

SAGE-Hindawi Access to Research  
Cardiology Research and Practice  
Volume 2011, Article ID 313179, 7 pages  
doi:10.4061/2011/313179

## Review Article

# Adiponectin Provides Cardiovascular Protection in Metabolic Syndrome

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Received 24 November 2010; Accepted 19 December 2010

Academic Editor: Rei Shibata

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Adipose tissue plays a central role in the pathogenesis of metabolic syndrome. Adiponectin (APN) is a bioactive adipocytokine secreted from adipocytes. Low plasma APN levels (hypoadiponectinemia) are observed among obese individuals and in those with related disorders such as diabetes, hypertension, and dyslipidemia. APN ameliorates such disorders. Hypoadiponectinemia is also associated with major cardiovascular diseases including atherosclerosis and cardiac hypertrophy. Accumulating evidence indicates that APN directly interacts with cardiovascular tissue and prevents cardiovascular pathology. Increasing plasma APN or enhancing APN signal transduction may be an ideal strategy to prevent and treat the cardiovascular diseases associated with metabolic syndrome. However, further studies are required to uncover the precise biological actions of APN.

## 1. Introduction

Obesity is one of the most common disorders in industrialized countries and is fast becoming a worldwide health problem. Metabolic disorders such as hypertension, dyslipidemia, and glucose intolerance frequently, but not incidentally, cluster in an individual with obesity, resulting in atherosclerotic cardiovascular diseases. This pathophysiology, based on excess visceral fat accumulation, has been conceptualized as “syndrome X,” “deadly quartet,” or “visceral fat syndrome,” which are currently recognized as “metabolic syndrome [1].”

Adipose tissue plays a pivotal role in metabolic syndrome. Accumulating evidence indicates that adipose tissue secretes a variety of bioactive adipocytokines such as tumor necrosis factor (TNF $\alpha$ ), plasminogen activator inhibitor type 1, retinol binding protein-4, monocyte chemoattractant protein-1, and adiponectin (APN). Of these, APN has been cloned and is the most abundant. In the past decade, a large number of clinical and experimental studies have uncovered a variety of biological functions for APN. This paper updates the protective roles of APN in cardiovascular diseases and discusses the association of APN with metabolic syndrome.

## 2. Clinical Features of Low Plasma APN (Hypoadiponectinemia)

**2.1. Obese Subjects and Patients with Coronary Risk Factors.** The first clinical study of APN was conducted to observe plasma levels of APN among obese subjects. Although plasma levels of most other adipocytokines are higher in obese individuals, Arita et al. reported that plasma levels of APN are lower in obese individuals and are negatively correlated with body mass index (BMI) [2]. Subsequent studies demonstrated that plasma APN is lower (hypoadiponectinemia) in patients with diabetes, hypertension, and dyslipidemia than BMI-matched controls [3–5], indicating that hypoadiponectinemia is associated with an increased prevalence of coronary risk factors.

**2.2. Coronary Artery Diseases.** Subsequently, a series of clinical studies reported an association between hypoadiponectinemia and coronary artery diseases (CAD). Plasma APN is significantly lower in patients with CAD than control subjects, and male patients with hypoadiponectinemia have a twofold increase in CAD prevalence, independent of well-

known risk factors [6, 7]. Another prospective study revealed that high plasma APN concentrations are associated with a lower risk for myocardial infarction in men, independent of inflammation and glycemic status [8]. Moreover, Otsuka et al. reported that patients with acute coronary syndrome have lower APN levels than patients with stable CAD and that plasma APN levels are significantly associated with coronary lesion complexity in men with CAD [9]. Several studies of patients undergoing percutaneous coronary intervention (PCI) indicate that hypo adiponectinemia is an independent predictor for in-stent restenosis [10, 11]. Recently, a multiple regression analysis revealed that levels of high molecular weight (HMW) APN correlate negatively with glycated hemoglobin in nondiabetic patients but positively with high-density lipoprotein cholesterol in diabetic patients with CAD [12]. These results indicate that total or HMW hypo adiponectinemia is an independent risk factor for CAD and that APN may directly protect against abnormal vascular remodeling.

**2.3. Cardiac Diseases.** Obesity is strongly associated with pathological cardiac remodeling, and several studies have investigated the association between plasma APN levels and cardiac diseases. Hypo adiponectinemia is associated with the progression of left ventricular hypertrophy (LVH) with diastolic dysfunction among patients with essential hypertension [13]. Even among healthy subjects, APN concentration is inversely and independently associated with LVH diagnosed by electrocardiography in Japanese men [14]. Another study using echocardiography revealed that circulating total APN and HMW APN are related to left ventricular wall thickness and diastolic function independent of age and metabolic factors [15]. These data suggest that APN may regulate hypertrophic progression of cardiomyocytes.

