Am J Physiol Heart Circ Physiol 292: H1655–H1663, 2007.
First published December 1, 2006; doi:10.1152/ajpheart.01072.2006.

Invited Review

Adiponectin and cardiovascular disease: state of the art?

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Szmitko PE, Teoh H, Stewart DJ, Verma S. Adiponectin and cardiovascular disease: state of the art? *Am J Physiol Heart Circ Physiol* 292: H1655–H1663, 2007. First published December 1, 2006; doi:10.1152/ajpheart.01072.2006.—The cardiometabolic syndrome, associated with increased cardiovascular disease risk in the industrialized world, is estimated to affect one in four adults. Although the mechanisms linking obesity and cardiovascular disease remain unclear, research continues to unravel the molecular pathways behind this pandemic. Adipose tissue has emerged as a metabolically active participant in mediating vascular complications, serving as an active endocrine and paracrine organ secreting adipokines, which participate in diverse metabolic processes. Among these adipokines is adiponectin, which seems to possess antiatherogenic and anti-inflammatory effects and may be protective against cardiovascular disease development. The current review describes the pathophysiology of adiponectin in atherosclerotic disease.

atherosclerosis; adipokines; cardiometabolic syndrome

OBESITY AND ITS ASSOCIATED adverse cardiovascular effects represent a worldwide pandemic (96). The cardiometabolic syndrome, the cluster of obesity-related metabolic disorders in one individual, is estimated to affect one in four adults, making it the leading public health issue associated with increased cardiovascular disease risk in the industrialized world (20). Although the mechanisms linking obesity and cardiovascular disease remain unclear, research continues to unravel the molecular pathways behind this pandemic with the goal of developing novel, protective therapies. Recently, adipose tissue has shed its label as a sedentary storage depot of excess energy and has emerged as a metabolically active participant in mediating vascular complications. Adipose tissue serves as an active endocrine and paracrine organ secreting an ever increasing number of mediators, known as adipokines, which participate in diverse metabolic processes (46). Though most adipokines appear to promote vascular disease, adiponectin seems to possess antiatherogenic and anti-inflammatory effects and may be protective against cardiovascular disease development. The current review describes the pathophysiology of adiponectin in atherosclerotic disease. The role of adiponectin in insulin resistance, diabetes, and the cardiometabolic syndrome will only be briefly discussed, and we direct the reader to a recent review for a more detailed discussion of these topics (4).

What Is Adiponectin?

Adiponectin, the most abundant known secreted factor produced by adipocytes, was originally identified by four independent groups in the mid-1990s using different experimental approaches, in both mice and humans (27, 48, 54, 70). Therefore, adiponectin is also called Acrp30 (70), AdipoQ (27), apM1 (48), and GBP28 (54). The adiponectin gene itself, located on chromosome 3q27 in humans (79), a locus that has been linked with diabetes susceptibility (42), encodes a secretory protein that structurally belongs to the complement 1q family. Full-length adiponectin contains 247 amino acids, including a collagen-like fibrous domain at the NH_2 terminus and a COOH-terminal globular region. The circulating plasma range of adiponectin in human subjects is 3–30 μg/ml, accounting for 0.01% of total plasma protein, being considerably more abundant than other adipokines, such as leptin (2–8 μg/l) or tumor necrosis factor (TNF)-α (<8 ng/l) (3). In plasma, adiponectin combines via its globular or collagen domains to form various multimer complexes. The three major complexes in plasma are a low-molecular-weight trimer (via globular domain interactions), a middle-molecular-weight hexamer, and a high-molecular-weight 12- to 18-mer (via collagenous domain interactions) (63). Also, existing in lower quantities is a smaller form of adiponectin that consists of globular domains cleaved from full-length adiponectin (63). Whereas there is no consensus concerning the biological significance of the various adiponectin isoforms, it is currently believed that circulating adiponectin complex distribution, specifically higher proportions of high-molecular-weight multimers, and not the absolute amount of plasma adiponectin, may be more clinically relevant, at least with respect to diabetes and coronary artery diseases (5, 38, 64). However, this theory remains largely unproven since until recently, the main means of profiling the individual adiponectin components was limited to semiquantitative methods. Molecular assays that are capable of differentiating between the various adiponectin multimers are currently being developed as investigators endeavor to determine which, if any, of the adiponectin complexes are more biologically active (5, 38).

