EDITORIAL COMMENT

A Big Fat Wedding

Association of Adiponectin With Coronary Vascular Lesions*

Mandeep Bajaj, MD,†
Ori Ben-Yehuda, MD, FACC‡

Galveston, Texas; and San Diego, California

Increasing obesity rates and a sedentary lifestyle worldwide have led to a marked increase in rates of type 2 diabetes as well as the metabolic syndrome (MetS), which is characterized by a clustering of cardiovascular risk factors (1). The two main etiologic factors for the MetS, obesity and insulin resistance, often are interrelated and concomitantly present. Despite recent claims that the cardiovascular risk associated with the MetS is simply the additive risk of the individual risk factors identified in patients with MetS, the concept is still clinically useful given the clustering of risk factors and the underlying etiologic factors of insulin resistance and obesity (2).

The realization that adiposity and particularly visceral adiposity (3) are potent risk factors for the development of type 2 diabetes has focused renewed attention on the role of the adipocyte in the development of both diabetes and cardiovascular disease. Once regarded as a relatively inert storage depot for fat, adipose tissue is now recognized as an important endocrine organ. The adipocyte, in response to specific extracellular stimuli or changes in metabolic conditions, releases a host of hormones and cytokines. These secreted proteins, which include tumor necrosis factor-alpha, leptin, resistin, adiponectin, and others, perform diverse functions. They have been collectively referred to as adipokines and are postulated to play an important role in the pathogenesis of insulin resistance, as well as the often-associated hypertension, disorders of coagulation, and dyslipidemia. An associated low-grade inflammatory state also is present in the MetS and diabetes, and may be mediated by adipokines (4).

The most abundant adipokine produced by visceral fat cells is adiponectin, an adipose tissue-specific 30-kDa protein, which is cleaved proteolytically to release a C-terminal globular domain (5,6). Insulin resistance, type 2 diabetes, and coronary artery disease are characterized by decreased circulating concentrations of adiponectin (7–9). Although adiponectin is produced by adipose cells, blood levels actually are inversely proportional to visceral adiposity (10).

A strong relationship has been demonstrated between plasma adiponectin levels and both hepatic and peripheral tissue insulin sensitivity in patients with type 2 diabetes (7). One of the primary effects of adiponectin is to increase fatty acid oxidation in muscle, leading to a decrease in intracellular fatty acid metabolites, i.e., fatty acyl coenzyme A, diacylglycerol, ceramides, and enhanced insulin signal transduction. Treatment with a thiazolidinedione (TZD) increases circulating adiponectin concentrations by almost 3-fold in patients with type 2 diabetes (7). Exercise has also been shown to increase adiponectin levels (8). Circulating adiponectin exists in at least two forms in serum, as a hexamer referred to as a low molecular weight (LMW) complex and as a high molecular weight (HMW) complex consisting of 12 to 18 subunits (9). The ratio between these two oligomeric forms (HMW to LMW) is critical in determining TZD-mediated increase in insulin sensitivity (11).

Adiponectin has been shown to have antiatherogenic and anti-inflammatory effects in rodents (12). In genetic studies, a strong linkage is observed between the chromosomal region encompassing the adiponectin gene (APM1) and risk factors for cardiovascular disease (13). The I164T mutation in the adiponectin gene also has been shown to be a common genetic polymorphism associated with the metabolic syndrome and coronary artery disease (CAD) in the Japanese population (14). Hypoadiponectinemia is closely associated with increased plasma levels of inflammatory markers such as C-reactive protein (15). Adiponectin inhibits tumor necrosis factor-alpha–induced activation of nuclear factor-kappa-B-dependent proinflammatory pathways, expression of endothelial adhesion molecules, macrophage-to-foam cell transformation, lipid accumulation in macrophages, and smooth muscle cell proliferation (16,17). Furthermore, adiponectin has been shown to prevent angiotensin II–induced human endothelial cell apoptosis (18). It remains to be investigated whether low plasma adiponectin levels contribute directly or indirectly (by aggravating the individual components of the metabolic syndrome, including insulin resistance) to accelerated atherosclerosis in patients with metabolic syndrome.