However, the role of APN in heart failure is controversial. Several studies have shown that plasma APN levels are high in patients with chronic heart failure (CHF) and are associated with CHF severity or mortality despite the protective effect of APN on CHF in mice [16–19].  $\beta$ -blocker therapy correlates with lower APN levels in patients with CHF, especially in nonobese patients, suggesting that this relationship should be considered when assessing plasma APN among patients with CHF [20]. Further careful studies may be required to clarify the relationship between APN and heart failure.

**2.4. Chronic Kidney Disease (CKD).** Increased albuminuria among patients with obesity and diabetes is a risk factor for cardiovascular and renal disease, and patients with CKD are at high risk for cardiovascular events. CKD patients show higher plasma APN levels than healthy subjects due to the low renal clearance rate of APN [21]. A prospective study of patients with renal failure demonstrated that patients who experience new cardiovascular events had lower plasma APN levels than event-free patients [22]. Several other studies have also indicated that increases in plasma APN in patients with CKD decrease their risk for cardiovascular disease and increase survival rate [23, 24]. In contrast, a

high APN level is associated with mortality, independent of risk markers for CHF severity among patients with CKD [16, 25]. Therefore, the cardioprotective role of APN in CKD remains controversial. A recent report by Komura et al. revealed that the loss of the vascular protective function of APN in the presence of high cystatin C levels in patients with CKD indicates that cystatin C may mask the beneficial effect of APN in patients with CKD despite high plasma APN levels [21].

### 3. Biological Features of APN

#### 3.1. Atherosclerosis

**3.1.1. In Vitro.** After initial clinical findings of the association between CAD and hypo adiponectinemia were reported, several experimental studies have been conducted to elucidate the biological effect of APN in atherosclerosis. APN has structural similarity with complimentary C1q or the collagen families [1]. APN specifically binds to collagen types I, III, and V, which are present in vascular intima and detected in the subendothelial space of rat balloon-injured arteries, implying an interaction between APN and vascular pathology [26].

When atherosclerosis commences, low-density lipoprotein (LDL) particles in the blood become oxidized (oxLDL) and induce the expression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1, in endothelial cells (ECs). Leukocytes in blood attach to the endothelial layer and induce proinflammatory chemokines that attract leukocytes into the subendothelial space [27]. APN inhibits the expression of these adhesion molecules in TNF $\alpha$ -activated endothelial cells by suppressing inflammatory transcriptional factors and activating nuclear factor (NF)- $\kappa$ B [6, 28]. Additionally, APN inhibits TNF $\alpha$ -inducible interleukin (IL)-8 synthesis in ECs by inactivating NF- $\kappa$ B and activating Akt [29]. An *in vivo* study in mice demonstrated that APN deficiency increases leukocyte-endothelium interactions with impaired endothelial nitric oxide signaling (eNOS) via upregulation of endothelial cell adhesion molecules [30].

The recruited inflammatory cells subsequently enhance the oxidization of LDL and various inflammatory reactions. Monocytes migrate to the subendothelial space in the atherosclerotic lesion and become lipid-laden macrophages. Monocytes change into macrophages in the subendothelial space by taking up oxLDL via scavenger receptors and form cells with accumulated cholesterol esters. APN suppresses scavenger receptor type A (SR-A) in macrophages and the internal cholesterol ester content. However, macrophages play an important role in reverse cholesterol transport (RCT), a protective system against atherosclerosis. APN increases apoA-I-mediated cholesterol efflux from macrophages through an ATP-binding cassette transporter A1-dependent pathway, indicating that APN may prevent atherosclerosis by accelerating RCT [31]. Macrophages sustain and amplify the inflammatory process by releasing several growth factors, cytokines, and chemokines that may further recruit immune cells, including monocyte/

macrophages, T lymphocytes, or vascular smooth muscle cells. Pretreatment with recombinant APN significantly suppresses the production of cytokines/chemokines, such as TNF $\alpha$ , and CXCR3 ligand chemokines, such as IFN-inducible protein of 10 kDa (IP-10), monokine induced by IFN- $\gamma$ , and IFN-inducible T cells, which is a chemoattractant in lipopolysaccharide-stimulated macrophages [32, 33]. The inflammatory process includes enzymes that can destroy the arterial extracellular matrix such as metalloproteinases (MMPs). APN treatment also induces anti-inflammatory IL-10 and subsequent tissue inhibition of MMP-1 production, suggesting that APN may stabilize atherosclerotic plaques and prevent their rupture [34].

