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STATE-OF-THE-ART PAPER

Adiponectin and Vulnerable Atherosclerotic Plaques

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High-risk plaques that are vulnerable to rupture demonstrate distinct morphological characteristics. They are differentiated from the lesions responsible for stable coronary artery disease by their large necrotic cores, thin-inflamed fibrous caps, and positive remodeling. Adiponectin is an adipocytokine that is reduced in obesity and type 2 diabetes. Hypoadiponectinemia has been associated with an increased risk of coronary artery disease and acute coronary syndrome in several though not all studies. The involvement of adiponectin provides clues to the inflammatory and atherogenic mechanisms associated with pathological coronary disease progression. (J Am Coll Cardiol 2011;57:761–70) © 2011 by the American College of Cardiology Foundation

Heart disease is the leading cause of death in the world (1). Acute coronary events are a consequence of thrombotic occlusions of coronary arteries, and thrombosis is believed to be caused by plaque rupture in 75% of patients (2). Thus it is consequently accepted as the critical event leading to acute coronary syndrome (ACS) (3,4). These vulnerable plaques are often large and consist of a necrotic core that forms a significant portion of the plaque. Covered by a thin inflamed fibrous cap, the necrotic core is often associated with intraplaque neovascularization and hemorrhage and adventitial vasa vasorum proliferation (5). Because vulnerability is associated with inflammation, neovascularization, and the necrotic core formation, it is prudent to investigate the mediators of coronary artery disease and plaque vulnerability.

One important mediator of coronary artery disease (CAD) progression is adiponectin. Adiponectin is a protein secreted by adipose tissue (adipocytokine). A strong relationship has been demonstrated between plasma adiponectin levels and both hepatic and peripheral tissue insulin sensitivity in humans (6). One of the primary effects of adiponectin in rodents is to increase fatty acid oxidation in muscle, leading to a decrease in intracellular fatty acid metabolites (i.e., long chain fatty acyl coenzyme A, diacylglycerol, ceramides, and enhanced insulin signal transduction), resulting in an improvement in insulin sensitivity (7). Hypoadiponectinemia in insulin-resistant states such as obesity and type 2 diabetes is associated with increased plasma levels of inflammatory markers such as C-reactive protein (8,9) as well as an increased risk for CAD. Adiponectin inhibits tumor necrosis factor (TNF) 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. 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. Hypoadiponectinemia has been associated with coronary lesion complexity (10) and ACS (11). Adiponectin's involvement in the development of atherosclerosis appears to be more related to the stability of atherosclerotic plaque rather than the atherosclerotic burden (11,12). Thus adiponectin may be involved in the pathogenesis of vulnerability of coronary lesions.

Structure, Origin, and Characteristics of Adiponectin

Adipocytes release hormones and cytokines that are functionally diverse and include adiponectin as well as interleukin (IL)-1, IL-6, IL-8, TNF-alpha, leptin, resistin, and others (13,14). Adiponectin was originally discovered in the mid 1990s and named Acrp30 (15), AdipoQ (16), apM1 (17), and GBP28 (18) by 4 independent groups. It is the most abundant adipokine released by adipocytes in response to extracellular stimuli and metabolic changes. Adiponectin is predominately, but not exclusively, produced by adipose tissue. Recent studies suggest that it is also synthesized and secreted by human cardiomyocytes (19). The adiponectin gene is located on chromosome 3q27 in humans (20) and expresses a secretory protein that consists of 247 amino acids including a carboxyl-terminal globular domain and an amino-terminal collagen domain (21) and has a structure similar to complement 1q (22) (Fig. 1).

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Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
AMP = adenosine monophosphate
AMPK = adenosine monophosphate-activated protein kinase
BMI = body mass index
CAD = coronary artery disease
cAMP = cyclic adenosine monophosphate
COX = cyclooxygenase
CRP = C-reactive protein
eNOS = endothelial nitric oxide synthase
HMW = high molecular weight
IL = interleukin
LMW = low molecular weight
MMP = matrix metalloproteinase
MMW = middle molecular weight
NO = nitric oxide
TCFA = thin-cap fibroatheroma
TIMP = tissue inhibitor of metalloproteinase
TNF = tumor necrosis factor
TZD = thiazolidinedione
VEGF = vascular endothelial growth factor
VH-IVUS = virtual histology intravascular ultrasound

Circulating serum adiponectin levels in Japanese non-obese subjects have been approximated at 3 to 30 μg/ml (23) with a significant reduction (>50%) noted in obese subjects (24). Although adiponectin is produced by adipocytes, plasma levels actually are inversely proportional to body mass index (BMI) and visceral adiposity (14,24). Adiponectin exists in plasma as complexes and binds by its globular and collagen domain to form 3 major oligomeric multimers: a low-molecular-weight (LMW) trimer, a middle-molecular-weight (MMW) hexamer, and high-molecular-weight (HMW) 12- to 18-multimer (25) (Fig. 1). A fourth form found in the circulation consists of a trimer bound to albumin (Alb-LMW) (26). MMW and LMW forms account for 25% of the total adiponectin, whereas HMW accounts for 50% of the total adiponectin in humans (26). Plasma levels of the HMW multimer have stronger associations with insulin sensitivity than the ratio of HMW multimer to total adiponectin and total adiponectin alone, suggesting that the HMW multimer is the active form (27). Thus measurements of specific multimeric forms may be more valuable than simply measuring total adiponectin levels. Two adiponectin receptors have been identified in mice (Fig. 1). AdipoR1 is abundantly expressed in skeletal muscle and is also seen in endothelial cells (28), cardiomyocytes (19,29), and pancreatic-beta cells (30), whereas AdipoR2 is predominately in the liver (31) and is also expressed in endothelial cells (32). These receptors are also expressed in human monocytes and macrophages (33). Adiponectin appears to mediate its actions via the activation of the cyclic adenosine monophosphate (cAMP)–dependent, AMP-activated protein kinase (AMPK), cyclooxygenase (COX)-2, and peroxisome proliferator-activated receptor-alpha pathways (34–37).

Adiponectin and ACS

Hypoadiponectinemia has been associated with CAD and ACS in several (38–45) but not all studies (46–49) (Table 1). Patients with plasma adiponectin levels <4.0 μg/ml have a 2-fold increase in the prevalence of angiographically determined CAD independent of other well-known risk factors, including diabetes mellitus, dyslipidemia, hypertension, smoking, and increased BMI (50). In a 10-year follow-up of healthy elderly patients, higher adiponectin levels were associated with a lower risk of CAD independent of other risk factors such as increased BMI and insulin resistance (51). Serum adiponectin levels are also inversely related to the severity of CAD in nondiabetic patients (52,53). In a study of 207 men, those with stable CAD and complex coronary lesions had significantly lower plasma adiponectin levels than those with stable CAD and simple lesions (54,55). Furthermore, those with multiple complex lesions had significantly lower levels of adiponectin than those with single complex lesions in ACS, suggesting that adiponectin is also an independent predictor of coronary lesion complexity in ACS (54). In the event of ACS, plasma levels of adiponectin are significantly lower than in patients with stable CAD (54–56). The early phase of myocardial infarction in particular has been associated with a reduction in adiponectin levels (57). Higher levels of adiponectin have been linked to decreased prevalence of CAD in both men and women and show a beneficial association with a lower risk of nonfatal myocardial infarction in men without pre-existing CAD, although they have failed to predict future CAD events in women (Table 1, Rancho Bernardo Study) (49).