The secretion of adiponectin by adipocytes appears to be hormone regulated. Adiponectin expression declines following stimulation with insulin, TNF-α, endothelin-1, and glucocorticoids, whereas transcription appears to increase with IGF-I treatment (24). Initially, adiponectin was thought to be exclusively synthesized by adipocytes; however, a recent study

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suggests that adiponectin is also synthesized and secreted by human cardiomyocytes (65). Adiponectin acts through its two receptors, designated AdipoR1 and AdipoR2, which are primarily expressed in skeletal muscle and liver, respectively (90). Subsequent studies have shown that AdipoR1 is also present in endothelial cells (53), cardiomyocytes (65), and pancreatic-β cells (35), whereas AdipoR2 is also expressed in endothelial cells (81). These observations provide a potential molecular pathway through which adiponectin may exert its effects on these tissues. Both receptors have seven transmembrane domains but differ structurally from G protein-coupled receptors and serve to bind both globular and full-length forms of adiponectin (90). The expression of both AdipoR1 and AdipoR2 is significantly decreased in muscle and adipose tissue in hyperinsulinemic and hyperglycemic states (84). The molecular pathways through which adiponectin mediates its effects appear to involve activation of the AMP-activated protein kinase (AMPK), the peroxisome proliferator-activated receptor (PPAR)-α, and the p38 mitogen-activated protein kinase (MAPK)-signaling pathways (31).

When compared with other adipokines, such as leptin and resistin, both considered to be proinflammatory, adiponectin exerts anti-inflammatory effects on the vasculature. Leptin acts as a satiety signal, acting on the hypothalamus to suppress food intake and stimulate energy expenditure, and thus plays an important role in controlling body fat stores (39). In contrast to adiponectin, circulating leptin levels are elevated in both obese individuals and patients with Type 2 diabetes and are associated with increased coronary artery calcification, a measure of coronary atherosclerosis (68). Furthermore, leptin appears to promote a proinflammatory milieu, by increasing the secretion of TNF, IL-6, and activating neutrophils and increasing the generation of reactive oxygen species, all of which promote endothelial dysfunction and vascular inflammation, prerequisites for atherogenesis (82). Clinically, in patients with angiographically confirmed coronary atherosclerosis, plasma leptin serves as a predictor of future cardiovascular events independent of other risk factors such as lipid or C-reactive protein (CRP) levels (89). Likewise, resistin, an adipokine that appears to play a role in obesity-associated insulin resistance, counteracts the vasculoprotective effects of adiponectin. Resistin exerts potent proinflammatory properties by upregulating inflammatory cytokines such as TNF, IL-1, and IL-6 (82), inducing endothelial adhesion molecule expression (86) and decreasing nitric oxide (NO) expression in endothelial cells (43). Thus adiponectin appears to serve as the protective adipocytokine, balancing the detrimental, proinflammatory actions of both leptin and resistin.

Adiponectin As a Clinical Marker of Cardiometabolic Disease

Despite being the most abundant adipokine secreted by adipose tissue, the initial clinical studies measuring plasma adiponectin levels in obese subjects yielded a surprising result. Obese subjects had significantly lower levels of plasma adiponectin when compared with nonobese subjects, and the adiponectin levels were negatively correlated to body mass index (BMI) in both male and female subjects ($r = -0.71$, $P < 0.0001$ and $r = -0.51$, $P < 0.0001$, respectively) (4). The same relationship exists in rodent models of obesity (27). Subsequent studies have confirmed this initial finding in humans and have further shown that circulating adiponectin concentrations are correlated more negatively with visceral fat area than with subcutaneous adiposity (10), suggesting a link with the metabolic syndrome. Thus, since adiponectin was decreased in individuals with more adipose tissue, it may serve as a biologically protective rather than detrimental molecule. The mechanism behind concomitant reductions in plasma adiponectin levels with increased visceral fat remains to be clarified. The current literature suggests that this phenomenon may be secondary to elevated levels of detrimental adipokines secreted in states of increased adiposity, such as TNF-α, which inhibit adiponectin secretion, leading to reduced plasma levels (6, 50).

A similar relationship exists between plasma adiponectin levels, insulin resistance, and Type 2 diabetes. In the initial study measuring plasma adiponectin levels in Type 2 diabetic patients, adiponectin concentrations were significantly lower compared with those of age- and BMI-matched control men and women (26). Type 2 diabetic patients with macrovascular disease had lower circulating adiponectin levels than those without (26). Importantly, hypoadiponectinemia appears to place an individual at risk for the development of insulin resistance and progression toward diabetes. In a case-control series conducted among the Pima Indians of Arizona, a population with a high prevalence of obesity, Type 2 diabetes, and insulin resistance, it was reported that plasma adiponectin levels strongly correlated with reduced insulin sensitivity. Moreover, individuals with higher concentrations of circulating adiponectin were less likely to develop Type 2 diabetes compared with those with lower plasma adiponectin concentrations [incidence rate ratio, 0.63; 95% confidence interval (CI), 0.43–0.92; $P = 0.02$] (47). High levels of circulating adiponectin provided greater protection against Type 2 diabetes among Pima Indians than do age, fasting glucose, fasting insulin, or waist circumference (47). A similar protective role of adiponectin was demonstrated among Japanese subjects followed over a 5-yr period where patients with serum levels of adiponectin in the lowest tertile developed diabetes 9.3 times more often than those in the highest third ($P = 0.046$) (14).