Studies have provided evidence for a link between hypoadiponectinemia and impaired nitric oxide generation. Diminished brachial arterial endothelium-dependent vasodilation has been associated with reduced adiponectin levels in subjects with type 2 diabetes and with hypertension (19). Animal models of adiponectin deficiency are characterized by severe neointimal hyperplasia that can be reversed with adiponectin repletion (12). Recent in vitro studies (20) using bovine aortic endothelial cells have shown that adiponectin stimulates nitric oxide (NO) production by increasing endothelial nitric oxide synthase (eNOS) enzyme activity and eNOS expression via a phophatidylinositol 3-kinase–dependent pathway that causes phosphorylation/activation...
of eNOS at Ser1179 by AMP-activated protein kinase. In a rat model of NO synthesis deficiency produced by L-NAME, plasma adiponectin concentration and adiponectin messenger RNA levels in the aorta were noted to be reduced (21). Treatment using TZD increased fat adiponectin messenger RNA levels and normalized the plasma adiponectin concentration in association with an increase in NO synthesis in arterial tissue. These results provide evidence that, in rodents in vivo, adiponectin is an important regulator of NO synthesis and could explain some of the observed vasoprotective properties of adiponectin.

The identification of two adiponectin receptors in mice represents a significant breakthrough in our understanding of the mechanism of adiponectin action (22). Adiponectin is abundantly expressed in skeletal muscle, whereas AdipoR2 is predominantly expressed in the liver. AdipoR1 and AdipoR2 serve as receptors for globular and full-length adiponectin and mediate stimulation of AMP-activated protein kinase, fatty acid oxidation, and glucose uptake. More recently, the expression of adiponectin has been demonstrated in human monocytes and macrophages (23). Skeletal muscle adiponectin receptors AdipoR1 and AdipoR2 expression levels are strongly related to peripheral (muscle) insulin sensitivity in humans in vivo (24).

In this issue of the Journal, Otsuka et al. (25) demonstrate that low plasma adiponectin levels are associated with complexity of angiographic coronary lesions in men both in stable CAD and in acute coronary syndrome (ACS). Given the association of plaque complexity with plaque vulnerability, they suggest that hypoadiponectinemia may contribute to coronary plaque vulnerability. In addition, they demonstrate that patients with ACS have lower plasma adiponectin concentration than patients with stable coronary artery disease. Their findings are important given the higher prevalence of diabetes and impaired glucose tolerance in patients with ACS (26) and suggest that hypoadiponectinemia may be an important link between type 2 diabetes, CAD, enhanced plaque vulnerability, and ACS. An increase in plasma adiponectin levels after treatment with TZD may be particularly valuable in enhancing coronary plaque stability and preventing ACS in patients with type 2 diabetes. The recent results of the PROActive (PROspective pioglitAzone Clinical Trial In macroVascular Events) trial (27), demonstrating a reduction in myocardial infarction rate over the course of 2 years of treatment with the TZD pioglitazone, may be the first evidence that pharmacologic intervention that increases adiponectin levels (among other interrelated effects of the TZDs) may be clinically relevant.

The complexity of atherosclerosis and plaque instability undoubtedly involves multiple interrelated risk factors and mediators. Given the relatively small size of the study by Otsuka et al. (25), the clinical utility of adiponectin as a biomarker remains to be determined in much larger studies. Whether adiponectin provides incremental predictive value to established risk factors such as cholesterol/high-density lipoprotein and the diagnosis of metabolic syndrome or diabetes itself remains to be determined in larger prospective studies. Moreover, whether adiponectin’s role in atherosclerosis is direct or whether its effects are mediated through other interrelated metabolic players such as high-density lipoprotein cholesterol also remains to be fully elucidated. And although the routine use of adiponectin as a biomarker in medicine is still premature, it remains an important target for study, not only as a potential marker of disease but also as a target for pharmacologic intervention.

REFERENCES

17. Ouchi N, Kihara S, Arita Y, et al. Adiponectin, suppresses lipid accumulation and class A scavenger