Aortic smooth muscle cells (AoSMCs) are another major player in atherosclerosis, and their pathological migration and proliferation in the intima relates to restenosis of coronary arteries after PCI. APN suppresses growth factor-stimulated AoSMC proliferation and migration by inhibiting the ERK signal [35].

**3.1.2. *In Vivo*.** Several experimental studies have demonstrated the effect of APN on atherogenesis. The increment of total APN or globular APN significantly attenuates the progression of atherosclerosis in apoE knockout mice [36, 37]. In atherosclerotic lesions, APN accumulates to form cells in fatty streaks and inhibits the expression of VCAM-1, SR-A, and TNF $\alpha$  [36]. In addition, APN/apoE double knockout mice show advanced atherosclerotic lesions with increased T-lymphocyte accumulation and higher plasma IP-10 levels compared with apoE single knockout mice (Figure 1) [33]. Moreover, APN deficiency worsens neointimal formation after endothelial injury in mice, while APN supplements reverse the abnormal vascular remodeling [38]. These data support the *in vitro* bioactivity of APN as an anti-inflammatory adipocytokine in the atherosclerotic process.

**3.2. *Cardiac Diseases*.** Clinical studies have demonstrated that APN is associated with myocardial pathophysiology. APN deficiency causes severe concentric cardiac hypertrophy in mice after pressure overload with increased extracellular signal-regulated kinase, diminishes AMP-activated protein kinase (AMPK) signaling in the myocardium, and increases mortality [39]. Supplementing APN with an adenovirus vector attenuates the pathological cardiac hypertrophy. In an ischemia/reperfusion myocardium injury model, APN knockout mice exhibit increases in myocardial infarct size, apoptosis, and TNF $\alpha$  expression compared with controls. In cultured cardiomyocytes, APN inhibits TNF $\alpha$  production by inducing cyclooxygenase-2-dependent synthesis of prostaglandin E 2 [40]. A similar experiment showed that globular APN protects myocardium from ischemia/reperfusion injury by inhibiting inducible NOS and nicotinamide adenine dinucleotide phosphate oxidase protein expression and resultant oxidative/nitrate stress [41]. Two recent reports demonstrated that APN knockout mice show enhanced cardiac fibrosis following permanent ligation of the left anterior descending artery or angiotensin II infusion. APN accumulates in the injured cardiomyocytes

and protects it against fibrosis by reducing apoptosis and AMPK-dependent peroxisome proliferator-activated receptor (PPAR $\alpha$ ) activation [19, 42]. Despite the potential association between heart failure and high plasma APN shown by several clinical studies, other experimental studies have demonstrated a beneficial, protective effect of APN on myocardium. Elevated plasma levels of APN among patients with heart failure can be a reflection of accompanying renal dysfunction or “APN resistance” including impaired APN signal transduction in myocardium.

**3.3. *APN and Pulmonary Artery Remodeling*.** Pulmonary arterial hypertension (PAH) is an idiopathic disease characterized by an increase in the thickness of pulmonary artery wall. APN suppresses platelet-derived growth factor BB-mediated proliferation of pulmonary artery smooth muscle cells harvested from mice [43], indicating that APN may play a role in the prevention of PAH. In a mouse model of chronic airway inflammation, APN deficiency causes pathological pulmonary arterial wall thickness and elevates right ventricular systolic pressure, indicating PAH [44]. APN knockout mice also show thickening of pulmonary arterial wall under chronic hypoxic exposure, and APN overexpression significantly decreases the wall remodeling and right ventricular hypertrophy [45].

**3.4. *APN and Endothelial Function, Angiogenesis, and Hypertension*.** APN serves as an angiogenic factor. In a mouse hindlimb ischemia model, APN deficiency impairs revascularization, whereas adenovirus-mediated APN administration recovers angiogenesis [46]. APN stimulates blood vessel growth in the *in vivo* mouse Matrigel plug implantation and rabbit corneal models of angiogenesis by promoting cross-talk between AMP-activated protein kinase and Akt signaling within endothelial cells [47]. APN also dose dependently suppresses endothelial cell apoptosis and proliferation, migration, and premature diabetic senescence of endothelial progenitor cells [48–50].

Hypoadiponectinemia is associated with impaired endothelial dysfunction related to vasorelaxation. APN knockout mice show a significantly reduced endothelium-dependent vasodilation in response to acetylcholine compared with wild-type mice [51]. Another experiment demonstrated that APN knockout mice develop hypertension when maintained on a high-salt diet (8% NaCl) without insulin resistance [52]. Notably, all of these APNs protective effects on endothelial function are mediated through an increase in the production of eNOS [51, 53–55].