However, despite these clinical associations, it still remains unclear as to whether decreased adiponectin levels facilitate the onset of insulin resistance or are merely a consequence of the physiological changes associated with the onset of the cardiometabolic syndrome at its earliest stages. On the basis of animal studies, as discussed below, adiponectin appears to be required for maintaining normal glucose metabolism, and in its absence, insulin resistance occurs. Furthermore, mutations, in the adiponectin gene itself, are associated with the metabolic syndrome. These results provide the biological plausibility for considering the concept that hypoadiponectinemia leads directly to the development of insulin resistance and diabetes mellitus and does not merely serve as a consequence of the metabolic syndrome. Clinical research in newborns, children, and adolescents may provide further insight into the time line of diabetes development and the association with adiponectin levels. Low birth weight has been associated with an increased risk of obesity, insulin resistance, and diabetes in adulthood, and small-for-gestational-age infants have been demonstrated, in at least one study, to have significantly lower levels of circulating adiponectin compared with that of appropriate-for-

gestational-age neonates (33). It will be interesting to follow this cohort of patients to see whether lower adiponectin levels at birth may serve as a predisposing factor for the development of insulin resistance, suggesting adiponectin plays a very early role in the pathogenesis of diabetes. Further support for adiponectin playing an early role in disease progression comes from the pediatric literature. In children aged 10–19 yr, the adiponectin serum concentration appeared to decrease as the number of metabolic syndrome component criteria increased (69). Thus it appears that adiponectin plays a primary role in the pathobiology of the cardiometabolic syndrome and is not merely a consequence of disease progression.

Mutations within the adiponectin gene appear to be associated with obesity, insulin resistance, and diabetes. The frequency of the missense mutation I164T was significantly higher in Type 2 diabetic patients compared with that of age- and BMI-matched controls ($P < 0.01$) and was associated with a significantly lower plasma adiponectin concentration (42). The mutation was also appreciably higher in patients with the metabolic syndrome, and angiographically confirmed coronary artery disease (56). Likewise, the single nucleotide polymorphism G276T appears to be associated with lower levels of adiponectin and with the earlier onset of coronary artery disease (19). Variation within the adiponectin gene promoter region, namely, the single nucleotide polymorphisms -11391G>A and -11377C>G, appears to result in lower adiponectin levels and places individuals at increased risk for developing Type 2 diabetes (72). Accordingly, adiponectin appears to be crucial in the alliance between obesity, insulin resistance, and Type 2 diabetes.

Lower concentrations of plasma adiponectin have been associated with both essential hypertension and dyslipidemia. Patients with essential hypertension appear to have significantly lower levels of plasma adiponectin when compared with normotensive patients (9.1 ± 4.5 vs. 13.7 ± 5.2 μg/ml; $P < 0.001$) (1). In another case-control study, after adjusting for confounding factors such as obesity, insulin resistance, and diabetes, significantly lower concentrations of circulating adiponectin were present in patients with hypertension compared with those without (5.2 ± 0.2 vs. 6.1 ± 0.2 μg/ml; $P < 0.001$) (30). The mechanism accounting for this observation may involve the effect of angiotensin II. Infusion of angiotensin II in rats decreased plasma adiponectin levels via signaling through the angiotensin II type 1 receptor (67). In human patients with essential hypertension, blockade of the renin-angiotensin system via treatment with angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors resulted in an increase in adiponectin concentrations and improved insulin sensitivity (21). Likewise, subjects with low plasma adiponectin levels appear to have smaller low-density lipoprotein (LDL) particle size, low lipoprotein lipase activity, lower high-density lipoprotein (HDL) cholesterol levels, and higher triglyceride levels when compared with individuals with higher levels of adiponectin (57). These associations tend to persist following adjustment for potential confounding variables such as comorbid conditions or obesity-associated variables.

