0021-972X/04/$15.00/0
*Printed in U.S.A.*

The Journal of Clinical Endocrinology & Metabolism 89(6):2563–2568

doi: 10.1210/jc.2004-0518

# Adiponectin: A Novel Adipokine Linking Adipocytes and Vascular Function

BARRY J. GOLDSTEIN AND ROSARIO SCALIA

*Dorrance H. Hamilton Research Laboratories, Division of Endocrinology, Diabetes and Metabolic Diseases (B.J.G.), Department of Medicine, and Department of Physiology (R.S.), Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania 19107*

**Cardiovascular disease accounts for an overwhelming proportion of the morbidity and mortality suffered by patients with obesity and type 2 diabetes mellitus, and recent work has elucidated several potential mechanisms by which increased adiposity enhances cardiovascular risk. Excess adipose tissue, especially in certain compartments, leads to reduced insulin sensitivity in metabolically responsive tissues, which is frequently associated with a set of cardiovascular risk factors, including hyperinsulinemia, hypertension, dyslipidemia, and glucose intolerance. Increasing attention has also been paid to the direct vascular effects of plasma proteins that originate from adipose tissue, especially adiponectin, which exhibits potent antiinflammatory and antiatherosclerotic effects. This brief review will summarize recent work on the vascular actions of adiponectin, which complements the growing body of information on its insulin-sensitizing effects in glucose and lipid metabolism. Adiponectin is now a recognized component of a novel signaling network among adipocytes, insulin-sensitive tissues, and vascular function that has important consequences for cardiovascular risk. (*J Clin Endocrinol Metab* 89: 2563–2568, 2004)**



*"To lengthen thy Life, lessen thy Meals"*
Benjamin Franklin *in* Poor Richard's Almanack, June 1733

THE GROWING EPIDEMIC of cardiovascular disease in developed countries and the third world is closely associated with an increased prevalence of insulin resistance and type 2 diabetes due to excess body weight and sedentary lifestyles (1). Insulin resistance, a failure of circulating insulin to elicit its expected responses in glucose and lipid metabolism, plays a key role in the development of the metabolic syndrome, a complex set of risk factors, including hyperinsulinemia, hypertension, glucose intolerance, and dyslipidemia, that dramatically heightens cardiovascular risk (2, 3). The pathogenic relationships among obesity, the metabolic syndrome, and its cardiovascular complications, however, remain poorly understood, and intensive research efforts are underway to elucidate the mechanisms by which excess adiposity, especially in visceral compartments, causes both insulin resistance and vascular dysfunction.

Endothelial dysfunction, characterized by several abnormalities, including a deficiency of nitric oxide (NO) production in response to normal secretion signals, is a key abnormality found in insulin-resistant states (4). When endothelial dysfunction is present, the relative lack of NO production contributes to hypertension and several concomitant alterations, including increased expression of adhesion molecules on the endothelial cell surface and other inflammatory changes that underlie the early processes of atherosclerosis. A variety of humoral substances that adversely influence endothelial function have been recognized, including free fatty acids, cytokines such as TNF$\alpha$, and prooxidant molecules, including oxidized low density lipoprotein (oxLDL). These mediators activate signaling kinases and are also closely linked to the endothelial production of reactive oxygen species (ROS; superoxide and $H_2O_2$), a central component of the inflammatory milieu that contributes to atherogenesis in the metabolic syndrome and in frank diabetes (5–9). ROS can reduce NO availability, consuming NO in the chemical formation of peroxynitrite, which has also been postulated to alter the catalytic activity of endothelial NO synthase (eNOS), diverting its synthesis from NO toward increased superoxide production (10). The duration and magnitude of ROS exposure also affect endothelial cell growth and determine whether these cells undergo proliferation or apoptosis (11).

Much of the recent work on obesity has highlighted the key role of adipose tissue as an endocrine organ that secretes a number of factors, termed adipokines, that mediate many of the vascular and metabolic complications of adiposity (12, 13). As the visceral adipose mass is expanded, the secretion of many of these products is increased, including free fatty acids, TNF$\alpha$, ILs, resistin, leptin, and complement factors, which reduce insulin sensitivity and contribute to endothelial dysfunction (14).

### *Potential role of adiponectin*

Adiponectin is a relatively abundant, approximately 30-kDa plasma protein secreted specifically from adipose tissue that is found in multimeric complexes in the circulation at relatively high levels in healthy human subjects (~2 to 10

Abbreviations: eNOS, Endothelial NO synthase; fAd, full-length adiponectin; gAd, globular C-terminal domain of adiponectin; NO, nitric oxide; oxLDL, oxidized low-density lipoprotein; PDGF-BB, platelet-derived growth factor-BB; ROS, reactive oxygen species; VCAM-1, vascular cell adhesion molecule-1.

**JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.**

$\mu$g/ml) (see Refs. 15–17 for recent reviews). In contrast to the dramatic increase in plasma levels of several of the adipokines observed in visceral adiposity, the plasma levels of adiponectin are markedly reduced. Thus, adiponectin levels correlate negatively with percent body fat, central fat distribution, fasting plasma insulin, and oral glucose tolerance and positively with glucose disposal during euglycemic insulin clamp. Adiponectin levels are also significantly lower in patients with coronary artery disease than in matched control subjects, suggesting a possible association of reduced adiponectin in vasculopathic states (18, 19).

Adiponectin exists in the circulation as a full-length protein (fAd) as well as a putative proteolytic cleavage fragment consisting of the globular C-terminal domain (gAd), which may have enhanced potency (20). Interestingly, two receptor forms have been cloned for adiponectin that have unique distributions and affinities for the molecular forms of the protein. AdipoR1 is a high affinity receptor for gAd with very low affinity for fAd, and AdipoR2 has intermediate affinity for both forms of adiponectin (21). Interestingly, AdipoR1 is abundantly expressed in skeletal muscle and at moderate levels in other tissues, whereas AdipoR2 is predominantly expressed in the liver. These findings are consistent with the observation that fAd has a greater effect on hepatic metabolic signaling, whereas both gAd and fAd elicit metabolic effects in skeletal muscle (21–23). Aortic endothelial cells express both adiponectin isoforms, but appear to preferentially express mRNA for AdipoR1, suggesting a signaling role for gAd in this cell type (24, 25).

### *Effects of adiponectin on vascular structure and function (Table 1)*

Studies in animal models and human subjects have demonstrated an association between circulating adiponectin levels and endothelial function. Forearm blood flow in human subjects during reactive hyperemia is highly correlated in a negative fashion with adiponectin, indicating that adiponectin is closely associated with endothelium-dependent vasodilation (25–27). In human subjects, independent of a correlation with insulin sensitivity, circulating adiponectin levels are positively associated with arterial vasodilation in response to nitroglycerin, a measure of endothelium-independent vasodilation (28).

**TABLE 1.** Cellular effects of adiponectin in the vasculature

| |
|---|
| Enhanced endothelium-dependent vasodilation |
| Enhanced endothelium-independent vasodilation |
| Suppression of atherosclerosis |
| Suppressed expression of vascular adhesion molecules scavenger receptors |
| Reduced levels of TNF$\alpha$ and suppression of inflammatory TNF$\alpha$ effects on endothelial function |
| Attenuation of growth factor effects on smooth muscle cells |
| Inhibition of endothelial cell effects of oxidized LDL, including suppression of proliferation, superoxide generation and the activation of MAPK |
| Enhanced NO production |
| Stimulation of angiogenesis |
| Reduced neointimal thickening and proliferation of smooth muscle cells in mechanically injured arteries |
| Inhibition of endothelial cell proliferation and migration |

### *In vivo studies in mouse models*

Using a more direct approach to determine the role of adiponectin in the vasculature, several groups have generated mice that completely lack adiponectin expression. These knockout mice show striking vascular alterations, including severe neointimal thickening and increased proliferation of vascular smooth muscle cells in mechanically injured arteries (29). Importantly, replenishment of fAd by infection with a recombinant adenovirus attenuated neointimal proliferation (30).

Related *in vivo* studies have shown that both forms of adiponectin can suppress the development of atherosclerosis in susceptible mice. Apolipoprotein E-deficient mice treated with recombinant adenovirus to increase the circulating levels of fAd demonstrated a 30% decrease in lesion formation compared with mice expressing a control protein (31). Adiponectin associated with foam cells in the fatty streak lesions, suppressed the expression of vascular cell adhesion molecule-1 (VCAM-1) and class A scavenger receptors, and tended to reduce levels of TNF$\alpha$ (31). Similarly, transgenic mice overexpressing gAd ameliorated atherosclerotic lesion formation when crossed onto an apolipoprotein E-deficient background, an effect that was associated with decreased expression of class A scavenger receptors and TNF$\alpha$ (32).

