

Adiponectin receptor: A Potential Target For Diabetes, Obesity And Other Disorders

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Summary

Adipose tissue acts as an endocrine organ producing a number of substances with an important role in the regulation of food consumption, energy expenditure and a variety of metabolic processes. Adiponectin is a collagen-like plasma protein secreted by adipocytes that has been recommended to play a substantial role in the development of insulin resistance and obesity. A number of studies have shown that obesity, insulin resistance and atherosclerosis are associated with decreased level of adiponectin and its replacement during experimentation is able to diminish insulin resistance, increases insulin sensitivity and reduces lipids and atherogenesis. Chronic and central adiponectin treatment reduces weight, glucose and lipids. Adiponectin is exclusively secreted from adipose tissue into the bloodstream and is very abundant in plasma relative to many hormones. Previous findings showed that its level is decreasing in person with increasing body mass index. The adiponectin receptors, AdipoR1 and AdipoR2, which regulate the antidiabetic actions of adiponectin, have been cloned and are down regulated in obesity-linked insulin resistance. Up regulation of adiponectin is a partial cause of the insulin- sensitizing and antidiabetic actions of thiazolidinediones. Therefore, adiponectin and adiponectin receptors represent potential versatile therapeutic targets to combat obesity-linked diseases characterized by insulin resistance. The aim of this review is to recapitulate the current knowledge about the physiology and pathophysiology of adiponectin and evaluation of adiponectin receptor as a target of diabetes (insulin resistance), obesity and atherosclerosis and asthma.

Key words: Adiponectin, Obesity, AMPK, PPAR- γ , Diabetes, Asthma.

Introduction

Newer studies in Pharmaceutical and medical sciences are continuously redefine the role of different tissues in our body. The adipose tissue represents one of the most emblematical illustrations at this point. It is now seen that in addition to its main function as an energy storage depot, adipose tissue involve as an important and very active endocrine organ that produces a number of hormones and other substances with significant roles in the regulation of insulin

sensitivity and other physiological processes [1]. Adiponectin is secreted by white adipose tissue and exists as the most abundant adipokine in the human plasma [2]. Adiponectin is an adipokine whose biosynthesis is deranged in obesity, diabetes mellitus and atherosclerosis [3]. Evidence suggests that adiponectin has anti-atherogenic properties by improving endothelial function and having anti-inflammatory effects in the vascular wall [4]. In addition, adiponectin modifies vascular intracellular redox signalling and exerts indirect antioxidant effects on human myocardium [5]. However, its clinical role in cardiovascular disease is doubtful. Adiponectin's positive prognostic value in coronary artery disease had been widely supported over the last years, but this view has been questioned recently [6]. High adiponectin levels are paradoxically associated with poorer prognosis in heart failure syndrome. These controversial findings seem surprising as adiponectin has been viewed overall as an anti-atherogenic molecule. Therefore, any certain conclusion about adiponectin's role in cardiovascular disease seems untimely and early [7]. Despite the rapidly accumulating literature on this adipokine, it is still unclear whether adiponectin is a key mediator or a bystander in cardiovascular disease. It is still uncertain whether adiponectin levels have any importance for risk of cardiovascular disease or they just reflect the activation of complex and opposing underlying mechanisms [8].

Recent studies have indicated that plasma adiponectin levels are inversely correlated with body mass index (BMI) and insulin resistance [9]. Reduction of plasma adiponectin levels is commonly observed in the patients with type-2 diabetes and/or in those who are obese in comparison with healthy control individuals [10]. The reason for the deep interest in adipose tissue-derived hormones lies in the growing incidence of obesity in the developed countries of the Western World [11]. It is now clear that the presence of obesity substantially increases the risk of related comorbidities such as insulin resistance, diabetes, dyslipidemia, hypertension and others [12]. Two novel adiponectin receptor types (AdipoR1 and AdipoR2) were very recently identified. AdipoR1 is ubiquitously expressed, most abundantly in skeletal muscle [13], and exhibits high affinity, whereas AdipoR2 is predominantly expressed in the liver and exhibits intermediate affinity to ligands [14]. Adiponectin receptors were also demonstrated to mediate increased AMP kinase and peroxisome proliferator-activated receptor- α ligand activities, resulting in enhancements of fatty acid oxidation and glucose transport activity when stimulated with ligands [15].