As a result of its association with the individual components of the metabolic syndrome, as expected, hypoadiponectinemia is associated with an increased risk for atherosclerotic cardiovascular disease. Both men and women with documented coronary artery disease, when compared with age- and BMI-matched control subjects, exhibit significantly lower plasma adiponectin levels (3.4 ± 1.8 vs. 7.4 ± 3.5 μg/ml in men, $P < 0.01$, and 4.3 ± 1.5 vs. 9.3 ± 6.8 μg/ml in women, $P < 0.05$) (59). Among male patients who underwent coronary angiography, a multiple logistic regression analysis, including plasma adiponectin level, diabetes, dyslipidemia, hypertension, smoking habits, and BMI revealed that hypoadiponectinemia was significantly and independently correlated with coronary artery disease ($P < 0.0088$) (45). This study further demonstrated that hypoadiponectinemic patients (adiponectin levels <4.0 μg/ml) had a significant twofold increase in coronary artery disease prevalence, independent of other cardiac risk factors (45).

A prospective, nested case-control study among 18,225 male participants in the Health Professionals Follow-up Study suggested that, after adjustment for family history of myocardial infarction (MI), BMI, alcohol consumption, physical activity, diabetes, and the presence of hypertension, participants in the highest compared with the lowest quintile of circulating adiponectin levels had a significantly decreased risk of MI [relative risk (RR), 0.41; 95% CI, 0.24–0.70, $P < 0.001$] (66). Among patients with renal failure, those who experienced new cardiovascular events had lower plasma adiponectin levels than those of event-free patients, with a relative risk of adverse cardiac events of 1.56 times higher among patients with adiponectin levels in the lowest third compared with those with levels in the highest third (95% CI, 1.12–1.99 times) (97). It was estimated that for each 1 μg/ml increase in plasma adiponectin level, risk decreased by 3% (97). Similarly, among Type 2 diabetic men, increased circulating adiponectin levels were associated with a decrease in cardiovascular risk (RR, 0.71; 95% CI, 0.53–0.95) (71). In patients with Type 1 diabetes, increased adiponectin concentrations were likewise associated with a lower risk of coronary artery disease after adjusting for standard risk factors (13). Plasma adiponectin levels also appear to be lower among patients presenting with acute coronary syndromes, possibly secondary to adiponectin consumption in a hyperinflammatory state (acutely elevated CRP levels), though the significance of this observation in relation to mortality or morbidity is unknown (41). Finally, circulating adiponectin concentrations may be associated with the occurrence of coronary in-stent restenosis. In end-stage renal disease patients undergoing hemodialysis who received stenting for a single coronary lesion, patients with restenosis tended to have lower plasma adiponectin concentrations than those without (6.2 ± 2.2 μg/ml, $n = 37$ vs. 27.2 ± 10.8 μg/ml, $n = 34$; $P = 0.0001$) (55).

The association of hyopadiponectinemia with atherosclerotic disease extends beyond the coronary vasculature. In a case-control study among individuals with or without ischemic cerebrovascular disease, decreasing concentrations of adiponectin were independently and significantly associated with a higher risk of stroke (9). Furthermore, patients with lower plasma adiponectin levels presenting with a first-ever ischemic stroke had an increased risk of 5-yr mortality compared with patients with higher adiponectin levels, independently of other adverse predictors (17). The relative risk of death was 8.1 (95% CI, 3.1–24.5; $P < 0.001$) for patients with adiponectin levels in the lowest tertile compared with the highest tertile (17). Hypoadiponectinemia appears to be associated with peripheral arterial disease as well. Plasma adiponectin concentrations were significantly lower in patients with peripheral arterial disease and were independently associated with ankle-brachial

index, suggesting that circulating adiponectin levels are decreased in proportion to the severity of disease (29). Likewise, in the Linz Peripheral Arterial Disease study, low plasma levels of adiponectin were associated with the presence of symptomatic peripheral arterial disease, independent of traditional risk factors (16). However, this same inverse relationship does not appear to exist in patients with chronic heart failure.

