ADIPONECTIN AND IL-10 IN CARDIOVASCULAR DISEASE

Nitin Tyagi¹, Jayeeta Bhadra², Subhra Sucharita Sahoo³, Anu RI¹, Peyir Bagra⁵, Charanjeet Kaur⁶

¹,²,³MBBS, MD(Post Graduate Student)
⁴Senior Resident, Department of biochemistry
⁵Director-Professor, Department of Biochemistry
College Building, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi-110029.

*Corresponding Author: Nitin Tyagi
MBBS, MD(Post Graduate Student), College Building, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi-110029.

ABSTRACT
Adiponectin is a protein secreted specifically by adipose cells that may couple regulation of insulin sensitivity with energy metabolism and serve to link obesity with insulin resistance. Obesity-related disorders including the metabolic syndrome, diabetes, atherosclerosis, hypertension, and coronary artery disease are associated with decreased plasma levels of adiponectin, insulin resistance, and endothelial dysfunction. Adiponectin has insulin-sensitizing effects as well as antiatherogenic properties. Lifestyle modifications and some drug therapies to treat atherosclerosis, hypertension, and coronary heart disease have important effects to simultaneously increase adiponectin levels, decrease insulin resistance, and improve endothelial dysfunction. In this review, we discuss insights into the relationships between adiponectin levels, insulin resistance, and endothelial dysfunction that are derived from various therapeutic interventions. The effects of lifestyle modifications and cardiovascular drugs on adiponectin levels and insulin resistance suggest plausible mechanisms that may be important for treating atherosclerosis and coronary heart disease.

INTRODUCTION
Elevated levels of free fatty acids associated with insulin resistance, obesity, diabetes, and the metabolic syndrome cause endothelial dysfunction by activating innate immune inflammatory pathways upstream of nuclear transcription factor kappa B (NF-κB). Thus, inflammation contributes to endothelial dysfunction[1,2]. The resultant decrease in nitric oxide (NO) bioactivity is important in the initiation, progression, and clinical expression of atherosclerosis. Insulin resistance[1], systemic hypertension, and hypercholesterolemia[2] all contribute independently to endothelial dysfunction accompanied by inflammation in the vessel wall, which promotes development of atherosclerosis and coronary heart disease.

Endothelial dysfunction is characterized by impaired NO release from endothelium and decreased blood flow to insulin target tissues[3]. This results in impaired delivery of substrate and hormone to skeletal muscle, which contributes to insulin resistance. The pathogenic relationships among obesity, the metabolic syndrome, and its cardiovascular complications are well established. However, mechanisms by which excess adiposity causes both insulin resistance and vascular dysfunction are not well understood. Increasing attention has been paid to the direct vascular effects of plasma proteins that originate from adipose tissue, especially adiponectin. Decreased plasma adiponectin levels are observed in patients with diabetes, metabolic syndrome, and coronary artery disease[4-5], and this may play a key role in the development of insulin resistance. Although the mechanisms underlying anti-inflammatory properties of adiponectin are not well understood[6], adiponectin’s anti-inflammatory and antiatherogenic properties may be related, in part, to its ability to stimulate production of NO from vascular endothelium[7]. In this review, we discuss the antiatherogenic effects of adiponectin and its properties to improve and mimic metabolic and vascular actions of insulin. Particular emphasis is given to insights derived from therapeutic interventions with diet, exercise, cardiovascular drugs, insulin sensitizers, and combination therapies that simultaneously raise adiponectin levels and improve insulin sensitivity and endothelial function.

BIOLOGY, REGULATION, AND METABOLISM OF ADIPONECTIN
The adipocyte is an active endocrine secretory cell releasing free fatty acids and producing several cytokines including tumor necrosis factor (TNF)-α, interleukins (ILs), leptin, and adiponectin[6]. Adiponectin is the most abundant adipokine secreted by adipose cells that may couple regulation of insulin sensitivity with energy metabolism. Adiponectin is a 30-kDa protein that...
consists of an N-terminal collagenous domain and a C-terminal globular domain.

Under normal conditions, the adiponectin gene (AMP1) located on chromosome 3q27 is expressed exclusively in adipose tissue, and recent genome-wide scans have mapped a diabetes susceptibility locus to this chromosome[8]. The concentration of adiponectin circulating in plasma is very high (2 to 20 g/ml)[9]. Plasma levels of adiponectin in the Japanese population is about 5 to 10 g/ml[10], and serum adiponectin is lower in Indo-Asians when compared with Caucasians (median 3.3 vs. 4.9 g/ml)[11]. Women have about 40% higher circulating levels of adiponectin than men[9].

Adiponectin exists in the circulation as a full-length protein and a putative proteolytic cleavage fragment consisting of the globular C-terminal domain. This globular domain of adiponectin is pharmacologically active and can regulate body weight and fatty acid oxidation in mice[12]. Adiponectin is found in multiple oligomeric forms in serum, as a trimer and a hexamer (2 trimers) of lower molecular weight (LMW) form: LMW isoform and high molecular weight (HMW) forms: HMW isoform[13]. The HMW form constitutes the major part of intracellular adiponectin, whereas the LMW form is predominant in the circulation. Levels of HMW isoform have better correlations with glucose tolerance than total adiponectin, suggesting that the HMW isoform of adiponectin is the active form[14]. The LMW and HMW isoforms of adiponectin activate NF-B[15]. The HMW isoform of adiponectin is suppressed in coronary artery disease patients, and it is elevated on weight loss, and it suppresses human umbilical vein endothelial cell apoptosis[16].