**3.5. *APN Strategies for Cardiovascular Protection in Metabolic Syndrome*.** Hypoadiponectinemia directly promotes the pathological reactions in cardiovascular system (Figure 2). Therefore, the increment of plasma APN is important to maximize the beneficial effects of APN. A reduction in body weight, especially visceral fat mass, with a combination of diet therapy and exercise is a safe and effective way to increase plasma APN levels.

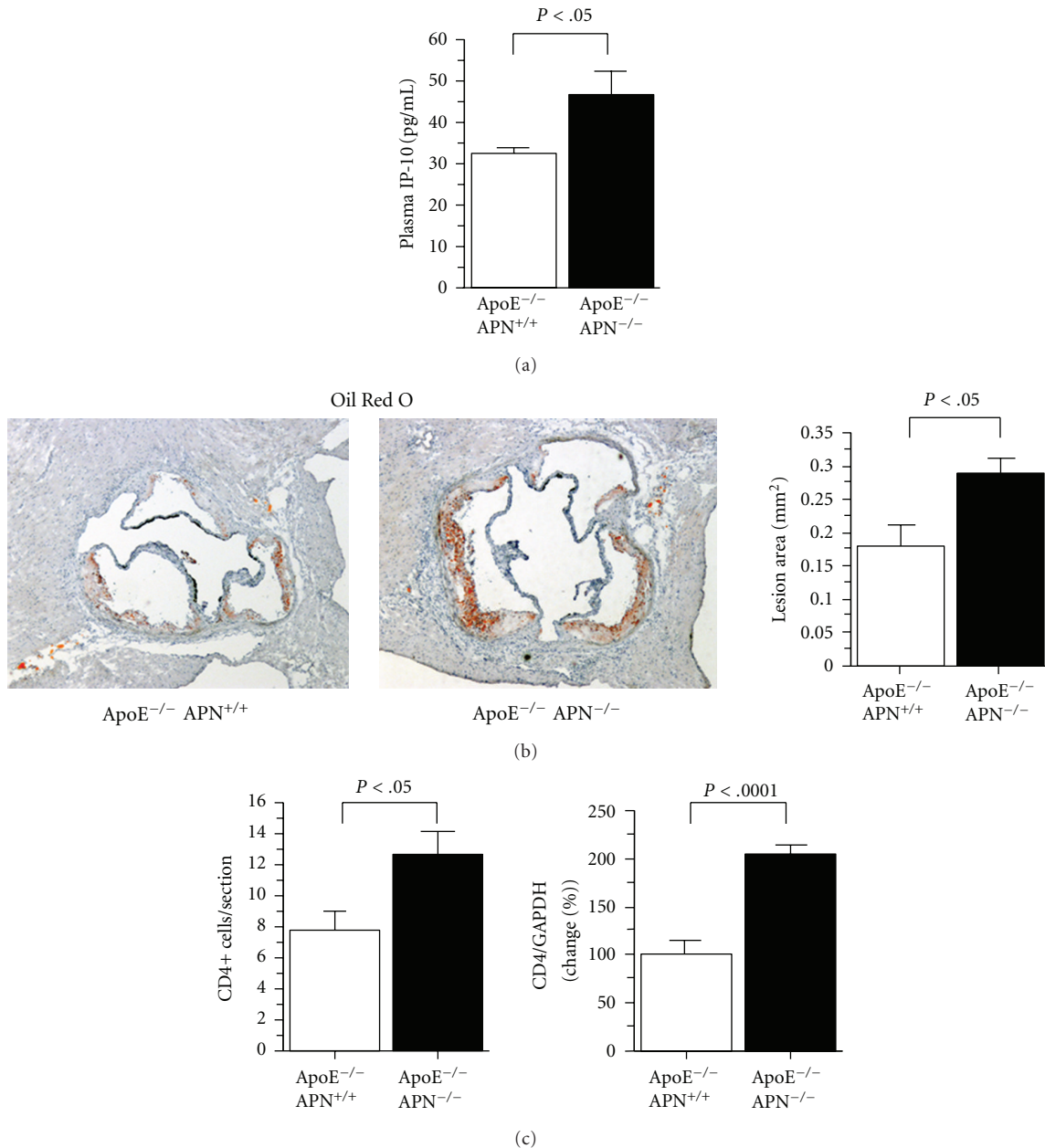


FIGURE 1: APN deficiency in apoE knockout mice. Compared with apoE single knockout mice, APN/apoE double knockout mice showed (a) higher plasma IP-10 levels, (b) advanced atherosclerosis, and (c) accelerated accumulation of T lymphocytes in atherosclerotic lesions (Adapted from [33]).

