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*Clin Appl Thromb Hemost* 2006; 12; 163

DOI: 10.1177/107602960601200203

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## The Role of Adiponectin in Atherosclerosis and Thrombosis

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**Summary:** Obesity is a major risk factor for morbidity and mortality from cardiovascular causes. Adiponectin has been identified recently as one of the adipocytokines with important metabolic effects. It can suppress atherogenesis by inhibiting the adherence of monocytes, reducing their phagocytic activity, and suppressing the accu-

mulation of modified lipoproteins in the vascular wall. In addition, as adiponectin decrease endothelial damage and stimulates production of NO from vascular endothelial cells, hypoadiponectinemia may be partially contribute to thrombus formation.

**Key Words:** Adiponectin—Atherosclerosis—Thrombosis.

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It is clear that obesity is a major risk factor for morbidity and mortality from cardiovascular causes (1). Current advanced knowledge has revealed that adipose tissue is not only a simple energy pool, but it also secretes metabolic hormones, enzymes, anti-fibrinolytic proteins, and inflammatory cytokines (2,3). These secretory proteins, which have been collectively named adipokines (3), include leptin (4), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) (5), plasminogen activator inhibitor type-1 (PAI-1) (6), adipsin (7), resistin (8), and adiponectin (9). In this review; we focus on the role of adiponectin in atherosclerotic disease and discuss its potential effects on thrombus formation.

### STRUCTURE, SYNTHESIS, AND METABOLIC FUNCTIONS OF ADIPONECTIN

Adiponectin has been identified recently as one of the adipocytokines with important meta-

bolic effects (9–11). The protein is present abundantly in the circulation, accounting for approximately 0.01% of the total plasma protein (12).

A description of the cDNA encoding adiponectin was first reported in 1995 by Scherer and colleagues (10). Adiponectin is a 244-amino acid protein produced by apM1 (adipose most abundant gene transcript) cDNA (9), and is also known as GPB28 (gelatin-binding protein of 28kDa) in humans. The mouse homology of adiponectin has been cloned as AcrP30 (adipocyte complement-related protein of 30 kDa) and adipoQ (10,11). The human adiponectin gene that is encoded by apM1 mRNA is located on chromosome 3q27, consisting of three exons and two introns (13,14). Furthermore, the cloning of DNAs encoding adiponectin receptors 1 (Adipo R1) and 2 (Adipo R2) was reported in June 2003 (15). These receptors are predicted to contain seven transmembrane domains, but do not seem to be coupled with G-protein (15).

Adiponectin is composed of four structurally distinct domains, an amino-terminal signal sequence, a variable region, a collagenous domain (cAd), and a carboxy-terminal globular domain (gAd) (10). On the basis of both its primary amino acid sequence and its subunit domain structure, adiponectin is most similar to C1q, a member of complement-related family of pro-

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teins (Fig. 1). However, X-ray crystallography of the globular fragment of adiponectin also reveals a striking structural homology to TNF- $\alpha$ , suggesting an evolutionary link between the TNF- $\alpha$  family members and adiponectin (16). Both C1q and TNF family play important roles in inflammation, the immune system, and atherosclerosis (17).

The synthesis and secretion of adiponectin is regulated by several mechanisms. Insulin stimulates adiponectin gene expression and its secretion from cultured 3T3-L1 adipocytes (10). Both insulin and insulin-like growth factor-1 (IGF-1) also increase adiponectin synthesis in adipocytes isolated from human visceral adipose tissue (18). Peroxisome proliferator-activated receptors (PPAR), which belong to the nuclear hormone superfamily, are involved in the regulation of adiponectin synthesis (19).

Once synthesized, mammalian adiponectin undergoes posttranslational hydroxylation and glycosylation modifications, yielding eight isoforms. Six of the adiponectin isoforms are glycosylated. O-linked glycosylation sites have been mapped to four lysine residues—68, 71, 80, 104—and one proline residue, 94, located within the collagenous domain (20). In addition, there is evidence that some of the O-linked glycans contain unique and adipocyte-specific disial-

ic acid residues, a newly recognized class of sialyl groups in glycoproteins (21).