At physiological levels, adiponectin exhibits specific and saturable binding to aortic endothelial cells, but readily binds to the walls of catheter-injured vessels, preferentially to intact vascular walls (33–35). Studies of vascular reactivity in aortic rings from adiponectin knockout mice showed reduced vasodilation in response to acetylcholine compared with wild-type mice, but not in response to sodium nitroprusside, indicative of an endothelial signaling defect (26).

### *Antiinflammatory effects of adiponectin*

Consistent with a protective effect on macrovascular disease, studies *in vitro* have provided insight into the direct effects of adiponectin on the function of vascular and inflammatory cells, including reversing some of the deleterious effects of TNF$\alpha$ on endothelial function. Without blocking TNF$\alpha$ binding, fAd inhibited TNF$\alpha$-induced expression of several adhesion molecules on the surface of endothelial cells, including VCAM-1, E-selectin, and intercellular adhesion molecule-1, and suppressed the effect of TNF$\alpha$ to induce the adhesion of monocytic THP-1 cells to cultured endothelial cells (18). Adiponectin (fAd) also suppresses TNF$\alpha$-induced inflammatory changes in endothelial cells by blocking inhibitory nuclear factor-$\kappa$B phosphorylation and nuclear factor-$\kappa$B activation without affecting TNF$\alpha$-mediated activation of c-Jun N-terminal kinase, p38, and Akt (33). Additional antiinflammatory effects of adiponectin (fAd) include suppression of leukocytic colony formation, reduction of phagocytic activity, and reduction of TNF$\alpha$ secretion from macrophages (34, 36).

Using aortic endothelial cells, we recently reported that gAd inhibited oxLDL-induced cell proliferation as well as basal and oxLDL-induced release of superoxide and the activation of p42/p44 MAPK by oxLDL (24). The uptake and oxidation of circulating LDL particles in the vascular wall can potentiate the formation of foam cells, inactivate eNO, in-

duce inflammatory responses, and stimulate the generation of ROS, all processes that are widely believed to be integral to atherogenesis (5, 37). Vascular ROS can lead to the proliferation or apoptosis of endothelial cells, processes that are integral to angiogenesis and vascular damage (11, 38, 39).

### *Effects of adiponectin on NO*

As one of the cardinal functions of endothelial cells is to generate NO, the salutary effects of adiponectin on the vasculature have been hypothesized to be associated with enhanced eNO generation. Consistent with this, concentrations of fAd similar to those found in the circulation have been shown to enhance NO production in cultured aortic endothelial cells (25, 40). In our studies of the effects of oxLDL on endothelial cells, gAd also enhanced NO production by ameliorating the suppression of eNOS activity by oxLDL (24).

### *Effects of adiponectin on angiogenesis*

Two very recently published studies have shown that adiponectin also has significant effects on small vessel angiogenesis. Ouchi *et al.* (41) showed that fAd exhibited chemoattractant properties and stimulated the differentiation of human umbilical vein endothelial cells into capillary-like structures *in vitro*; fAd also stimulated blood vessel growth *in vivo* in a corneal model of angiogenesis. In contrast, Bråkenhielm *et al.* (42) reported that fAd acts a negative regulator of angiogenesis, preventing new blood vessel growth in a chick chorioallantoic membrane assay as well as in mouse corneal angiogenesis assays, and *in vitro*, adiponectin potently inhibited endothelial cell proliferation and migration. These discordant results may arise from the source of the endothelial cells, large vessels (aorta) or small capillaries, or from technical differences in the corneal angiogenesis assays (42).

In addition to endothelial cell responses, the effects of adiponectin on vascular smooth muscle cells may also contribute to its influence on angiogenesis. Adiponectin (fAd) treatment of vascular smooth muscle cells in culture attenuated proliferation induced by a variety of growth factors and migration induced by heparin-binding-epidermal growth factor or platelet-derived growth factor-BB (PDGF-BB). The reduction in signaling effects of PDGF were possibly caused at least in part by binding of adiponectin to PDGF-BB, which inhibited PDGF cellular association (30, 43). Depending on the setting, angiogenesis can be either reparative (*e.g.* coronary neovascularization) or pathological (*e.g.* diabetic retinopathy), so it is difficult to predict what effects of adiponectin in cultured cell systems might correlate best with its observed role in protection from atherosclerosis in mouse models *in vivo*. Nevertheless, the available data indicate that adiponectin has dramatic effects on vascular remodeling that probably contribute to vascular function and growth in various disease states.