In two prospective studies conducted among heart failure patients, high circulating adiponectin levels were identified as independent predictors of mortality (23, 36). Kistorp et al. (36) measured plasma adiponectin levels, among other parameters, in 195 heart failure patients and followed this cohort for a median of 2.6 yr. After being adjusted for clinical variables associated with heart failure such as age, systolic blood pressure, left ventricular ejection fraction <25%, duration of congestive heart failure, creatinine clearance, and plasma NH_2-terminal pro-brain natriuretic peptide levels, the hazard ratio of mortality for adiponectin values in the two upper tertiles relative to the lowest tertile was 3.23 ($P = 0.032$). Similarly, George et al. (23) found that, among clinically controlled heart failure outpatients, adiponectin level in the highest quartile served as an independent predictor of total mortality and heart failure hospitalizations over a 2-yr prospective follow-up period. These results may be reflective of the known association between cardiac "wasting" and increased mortality, suggesting that the paradoxical increase of adiponectin levels in those with the highest mortality may have been secondary to weight loss, a known stimulator of adiponectin (2). Alternatively, the heightened inflammatory state of individuals with high risk coronary artery disease or severe end-stage heart failure may trigger the compensatory expression, synthesis, and release of adiponectin from the adipose tissue in an attempt to limit further endothelial damage, cardiac remodeling, or atherosclerotic change. However, in the advanced diseased state, the counterregulatory system is overwhelmed and any measured elevation in plasma adiponectin may cease to be adequately protective, translating into higher cardiovascular morbidity and mortality. Owing to previously discussed technical limitations, the majority of the epidemiological studies have only measured total adiponectin levels and were unable to comment on the relative distribution of the individual adiponectin fractions. It is therefore not unreasonable to speculate that patients with the worse odds ratio for heart failure may also have the lowest percentages of the biologically active adiponectin oligomer or, alternatively, a higher ratio of "inert" adiponectin complexes, despite high levels of total plasma adiponectin. Studies deemed at examining the various circulating isoforms of adiponectin are thus warranted, given that each isoform may have a variable physiological effect.

Adiponectin and Surrogates of Atherosclerosis

Plasma adiponectin levels have also been demonstrated to correlate to surrogate markers of atherosclerosis. Currently, atherosclerosis is largely considered an inflammatory disease (78), and individuals at high risk of developing atherosclerosis have high levels of circulating inflammatory markers such as CRP. CRP has emerged as not only an independent risk factor for cardiovascular disease but is also considered to be a biological mediator of atherosclerosis (88). In human male patients, plasma adiponectin and CRP levels were negatively correlated ($r = -0.29$, $P < 0.01$) (61). Decreased plasma adiponectin levels in women similarly demonstrated positive correlation with CRP elevation (51). Thus adiponectin appears to play an anti-inflammatory role in atherogenesis.

Endothelial dysfunction sets the stage for atherogenesis, and its clinical evaluation serves as a biomarker for vascular disease (87). Hypoadiponectinemia appears to be associated with impaired endothelium-dependent vasorelaxation (62). In a study conducted on 202 hypertensive patients, plasma adiponectin levels were measured along with forearm blood flow via strain-gauge plethysmography. Plasma adiponectin level was independently and highly correlated with the vasodilator response to reactive hyperemia ($r = 0.257$, $P < 0.001$), suggesting that hypoadiponectinemia is associated with impaired endothelium-dependent vasorelaxation (62). In a similar study conducted on Japanese subjects without a history of cardiovascular disease or diabetes, endothelial function was impaired in proportion to the severity of obesity, which was, in turn, closely related to plasma adiponectin levels (76). Likewise, plasma levels of adiponectin are associated with impaired endothelium-dependent vasodilation independent of diabetes mellitus (81).

Levels of adiponectin appear to be associated with direct measures of atheroma burden (28, 40). Adiponectin has a close relationship to intima-media thickness among patients with coronary artery disease ($P = 0.02$) (40). In the Salzburg Atherosclerosis Prevention Program in subjects at high individual risk (SAPHIR) study, a study conducted on 1,515 middle-aged healthy white subjects, common carotid artery intima-media thickness (CIMT) and the presence of atherosclerotic plaques were assessed by B-mode ultrasound. After adjustment for established risk factors, for every 1 μg/ml decrease in adiponectin level, CIMT increased by 3.48 μm in men (95% CI, 1.23–5.73 μm) and by 2.39 μm in women (95% CI, 0.50–4.27 μm) (28). Thus the negative association of adiponectin levels and CIMT suggests hypoadiponectinemia is a risk factor for the development of early atherosclerosis.

Adiponectin As a Molecular Regulator of Atherosclerosis

Clinically, adiponectin appears to serve as a biomarker for cardiovascular disease. However, as a biologically active molecule, adiponectin appears to protect the vasculature at each stage of atherogenesis. Atherosclerosis is largely considered to be an inflammatory disease (78). The first stage of atherogenesis involves endothelial dysfunction, which culminates from diminished production or availability of NO and/or an imbalance in the relative contribution of endothelium-derived relaxing and contracting factors, such as endothelin-1, angiotensin, and oxidants (85). NO is the key endothelium-derived relaxing factor that plays a pivotal role in the regulation of vascular tone and vasomotor function. In addition to its vasodilatory effect, NO also protects against vascular injury, inflammation, and thrombosis by inhibiting leukocyte adhesion to the endothelium, maintaining vascular smooth muscle in a nonproliferative state, and limiting platelet aggregation (78). However, in response to the traditional cardiovascular risk factors, such as hypertension, diabetes and hypercholesterolemia, the endogenous defenses of the vascular endothelium begin to break down. For example, oxidized LDL activates and changes the biological characteristics of the endothelium, in part, by reduc-

ing the intracellular concentration of NO (12). Adiponectin possesses anti-inflammatory properties, in part, by altering the level of NO at the level of the endothelium. In vitro, adiponectin induces NO production in human aortic endothelial cells via activation of the AMPK pathway and enhanced endothelial NO synthase (eNOS) mRNA and protein expression (8, 25). Furthermore, adiponectin suppresses superoxide generation and enhances eNOS activity in endothelial cells that are treated with oxidized LDL (53). Therefore, by promoting NO generation, adiponectin serves to protect against the onset of endothelial dysfunction.