Little is known about the degradation of plasma adiponectin; however, the kidney may be involved in this process because the plasma level of this protein markedly increases in patients with advanced renal failure (22).

Adiponectin may augment and mimic metabolic actions of insulin by increasing fatty acid oxidation and insulin-mediated glucose disposal in skeletal muscle as well as decreasing hepatic glucose output (23).

In the liver, the decreased free fatty acid influx and increased fatty acid oxidation contribute to reduced hepatic glucose output and very-low-density lipoprotein triglyceride synthesis. In vascular endothelium, adiponectin decreases monocyte adhesion to endothelium, suppresses macrophage-to foam cell transformation, and inhibits vascular smooth muscle cell proliferation and migration (24).

#### ADIPONECTIN AND ATHEROSCLEROSIS

Atherosclerosis has been regarded as an inflammatory disease. The initial atherosclerotic le-

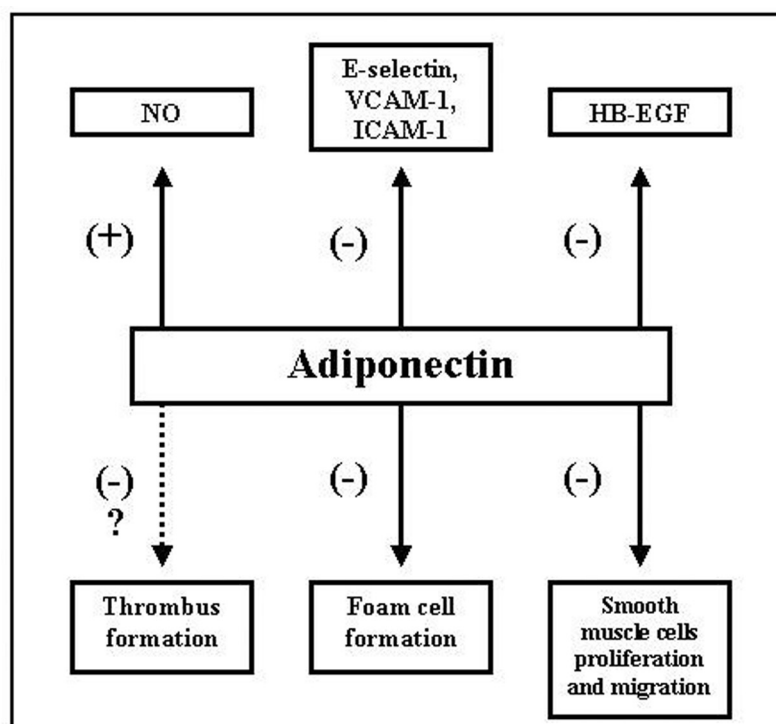


FIG. 1. Antiatherogenic effects of adiponectin.

sion consists of monocytes/macrophages and T lymphocytes (25). The first change that precedes the formation of lesions of atherosclerosis is endothelial injury, which is mediated by various inflammatory stimuli, including TNF- $\alpha$  (17).

Experimental studies have indicated that adiponectin has potential anti-atherogenic and anti-inflammatory properties (26–29). When the vascular endothelium is injured, adiponectin accumulates in the subintimal space of the arterial wall through its interaction with collagens in the vascular intima (30). Adiponectin dose-dependently inhibited TNF- $\alpha$ -induced monocyte adhesion and expression of endothelial-leukocyte adhesion molecule -1 (E-selectin), vascular cell adhesion molecule -1 (VCAM-1), and intracellular adhesion molecule -1 (ICAM -1) on the endothelium (31). It has been suggested that the intracellular signal by which adiponectin suppressed adhesion molecule expression is inhibition of endothelial NF- $\kappa$ B (nuclear transcription factor  $\kappa$ B) signaling through the activation of cAMP protein kinase A (32).

