# New Insight into the Relation between Adiponectin and Diabetes

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## Abstract

Diabetes mellitus is a group of metabolic diseases. Insulin resistance is defined as a state that needs more insulin to get the biological effects achieved by a lower amount of insulin in the normal state. Several molecules which are secreted through adipocytes have been involved in insulin resistance and type 2 diabetes mellitus. Adiponectin as a 244 amino acid protein is exclusively expressed in differentiated adipocytes. Recent studies indicated impaired multimerization of adiponectin is associated with type 2 diabetes development. Moreover, the relationship between adiponectin, insulin and insulin resistance is not known and many mechanisms have been proposed. Inverse relationship between adiponectin and insulin resistance may be mediated through insulin and other hormones like catecholamines or androgens. Moreover, intensive insulin treatment increased serum C-peptide and adiponectin level resulted to improving sensitivity of insulin and decreased CRP level. According to these studies, it seems that adiponectin may be an important modulator of insulin action for enhancing of sensitivity of insulin.

**Keywords**: Adiponectin, Diabetes, Insulin resistance

## Introduction

Diabetes mellitus is a group of metabolic diseases (1), with more than 200 million people (2). It is expected that the total number of these patients reaches 370 million worldwide in 2030 (3,4). It is caused by a combination of insulin resistance and impaired insulin secretion by pancreatic β cell (2-4). Insulin resistance is defined as a state that needs more insulin to get the biological effects achieved by a lower amount of insulin in the normal state (5). Several molecules which are secreted through adipocytes have been involved in insulin resistance and type 2 diabetes development in from animal models and humans (6). Thus, it seems that these signaling molecules can be as determinative agent of the incidence of type 2 diabetes mellitus (6).

Adiponectin is a 244 amino acid protein (7-9) exclusively expressed in differentiated adipocytes (10-16). Cardiac tissue, bone, mammary and salivary glands in limited quantities may express adiponectin (7). It is known as ACRP30 (9) (adipocyte complement related protein of 30kDa) (17-21) or GBP28 (gelatin binding protein of 28 kDa) (10). It



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exists on chromosome 3 locus 3q27 in adipose tissue (10). It circulates in the blood and acts as a protective factor for cardiovascular disease and increases insulin sensitivity (10). Other property of adiponectin is containing of three exons and two introns. It acts as a single monomer and contain four structurally domains named amino terminal domain, a changed domain, a collagen-like region and an amino terminal globular region (7). Adiponectin and globular fragments are similar with complement C1q protein and TNF-α. Circulating adiponectin is disulfide-linked oligomer and exists in trimers, hexamers and multimers status with high molecular mass. Several previous studies showed that the level of adiponectin is decreased in obese people (22).

The action of adiponectin is facilitated via two distinct receptors called AdipoR1 and AdipoR2 Only liver expressed AdipoR2 whereas AdipoR1 (mRNA) was detected in human platelets (7). The expression of these receptors (AdipoR1 and AdipoR2) has been detected in monocytes, and megakaryocyte cell lines. The existence of adiponectin receptors can be due to different isoforms of adiponectin which need different receptor conformations to bind with high affinity and wide biological actions of adiponectin in different tissues (7).

## Epidemiology

Concentration of adiponectin in circulation is 2 and 20 mg/ mL, accounting for up to 0.05% of total serum protein (7,19,23). Moreover, the level of plasma adiponectin is lower in obese subjects as compared with lean subjects (23). The amount of adiponectin in women is about 40% higher than men (19,20). It seems that androgens may play a main role in these differences, because androgens have an inhibitory effect on adiponectin (23,24).

## Adiponectin and its properties

Adiponectin has anti-inflammatory and anti atherogenic propertie (9). It acts through reduced expression of adhesion molecule-1, reduced macrophage chemotaxis needed to form fat cells and suppression of inflammatory signaling in endothelial tissue (10). It also has anti-angiogenic, and possibly anticancer properties (25). Moreover, its effect on glucose and lipid metabolism is detected (25). Indirect antineoplastic action may be due to decreased insulin resistance, hyperinsulinemia, and free IGF-I levels or via moderating neovascularization and inflammation (25).

Study on adipose tissue of rat showed that reduction of adiponectin expression about 60% increased insulin resistance (10). Nucleotide polymorphism in adiponectin which is caused by genetic or environmental factors can be a significant factor in reduction of insulin sensitizing action (10).

Evidence also showed that adiponectin has anti-neoplastic effect. The signaling pathways of adiponectin to inhibit tumorigenesis are several signaling pathways including 5' AMP activated protein kinase (AMPK), phosphatidylinositol 3-kinase (PI3K), mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription 3 (STAT 3), c-Jun NH2-terminal kinase (JNK), nuclear factor-κB (NFκB) and the sphingolipid way (36).

## Adiponectin and diabetes

Idea about the role of adiponectin in diabetes is contradictory. Some studies reported that the level of adiponectin is lower in type 2 diabetes mellitus and obese subjects (16,19-21). Furthermore low level of serum adiponectin auspicates the incidence of type 2 DM (26). The level of adiponectin is decreased prior to development of type 2 diabetes (23). In contrast, high level of adiponectin is associated with decreased level of type 2 diabetes (27).

Adiponectin administration is caused lower level of plasma glucose and increased insulin sensitivity (23). So that treatment of patients with intensive insulin increased the level of circulating adiponectin and improved insulin sensitivity (28,29). It seems that administration of adiponectin can change insulin sensitivity



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through increased oxidation of fatty acid, glucose uptake and utilization of skeletal muscle and adipose tissue (10), but it can also mediate numerous anti-atherosclerotic vascular functions like endothelial function, inhibition of smooth muscle cell proliferation and inhibition of macrophage conversion of foam cells (30).

Some study reported that insulin may regulate proteins which are secreted from fat cells. Moreover, insulin may affect expression of adiponectin gene and concentration of adiponectin in vitro (31,32). Albeit there is causal association between adiponectin level and insulin sensitivity in humans, regulation of adiponectin in old age and in people with inflammatory status is poorly understood and may be due to non-inflammatory mechanisms (27).

Moreover, intensive insulin treatment increased serum C-peptide and adiponectin level resulted to improving sensitivity of insulin (32) and decreased CRP level. It seems that decreased level of C -peptide is correlated to increased level of adiponectin in type 1 diabetes patients (32). Another study reported that there is no difference between adiponectin level in diabetic patients and control group (32). Perhaps, it is due to in type 2 diabetes, C-peptide is not decreased as in type 1 diabetes (32).

High level of adiponectin protects glucose metabolism impairment in obese patients and decreases the risk of type 2 diabetes development (31). However inverse relationship between adiponectin and insulin resistance may be mediated through insulin and other hormones like catecholamines or androgens (33-34) and pro-inflammatory cytokines and some medications (31). However, recent studies indicated impaired multimerization of adiponectin in type 2 diabetes development. Formation of adiponectin oligomers is dependent on intermolecular disulfide bonds mediated by the N-terminal Cys39 residue. Moreover, they explained capability of various adiponectin species to active AMP-activated protein kinase (AMPK) in hepatocytes and myocytes. While wild-type Adiponectin HMW complexes are able to activate AMPK in hepatocytes, but Cys39Ser in trimer and globular domain mutant condition are not able. Moreover, wild and mutant species can activate AMPK in monocyte (35).

## Conclusions

According to these studies, it seems that adiponectin may be an important modulator of insulin action for enhancing of sensitivity of insulin.

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