In addition to the direct relationship as above, there are multiple other markers of inflammation (which is an obligatory component of plaque instability) that correlate with adiponectin. Results of numerous studies have established a positive association between C-reactive protein (CRP) levels and BMI (58), CAD (59), unstable angina (60), and ACS (61). Hypoadiponectinemia, which is associated with future risk of myocardial infarction in men without CAD (41), is negatively correlated with CRP levels in CAD patients. Additionally, CRP has also been demonstrated to contribute to vascular inflammation by inhibiting nitric oxide (NO) production (62). The vasodilatory and protective effects of NO are impeded by such risk factors as oxidized low-density lipoproteins and CRP, which reduce endothelial NO synthase (eNOS) production (63,64). Diminished eNOS expression obstructs the ability of NO to ameliorate the vicious effects of inflammation. Adiponectin has been shown to promote eNOS synthesis via the AMPK pathway (65), thus enhancing the anti-inflammatory effect of NO. Adiponectin's inhibition of CRP also results in improved NO synthesis by reducing downregulation of eNOS.

Vulnerable plaques, also referred to as thin-cap fibroatheroma (TCFA) (66), are the most common morphology of rupture-prone plaques that result in ACS occlusions (67,68). Most culprit lesions in ACS have a large quantity of plaque. Their vulnerability is defined as a relatively large necrotic lipid-laden core, intraplaque hemorrhage, and/or calcification and abundant vasa vasorum. They are also

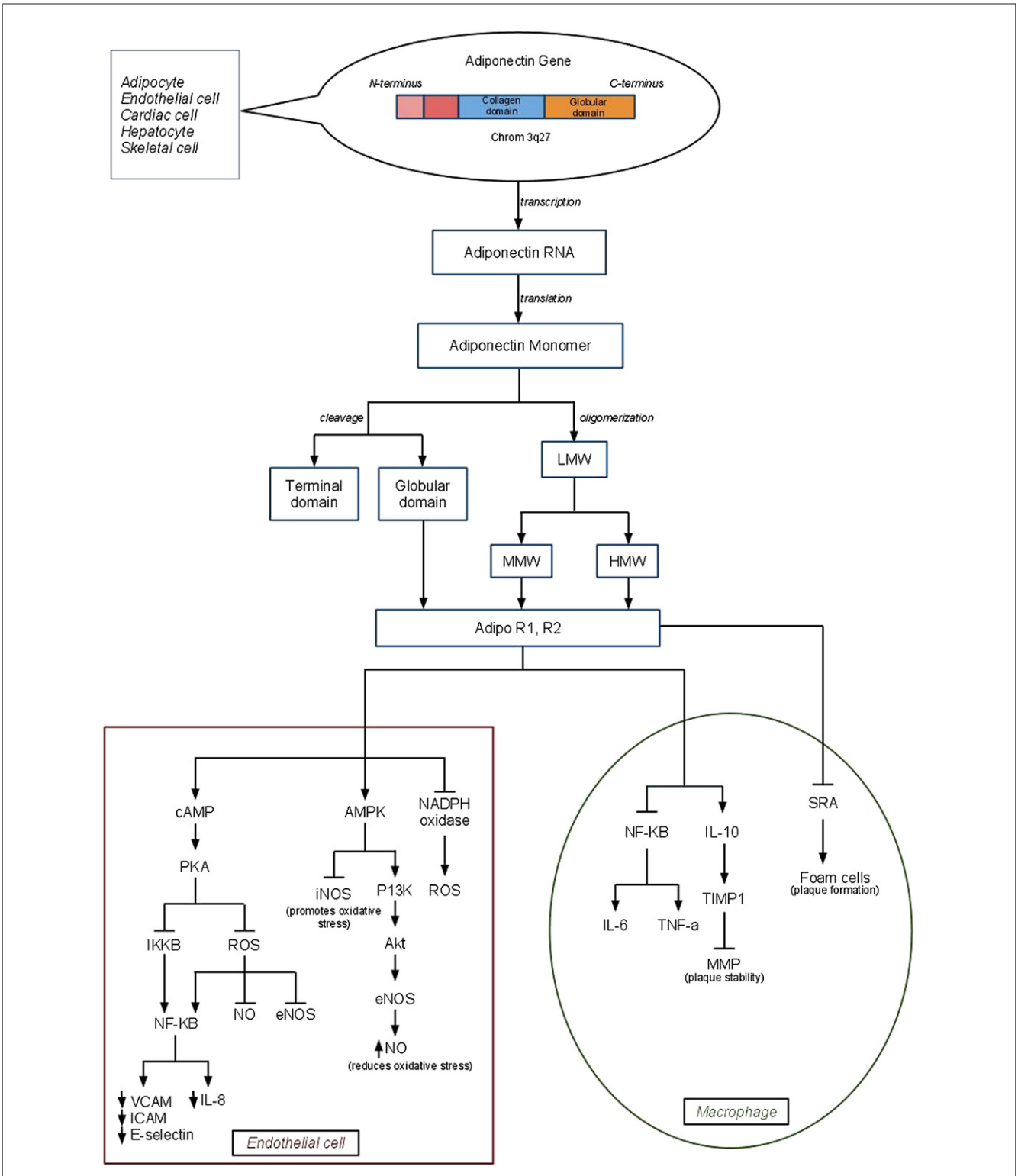

Figure 1 **Antiatherosclerotic Effects of Adiponectin**

Schematic representation of the effects of adiponectin on the endothelial cell and macrophage. Adipo = adiponectin receptor; AMPK = adenosine monophosphate-activated protein kinase; cAMP = cyclic adenosine monophosphate; eNOS = endothelial nitric oxide synthase; HMW = high molecular weight; ICAM = intercellular adhesion molecule; IKKB = IKB kinase; IL = interleukin; iNOS = inducible nitric oxide synthase; LMW = low molecular weight; MMP = matrix metalloproteinase; MMW = middle molecular weight; NADPH = nicotinamide adenine dinucleotide phosphate; NF-KB = nuclear factor-kappa B; NO = nitric oxide; P13K = phosphatidylinositol 3'-kinase; PKA = protein kinase A; RNA = ribonucleic acid; ROS = reactive oxygen species; SRA = class A scavenger receptor; TIMP = tissue inhibitor of metalloproteinase; TNF = tumor necrosis factor; VCAM = vascular cell adhesion molecule.