Another strategy to prevent cardiovascular disease using APN includes pharmacological changes in plasma APN levels. PPAR $\gamma$  agonists significantly increase plasma APN concentrations in insulin-resistant humans without affecting their body weight and in a mouse model of oxygen-induced retinopathy [56, 57]. Administering PPAR $\alpha$  ligands and angiotensin receptor blockers also increases plasma APN levels [53, 58–60]. Furthermore, several statins are also effective for elevating plasma APN [61, 62]. Changes in HMW APN as well as total APN may also be an ideal target. The natriuretic peptides including atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) also increased the production of APN in adipocytes and plasma APN levels

among patients with congestive heart failure [63]. Exogenous administration of adiponectin may be a therapeutic strategy as well. In a pig model, a single intracoronary administration of recombinant adiponectin protected myocardial ischemia/reperfusion injury by suppressing inflammation, apoptosis and oxidative stress [64].

APN receptors or candidate APN-receptor-binding proteins have been reported such as AdipoR1-R2, T-cadherin, and calreticulin [65–67]. Very recently, Denzel et al. reported that T-cadherin (glycosyl phosphatidylinositol-anchored cell surface glycoprotein) is critical for adiponectin-mediated cardioprotection by showing no effect of adenovirus-mediated adiponectin supplement in T-cadherin knockout

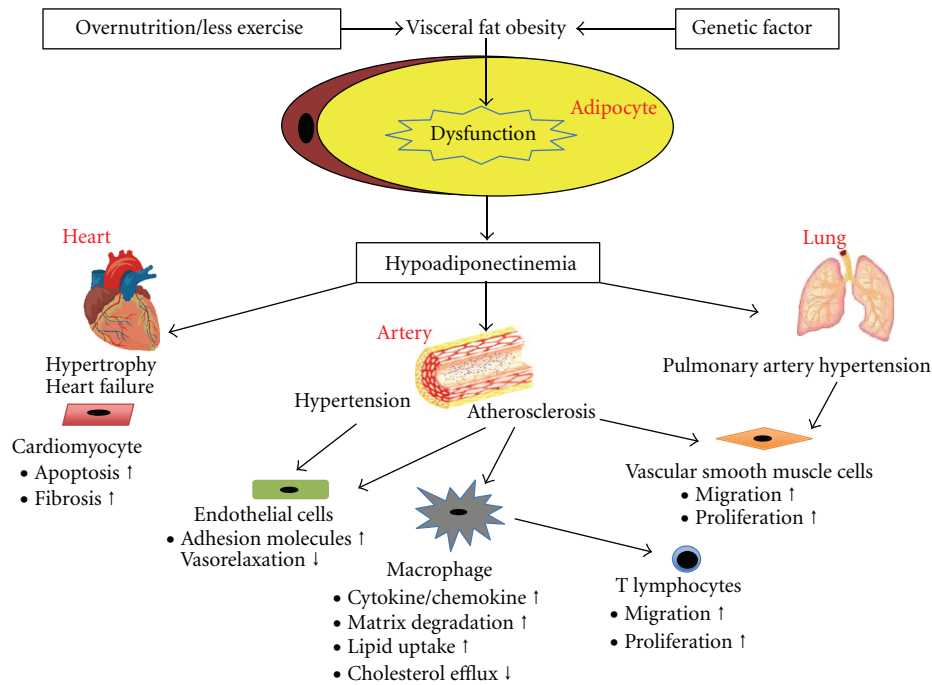


FIGURE 2: Hypoadiponectinemia directly promotes the pathological reactions in cardiovascular system.

mice [68]. Pharmacologically enhancing the expression of or activating APN receptors may be a good strategy for cardiovascular protection.

**4. Conclusion**

Adipose tissue stores not only excess body energy but also a variety of adipocytokines that regulate cardiovascular homeostasis directly and indirectly. Accumulating evidence has demonstrated that APN prevents diabetes, dyslipidemia, and hypertension, which are well-known risk factors for cardiovascular disease. Notably, APN directly interacts with cardiac and vascular tissues and mitigates pathological reactions. Generally, anti-inflammation is a key biological action of APN for cardiovascular protection. Further clinical and experimental studies will clarify the precise effects and mechanisms of APN action for future clinical use.

**Acknowledgment**

This work was supported by a grant from the Takeda Science Foundation.

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