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Adiponectin: linking the metabolic syndrome to its cardiovascular consequences

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KEYWORDS:
atherosclerosis, glucose and lipid
metabolism, metabolic syndrome,
vascular biology

Obesity and its related disorders, glucose intolerance, hypertension and hyperlipidemia, collectively named the metabolic syndrome, result in substantial cardiovascular morbidity and mortality. Recent data point to several underlying regulatory mechanisms through which obesity links these various outcomes. Adipose tissue is now understood to function not merely as a passive energy storage depot but as an active endocrine organ, producing a variety of bioactive substances termed adipocytokines. Adiponectin, an adipocytokine first described as the most abundant protein produced by adipocytes, appears to serve as a central regulatory protein in many of the physiologic pathways controlling lipid and carbohydrate metabolism, and to mediate various vascular processes. Adiponectin displays both anti-inflammatory and antiatherogenic properties. Unlike other adipocytokines, its levels are paradoxically decreased in obesity and insulin-resistance states including metabolic syndrome and diabetes, as well as hypertension and coronary artery disease. This review will detail the relationship of adiponectin to various features of obesity and insulin-resistance syndromes, as well as its relationship to the cardiovascular complications of these disorders.

Expert Rev. Cardiovasc. Ther. 3(3), 465–471 (2005)

Obesity and the related metabolic syndrome are rapidly becoming a global health issue even in nonindustrialized parts of the world [1]. Given the cardiovascular consequences of these disorders, there is a pressing imperative to understand their physiologic basis. Energy homeostasis, manifested as long-term weight stability, is controlled by a complex array of regulatory signals affecting multiple organs, skeletal muscle and the CNS. Accumulating evidence suggests that adipose tissue is not simply an energy storage depot, but also functions as an active endocrine organ through its secretion of various cytokines, such as leptin, plasminogen activator inhibitor Type 1, resistin, tumor necrosis factor (TNF)- α and adiponectin [2–4]. Adiponectin appears to mediate the direct metabolism of fatty acids [5], and modulate glucose metabolism by acting as an insulin sensitizer [6] and

by directly stimulating glucose uptake [7,8]. In addition, it influences endothelial cell function [9,10] and plays an anti-inflammatory role in the microvasculature [11]. Thus, adiponectin is associated not only with obesity but with the subsequent complication of insulin resistance, including the metabolic syndrome and frank diabetes mellitus, as well as the cardiovascular outcomes of these conditions.

Adiponectin is a protein abundantly produced by adipose tissue [12,13]. First described by four independent groups in the mid-1990s [12,14–16], it consists of four domains – an amino-terminal signal sequence, a variable region, a collagenous domain and a carboxy-terminal globular domain [14]. In plasma, it exists in full-length monomers forming trimers and hexamers known as the low-molecular-weight (LMW) forms and a high-molecular-weight (HMW) complex, as well as in a cleaved

globular form [17]. In males, the LMW form predominates, while females exhibit a more balanced distribution of the two forms. The different domains acting alone or as a whole molecule, in both the LMW or HMW form, appear to have different bioactivity depending upon the target tissue [5,6,18]. Thus, when adiponectin is unable to form multimers, its effect on hepatocyte AMP-kinase is abolished [19]. Recent observations by Pajvani and colleagues have also suggested that the HMW:total ratio may more accurately determine bioactivity [20].

Two adiponectin receptor subtypes have recently been cloned, AdipoR1 and AdipoR2 [21]. AdipoR1 is ubiquitously expressed but is particularly abundant in skeletal muscle. In humans, AdipoR2 is synthesized by both liver and skeletal muscle. Both receptors bind globular and full-length adiponectin; however, the globular form binds more avidly to skeletal muscle, while the reverse is true of hepatocytes, which principally bind the full-length form. The different receptors, as well as the type of adiponectin present, likely reflect the variable actions of adiponectin on glucose and lipid metabolism.