Table 1 Relationship of Adiponectin to CAD and ACS

Study/First Author (Ref. #)	Outcome	Cases	Controls	Study Population	Study Type	Correlation
Studies supporting relationship of hypoadiponectinemia to CAD and ACS						
Zoccali et al. (40)	Angina, MI, HF, arrhythmia, TIA, stroke, PVD, major arterial/venous thrombosis	95	132	ESRD on hemodialysis with pre-existing CAD	Prospective cross-sectional	Yes
HPFUS (41)	MI	266	532	Healthy men	Prospective nested case control	Yes
HPFUS (42)	Death from CAD, MI, CABG, coronary angioplasty	89	656	Men with type II DM without pre-existing CAD	Prospective nested	Yes
Becker et al. (43)	MI, CABG, angioplasty, stroke	10	167	CKD with and without pre-existing CAD	Prospective observational	Yes
Iwashima et al. (44)	MI, angina, stroke, TIA	31	119	Japanese men with CKD with and without CAD	Prospective cross-sectional, longitudinal	Yes
PEDCS (45)	Angina, MI, stenosis ≥50%, CABG, angioplasty, ischemic ECG changes	28	34	Youth with type I DM	Prospective case control	Yes
Studies not supporting relationship of hypoadiponectinemia to CAD and ACS						
BRHS (46)	MI	589	1,231	Men	Prospective nested case control	No
Strong Heart (47)	MI	251	251	American Indians without pre-existing CAD	Prospective case control	No
BWHSS (48)	Death from CAD, MI, angina, CABG, angioplasty	167	334	British women without pre-existing CAD	Prospective nested case control	No
Rancho Bernardo Study (49)	MI, revascularization	252	1,352	Older Caucasian men and women without CAD	Prospective cross-sectional	No

ACS = acute coronary syndrome; BRHS = British Regional Heart Study; BWHSS = British Women's Heart Health Study; CABG = coronary artery bypass graft; CAD = coronary artery disease; CKD = chronic kidney disease; DM = diabetes mellitus; ECG = electrocardiogram; HPFUS = Health Professionals Follow-Up Study; MI = myocardial infarction; PEDCS = Pittsburgh Epidemiology of Diabetes Complication Study; TIA = transient ischemic attack.

covered by a thin, inflamed, fibrous cap that may fissure (69,70). They often enlarge outward from the vessel lumen, which is referred to as positive vessel remodeling (66,71,72). In an effort to further evaluate adiponectin in stable CAD and its association with plaque vulnerability, the TCFA prevalence was identified using both virtual histology intravascular ultrasound (VH-IVUS) and optical coherence tomography. Patients with TCFA identified by this method had significantly lower adiponectin levels than patients without TCFA. In fact, levels of adiponectin were significantly lower in multivessel TCFA compared with those with single-vessel TCFA. The authors concluded that adiponectin is the strongest predictive factor of the presence of TCFA and suggested that adiponectin can be used as a biomarker for risk stratification in patients with vulnerable plaques on the basis of these findings (73). Because the degree of hypoadiponectinemia may be suggestive of the extent of plaque vulnerability (54,55), it is pertinent to determine adiponectin's involvement in the components of a vulnerable plaque.

Necrotic core. Necrotic core content is significantly correlated with plaque size in patients with ACS. Culprit plaques in patients with ACS have a larger amount of necrotic core plaque than those without ACS (12). VH-IVUS is superior for quantification of the plaque volume (74) and in detecting the necrotic core. In patients without diabetes, decreased adiponectin levels are associated with dyslipidemia; increased plaque volume; lipid-rich, noncalcified coronary plaque; and pathological intimal thickening, as evidenced by IVUS (75). Adiponectin is believed to be involved in regulating the development of necrotic core. A decrease in adiponectin is associated with an increase in necrotic core ratio in both culprit and nonculprit lesions in patients with ACS as demonstrated by VH-IVUS, suggesting that lower adiponectin levels reflect plaque vulnerability in this patient population (12). Additionally, this association of decreased plasma adiponectin level and increased necrotic core ratio has not been demonstrated in patients with stable CAD (12,73).

Neovascularization and intraplaque hemorrhage. Neovascularization has a dual role in atherosclerosis (76). Although it may be beneficial for its role in tissue hypoxia and promotion of collateral growth in the prevention of ischemia in tissues where circulation has been impaired, it is also associated with nascent friable vessels involved in the intraplaque hemorrhage that has shown to promote plaque growth, instability, and rupture (66,68,77,78). Similarly, adiponectin has demonstrated a dual role in the process of neovascularization by displaying both pro- and antiangiogenesis properties. Adiponectin's ability to promote angiogenesis (79) has been shown to be beneficial in its ability to prevent ischemia. In adiponectin knock-out animals, exogenous administration of adiponectin at 30 min before induction of ischemia, during ischemia, and 15 min after reperfusion demonstrated a reduction in the size of infarct (37). Neovascularization induced by transplanted endothe-

lial progenitor cells has shown to be an effective treatment for atherosclerosis and ischemic heart disease (80–82). Physiological plasma concentrations of adiponectin promote the migration of endothelial progenitor cells and contribute to the process of new vessel formation (81). These results suggest therapeutic neovascularization by adiponectin supplementation may be useful in patients with ischemia heart disease (81).

On the other hand, angiogenesis within the vessel wall is associated with atherosclerotic lesions responsible for vascular occlusions. The growing plaque and the increasing oxygen requirements of the vessel wall promote vasa vasorum proliferation. Increased proliferation of adventitial vasa vasorum accompanies neovascularization and intraplaque hemorrhage (82). Intraplaque hemorrhage has been associated with plaque vulnerability through the promotion of plaque growth, instability, and rupture (66,69,83). Although the exact mechanism of adiponectin in intraplaque neovascularization remains unknown, its role in certain elements of neovascularization has been elucidated. Adiponectin's protective role in plaque vulnerability is demonstrated in the ability of adiponectin to directly inhibit endothelial cell growth (84) and induce apoptosis in activated endothelial cells (85). Another key growth factor in angiogenesis is vascular endothelial growth factor (VEGF). VEGF is a potent stimulator of angiogenesis and functions in endothelial proliferation, permeability, and survival (78). VEGF has also been associated with plaque formation and plaque destabilization (86). The application of various concentrations of adiponectin to human coronary artery endothelial cells demonstrated suppression of VEGF-stimulated migration of human coronary artery endothelial cells, suggesting a regulatory role of adiponectin in vascular processes that have been associated with atherosclerosis (87).

Fibrous cap breakdown. Plaque vulnerability is further enhanced by thinning and fissuring of the fibrous cap. Macrophages and vascular smooth muscle cells promote the local release of matrix metalloproteinases (MMP), which degrade the supportive collagen, enabling fibrous cap instability and plaque rupture (88,89,90,91). MMP activity is controlled by tissue inhibitor of metalloproteinase (TIMP)-1, and adiponectin increases TIMP-1 expression in human monocyte-derived macrophages (88,92). The MMP-9/TIMP-1 ratio was demonstrated to be higher in patients with ACS compared with those with stable angina and in patients with complex lesions compared with those with simple lesions (88). Given these findings, the MMP-9/TIMP-1 ratio has been identified as an independent predictor of coronary plaque stability and CAD severity (88). Adiponectin has an inverse relationship with MMP-9/TIMP-1 ratio in patients with ACS (88). The inverse relationship found between adiponectin and the MMP-9/TIMP-1 ratio suggests that adiponectin modulates plaque stability through the balance of this ratio (88). The tipped balance between metalloproteinases and their inhibitors results in degradation of the fibrous cap and subsequent plaque rupture (83,93).

Positive remodeling. In positive remodeling, lumen area is preserved by outward expansion of the vessel wall despite plaque grow (74). It has been suggested that plaques with high lipid content and macrophage count are the plaques involved in positive outward remodeling (71). IVUS studies have shown that complex plaque anatomy and plaque rupture occurs in the presence of marked outward remodeling more frequently (71) and is often associated with plaque rupture in ACS (74). Associations between metabolic factors and coronary plaque growth or remodeling were elucidating using IVUS technology and compared with coronary arteriography. It was suggested that plasma adiponectin may be an independent risk factor for positive vascular remodeling (Remodeling Index [RI] >1) in patients with stable angina after demonstrating significantly lower levels of plasma adiponectin compared with those in the negative remodeling group (vessel shrinkage, RI ≤ 1) (94). Additionally, it has been demonstrated that adiponectin directly modulates vascular remodeling as opposed to systemically through its effects on glucose reduction and lipid metabolism modulation in a study of mice controlled for glucose and lipid profile (11,95,96).

