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 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.

**Adiponectin and Vulnerable Atherosclerotic Plaques**

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Irvine, California; and College Station and Houston, Texas

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

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**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).
 Patients with plasma adiponectin levels 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 a 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 (A1b–LMW) (26). MMW and HMW 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 non-diabetic 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

### 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
T2D = thiazolidinedione
VEGF = vascular endothelial growth factor
VH-IVUS = virtual histology intravascular ultrasound
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.
### Relationship of Adiponectin to CAD and ACS

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

**Note:** 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.

Adiponectin and CAD

February 15, 2011:761–70

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 endothel-
Adiponectin and CAD

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-

**Localization of Adiponectin in Atherosclerotic Lesions**

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).

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**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).

**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).

**Li-
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 nointimal 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).

### Table 2 Effect of Adiponectin on Atherosclerosis and the Vulnerable Plaque

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Endothelial Dysfunction</th>
<th>Monocyte Infiltration</th>
<th>Macrophage Scavenger Receptor Uptake</th>
<th>SMC Deficiency</th>
<th>Fibrous Cap Attenuation</th>
<th>Platelet Activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediators</td>
<td>↓ eNOS ↑ NO ↓ ROS</td>
<td>↓ Monocyte adhesion and migration</td>
<td>↓ Accumulation of modified lipoproteins</td>
<td>↓ SMC proliferation</td>
<td>↓ Fibrous cap thinning</td>
<td>↓ Platelet aggregation</td>
</tr>
<tr>
<td>Histopathological changes</td>
<td>↓ Endothelial cell activation, apoptosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

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