Adiponectin & its relationship to obesity

Adiponectin has a complex relationship with obesity, acting peripherally on skeletal muscle, visceral and subcutaneous fat, and centrally, on the brain. Adiponectin is secreted exclusively by adipose tissue and its gene expression is activated during adipogenesis. Despite being called the most abundant transcript by Maeda [12], its levels are paradoxically reduced in obesity [13,15] and unlike other adipocytokines, such as leptin and TNF- α , its expression is inversely related to visceral fat quantities [22,23]. In animal models of obesity, it was demonstrated that compared with wild-type mice, mRNA transcription was reduced in the steady state [15]. Although the gene is upregulated in the differentiation process of the normal adipocytes, it has also been demonstrated in obese mice that there is a downregulation of adiponectin gene expression in the differentiated hypertrophic adipocyte [24], suggesting a feedback inhibition during the development of obesity [25]. Such an outcome might occur due to higher levels of TNF- α and other cytokines, which may have a toxic effect on adiponectin gene expression in the obese individual. TNF- α , among other factors, such as corticosteroids and β -adrenergic stimulation, has been demonstrated to reduce adiponectin gene expression *in vitro* [26,27].

In human studies, the inverse relationship between visceral obesity and adiponectin has been shown repeatedly. Arita and colleagues demonstrated that the mean plasma adiponectin level was 3.7 μ g/ml in a group of obese patients compared with a mean level of 8.97 μ g/ml in normal-weight subjects [13]. Stefan and colleagues described decreased adiponectin levels with increasing adiposity in a group of children followed longitudinally over 10 years [28]. Several studies, including those by Matsubara and colleagues and Yamamoto and colleagues confirmed the inverse relationship between body mass index (BMI) and adiponectin, which held true in normal-weight subjects [29,30]. In addition, recent studies have demonstrated that weight reduction induces an increase in adiponectin levels. In a group

of 22 obese patients who had undergone gastric partition surgery, a 21% reduction in BMI was associated with a 46% increase in mean plasma adiponectin levels [31]. Similar results were observed in a group of obese Japanese adolescents following weight loss after psychoeducational intervention [32]. The correlation between obesity and plasma adiponectin is significantly stronger with visceral versus subcutaneous adipose tissue [22,23,33]. An *in vitro* study demonstrated that cultured visceral adipocytes actively secrete more adiponectin than subcutaneous adipocytes; however, such secretion by these adipocytes is negatively correlated with BMI in the study subjects [33]. In addition, clinical trials confirmed that adiponectin concentrations are primarily determined by the degree of visceral fat [22,23]. Interestingly, one study suggests that adiponectin plays a role in weight gain and loss. When the globular region of recombinant adiponectin was administered to mice, it induced weight loss despite a high-fat, high-sucrose diet. It was also associated with a reduction in glucose, free fatty acids (FFAs) and triglycerides [5].

Similarly, a recent study by Qi and colleagues points to a unique role of adiponectin in the CNS. In mice administered intravenous and intracerebral–intraventricular adiponectin, they verified intracerebral transport of adiponectin and demonstrated that weight loss occurs via increased energy expenditure and not decreased caloric intake [34]. These observations await further investigation.

Adiponectin & its relationship to insulin resistance & glucose metabolism

Adiponectin has repeatedly been demonstrated to be inversely correlated to the insulin-resistant state and plays an integral role in glucose homeostasis. The mechanisms underlying these findings are now being elucidated and are related to the actions of the peroxisome proliferator-activated receptor (PPAR) agonists, such as PPAR- γ , and several pathways mediated through the common enzyme AMP-kinase.

The inverse relationship between adiponectin levels and insulin-resistant states is evident throughout the literature [35–37]. In rhesus monkeys, plasma adiponectin declines at an early phase of obesity and remains decreased after the development of diabetes [36]. In adiponectin knockout mice, both homozygous and heterozygous adiponectin-deficient mice demonstrate insulin resistance, with the homozygous mice displaying glucose intolerance at a body weight equivalent to that of wild-type mice [37]. In another study, Maeda demonstrated that feeding adiponectin knockout mice a high-fat, high-sucrose diet induced insulin resistance after just 2 weeks. Administration of recombinant adiponectin lowers plasma glucose levels and improves glucose tolerance without stimulating insulin secretion in both normal mice and murine models of diabetes [6,18,38]. Notably, this effect is associated with lowering of hepatic glucose production, an indication of improved insulin function in the liver.