Localization of Adiponectin in Atherosclerotic Lesions

Adiponectin appears to have a protective effect on the cardiovascular system via its anti-atherogenic and anti-inflammatory effects (96,97), primarily through its actions on endothelial cells and macrophages (65) (Fig. 1). Adiponectin's role has been identified in endothelial activation (39), inflammatory factor propagation by adhesion molecules expression (39), monocyte adhesion to vascular endothelium (39) and migration into tunica intima, macrophage activation (98), macrophage-to-foam cell transformation (99,100), lipid accumulation in macrophages (99), smooth muscle cell (SMC) proliferation (23,95), SMC migration into the intima (23,95), and platelet aggregation (101) (Table 2).

Endothelial dysfunction is generally accepted as the initial step in atherogenesis and plays a critical role in the development of atherosclerosis. The endothelium is a major source of NO in the vasculature. NO plays a pivotal role in endothelial dysfunction. In physiological amounts, NO protects against vascular injury, inflammation, and thrombosis by prevention of leukocyte adhesion to the endothelium, inhibition of vascular smooth muscle proliferation, and limitation of platelet aggregation (63). Low levels of adiponectin have been associated with increased NO inactivation combined with decreased NO production, both of which contribute to endothelial dysfunction (102). In inflammatory states, NO may react with reactive oxygen species, such as nicotinamide adenine dinucleotide phosphate oxidase-induced superoxide, to produce highly reac-

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Table 2 Effect of Adiponectin on Atherosclerosis and the Vulnerable Plaque

Mechanism	Endothelial Dysfunction	Monocyte Infiltration	Macrophage Scavenger Receptor Uptake	SMC Deficiency	Fibrous Cap Attenuation	Platelet Activation
Mediators	↑ eNOS ↑ NO ↓ ROS	↓ NF-KB ↓ VCAM ↓ ICAM ↓ E-selectin ↓ IL-8	↓ Class A scavenger receptors (SR-As)	↑ PDGF-BB binding	↑ TIMP-1	? ↑ NO ? ↓ sCD40L
Histopathological changes	↓ Endothelial cell activation ↓ Endothelial cell apoptosis	↓ Monocyte adhesion and migration	↓ Accumulation of modified lipoproteins ↓ Foam cell formation	↓ SMC proliferation ↓ SMC migration	↓ Fibrous cap thinning	↓ Platelet aggregation ↓ Thrombus formation

eNOS = endothelial nitric oxide synthase; ICAM = intercellular adhesion molecule; IL = interleukin; NF-KB = nuclear factor kappa-B; NO = nitric oxide; PDGF = platelet-derived growth factor; ROS = reactive oxygen species; SMC = smooth muscle cells; TIMP = tissue inhibitor of metalloproteinase; VCAM = vascular cell adhesion molecule.

tive molecules (90,91). In vitro studies have demonstrated a decrease in reactive oxygen species in the presence of adiponectin (103,104). Hemeoxygenase has been identified as a protective agent against oxidative insults and has been shown to have a prolonged antidiabetic effect by working synergistically with adiponectin (105,106).

After the initiation of endothelial dysfunction, vascular inflammation characterized by increased adhesion molecule expression via proinflammatory cytokines such as IL-1, IL-8, and TNF-alpha can take place (63,107). Adiponectin partakes in inflammatory factor propagation by adhesion molecule expression (39). Inhibition of the TNF-induced activation of nuclear factor kappa-B–dependent proinflammatory cAMP pathway (35,36) reduces the expression of adhesion molecules such as vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and E selectin (39,108–110), all of which have been detected in atherosclerotic lesions (111). Local adiponectin to intima and adventitia of endothelial wall suppresses the expression of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 in vascular walls, suggesting that adiponectin improves atherosclerosis in part by inhibition of the expression of these inflammatory molecules in vivo (112). Adventitial fibroblasts play an important role in adventitial response to vascular injury. Adventitial fibroblast proliferation, migration, and adventitial fibroblast transformation to myofibroblasts is inhibited by the administration of adiponectin via the AdipoR1-AMPK-iNOS pathway, further demonstrating adiponectin's protective role in the vasculature (113). Recombinant adiponectin has been shown to attenuate monocyte attachment to endothelial cells (35,39,99,114). Upon adherence, monocytes migrate into the intima and transform into macrophages that express class A scavenger receptors that accumulate modified lipoproteins and form lipid-laden macrophages known as foam cells. These foam cells characterize the "fatty streak" and secrete proinflammatory cytokines. Adiponectin inhibits macrophage activation (98), macrophage-to-foam cell transformation (99,100), and lipid accumulation in macrophages (92), subsequently decreasing proinflammatory cytokines. The transformation from a nonatherosclerotic intimal lesion with intimal thickening with normal accumulation of SMCs and "fatty streak" formation with accumulation of foam cells to an atherosclerotic lesion with pathological intimal thickening requires the combination of such SMCs in a lipid-rich core. Adiponectin has been shown to decrease the progression of atherosclerosis by inhibiting both neointimal thickening and SMC proliferation and migration to the intima in vivo, suggesting a possible involvement in vascular remodeling (23,95,96). In cultured vascular smooth muscle cells, adiponectin suppressed vascular smooth muscle cell proliferation and migration via direct binding to platelet-derived growth factor-BB (23). Adiponectin also inhibits platelet aggregation and thrombus formation; however, the mechanism of action remains unclear (101,115,116). Macrophages add to the enlarging necrotic core when they succumb to necrotic and apoptotic cell death (117). The HMW form of adiponectin has been associated with suppression of endothelial cell apoptosis (118). Adiponectin also promotes the clearance of early apoptotic cells by macrophages (119).

Adiponectin as a Target for Stabilization of Plaque

In vitro and animal studies demonstrate that administration of adiponectin causes an increase in adiponectin plasma levels and exerts protective effects on atherosclerosis progression (96,120). High levels of adiponectin can reduce atherosclerosis by attenuating endothelial inflammation and macrophage to foam cell transformation (100). Local adiponectin to intima and adventitia of endothelial wall suppresses the expression of adhesion molecules in vascular walls (112), and recombinant adiponectin decreases monocyte attachment to endothelial cells (23).