TNF- $\alpha$  activates nuclear transcription factor NF- $\kappa$ B in endothelial cells by stimulating protein kinase NIK (NF- $\kappa$ B inducing kinase), which phosphorylates NF- $\kappa$ B inhibitor, I $\kappa$ B, initiating its degradation of I $\kappa$ B. The effect of adiponectin is specific for the I $\kappa$ B-NF- $\kappa$ B pathway. The inhibition of I $\kappa$ B phosphorylation is most likely mediated by the cAMP-protein kinase A pathway, because it is mimicked by the membrane-perme-

able cAMP analogue, dibutyryl-cAMP, and blocked by inhibitors of either adenylate cyclase or protein kinase A (32).

The expression of adhesion molecule plays an important role in the regulation of inflammatory reactions in various types of cells. If the excess inflammatory response could be neutralized by adiponectin, it might be possible to prevent the process of atherogenesis (31).

In addition, Ouchi and colleagues (31) found that adiponectin had effects on monocyte adhesion to endothelium, myeloid differentiation, and macrophage cytokine production and phagocytosis. Moreover, adiponectin also suppresses lipid accumulation in monocyte-derived macrophages through the suppression of macrophage scavenger receptor expression (28).

On the other hand, adiponectin suppressed the expression of HB-EGF in stimulated endothelial cells of injured vascular wall and also the proliferation and migration of smooth muscle cells stimulated by various growth factors such as PDGF, basic FGF, EGF, and HB-EGF. These suppressive effects of adiponectin on the production and action of growth factors in vascular stenosis indicate that it could prevent injury-induced intimal thickening (28).

A recent report demonstrated that adiponectin has the direct action of stimulating the production of nitric oxide (NO) in endothelial cells (Fig. 2). This direct stimulation depends on the pathway of phosphatidylinositol-3-kinase (PI3K) in-

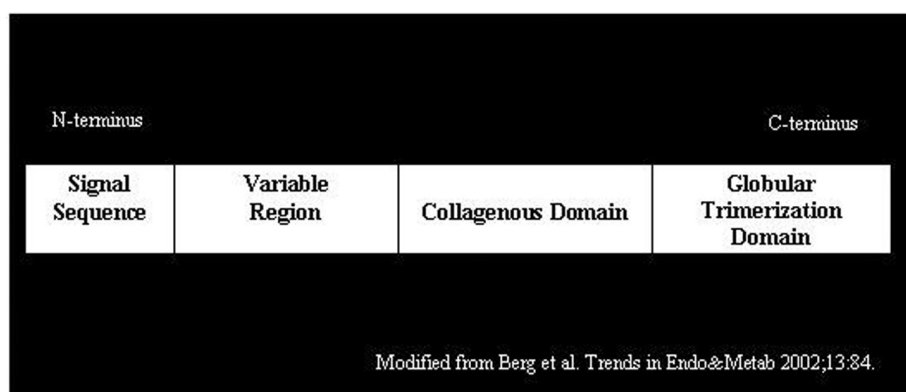


FIG. 2. Structure of adiponectin (16).

volving phosphorylation of endothelial NO synthase (eNOS) at ser 1179 by AMPK (23).

### EPIDEMIOLOGY OF ADIPONECTIN IN CORONARY ARTERY DISEASE

One of the most interesting features of adiponectin is that, in contrast to other adipocytokines that are markedly upregulated in obesity, its adipose tissue expression and plasma concentration is reduced in overweight and obese subjects. This has been observed in different animal models of obesity, as well as in obese humans (9,11,33). It is possible that although adiponectin expression is activated during adipogenesis, a feedback inhibition on its production may occur during the development of obesity. For example, adipocyte expression and secretion of adiponectin is reduced by TNF- $\alpha$  (34).

Levels are also lower in patients with essential hypertension (35) and in diabetic patients compared with nondiabetic subjects, and are particularly low in subjects with coronary artery disease (CAD) (36).