### *Adiponectin signal transduction mechanisms*

Studies in metabolically responsive cell types (liver, skeletal muscle, and adipose) have shown that activation of the pleiotropic enzyme AMP-activated protein kinase (AMP kinase) is integral to the signaling effects of adiponectin (22, 23, 44). AMP kinase is typically activated in a variety of cellular stress conditions associated with AMP accumulation, and it turns on catabolic pathways that generate ATP (45, 46). Interestingly, AMP kinase has recently been implicated in the mechanism of action of metformin in the liver (47) and potentially in the action of the thiazolidinedione insulin sensitizers (48, 49), suggesting that it may be an important mediator of antidiabetic metabolic effects, consistent with the insulin-sensitizing effects of adiponectin.

AMP kinase also appears to mediate adiponectin signaling in endothelial cells (40, 41). As in other cell types, AMP kinase activation in the endothelium increases fatty acid oxidation and net ATP synthesis (50, 51). As AMP kinase activates eNOS in endothelial cells (52), this enzyme system provides a potential signaling link between adiponectin and NO generation. Pharmacological AMP kinase activation also ameliorates the increased apoptosis observed in endothelial cells exposed to high glucose (53), suggesting that AMP kinase may mediate cellular growth and differentiation responses, as described above for adiponectin in endothelial cells.

What upstream or parallel pathway(s) modulates the activation of AMP kinase and eNOS by adiponectin? The available evidence at this early stage in our understanding of adiponectin signaling suggests that adiponectin influences a number of interrelated signaling pathways (Fig. 1). The hi-

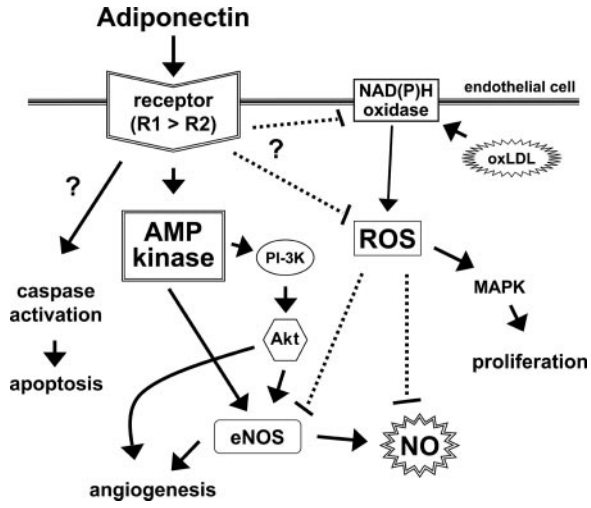


FIG. 1. Multiple potential signaling pathways for adiponectin in endothelial cells. Both isoforms of the adiponectin receptor (AdipoR1 and AdipoR2) are expressed in endothelial cells, but mRNA for the AdipoR1 receptor, with a higher affinity for gAd, is more abundant. As in metabolically responsive tissues, one of the major signaling effects of adiponectin in endothelial cells is activation of AMP kinase. AMP kinase, in turn, activates eNOS via a pathway that also appears to be dependent on Akt activation, which is linked upstream to phosphatidylinositol 3′-kinase (PI-3K) signaling. Both eNOS activation and Akt activation contribute to the effects of adiponectin on angiogenesis. Adiponectin also inhibits oxLDL-induced superoxide production, possibly through inhibition of cellular NAD(P)H oxidase activity. Reduced ROS generation may enhance NO production and diminish cell proliferation by adiponectin by ameliorating the suppression of eNOS activity and NO quenching by ROS and by blocking oxLDL-induced MAPK activation, respectively. Adiponectin can also lead to endothelial apoptosis via upstream caspase activation. The *solid arrows* and *dotted lines* reflect stimulatory and inhibitory effects, respectively. See text for discussion and pertinent references.

erarchy of these signaling responses has not been fully elucidated and is under active investigation. For example, the enhanced NO production in endothelial cells elicited by adiponectin is not only linked to AMP kinase activation, but is also dependent on signaling through the Akt kinase and its upstream mediator phosphatidylinositol 3′-kinase (40, 41). The effects of adiponectin on endothelial cell angiogenesis were also dependent on activation by adiponectin of both AMP kinase and Akt (41). AMP kinase appears to be upstream of Akt in adiponectin signaling in endothelial cells, because disrupting AMP kinase activation inhibited adiponectin-induced Akt phosphorylation. These findings are consistent with other examples of multiple parallel pathways that can elicit eNOS activation, including AMP kinase and Akt (54). Clearly, additional work will be required to map out the relative importance of specific upstream signals on adiponectin effects in endothelial cells. In addition, the signaling roles of the two adiponectin receptor isoforms are completely unknown at this time. As both AdipoR1 and AdipoR2 are expressed in endothelial cells (although more mRNA encoding R1 is present compared with R2), it is possible that they differ in their activation of various kinase-linked cascades in the endothelial cells.