Although direct adiponectin administration in humans warrants further investigation, adiponectin levels can be increased via indirect methods such as lifestyle modifications and pharmacological interventions (6,33,121–138) (Table 3). Large reductions in weight (almost 14% reduction of BMI) by changes in lifestyle or after gastric bypass have demonstrated an increase in adiponectin (135,137). Thiazolidinediones (TZDs), which act through peroxisome

Table 3 Interventions That Increase Adiponectin Levels

Site of Action	Intervention (Ref. #)
Adiponectin	ACE inhibitors (121,122) Angiotensin receptor blockers (123,124) Glimepiride (125) Nebivolol (126) Rimonabant (127) Dietary fish oils (128) Oolong tea (129) Moderate alcohol consumption (130)
Adiponectin receptors	Osmotin (131)
Adiponectin and adiponectin receptors	PPAR α (fenofibrate) (33,132) PPAR γ (TZDs) (6,33,133,134) Weight reduction (135,136,137) Calorie restriction (135) Exercise (136,138)

ACE = angiotensin-converting enzyme; PPAR = peroxisome proliferator activator receptor; TZD = thiazolidinedione.

proliferator activator receptors gamma, also increase serum adiponectin levels (6,133,134). The increase is almost 3-fold in diabetic patients (6). A meta-analysis of 19 studies confirmed an increase of endogenous adiponectin levels with TZD use (133). Recently, it has also been suggested that pioglitazone, a TZD, may stabilize coronary plaque contents by increasing adiponectin levels. In a study of diabetic subjects, pioglitazone therapy was not only correlated with an increase in adiponectin levels, but also with a reduction in the necrotic-core component in plaques based on VH-IVUS analysis (134). Although promising, knowledge of adiponectin's actions remains incomplete and creates a barrier against the possible future therapeutic development of adiponectin.

Conclusions

Adiponectin plays a significant role in CAD and plaque vulnerability, as demonstrated by its association with the stepwise progression of atherogenesis and, more importantly, the components of plaque vulnerability. However, most of the available data are epidemiological in nature and do not prove causal association (46,49,139–142). As more details of adiponectin's antiatherogenic, anti-inflammatory, and anti-remodeling properties continue to emerge, methods of increasing adiponectin may become a promising new therapy for the prevention and treatment of CAD and ACS.

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REFERENCES

1. World Health Organization. The top 10 causes of death. Fact Sheet No. 310. Updated October 2008. Available at: http://www.who.int/mediacentre/factsheets/fs310/en/index.html. Accessed September 14, 2009.
2. Davies MJ. Anatomic features in victims of sudden coronary death: coronary artery pathology (abstr). Circulation 1992;85:119–24.
3. Falk E, Shah PK, Fuster V. Coronary plaque disruption. Circulation 1995;92:657–71.
4. Ross R. Atherosclerosis–an inflammatory disease. N Engl J Med 1999;340:115–26.
5. Narula J, Garg P, Achenbach S, et al. Arithmetic of vulnerable plaques for noninvasive imaging. Nat Clin Pract Cardiovasc Med 2008;5 Suppl 2:2–10.
6. Bajaj M, Suraamornkul S, Piper P, et al. Decreased plasma adiponectin concentrations are closely related to hepatic fat content and hepatic insulin resistance in pioglitazone-treated type 2 diabetic patients. J Clin Endocrinol Metab 2004;89:200–6.
7. Bajaj M, Suraamornkul S, Romanelli A, et al. Effect of a sustained reduction in plasma free fatty acid concentration on intramuscular long-chain fatty Acyl-CoAs and insulin action in type 2 diabetic patients. Diabetes 2005;54:3148–53.
8. Putz DM, Goldner WS, Bar RS, et al. Adiponectin and C-reactive protein in obesity, type 2 diabetes, and monodrug therapy. Metabolism 2004;53:1454–61.
9. Ouchi N, Kihara S, Funahashi T, et al. Reciprocal association of C-reactive protein with adiponectin in blood stream and adipose tissue. Circulation 2003;107:671–4.
10. Otsuka F, Sugiyama S, Kojima S, et al. Plasma adiponectin levels are associated with coronary lesion complexity in men with coronary artery disease. J Am Coll Cardiol 2006;48:1155–62.
11. Wolk R, Berger P, Lennon RJ, et al. Association between plasma adiponectin levels and unstable coronary syndromes. Eur Heart J 2007;28:292–8.
12. Otake H, Shite J, Shinke T, et al. Relation between plasma adiponectin, high-sensitivity C-reactive protein, and coronary plaque components in patients with acute coronary syndrome. Am J Cardiol 2008;101:1–7.
13. Steppan C, Lazar M. Resistin and obesity-associated insulin resistance. Trends Endocrinol Metab 2002;13:18–23.
14. Bajaj M, Ben-Yehuda O. A big fat wedding: association of adiponectin with coronary vascular lesions. J Am Coll Cardiol 2006;48:1163–5.
15. Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1q, produced exclusively in adipocytes. J Biol Chem 1995;270:26746–9.
16. Hu E, Liang P, Spiegelman BM. AdipoQ is a novel adipose-specific gene disregulated in obesity. J Biol Chem 1996;271:10697–703.
17. Maeda K, Okubo K, Shimomura I, et al. cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPose Most abundant Gene transcript 1). Biochem Biophys Res Commun 1996;221:286–9.
18. Nakano Y, Tobe T, Choi-Miura NH, et al. Isolation and characterization of GBP28, a novel gelatin binding protein purified from human plasma. J Biochem (Tokyo) 1996;120:803–12.
19. Pineiro R, Iglesias MJ, Gallego R, et al. Adiponectin is synthesized and secreted by human and murine cardiomyocytes. FEBS Lett 2005;579:5163–9.
20. Takahashi M, Arita Y, Yamagata K, et al. Genomic structure and mutations in adipose-specific gene, adiponectin. Int J Obes 2000;24:861–8.
21. Jogi M, Bajaj M. Adiponectin and cardiovascular disease. In: Fonseca V, editor. Contemporary Endocrinology: Cardiovascular Endocrinology: Shared Pathways and Clinical Crossroads. New York, NY: Humana Press, 2009:171–84.
22. Scherer PE, Williams S, Fogliano M, et al. A novel serum protein similar to C1q produced exclusively in adipocytes. J Biol Chem 1995;270:26746–9.
23. Arita Y, Kihara S, Ouchi N, et al. Adipocyte-derived plasma protein adiponectin acts as a platelet-derived growth factor-BB-binding protein and regulates growth factor induced common postreceptor signal in vascular smooth muscle cell. Circulation 2002;105:2893–8.
24. Arita Y, Kihara S, Ouchi N, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 1999;257:79–83.
25. Pajvani UB, Du X, Combs TP, et al. Structure-function studies of the adipocyte-secreted hormone Acrp3/adiponectin. Implications for metabolic regulation and bioactivity. J Biol Chem 2003;278:9073–85.