Once endothelial dysfunction is established, endothelial cells undergo inflammatory activation, characterized by increased expression of adhesion molecules, and promote the progression of atherosclerosis. Adhesion molecule expression is induced by proinflammatory cytokines such as interleukin (IL)-1, IL-8, TNF-α, and the acute phase protein CRP. Once adherent to the adhesion molecules, the monocytes transmigrate into the tunica intima, passing between the endothelial cells, along a concentration gradient of monocyte chemoattractant protein-1. Within the arterial intima, the monocytes develop into macrophages and begin to express class A scavenger receptors (SR-As) that internalize modified lipoproteins, giving rise to lipid-laden macrophages or foam cells, which characterize early atherosclerotic lesions. Within the developing atheroma, the foam cells begin to secrete proinflammatory cytokines, maintaining the inflammatory milieu. In cultured cells, physiological concentrations of adiponectin exert an anti-inflammatory effect on the endothelium by attenuating the attachment of monocytes to endothelial cells by inhibiting the proinflammatory TNF-α- and IL-8-induced synthesis of adhesion molecules [e.g., intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, and E-selectin] by interfering with nuclear factor-κB activation (37, 59). Adiponectin suppresses the expression of macrophage SR-As, resulting in the reduction of foam cell formation and decreasing the secretion of proinflammatory cytokines (60). Foam cell formation is further reduced by adiponectin-induced downregulation of acyl-coenzyme A:cholesterol acyltransferase-1 in macrophages, the enzyme that catalyzes the formation of cholesteryl esters (22), and by adiponectin-mediated induction of anti-inflammatory cytokine IL-10 secretion from macrophages (44). Accordingly, adiponectin limits the initiation of atherosclerotic plaque formation.

The evolution of a fatty streak toward a complex lesion is typified by the proliferation of smooth muscle cells (SMCs), their migration toward the intima, and their synthesis of collagen. Physiological concentrations of adiponectin significantly suppress both the proliferation and migration of human aortic SMCs in vitro, induced by platelet-derived growth factor (PDGF)-BB (3). Adiponectin exerts its effect by directly binding PDGF-BB and inhibiting growth-factor-stimulated extracellular signal-regulated kinase signaling. Thus adiponectin may act as a modulator for vascular remodeling. Accumulation of oxidized LDL has toxic effects on macrophages and SMCs, leading to the formation of a necrotic core and a reduction in collagen synthesis that leads to fibrous cap thinning. The thinning of the fibrous cap is further enhanced by the overexpression of matrix metalloproteinases, which degrade supportive collagen, leaving the plaque vulnerable to rupture and eventual thrombosis. Adiponectin selectively increases the expression of tissue inhibitor of metalloproteinase-1 in human monocyte-derived macrophages by inducing IL-10 secretion (44). Therefore, adiponectin may favor plaque stabilization (see Fig. 1).

In vivo studies in mice have confirmed the antiatherogenic properties of adiponectin observed in vitro. Adiponectin-deficient or knockout mice, as compared with wild-type controls, show neointimal thickening and increased proliferation of vascular SMCs after mechanical injury to arteries (52). Adenovirus-mediated reexpression of adiponectin in these mice attenuated the extent of neointimal proliferation considerably (52).

Studies with adiponectin-deficient mice further revealed adiponectin as a potential endogenous antithrombotic factor