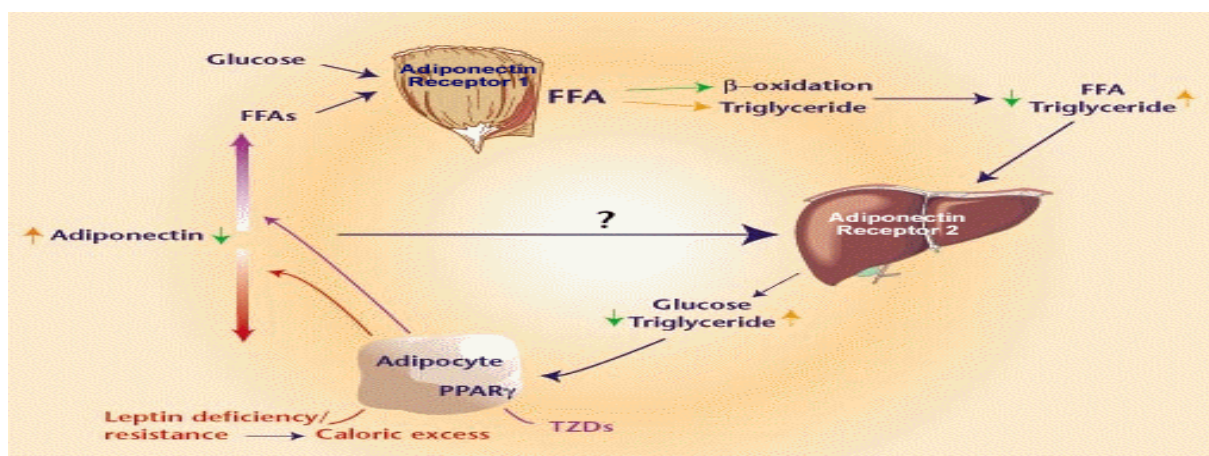


Figure 1: shows the effect of adiponectin via adiponectin receptor 1 & 2 in skeletal muscle and liver respectively

AdipoRs (Adiponectin Receptors)

Two adiponectin receptors (AdipoR1 and Adipo R2) isoforms, whose copy has been shown to be regulated by PPAR and liver X receptor ligands, were recently identified and it has been suggested that additional receptors may be present [16-18]. These AdipoR1 and AdipoR2 are predicted to have seven transmembrane domains and AdipoR1 has a high affinity for gAd and low affinity for fAd oligomeric forms, whereas AdipoR2 exhibits intermediate binding affinity for both gAd and fAd forms.