In humans, accumulating evidence strongly and inversely correlates plasma adiponectin to insulin sensitivity [39–42]. In a study conducted on 23 Caucasians and 121 Pima Indians,

hypoadiponectinemia was more strongly related to the degree of insulin resistance and hyperinsulinemia than that of adiposity or glucose intolerance. This suggests that insulin resistance and hyperinsulinemia are major determinants of hypoadiponectinemia in obesity and Type II diabetes [39]. The correlation of adiponectin to insulin sensitivity appears to hold true both in glucose uptake in muscle [41,43] and liver gluconeogenesis [40]. This insulin sensitivity also correlated independently of adiposity [40]. Finally, not only are adiponectin gene expression and circulating levels lower in patients with Type II diabetes than in nondiabetic counterparts [44,45], but high levels of adiponectin also predict a lower rate of diabetes, independent of obesity [42].

Further evidence establishing the connection between adiponectin and insulin activity is derived from data obtained from studying the activity of PPAR agonists. PPAR- γ , found in adipose but not skeletal muscle, is stimulated by the thiazolidinediones (TZDs). Initially developed as agents that reduce hyperglycemia by reducing peripheral insulin resistance, they were subsequently discovered to be potent, specific stimulators of PPAR- γ [46]. Administration of TZDs increases adiponectin mRNA levels in cultured adipocytes, as well as in the adipose tissue of obese mice [47]. The TZDs also markedly enhance the activity of the adiponectin gene promoter by blocking the inhibitory effect of TNF- α [48] on the adiponectin gene promoter [49]. In diabetic mice models, chronic treatment with PPAR- γ agonists induced a significant increase in plasma adiponectin levels, whereas, treatment with fibrates-PPAR- α agonists, or metformin did not [50]. Similar findings were also observed in insulin-resistant humans [47,50-52].

The exact relationship between PPAR- γ and adiponectin remains somewhat enigmatic. Certain dominant-negative PPAR- γ mutations in humans are associated with severe insulin resistance and reduced levels of adiponectin [53]. Other studies involving another mutation, PPAR- γ 2 Pro12Ala, have yielded conflicting results. Healthy Japanese subjects with this mutation demonstrated reduced adiponectin levels, but subjects with polycystic ovary syndrome and healthy Europeans with the same polymorphism demonstrated elevated levels, perhaps reflecting other genetic influences on adiponectin and PPAR- γ [54-57]. This possibility is supported in a recent paper by Menzaghi and colleagues, which suggested that adiponectin levels were controlled by several genes, including variations at the adiponectin gene itself, as well as an as yet unidentified gene on the 14q13 locus [58]. Further research concerning PPAR- γ , adiponectin's apM1 locus and other chromosomal foci may enable the targeting and enhancing of adiponectin expression and secretion. This may represent another potential mechanism for increasing insulin sensitivity through its effect on PPAR- γ .

Physiologically, adiponectin has numerous effects on glucose metabolism through its effect on insulin action, as well as by directly stimulating glucose uptake. It has been demonstrated to improve insulin sensitivity in animal models and humans by increasing insulin-induced tyrosine phosphorylation of the insulin receptor [5,18,59,60]. In human studies involving Pima

Indians, insulin receptor tyrosine phosphorylation correlated positively with adiponectin levels [59]. When adiponectin is administered to mice, glucose and fat metabolism improves, as evidenced by increased FFA oxidation [18] and decreased skeletal muscle triglyceride content [60], a marker of insulin activity [5]. Although information regarding insulin's effect on adiponectin remains unresolved, with an acute effect of insulin on adiponectin not ruled out, adiponectin appears to determine insulin resistance and not the reverse. This is supported by Combs and colleagues who demonstrated that an increase in adiponectin precedes increased insulin sensitivity [50].

Adiponectin also directly stimulates glucose uptake in adipocytes and muscle by stimulating AMP-activated protein kinase [7,8]. In hepatocytes, adiponectin-stimulated, insulin-mediated AMP-kinase activation reduces gluconeogenesis [7]. This action in the liver appears to be the major factor in reducing systemic glucose levels [61].

Adiponectin & lipid metabolism associated with insulin resistance

Visceral adiposity is characterized by enhanced lipolysis and increased FFA flux, especially into the portal circulation. Such increased inflow raises FFA influx to the liver and is thought to delay insulin clearance and stimulate lipid synthesis. This may result in peripheral hyperinsulinemia and hyperlipidemia. Excess FFAs, therefore, are an established indicator of insulin resistance. They have also been demonstrated to induce hepatic insulin resistance by inhibiting insulin suppression of glycogenolysis during euglycemic-hyperinsulinemic clamp studies [60]. Adiponectin decreases circulating and tissue FFA levels via a number of related mechanisms. Similar to metformin [62], it stimulates fatty acid oxidation by skeletal muscle via the AMP-kinase pathway [5,8,18], and hence serves to decrease circulating FFA levels. This leads to decreased triglyceride content in muscle, a sign of improved insulin sensitivity [60]. Liver FFA influx is also reduced in the presence of adiponectin, either indirectly through decreased circulating FFA, or directly via decreased fatty acid hepatocyte uptake [18]. Decreased FFA influx may lead to decreased hepatic triglyceride content, which theoretically leads to improved insulin sensitivity and reduced hepatic glucose output.