26. Ebinuma H, Miyazaki O, Yago H, et al. A novel ELISA system for selective measurement of human adiponectin multimers by using proteases. Clin Chim Acta 2006;372:47–53.
27. Lara-Castro C, Luo N, Wallace P, et al. Adiponectin multimeric complexes and the metabolic syndrome trait cluster. Diabetes 2006; 55:249–59.
28. Motoshima H, Wu X, Mahadev K, et al. Adiponectin suppresses proliferation and superoxide generation and enhances eNOS activity in endothelial cells treated with oxidized LDL. Biochem Biophys Res Commun 2004;315:264–71.
29. Ouchi N, Shibata R, Walsh K. Cardioprotection by adiponectin. Trends Cardiovasc Med 2006;16:141–6.
30. Kharroubi I, Rasschaert J, Eizirik DL, et al. Expression of adiponectin receptors in pancreatic beta cells. Biochem Biophys Res Commun 2003;312:1118–22.
31. Yamauchi T, Kamon J, Ito Y, et al. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature 2003;423:762–9.
32. Tan KC, Xu A, Chow WS, et al. Hypoadiponectinemia is associated with impaired endothelium-dependent vasodilation. J Clin Endocrinol Metab 2004;89:765–9.
33. Chinetti G, Zawadski C, Fruchart JC, et al. Expression of adiponectin receptors in human macrophages and regulation by agonists of the nuclear receptors PPARalpha, PPARgamma, and LXR. Biochem Biophys Res Commun 2004;14:151–8.
34. Kadowaki T, Yamauchi T, Kubota N, et al. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest 2006;116:1784–92.
35. Ouchi N, Kihara S, Arita Y, et al. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-κB signaling through a cAMP-dependent pathway. Circulation 2000;102:1296–301.
36. de Winther MP, Kanters E, Kraal G, et al. Nuclear factor kappaB signaling in atherogenesis. Arterioscler Thromb Vasc Biol 2005;25: 904–14.
37. Shibata R, Sato K, Pimentel DR, et al. Adiponectin protects against myocardial ischemia-reperfusion injury through AMPK- and COX-2-dependent mechanisms. Nat Med 2005;11:1048–9.
38. Hotta K, Funahashi T, Arita Y, et al. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 2000;20:1595–9.
39. Ouchi N, Kihara S, Arita Y, et al. Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. Circulation 1999;100:2473–6.
40. Zoccali C, Mallamaci F, Tripepi G, et al. Adiponectin, metabolic risk factors, and cardiovascular events among patients with end-stage renal disease. J Am Soc Nephrol 2002;13:134–41.
41. Pischon T, Girman CJ, Hotamisligil GS, et al. Plasma adiponectin levels and risk of myocardial infarction in men. JAMA 2004;291: 1730–7.
42. Schulze MB, Shai I, Rimm EB, et al. Adiponectin and future coronary heart disease events among men with type 2 diabetes. Diabetes 2005;54:534–9.
43. Becker B, Kronenberg F, Kielstein JT, et al. Renal insulin resistance syndrome, adiponectin and cardiovascular events in patients with kidney disease: The mild and moderate kidney disease study. J Am Soc Nephrol 2005;16:1091–8.
44. Iwashima Y, Horio T, Kumada M, et al. Adiponectin and renal function, and implication as a risk of cardiovascular disease. Am J Cardiol 2006;98:1603–8.
45. Costacou T, Zgibor JC, Evans RW, et al. The prospective association between adiponectin and coronary artery disease among individuals with type 1 diabetes. The Pittsburgh Epidemiology of Diabetes Complications Study. Diabetologia 2005;48:41–8.
46. Sattar N, Wannamethee G, Sarwar N, et al. Adiponectin and coronary heart disease: a prospective study and meta-analysis. Circulation 2006;114:623–9.
47. Lindsay RS, Resnick HE, Zhu J, et al. Adiponectin and coronary heart disease: the Strong Heart Study. Arterioscler Thromb Vasc Biol 2005;25:e15–6.
48. Lawlor DA, Davey Smith G, Ebrahim S, et al. Plasma adiponectin levels are associated with insulin resistance, but do not predict future risk of coronary heart disease in women. J Clin Endocrinol Metab 2005;90:5677–83.
49. Laughlin GA, Barrett-Connor E, May S and Langenberg C. Association of adiponectin with coronary heart disease and mortality: the Rancho Bernardo Study. Am J Epidemiol 2007;165:164–74.
50. Kumada M, Kihara S, Sumitsuji S, et al. Association of hypoadiponectinemia with coronary artery disease in men. Arterioscler Thromb Vasc Biol 2003;2:85–9.
51. Frystyk J, Berne C, Berglund L, et al. Serum adiponectin is a predictor of coronary heart disease: a population-based 10-year follow up study in elderly men. J Clin Endocrinol Metab 2007;92:571–6.
52. Cesari M, Pessina AC, Zanchetta M, et al. Low plasma adiponectin is associated with coronary artery disease but not with hypertension in high-risk nondiabetic patients. J Intern Med 2006;260:474–83.
53. Hara K, Yamauchi T, Imai Y, et al. Reduced adiponectin level is associated with severity of coronary artery disease. Int Heart J 2007;48:149–53.
54. Otsuka F, Sugiyama S, Kojima S, et al. Plasma adiponectin levels are associated with coronary lesion complexity in men with coronary artery disease. J Am Coll Cardiol 2006;48:1155–62.
55. Wang XY, Guo YH, Guo LJ. Association between plasma adiponectin levels and coronary lesion complexity. Beijing Da Xue Xue Bao 2007;39:599–602.
56. Nakamura Y, Shimada K, Fukuda D, et al. Implications of plasma concentrations of adiponectin in patients with coronary artery disease. Heart 2004;90:528–33.
57. Kojima S, Funahashi T, Sakamoto T, et al. The variation of plasma concentrations of a novel, adipocyte derived protein, adiponectin, in patients with acute myocardial infarction. Heart 2003;89:667–8.
58. Mendall MA, Patel P, Ballam L, et al. C reactive protein and its relation to cardiovascular risk factors: A population based cross sectional study. BMJ 1996;312:1061–5.
59. Nakamura T, Nishida M. Kumada M, et al. Reciprocal association of c-reactive protein with adiponectin in blood stream and adipose tissue. Circulation 2003;107:671–4.
60. Liuzzo G, Biasucci LM, Gallimore JR, et al. The prognostic value of c-reactive protein and serum amyloid a protein in severe unstable angina. N Engl J Med 1994;331:417–24.
61. Lindahl L, Toss H, Siegbahn A, et al. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. N Engl J Med 2000;343:1139–47.
62. Verma S, Wang C-H, Li S-H, et al. A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. Circulation 2002;106:913–9.
63. Szmitko PE, Wang CH, Weisel RD, et al. New markers of inflammation and endothelial cell activation. Circulation 2003;108: 1917–23.
64. Behrendt D, Ganz P. Endothelial function: from vascular biology to clinical applications. Am J Cardiol 2002;90:40L–8L.
65. Ouchi N, Walsh K. Adiponectin as an anti-inflammatory factor. Clinica Chimica Acta 2007;380:24–30.
66. Kolodgie FD, Virmani R, Burke AP, et al. Pathologic assessment of the vulnerable human coronary plaque. Heart 2004;90:1385–91.
67. Burke A, Farb A, Malcom G, et al. Coronary risk factors and plaque morphology in men with coronary artery disease who died suddenly. N Engl J Med 1997;336:1276–82.
68. Virmani R, Burke AP, Farb A, et al. Pathology of the vulnerable plaque. J Am Coll Cardiol 2006;47:C13–8.
69. Virmani R, Kolodgie FD, Burke AP, et al. Atherosclerotic plaque progression and vulnerability to rupture: angiogenesis as a source of intraplaque hemorrhage. Arterioscler Thromb Vasc Biol 2005;25: 2054–61.
70. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: A call for new definitions and risk assessment strategies: Part I. Circulation 2003;108:1664–72.
71. Varnava AM, Mills PG, Davies MJ. Relationship between coronary artery remodeling and plaque vulnerability. Circulation 2002;105: 939–43.
72. Burke AP, Farb A, Malcolm GT, et al. Plaque rupture and sudden death related to exertion in men with coronary artery disease. JAMA 1999;281:921–6.
73. Sawada T, Shite J, Shinke T, et al. Low plasma adiponectin levels are associated with presence of thin-cap fibroatheroma in men with stable coronary artery disease. Int J Cardiol 2010;142:250–6.