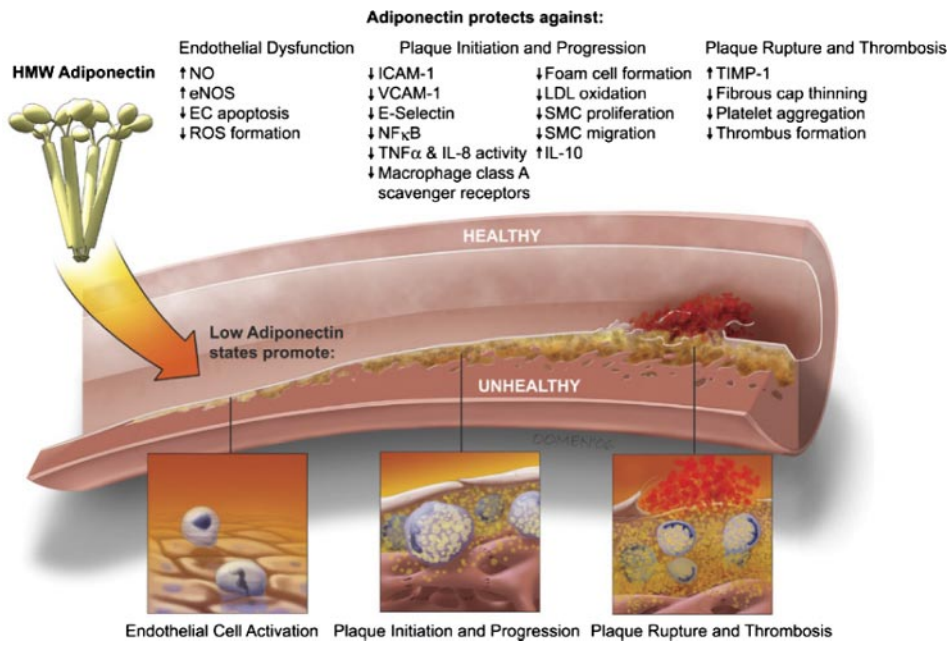

Fig. 1. Adiponectin, via its anti-inflammatory actions on the vascular endothelium, is a molecular regulator of atherosclerosis. Adiponectin appears to protect against all stages of atherosclerotic plaque formation, maintaining a functional, healthy endothelium; preventing plaque initiation, formation, and progression; and protecting against plaque rupture and thrombosis. NO, nitric oxide; eNOS, endothelial NO synthase; EC, endothelial cell; ROS, reactive oxygen species; TNF, tumor necrosis factor; IL, interleukin; SMC, smooth muscle cell; HMW, high-molecular weight; TIMP-1, tissue inhibitor of metalloproteinase-1.

(34). When compared with wild-type control mice, adiponectin-deficient mice demonstrated enhanced thrombus formation and platelet aggregation at sites of vascular injury (34). Furthermore, treatment of apolipoprotein E (apoE)-deficient mice—mice that develop early atherosclerosis—with adiponectin-expressing adenoviruses resulted in a 30% decrease in atherosclerotic lesion formation as compared with control mice (58). Immunohistochemical analysis indicated that adenovirus-mediated adiponectin colocalized with foam cells in the fatty streak lesions and resulted in suppression of VCAM-1, SR-A, and TNF-α expression (58). In a similar experimental setting, apoE knockout mice overexpressing globular adiponectin had fewer atherosclerotic lesions when compared with control apoE knockout mice, despite similar plasma glucose and lipid levels (92).

Adiponectin As a Molecular Regulator of Insulin Resistance and Diabetes

In addition to being a clinical marker of susceptibility toward developing insulin resistance and diabetes, several animal studies have demonstrated the molecular association of adiponectin with impaired glucose metabolism. Adiponectin appears to modulate insulin sensitivity by stimulating glucose utilization and fatty acid oxidation via the phosphorylation and activation of AMPK in both muscle and liver cells (83, 91). During consumption of a high-fat and sugar diet, but not with a regular diet, adiponectin knockout mice exhibit delayed clearance of free fatty acid in plasma, high levels of TNF-α mRNA in adipose tissue, and severe diet-induced insulin resistance with reduced insulin-receptor substrate 1-associated phosphatidylinositol 3-kinase (PI3-kinase) activity in muscle (49). However, with replenishment of adiponectin, these changes were reversed, decreasing the extent of insulin resistance. These findings suggest that restoration of adiponectin levels may provide a novel treatment for the metabolic syndrome (49, 93).

Adiponectin and Cardioprotection

Aside from protecting the vasculature from atherogenesis, adiponectin may serve to limit pathological cardiac remodeling, which leads to hypertrophy and diastolic dysfunction, as well as to provide protection from ischemic damage. In adiponectin-deficient mice, pressure overload resulted in enhanced concentric cardiac hypertrophy and increased mortality compared with control mice (74). These hypertrophic changes were associated with increased extracellular signal-regulated kinase and decreased AMPK signaling in the myocardium. Supplementation with adiponectin attenuated cardiac hypertrophy in part by activating AMPK signaling (74).