Plasma levels of adiponectin were significantly decreased in patients with CAD than in age- and BMI-adjusted control subjects (31). A recent study reported that hypoadiponectinemia was significantly and independently correlated with CAD even after adjustment for several coronary risk factors (37). Moreover, in a very recent report, Nakamuro and colleagues reported that measurement of plasma concentrations of adiponectin may be used for assessing the risk of CAD and may be related to the development of acute coronary syndrome (ACS) (38).

High sensitive C-reactive protein (hs-CRP) is a well-known marker and risk factor for coronary artery disease. It was recently shown that CRP mRNA is expressed in human adipose tissue. A significant inverse correlation has been observed between CRP and adiponectin mRNA levels in subcutaneous adipose tissue of human subjects with atherosclerosis (28). Therefore, the expression of CRP may be negatively regulated by adiponectin in adipose tissue. Indeed, the reciprocal relationship was found between adiponectin and TNF- $\alpha$  on their production in adipose tissue. CRP production modulated by TNF- $\alpha$  might be regulated by adiponectin in adipose tissue.

In addition, it is clear that most patients with CAD have metabolic syndrome, which is closely related to insulin resistance (39). Hyperinsul-

inemia associated with an insulin resistant state may lead to a decrease of production of adiponectin. These findings suggest that the decreased plasma adiponectin levels may relate to the development of CAD.

### ADIPONECTIN AND THROMBOSIS

Platelets play an important role in arterial thrombosis and the onset of acute myocardial infarction after atherosclerotic plaque rupture. Inhibition of platelet aggregation has become a critical step in preventing thrombotic events that are associated with stroke, heart attack, and peripheral arterial thrombosis (40).

Endothelial cells play a vital physiologic role in dividing blood from tissue. These cells actively inhibit the activation of the hemostatic mechanism and maintain blood circulation and fluidity, limit the efflux of cells from the bloodstream, and participate in the maintenance of normal vasomotor tone (41).

Vascular endothelial dysfunction plays a pivotal role in the pathogenesis of atherosclerosis and enhances the risk of future cardiovascular events (42). Because adiponectin may protect the endothelium from early atherosclerotic events such as the expression of adhesion molecules (31) or the attachment of monocytic cells (43), hypoadiponectinemia could be related to endothelial damage.

On the other hand, loss of plasma adiponectin may accelerate early atherosclerotic vascular damage and reduce various physiologic roles of endothelial cells, including NO synthesis and supply.

The localization of the platelet to areas of inflammation is mediated by adhesion molecules. Platelets contain integrins of the  $\beta 1$  and  $\beta 3$  subfamilies, and platelet activation occurs as a result of integrin binding to adhesion molecules expressed by injured or inflamed endothelium or to the exposed subendothelium. The activated platelet expresses the integrin  $\alpha IIb\beta_3$ , which allows the platelet to bind bivalent fibrinogen and thereby crosslink with other platelets (ie, aggregate) (44).

Furthermore, Chen and colleagues demonstrated that adiponectin at physiologic concentrations stimulated production of NO (nitric oxide) from vascular endothelial cells (23). During the past several years, clear evidence has emerged that a concerted action of nitric oxide (NO) generated by either endothelial or platelet NO synthases

regulates platelet activation, causing inhibition of adhesion and aggregation (45–47). Activation of guanylyl cyclase, inhibition of the PI3K pathway, and suppression of both P-selectin expression and conformational change in glycoprotein  $\alpha\text{IIb}\beta_3$ , are required for fibrinogen binding (48).

As adiponectin decreases endothelial damage and stimulates production of NO from vascular endothelial cells, hypo adiponectinemia may partially contribute to thrombus formation, especially in patients with CAD.

### CONCLUSIONS

Adiponectin is an adipocyte-specific plasma protein, which acts as an endogenous regulator of endothelial cells in response to inflammatory stimuli. It can suppress atherogenesis by inhibiting the adherence of monocytes, reducing their phagocytic activity, and suppressing the accumulation of modified lipoproteins in the vascular wall. In addition, the loss of adiponectin effects enhances endothelial dysfunction and thrombus formation and may be associated with future cardiovascular events.

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