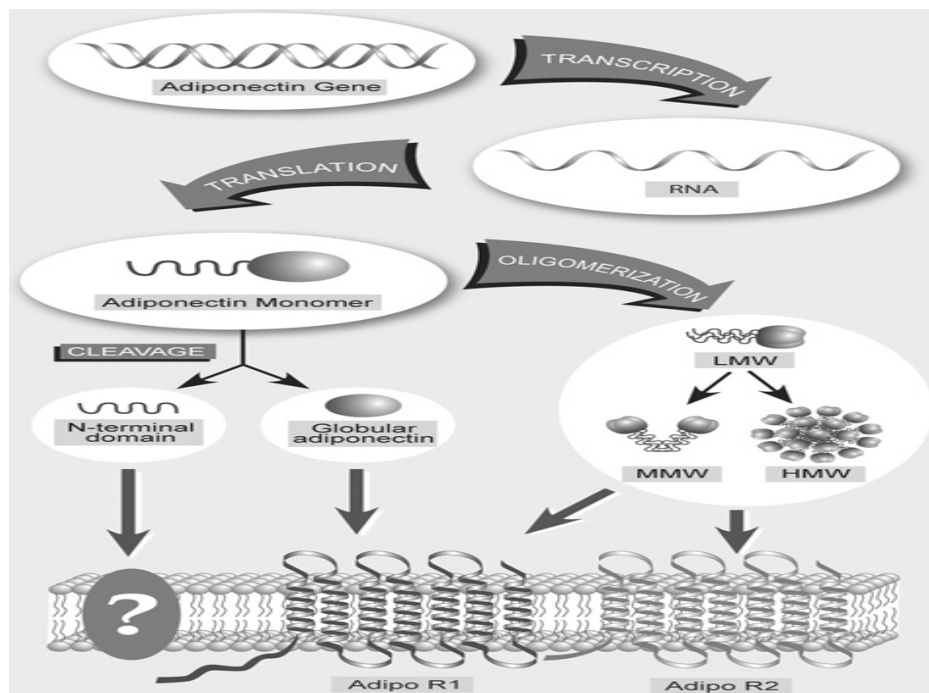


Figure 2: Regulation of adiponectin synthesis and function As highlighted in this Figure, the function of adiponectin can be regulated at many levels, including: transcription of the adiponectin gene; translation of RNA to protein; post-translational modifications resulting in oligomerization of fAd into trimers (LMW), hexamers (MMW) and oligomers (HMW); protease-mediated cleavage of fAd to produce the N-terminal fragment and the C-terminal globular domain. Binding of adiponectin forms to membrane receptors (e.g. gAd has high affinity only for AdipoR1) and LMW, MMW and HMW forms of fAd and gAd can mediate distinct cellular effects. It has also been suggested that the N-terminal fragment may mediate cellular responses.

A potential pathophysiological role for alterations in AdipoRs is supported by a strong relation between receptor expression in skeletal muscle with insulin resistance and plasma insulin levels, lower skeletal-muscle AdipoR1 and AdipoR2 expression in patients with a family history of diabetes and altered AdipoR1 expression in *ob/ob*, *db/db* or STZ (streptozotocin) diabetic mice [19–21]. The importance of AdipoR is being further highlighted by a recent study on their regulation in response to changes in nutritional conditions, metabolic alterations and antidiabetic agents. We have performed *in vitro* studies to examine direct regulation of AdipoR expression by

hyperinsulinaemia and hyperglycaemia [22]. Both conditions decreased AdipoR1 mRNA levels and, importantly, reduced the metabolic effects of gAd in skeletal muscle. Hyperinsulinaemia also increased AdipoR2 and increased sensitivity of muscle cells to fAd (Figure 2). Demonstration of this potential for conditions prevailing during the progression of Type 2 diabetes to alter AdipoR expression and consequently the function of different forms of adiponectin confirms the recently proposed concept of gAd resistance, resulting in a vicious cycle of events that exacerbates the development of diabetes [23].

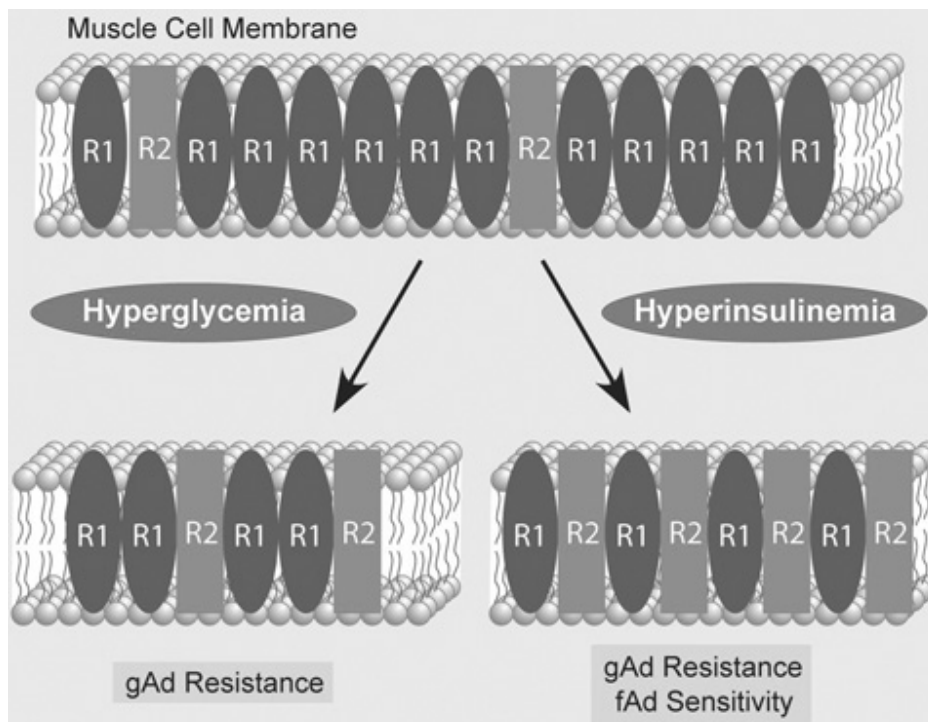


Figure 3: Regulation of AdipoR isoform expression and adiponectin-sensitivity by hyperglycaemia and hyperinsulinaemia In extensor digitorum longus or L6 muscle cells, there is approx. 6-fold more AdipoR1 than AdipoR2. Hyperinsulinaemia or hyperglycaemia can reduce AdipoR1 mRNA expression, resulting in gAd resistance, while hyperinsulinaemia also induced a switch towards increased fAd-sensitivity by enhancing AdipoR2 expression.