Furthermore, adiponectin appears to act directly on the heart to ameliorate cardiac ischemic injury. Ischemia-reperfusion in adiponectin-deficient mice resulted in increased MI size, apoptosis, and TNF-α expression when compared with wild-type mice (75). Administration of adiponectin attenuated these detrimental effects via the activation of both AMPK and cyclooxygenase (COX)-2 dependent mechanisms (75). Thus both AMPK-mediated antiapoptotic actions and COX-2 mediated anti-inflammatory actions serve to protect the myocardium from ischemia-reperfusion injury. By activating COX-2, adiponectin appears to be linked with prostaglandins, which themselves serve to protect various organs from ischemic insult. Therefore, adiponectin itself may one day serve as a potential therapy for acute MI.

Modifying Adiponectin Levels To Combat Cardiometabolic Disease

Since low plasma adiponectin concentrations correlate closely with obesity-related disorders, strategies that increase plasma adiponectin may serve to enhance overall health by preventing the development of the metabolic syndrome. Weight reduction, consumption of a Mediterranean-type diet, increased physical activity, and moderate alcohol intake appear to elevate plasma adiponectin levels (18, 73, 95).

Pharmacological interventions, namely, with PPAR-γ agonists or thiazolidinediones, appear to enhance adiponectin expression. Used clinically to treat Type 2 diabetes by improving insulin sensitivity, thiazolidinediones increase adiponectin mRNA expression and secretion in adipose tissue by activating the adiponectin promoter (50). In a randomized, double-blind placebo-controlled trial conducted on patients with Type 2 diabetes, rosiglitazone therapy for 6 mo resulted in a significant increase in circulating plasma levels compared with placebo (94). Additionally, rosiglitazone therapy has been reported to selectively elevate plasma high-molecular-weight adiponectin in humans and rodents (64). Pioglitazone exerts a similar effect on adiponectin levels (11) and increases the secretion of the high-molecular-weight form of adiponectin (7). Furthermore, PPAR-γ agonists appear to enhance the expression of AdipoR1 and AdipoR2 in skeletal muscle and adipose tissue and thereby may enhance adiponectin intracellular signaling pathways that promote glucose utilization and antiatherosclerotic conditions (80). In addition to PPAR-γ agonists, treatment with both angiotensin-converting enzyme inhibitors and angiotensin receptor blockers increased adiponectin concentrations in insulin-resistant hypertensive patients, without affecting BMI; however, the molecular mechanisms involved remain to be elucidated (21). Recently, the Rimonabant in Obesity-Lipids (RIO-Lipids) study examined the effects of rimonabant, a selective cannabinoid-1 receptor blocker, on metabolic risk factors (15). Rimonabant is believed to induce significant weight loss in obese patients via the activation of the endocannabinoid system through CB1, which plays an important role in both the central and peripheral regulation of energy balance, body weight, and food intake (77). Rimonabant, at a dose of 20 mg daily, resulted in a significant increase in plasma adiponectin, at levels above those that could be explained by weight loss alone (15). Finally, as the beneficial molecular properties of adiponectin continue to emerge, a recombinant form of adiponectin may become available for therapeutic use or, alternatively, an adiponectin receptor-specific agonist may be developed to optimize the favorable cellular effects of adiponectin.

Conclusion

Adiponectin has emerged as an antiatherogenic, anti-inflammatory, cardioprotective, insulin-sensitizing adipokine that appears to protect against obesity-related metabolic disease. A series of clinical and experimental studies have highlighted these biological roles. Pharmacological approaches that increase circulating plasma adiponectin levels or enhance the molecular signaling of adiponectin will certainly form the basis

for future therapeutic interventions. Further experimental studies should shed light on the pathophysiological mechanisms of adiponectin and may provide promising targets for the prevention and treatment of obesity, the metabolic syndrome, and cardiovascular disease.

NOTE ADDED IN PROOF

During the review process, a few more key insights into the link between adiponectin and cardiovascular disease emerged. Yamauchi et al. (93a) demonstrated that the simultaneous disruption of both AdipoR1 and -R2 in mice abolished adiponectin binding and actions, resulting in increased inflammation, oxidative stress, and tissue triglyceride content, and subsequent insulin resistance and glucose intolerance. Therefore, AdipoR1 and -R2 appear to serve as the primary receptors for adiponectin in vivo and assume an important role in glucose and lipid metabolism. To further support the protective role of adiponectin from systemic inflammation, Takemura et al. (79a) demonstrated that adiponectin was capable of opsonizing apoptotic cells, which were subsequently phagocytosed by the binding of adiponectin to calreticulin on the macrophage cell surface.

GRANTS

This study was supported by grants from the Heart and Stroke Foundation of Canada (to S. Verma) and The Physicians' Services Incorporated Foundation (P. E. Szmitko). P. Szmitko is the recipient of the MerckFrosst Canada Traineeship in Diabetes and Cardiovascular Disease.

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