Adiponectin in the development of cardiovascular disease

In addition to its role as a modulator of insulin's effect on reducing hyperglycemia and the inherent toxicity of hyperglycemia on the vasculature, adiponectin plays a role in the development of cardiovascular disease at the level of the endothelium, as an anti-inflammatory substance, and in myocardial cell remodeling. Endothelial dysfunction plays a significant role in the evolution of atherosclerosis and thrombosis [63,64]. In conjunction with oxidative stress and inflammation, it contributes to obesity-related insulin resistance and diabetes, hypertension and dyslipidemia [65]. Impaired nitric oxide (NO)-mediated vasorelaxation, the hallmark of endothelial dysfunction, is common in patients with

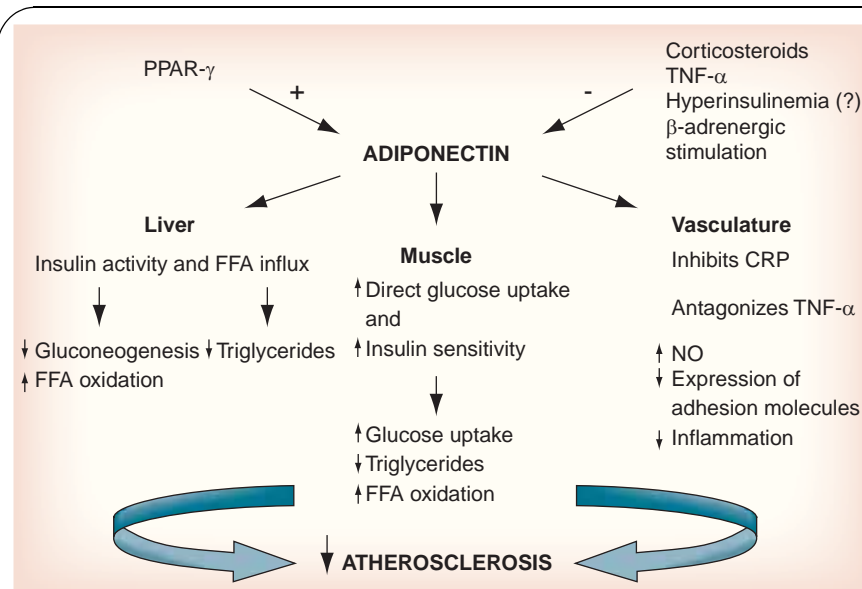


Figure 1. The role of adiponectin in the pathophysiology of the metabolic syndrome and its cardiovascular complications.

CRP: C-reactive protein; FFA: Free fatty acid; NO: Nitric oxide;

PPAR: Peroxisome proliferator-activated receptor; TNF: Tumor necrosis factor.

the metabolic syndrome [66]. Recent animal and human studies report the association of a low plasma level of adiponectin with endothelial dysfunction. In adiponectin-knockout mice, acetylcholine-induced endothelium-dependent vasodilatation was significantly reduced compared with wild type [9]. In humans, forearm blood flow during reactive hyperemia was impaired in proportion to the severity of obesity and inversely related to adiponectin levels [10], and endothelium-dependent vasodilatation was negatively correlated with plasma levels of adiponectin [9].

Adiponectin plays a role in protecting the vasculature at many levels. It enhances endothelial production of NO [67]. Through its modulation of insulin action, it protects against the deleterious effects of glucose on endothelial cells [66]. By decreasing FFA levels [35], inhibiting oxidized low-density lipoprotein superoxide generation [68] and antagonizing TNF- α and C-reactive protein (CRP) [69,70], all of which reduce the availability of NO, adiponectin enhances endothelial function. Furthermore, expression of adhesion molecules on endothelial cells, a pivotal characteristic of dysfunctional endothelial cells, is downregulated by adiponectin [71].