Linkage of adiponectin with insulin resistance, diabetes, obesity and other metabolic disorders

The *Adiponectin* gene encodes a secreted protein expressed exclusively in both white adipose tissue (WAT) and brown adipose tissue [24]. Adiponectin has a carboxyl-terminal globular domain and an amino-terminal collagen domain and is structurally analogous to complement 1q [25-27], which belongs to a family of proteins that form specialized multimers [28]. Adiponectin presents in a wide range of multimer complex forms in plasma and attaches via its collagen domain to make three major oligomeric forms: a low-molecular weight (LMW) trimer, a middle-molecular weight (MMW) hexamer, and high-molecular weight (HMW) 12- to 18-mer adiponectin [29]. In contrast to the expression of adipokines such as TNF- α and resistin, which cause insulin resistance, adiponectin expression is reduced in obese, insulin-resistant rodent

models [30]. Importantly, a decrease in plasma adiponectin levels preceded the onset of diabetes in these animals and decreased insulin sensitivity [31]. Plasma adiponectin levels have also been reported to be decreased in humans with high body mass index, particularly those with visceral obesity, and to correlate inversely with lower insulin effect [32]. Hypo-adiponectinemia has also been suggested to be independently connected with the metabolic disorders like diabetes — indeed, more strongly than are any other markers for inflammation [33]. There is a sexual dimorphism in the circulating levels of adiponectin. Indeed, female humans and rodents have higher plasma adiponectin levels than males, suggesting that sexual hormones regulate the production of adiponectin, although it is controversial how these hormones, such as estrogen and testosterone, are involved in the regulation of plasma adiponectin level [34]. Nevertheless, this may partly account for the fact that females are more sensitive to insulin than males. Some dietary factors, such as soy protein, fish oils, and linoleic acid, are also suggested to increase plasma adiponectin levels, which is consistent with the fact that intake of these factors is thought to have a protective effect on the development of diabetes [35] while a diet rich with carbohydrates appears to decrease plasma adiponectin level [36]. The plasma adiponectin level is changed by different factors, including gender, aging, and lifestyle [37, 38].

Mode of Action of Adiponectin: Adiponectin signaling

A. Insulin-sensitizing actions

1. Adiponectin decreases tissue triglyceride content and enhance insulin signaling; in skeletal muscle, adiponectin up regulate the expression of molecules involved in fatty-acid transport such as CD36, in combustion of fatty-acid such as acylcoenzyme a oxidase, and in energy dissipation such as uncoupling protein [39, 40]. These changes led to decreased tissue TG content in skeletal muscle [31]; increased tissue TG content has been reported to interfere with insulin-stimulated phosphatidyl-inositol (PI) 3-kinase activation and subsequent glucose transporter 4 translocation and glucose uptake, leading to insulin resistance Decreased tissue TG content in muscle may contribute to improved insulin signaling [41]. This was demonstrated in skeletal muscle of lipoatrophic mice treated with adiponectin, in which increases in insulin-induced tyrosine phosphorylation of insulin receptor and insulin receptor substrate-1 and insulin-stimulated phosphorylation of Akt were seen [39].

2. Adiponectin activates PPAR- γ signaling

Based on the data that treatment of lipoatrophic or obese diabetic mice with adiponectin or over-expression of adiponectin in ob/ob mice resulted in increased expression levels of PPAR- γ target genes such as CD36, acyl-coenzyme A oxidase, and uncoupling protein 2, we hypothesized that adiponectin could activate PPAR- γ [42]. Consistent with this hypothesis, adiponectin indeed increased the expression levels of PPAR- γ *in vivo* [43]. These data suggested that adiponectin increased fatty-acid combustion and energy consumption, presumably via PPAR- γ activation at least in part, which led to decreased TG content in the liver and skeletal muscle and thus coordinately increased *in vivo* insulin sensitivity [44].

