitivity and to reductions in markers of oxidative stress and inflammation, as well as to reductions in blood pressure, albuminuria, and carotid intima-media thickness.^{42,43}

KEY POINT

Weight loss in obese and overweight persons has been found to increase adiponectin levels. Therefore, this nonpharmacologic measure must be an integral component of any strategy to increase adiponectin levels. However, pharmacologic strategies may also be required.

There is also emerging evidence that blockade of CB₁ receptors is associated with increases in adiponectin levels in both obese rodents^{44,45} and humans,^{45,46} in conjunction with improvement in insulin sensitivity and reduced systemic markers of inflammation. In a study by Bensaid et al,⁴⁴ the mechanism involved in these effects of CB₁ receptor blockade was explored using fat cells in vitro. The investigators found that CB₁ receptor blockade with the investigational drug rimonabant stimulated adiponectin gene expression in the cultured fat cells. Furthermore, CB₁ receptors were found to be upregulated in the adipose tissue of obese rodents.⁴⁴ The impact of CB₁ receptor blockade on circulating levels of multimeric forms of adiponectin, as well as upregulation of adiponectin receptors on target tissues, also may contribute to the reduction in insulin resistance, improvement in lipid profiles, and reduction in blood pressure observed with rimonabant therapy in patients with CMS and type 2 DM.^{45–50}

Current therapeutic strategies aimed at increasing active forms of adiponectin include nonpharmacologic weight reduction strategies and treatment with TZDs.

Future strategies may include the CB₁ antagonist rimonabant. Long-term therapeutic strategies directed at increasing circulating levels of active multimeric forms of adiponectin need to be tested to determine if these strategies are also associated with reductions in CVD and CKD.

CONCLUSIONS

The adipocyte-derived cytokine, adiponectin, improves insulin sensitivity, increases rates of fatty acid oxidation, decreases muscle lipid content, and reduces inflammation and vascular injury. However, adiponectin levels are reduced in persons with obesity and type 2 DM and are inversely associated with TNF- α and CRP levels. Receptors for adiponectin have been found to be hormonally regulated, with increased insulin levels causing a reduction in their abundance. To fully assess the clinical role of adiponectin, the multimeric forms of the adiponectin molecule need to be measured and evaluated in relation to associated metabolic, cardiovascular, and renal functions, and strategies to measure the numbers of adiponectin receptors present on available tissues need to be developed.

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Address correspondence to: James R. Sowers, MD, University of Missouri–Columbia School of Medicine, D109 Diabetes Center, UHC, One Hospital Drive, Columbia, MO 65212. E-mail: sowersj@health.missouri.edu

Dialogue Box

EDITORIAL BOARD

What determines whether a fat cell produces adiponectin versus inflammatory adipokines?

SOWERS

I don't know that there is anything that directly affects a cell's production of adiponectin. However, to the best of my knowledge, peripheral fat cells, which are the more mature cells, are more likely to produce bioavailable or bioactive adiponectin. Central visceral adipose cells are not only less likely to produce adiponectin but also disproportionately less full-length adiponectin. As point of fact, there is almost an inverse relationship between the production of inflammatory adipokines and that of adiponectin. Thus, central fat cells produce more of the inflammatory cytokines such as interleukin-6 and less adiponectin. Weight loss and exercise both seem to effect an increase in the production of adiponectin and there is evidence that thiazolidinediones (TZDs), angiotensin receptor blockers (ARBs), and angiotensin-converting enzyme (ACE) inhibitors do this as well. This may have to do with the differentiation of fat from immature central fat cells to more mature peripheral fat cells.

EDITORIAL BOARD

Does this mean that the location of the fat cell influences the adipokines produced?

SOWERS

Centrally located fat does produce more inflammatory cytokines such as interleukins and tumor necrosis factor- α than does peripherally located fat, and part of the differentiation of fat cells has to do with whether they are located centrally or peripherally. The initial production of immature fat cells occurs in a central location and the initial production of more mature fat cells occurs in a peripheral location. If we are to use a TZD in the treatment of our patient, the TZD does not simply move the fat cell—it differentiates the fat cell, which results in greater numbers of peripheral, well-differentiated, biologically effective fat cells that take up lipids and

produce adiponectin. The process has to do with maturation, that is, differentiation into the more mature, and if you will, biologically effective, peripheral fat cell.

EDITORIAL BOARD

What happens in the patient who overeats and gains weight?

SOWERS

The initial accumulation of fat appears to be more centrally located in the visceral region, and this fat tissue may be relatively less mature and more inflammatory. When you gain weight and when you lose weight, the first action appears to be in visceral fat. So the good news is, particularly in a male, when you lose weight, the fat lost initially is central fat. That is the reason why a little weight loss is good.

EDITORIAL BOARD

Would that also explain why CB₁ blockers seem to have the same effect?

SOWERS

Yes, any strategy to lose weight would result in initial loss of this central, more inflammatory, and dysmetabolic fat. I think when you talk about the endocannabinoid receptor antagonists, TZDs, ARBs, or even exercise, it has more to do with the production of more mature fat cells, which are located peripherally, preferentially, over the visceral region.

EDITORIAL BOARD

Do you foresee it being possible soon to assess a patient's adiponectin status?

SOWERS

We will be able to more accurately measure the biologically active components of adiponectin with development of newer assays in the future. But I am not aware of any commercially available adiponectin assays at this time. When, and if, one does become available, I think it is going to be important to know whether it is measur-

Dialogue Box

ing the full length of the multiplex adiponectin, or its fragments. Laboratories may spring up that can measure different types of adiponectin, but it does make a difference whether you are measuring the full length versus segments of the adiponectin molecule.