Regarding its role as an anti-inflammatory, adiponectin impacts the formation of atherosclerosis at many levels. In the development of the fatty streak, it suppresses the transformation of macrophages to foam cells [11,72], inhibits vascular smooth muscle and endothelial cell proliferation and migration [73,74], and suppresses CRP production [70]. Finally, adiponectin decreases neointimal hyperplasia after vascular injury [75]. Collectively, these properties limit the progression of atherosclerosis. Indeed, in animal and human studies, adiponectin levels are inversely related to the development of hypertension and coronary artery disease [75–77].

Recently, adiponectin has been directly linked to the development of hypertrophic cardiac disease, already known to be associated with hypertension and insulin resistance. A recent study by Shibata and colleagues demonstrated that artificially pressure-overloaded, adiponectin-deficient mice developed concentric cardiac hypertrophy associated with increased mortality [78]. This effect was mediated, in part, by diminished levels of AMP-kinase and was attenuated by adenovirus-mediated administration of adiponectin. Cultured myocytes demonstrated that adiponectin activated AMP-kinase and inhibited agonist-stimulated hypertrophy. In general, this study suggests that, similar to other tissues, adiponectin inhibits myocardial hypertrophy through the activation of AMP-kinase.

Expert opinion & five-year view

The comprehensive understanding of the association between obesity, insulin resistance and other components of the metabolic syndrome to the eventual development of cardiovascular disease remains enigmatic. Studying the role of adipose tissue as an endocrine organ has provided a window through which we can begin to elucidate these inter-relationships. Among adipose tissue hormones, adiponectin plays a central and unique role in the pathophysiology of the metabolic syndrome and its complications (FIGURE 1). Unlike other adipocytokines, adiponectin levels are inversely related to the degree of adiposity, as well as to the degree of insulin resistance independent of adiposity. Low levels are not only associated with the development of the metabolic syndrome but also predict its consequences, namely, the development of diabetes, hypertension and coronary artery disease. Collectively, adiponectin's effect on inflammation, the vasculature and various organs including the liver and skeletal and cardiac muscle, acting through PPAR- γ and ubiquitous pathways such as AMP-kinase, emphasizes adiponectin's central role in regulating energy homeostasis ending in the pathologic state of the metabolic syndrome and linking the insulin-resistant state to its cardiovascular consequences.

Investigations directed at developing adiponectin available for human study may provide a potential alternative treatment for obesity and the metabolic syndrome, before clinical complications ensue. Animal studies have already demonstrated the beneficial effect of adiponectin administration, impacting obesity directly through weight loss and indirectly by improving insulin sensitivity and limiting vascular injury. Future human pharmacologic intervention can potentially be aimed at using adiponectin directly as an antiobesity drug for primary prevention of Type II diabetes and ischemic heart

disease, as well as secondary prevention of their complications. Other possible mechanisms, which aim to raise endogenous adiponectin production and sensitivity using medications such as the TZDs and blockers of the renin–angiotensin system, may also prevent the consequences of these disorders.

The growing worldwide obesity problem underscores the need to prevent and treat obesity, the metabolic syndrome and their complications. Future basic and clinical research on adipose tissue and adiponectin, as well as its target organs, will contribute to that ultimate goal.

Key issues

- Adiponectin, a specific adipose tissue cytokine, is inversely related to insulin resistance, obesity, the metabolic syndrome and overt diabetes.
- Adiponectin plays a central role in glucose and lipid metabolism, acting directly on muscle cells as well as indirectly through insulin, by acting as an insulin sensitizer.
- Adiponectin acts as an antiatherogenic substance through various mechanisms including as an anti-inflammatory, diminishing of adhesion of inflammatory cells and inhibition of the C-reactive protein, as well as tumor necrosis factor- α .
- Adiponectin improves endothelial function through various mechanisms that lead to the increased production of nitric oxide.
- Adiponectin levels are inversely correlated to the development of hypertension, coronary artery disease and cardiac hypertrophy.
- Adiponectin is upregulated by activation of peroxisome proliferator-activated receptor- γ , such as the thiazolidinediones.
- Adiponectin may potentially serve in the future as a therapeutic agent in the treatment of metabolic syndrome and its consequences.
- Issues to be clarified revolve around the regulation of adiponectin production, secretion and activity, its signaling pathways and the interrelations between adiponectin and insulin.

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