Additional signaling systems have also been implicated in at least some of the endothelial effects of adiponectin. The inhibitory effect of adiponectin on TNF$\alpha$ signaling in endothelial cells was accompanied by cAMP accumulation and was blocked by an inhibitor of either adenylate cyclase or protein kinase A. These observations suggest that adiponectin may modulate inflammatory signaling in endothelial cells through cross-talk between the cAMP-protein kinase A and nuclear factor-$\kappa$B pathways (33). As oxLDL-induced superoxide generation in endothelial cells is linked to an NAD(P)H oxidase pathway, the suppression of this process by gAd may involve regulation of the activity of certain isoforms of NADPH oxidase or its protein subunits in the vascular cells (24, 55, 56). Finally, the activation of endothelial cell apoptosis by adiponectin in the system reported by Bråkenhielm and colleagues (42) is mediated by specific cellular caspases (caspases-8, -9, and -3), which may be coupled to unique upstream signaling cascades.

### *Vascular effects of leptin and resistin*

Although the role of the adipokine leptin in human obesity and insulin resistance has yet to be fully clarified (57), recent studies have provided evidence that leptin also has significant effects on vascular development and repair. Treatment of endothelial cells with leptin increased cell number and enhanced the formation of capillary-like tubular structures *in vitro* and evidence of neovascularization *in vivo* (58). Leptin acts synergistically with fibroblast growth factor-2 and vascular endothelial growth factor to stimulate angiogenesis and can also influence vascular permeability (59). Leptin induced neovascularization in corneas from normal rats, but not in corneas from leptin receptor-deficient (*fa/fa*) rats, indicating that the vascular effects were mediated via the leptin receptor (60). Leptin administration also increased vascular lesion formation in injured arteries in leptin-deficient (*ob/ob*) mice, but this response was markedly attenuated in leptin receptor-deficient (*db/db*) mice, providing strong evidence for direct effects of leptin on the arterial wall (61, 62).

The adipokine resistin, which mediates glycemia in obesity (63), has been shown to promote endothelial cell activation, with increased endothelin-1 transcription and release and increased expression of the adhesion molecule VCAM-1 and the chemotactic protein VCAM-1 (64). To make matters even more complex, adiponectin reportedly inhibits the induction of the adhesion molecules VCAM-1 and intercellular adhesion molecule-1 in endothelial cells by resistin, suggesting that the balance of the opposing effects of these adipokines at the level of the endothelial cell is an important determinant of the development of vascular inflammation, leukocyte adherence, and early atherosclerosis (65). In future work, additional circulating adipokines are likely to add to our growing understanding of the complex relationship between adipose tissue and vascular proliferation and function.

### *Perspective*

Adiponectin is an important adipokine specifically secreted by adipocytes that circulates at relatively high levels in the bloodstream. Adiponectin exhibits potent antiinflammatory and atheroprotective responses in vascular tissue in addition to its insulin-sensitizing effects in tissues involved in glucose and lipid metabolism. Thus, the reduced circulating levels of adiponectin in visceral adiposity are now known to contribute not only to insulin resistance and dysglycemia, but also to the endothelial vascular dysfunction that is characteristic of the metabolic syndrome. Ongoing studies will help delineate the roles of the two adiponectin receptor isoforms (gAd and fAd) as well as their oligomeric complexes, which may activate specific regulatory signaling pathways that mediate the cellular effects of adiponectin in the vasculature, as has begun to be appreciated for metabolically responsive tissues (66–68). A detailed characterization of the adiponectin signaling cascade in vascular tissues will potentially provide insight into novel therapeutic approaches that modulate this system to ameliorate the heightened cardiovascular risk associated with obesity and type 2 diabetes.

## Acknowledgments

The authors are grateful to Hiroyuki Motoshima, Xiangdong Wu, and Mahadev Kalyankar for their contributions to the research performed in their laboratories.

Received March 16, 2004. Accepted March 17, 2004.

Address all correspondence and requests for reprints to: Dr. Barry J. Goldstein, Division of Endocrinology, Diabetes and Metabolic Diseases, Jefferson Medical College, Suite 349, 1020 Locust Street, Philadelphia, Pennsylvania 19107. E-mail: barry.goldstein@jefferson.edu.

This work was supported by a grant from the American Diabetes Association.

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