Two adiponectin receptor forms have been cloned. AdipoR1 is a high-affinity receptor for the globular C-terminal domain of adiponectin with very low affinity for full-length adiponectin. AdipoR1 is abundantly expressed in skeletal muscle whereas AdipoR2 is most abundant in the liver where it has intermediate affinity for both forms of adiponectin[17]. Overexpression or knock-down of AdipoR1/R2 suggests that these receptors mediate increased adenosine monophosphate (AMP) kinase and peroxisome proliferator-activated receptor (PPAR) ligands activities, as well as fatty-acid oxidation and glucose uptake by adiponectin[17]. Adiponectin receptors are expressed in pancreatic β-cells[18], macrophages, and atherosclerotic lesions[19]. Adiponectin receptor expression is increased by beta-cell exposure to the unsaturated free fatty acid oleate, and treatment of insulin-producing cells with globular adiponectin induces lipoprotein lipase expression[18].

Adiponectin itself is controlled in conditions of metabolic stress and by a number of hormones and factors involved inregulation of metabolic function. Insulin lowers adiponectin expression in both mice and humans[20]. Thiazolidinediones, as potent PPAR-

agonists, increase the expression of adiponectin[20,21]. Most factors with a significant impact on adiponectin regulation have inhibitory effects. These include catecholamines, glucocorticoids, cytokines (IL-6 and TNFα), prolactin, growth hormone, and androgens[22].

Adiponectin also influences IL-10 levels which is an anti-inflammatory cytokine. IL-10 protects against atherosclerosis by exerting an anti-apoptotic and anti-inflammatory action causing down regulation of Th1 response, inhibiting matrix degrading Matrix Metalloproteins (MMPs) and tissue factor(TF) thereby preventing plaque instability[23]. Adiponectin induces expression of IL-10 in human macrophages which then mediates its anti-atherogenic properties. Adiponectin also increases expression of TIMP (tissue inhibitor of metalloproteinases) by upregulating IL-10 synthesis[24] thereby providing an anti-atherogenic local environment.

**ADIPONECTIN AND IL-10 IN CORONARY ARTERY DISEASE**

Atherosclerosis is an inflammatory disease. Adiponectin prevents the process of atherogenesis by neutralizing the excess inflammatory response.

The physiological concentrations of adiponectin inhibits monocyte adhesion and expression of adhesion molecules such as VCAM-1, E-selectin, and ICAM-1 which aids in transendothelial migration of inflammatory cells thereby promoting atherosclerosis[12].

Adiponectin also hypothesized to stimulate nitric oxide (NO) production in vascular endothelium by AMPK-dependent pathways[13] which helps in vasorelaxation.

Adiponectin inhibits TNF-alpha induced NF-kBactivation thereby preventing release of proinflammatory cytokines and adhesion molecules[14] providing an antiatherogenic environment. Hence, according to Ouchi et al adiponectinaply acts as an endogenous modulator of endothelial cell function[18].

Adiponectin rapidly accumulates in the vascular wall when the endothelial barrier is injured and modulates the macrophage-to-foam cell transformation in vivo. This shows that adiponectin is not only a negative regulator of the endothelial adhesion molecule expression, but also a modulator for macrophage foam cell formation, thus providing a fundamental mechanism for the link between itself and atherosclerosis.

It is known that excessive lipid accumulation in macrophages plays an important role in the development of atherosclerosis. The scavenger receptor family proteins, such as class A macrophage scavenger receptor (MSR) and class B MSR (CD36), are responsible for lipid accumulation and foam cell formation by taking up modified LDL. Adiponectin’s role is in suppression of the macrophage-to-foam cell transformation by
inhibition of this class A macrophage scavenger receptor[2]. This in turn leads to less lipid accumulation in the macrophage and foam cell formation thereby preventing formation of atherosclerotic plaque.

Most coronary artery thrombi are triggered by the rupture of atherosclerotic plaque lesions, which are controlled by the balance between matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinases (TIMPs), mainly secreted from activated macrophages. Adiponectin selectively increases TIMP-1 expression in human monocyte-derived macrophages. Adiponectin is able to execute this action by inducing expression of IL-10 in human macrophages and IL-10 then exerts its anti-inflammatory role by inhibiting MMPs, which degrade the matrix, and by inducing TIMPs which prevent plaque formation in the vessel[3].

FUTURE PROSPECTS
Adiponectin is a target for future research in reducing morbidity and mortality of atherosclerotic disease. Diet, exercise, cardiovascular drugs, and insulin sensitizers improve endothelium-dependent vascular function, increase adiponectin levels, and reduce inflammation and insulin resistance by distinct mechanisms (Fig. 2). This may help explain beneficial effects of combination therapies in recent clinical trials. Thus, there is a scientific rationale for recommending a combination of lifestyle modifications and multiple drugs from separate classes to prevent atherosclerosis and coronary heart disease. Recent evidence suggests that cross-talk between inflammatory signaling pathways and insulin signaling pathways causes both metabolic insulin resistance and endothelial dysfunction that synergize to predispose to cardiovascular disorders in the metabolic syndrome (3,80). Prospective studies are needed to examine the ability of increases in adiponectin levels and insulin sensitivity to improve primary end points including incidence of diabetes and outcomes of cardiovascular events. It is possible that recombinant adiponectin may have a beneficial therapeutic role in the treatment and prevention of cardiovascular diseases in the future.

REFERENCES