74. Yasu T. Low adiponectin level causes vascular remodeling? A perspective through intravascular ultrasound. Hypertens Res 2008; 31:2099–101.
75. Marso SP, Mehta SK, Frutkin A, et al. Low adiponectin levels are associated with atherogenic dyslipidemia and lipid-rich plaque in non-diabetic coronary arteries. Diabetes Care 2008;31:989–94.
76. Ribatti D, Levi-Schaffer F, Kovanen PT. Inflammatory angiogenesis in atherogenesis—a double-edged sword. Ann Med 2008;40:606–21.
77. Narula J, Strauss HW. The popcorn plaques. Nat Med 2007;13: 634–41.
78. Di Stefano R, Felice F, Balbarini A. Angiogenesis as risk factor for plaque vulnerability. Curr Pharm Des 2009;15:1095–106.
79. Shibata R, Ouchi N, Kihara S, et al. Adiponectin stimulates angiogenesis in response to tissue ischemia through stimulation of AMP-activated protein kinase signaling. J Biol Chem 2004;279: 28670–4.
80. Kalka C, Masuda H, Takahashi T, et al. Transplantation of ex vivo expanded endothelial progenitor cells for therapeutic neovascularization. Proc Natl Acad Sci U S A 2000;97:3422–7.
81. Nakamura N, Naruse K, Matsuki T, et al. Adiponectin promotes migration activities of endothelial progenitor cells via Cdc42/Rac1. FEBS Lett 2009;583:2457–63.
82. Kwon HM, Sangiorgi G, Ritman EL, et al. Enhanced coronary vasa vasorum neovascularization in experimental hypercholesterolemia. J Clin Invest 1998;101:1551–6.
83. Libby P. Molecular bases of the acute coronary syndromes. Circulation 1995;91:2844–50.
84. Polowinczak-Przybylek J, Melen-Mucha G. The inhibitory influence of adiponectin on the growth of the murine endothelial cell line HECa 10 in vitro. Endokrynol Pol 2009;60:166–71.
85. Brakenhielm E, Veitonmaki N, Cao R, et al. Adiponectin induced antiangiogenesis and antitumor activity involve caspase-mediated endothelial cell apoptosis. Proc Natl Acad Sci U S A 2004;101: 2476–81.
86. Holm PW, Slart RH, Zeebregts CJ, et al. Atherosclerotic plaque development and instability: a dual role for VEGF. Ann Med 2009;41:257–64.
87. Mahadev K, Wu X, Donnelly S, et al. Adiponectin inhibits vascular endothelial growth factor-induced migration of human coronary artery endothelial cells. Cardiovasc Res 2008;78:376–8.
88. Cheng M, Hashmi S, Mao X, et al. Relationships of adiponectin and matrix metalloproteinase- to tissue inhibitor of metalloproteinase-1 ratio with coronary plaque morphology in patients with acute coronary syndrome. Can J Cardiol 2008;24:385–90.
89. Galis ZS, Muszynski M, Sukhova GK, et al. Enhanced expression of vascular matrix metalloproteinases induced in vitro by cytokines and in regions of human atherosclerotic lesions. Ann N Y Acad Sci 1995;748:501–7.
90. Griendling KK, FitzGerald GA. Oxidative stress and cardiovascular injury: Part I: basic mechanisms and in vivo monitoring of ROS. Circulation 2003;108:1912–6.
91. Griendling KK, FitzGerald GA. Oxidative stress and cardiovascular injury: part II: animal and human studies. Circulation 2003;108: 2034–40.
92. Kumada M, Kihara S, Ouchi N, et al. Adiponectin specifically increased tissue inhibitor of metalloproteinase-1 through interleukin-10 expression in human macrophages. Circulation 2004;109:2046–9.
93. Shah PK, Falk E, Badimon JJ, et al. Human monocyte-derived macrophages induce collagen breakdown in fibrous caps of atherosclerotic plaques. Potential role of matrix-degrading metalloproteinases and implications for plaque rupture. Circulation 1995;92: 1565–9.
94. Iwata A, Miura S, Mori K, et al. Associations between metabolic factors and coronary plaque growth or arterial remodeling as assessed by intravascular ultrasound in patients with stable angina. Hypertens Res 2008;31:1879–86.
95. Matsuda M, Shimomura I, Sata M, et al. Role of adiponectin in preventing vascular stenosis. The missing link of adipo-vascular axis. J Biol Chem 2002;277:37487–91.
96. Kubota N, Terauchi Y, Yamauchi T, et al. Disruption of adiponectin causes insulin resistance and neointimal formation. J Biol Chem 2002;277:25863–6.
97. Szmitko PE, Teoh H, Stewart DJ, et al. Adiponectin and cardiovascular disease: state of the art? Am J Physiol Heart Circ Physiol 2007;292:H1655–63.
98. Park PH, McMullen MR, Huang H, et al. Short-term treatment of RAW264.7 macrophages with adiponectin increases tumor necrosis factor-a (TNF-a) expression via ERK1/2 activation and Egr-1 expression: role of TNF-a in adiponectin stimulated interleukin-10 production. J Biol Chem 2007;282:21695–703.
99. Ouchi N, Kihara S, Arita Y, et al. Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. Circulation 2001;103:1057–63.
100. Okamoto Y, Kihara S, Ouchi N, et al. Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. Circulation 2002;106: 2767–70.
101. Kato H, Kashiwagi H, Shiraga M, et al. Adiponectin acts as an endogenous antithrombotic factor. Arterioscler Thromb Vasc Biol 2006;26:224–30.
102. Cao Y, Tao L, Yuan Y, et al. Endothelial dysfunction in adiponectin deficiency and its mechanisms involved. J Mol Cell Cardiol 2009;46: 413–9.
103. Mossalam M, Jeong JH, Abel ED, et al. Reversal of oxidative stress in endothelial cells by controlled release of adiponectin. J Control Release 2008;130:234–7.
104. Li R, Wang WQ, Zhang H, et al. Adiponectin improves endothelial function in hyperlipidemic rats by reducing oxidative/nitrative stress and differential regulation of eNOS/iNOS activity. Am J Physiol Endocrinol Metab 2007;293:E1703–8.
105. Yamauchi T, Kamon J, Minokoshi, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med 2002;8:1288–95.
106. Ndisang JF and Jadhav A. Up-regulating the hemeoxygenase system enhances insulin sensitivity and improves glucose metabolism in insulin-resistant diabetes in Goto-Kakizaki rats. Endocrinology 2009;150:2627–36.
107. Ouedraogo R, Gong Y, Berzins B, et al. Adiponectin deficiency increases leukocyte-endothelium interactions via upregulation of endothelial cell adhesion molecules in vivo. J Clin Invest 2007;117: 1718–26.
108. Murakami T, Mataki C, Nagao C, et al. The gene expression profile of human umbilical vein endothelial cells stimulated by tumor necrosis factor alpha using DNA microarray analysis (abstr). J Atheroscler Thromb 2000;7:39–44.
109. Kevil CG, Patel RP, Bullard DC. Essential role of ICAM-1 in mediating monocyte adhesion to aortic endothelial cells. Am J Physiol Cell Physiol 2001;281:C1442–7.
110. Karaduman M, Sengult A, Oktenli C, et al. Tissue levels of adiponectin, tumour necrosis factor-alpha, soluble intercellular adhesion molecule-1 and heart-type fatty acid-binding protein in human coronary atherosclerotic plaques. Clin Endocrinol (Oxf) 2006;64: 196–202.
111. Davies MJ, Gordon JL, Gearing AJ, et al. The expression of the adhesion molecules ICAM-1, VCAM-1, PECAM, and E-selectin in human atherosclerosis. J Pathol 1993;171:223–9.
112. Li CJ, Sun HW, Zhu FL, et al. Local adiponectin treatment reduces atherosclerotic plaque size in rabbits. J Endocrinol 2007;193:137–45.
113. Cai XJ, Chen L, Li L, et al. Adiponectin inhibits lipopolysaccharide-induced adventitial fibroblast migration and transition to myofibroblasts via AdipoR1-AMPK-iNOS pathway. Mol Endocrinol 2010; 24:218–28.
114. Okamoto Y, Arita Y, Nishida M, et al. An adipocyte derived plasma protein, adiponectin, adheres to injured vascular walls. Horm Metab Res 2000;32:47–50.
115. Restituto P, Colina I, Varo JJ, et al. Adiponectin diminishes platelet aggregation and sCD40L release. Potential role in the metabolic syndrome. Am J Physiol Endocrinol Metab 2010;298:e1072–7.
116. Sogo N, Magid KS, Shaw CA, et al. Inhibition of human platelet aggregation by nitric oxide donor drugs: relative contribution of cGMP-independent mechanisms. Biochem Biophys Res Commun 2000;279:412–9.
117. Kolodgie FD, Narula J, Burke AP, et al. Localization of apoptotic macrophages at the site of plaque rupture in sudden coronary death. Am J Pathol 2000;157:1259–68.

118. Kobayashi H, Ouchi N, Kihara S, et al. Selective suppression of endothelial cell apoptosis by the high molecular weight form of adiponectin. Circ Res 2004;94:e27–31.
119. Takemura Y, Ouchi N, Shibata R, et al. Adiponectin modulates inflammatory reactions via calreticulin receptor dependent clearance of early apoptotic bodies. J Clin Invest 2007;117:375–86.
120. Yamauchi T, Kamon J, Waki H, et al. Globular adiponectin protected ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis. J Biol Chem 2003;278:2461–8.
121. Hermann TS, Li W, Dominguez H, et al. Quinapril treatment increases insulin-stimulated endothelial function and adiponectin gene expression in patients with type 2 diabetes. J Clin Endocrinol Metab 2006;91:1001–8.
122. Krysiak R, Sierant M, Marek B, et al. The effect of angiotensin-converting enzyme inhibitors on plasma adipokine levels in normotensive patients with coronary artery disease. Endokrynol Pol 2010; 61:280–7.
123. Makita S, Abiko A, Naganuma Y, et al. Effects of telmisartan on adiponectin levels and body weight in hypertensive patients with glucose intolerance. Metabolism 2008;57:1473–8.
124. Mori Y, Itoh Y, Tajima N. Telmisartan improves lipid metabolism and adiponectin production but does not affect glycemic control in hypertensive patients with type 2 diabetes. Adv Ther 2007;24: 146–53.
125. Araki T, Emoto M, Konishi T, et al. Glimepiride increases high-density lipoprotein cholesterol via increasing adiponectin levels in type 2 diabetes mellitus. Metabolism 2009;58:143–8.
126. Celik T, Iyisoy A, Kursaklioglu H, et al. Comparative effects of nebivolol and metoprolol on oxidative stress, insulin resistance, plasma adiponectin and soluble P-selectin levels in hypertensive patients. J Hypertens 2006;24:591–6.
127. Bensaid M, Gary-Bobo M, Esclangon A, et al. The cannabinoid CB1 receptor antagonist SR141716 increases Acrp30 mRNA expression in adipose tissue of obese *fa/fa* rats and in cultured adipocyte cells. Mol Pharmacol 2003;63:908–14.
128. Itoh M, Suganami T, Satoh N, et al. Increased adiponectin secretion by highly purified eicosapentaenoic acid in rodent models of obesity and human obese subjects. Arterioscler Thromb Vasc Biol 2007;27: 1918–25.
129. Shimada K, Kawarabayashi T, Tanak A, et al. Oolong tea increases plasma adiponectin levels and low-density lipoprotein particle size in patients with coronary artery disease. Diabetes Res Clin Pract 2004;65:227–34.
130. Joosten MM, Beulens JW, Kersten S, et al. Moderate alcohol consumption increases insulin sensitivity and ADIPOQ expression in postmenopausal women: a randomised, crossover trial. Diabetologia 2008;51:1375–81.
131. Narasimhan ML, Coca MA, Jin J, et al. Osmotin is a homolog of mammalian adiponectin and controls apoptosis in yeast through a homolog of mammalian adiponectin receptor. Mol Cell 2005;17: 171–80.
132. Koh KK, Han SH, Quon MJ, et al. Beneficial effects of fenofibrate to improve endothelial dysfunction and raise adiponectin levels in patients with primary hypertriglyceridemia. Diabetes Care 2005;28: 1419–24.
133. Riera-Guardia N, Rothenbacher D. The effect of thiazolidinediones on adiponectin serum level: a meta-analysis. Diabetes Obes Metab 2008;10:367–75.
134. Ogasawara D, Shite J, Shinke T, et al. Pioglitazone reduces the necrotic-core component in coronary plaque in association with enhanced plasma adiponectin in patients with type 2 diabetes mellitus. Circ J 2009;73:343–51.
135. Yang WS, Lee WJ, Funahashi T, et al. Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. J Clin Endocrinol Metab 2001;86:3815–9.
136. Esposito K, Pontillo A, Di Palo C, et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. JAMA 2003;289:1799–804.
137. Kopp HP, Krzyzanowska K, Mohlig M, et al. Effects of marked weight loss on plasma levels of adiponectin, markers of chronic subclinical inflammation and insulin resistance in morbidly obese women. Int J Obes Relat Metab Disord 2005;29:766–71.
138. Bluher M, Williams CJ, Kloting N, et al. Gene expression of adiponectin receptors in human visceral and subcutaneous adipose tissue is related to insulin resistance and metabolic parameters and is altered in response to physical training. Diabetes Care 2007;30: 3110–5.
139. Nawrocki AR, Hofmann SM, Teupser D, et al. Lack of Association Between Adiponectin Levels and Atherosclerosis in Mice. Arterioscler Thromb Vasc Biol 2010;30:1159–65.
140. Holewijn S, den Heijer M, van Tits LJ, et al. Impact of waist circumference versus adiponectin level on subclinical atherosclerosis: A cross-sectional analysis in a sample from the general population. J Intern Med 2010;267:588–98.
141. von Eynatten M, Hamann A, Twardella D, et al. Atherogenic dyslipidaemia but not total- and high-molecular weight adiponectin are associated with the prognostic outcome in patients with coronary heart disease. Eur Heart J 2008;29:1307–15.
142. Aso Y, Yamamoto R, Wakabayashi S, et al. Comparison of serum high-molecular weight (HMW) adiponectin with total adiponectin concentrations in type 2 diabetic patients with coronary artery disease using a novel enzyme-linked immunosorbent assay to detect HMW adiponectin. Diabetes 2006;55:1954–60.

Key Words: acute coronary syndrome ■ adventitia ■ atherosclerosis ■ biomarkers ■ intraplaque hemorrhage ■ necrotic core ■ plaque rupture ■ thin-cap fibroatheroma ■ vasa vasorum.