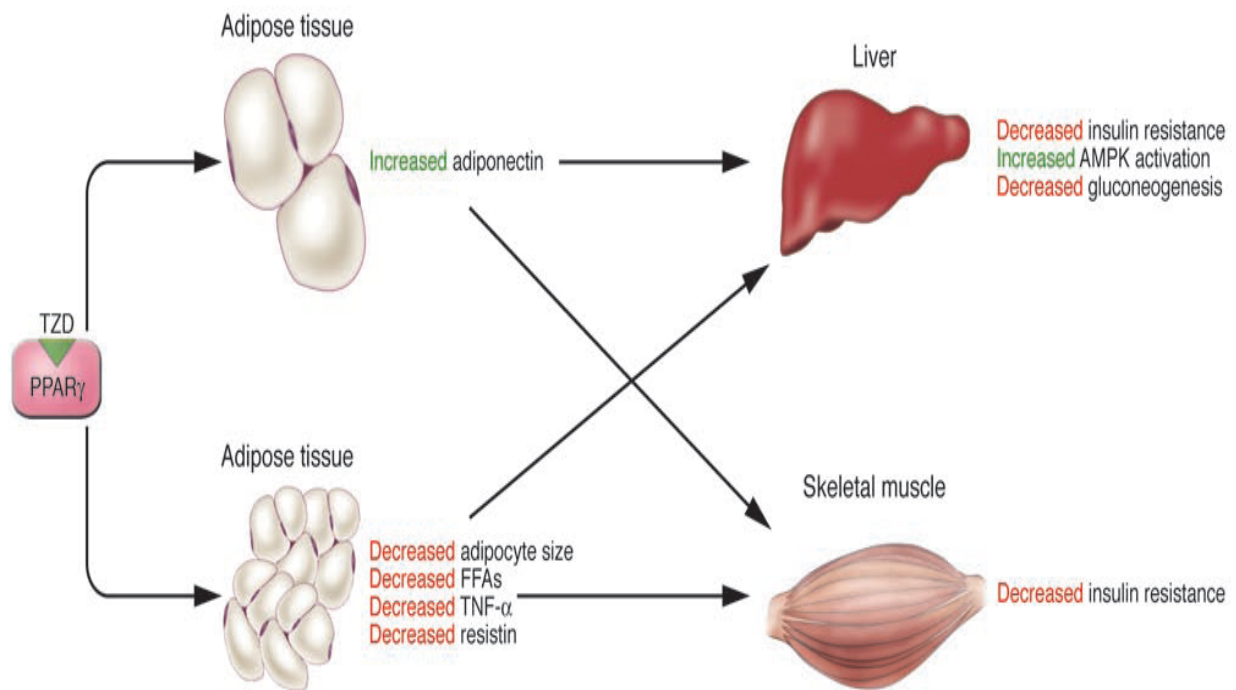


Figure 4: TZDs ameliorate insulin resistance and diabetes by both adiponectin-dependent and -independent pathways. We propose that there are 2 different pathways in the amelioration of insulin resistance induced by the PPAR γ agonists TZDs, such as pioglitazone and probably rosiglitazone.

3. Effect of adiponectin in AMPK receptors

Globular adiponectin and full-length adiponectin stimulated phosphorylation and activation of AMPK in skeletal muscle, whereas only full-length adiponectin did so in the liver [45]. In parallel with its activation of AMPK, adiponectin stimulated phosphorylation of acetyl coenzyme-A carboxylase (ACC), fatty-acid combustion, glucose uptake, and lactate production in myocytes, and also stimulated phosphorylation of ACC and caused a reduction in molecules involved in gluconeogenesis in the liver, which can account for the acute glucose-lowering effects of adiponectin *in vivo* [46].

The group of Lodish and Ruderman also showed that the adiponectin/ACRP30 globular domain enhanced muscle fat oxidation and glucose transport via AMPK activation and ACC inhibition [47]. In recent studies it was reported that AMPK involved in glucose uptake stimulated by the globular domain of adiponectin in primary rat adipocytes [48]. Because leptin has also been shown to stimulate AMPK in skeletal muscle, activation of AMPK may be a common mechanism by which insulin-sensitizing adipokines such as adiponectin and leptin increase insulin sensitivity [49].

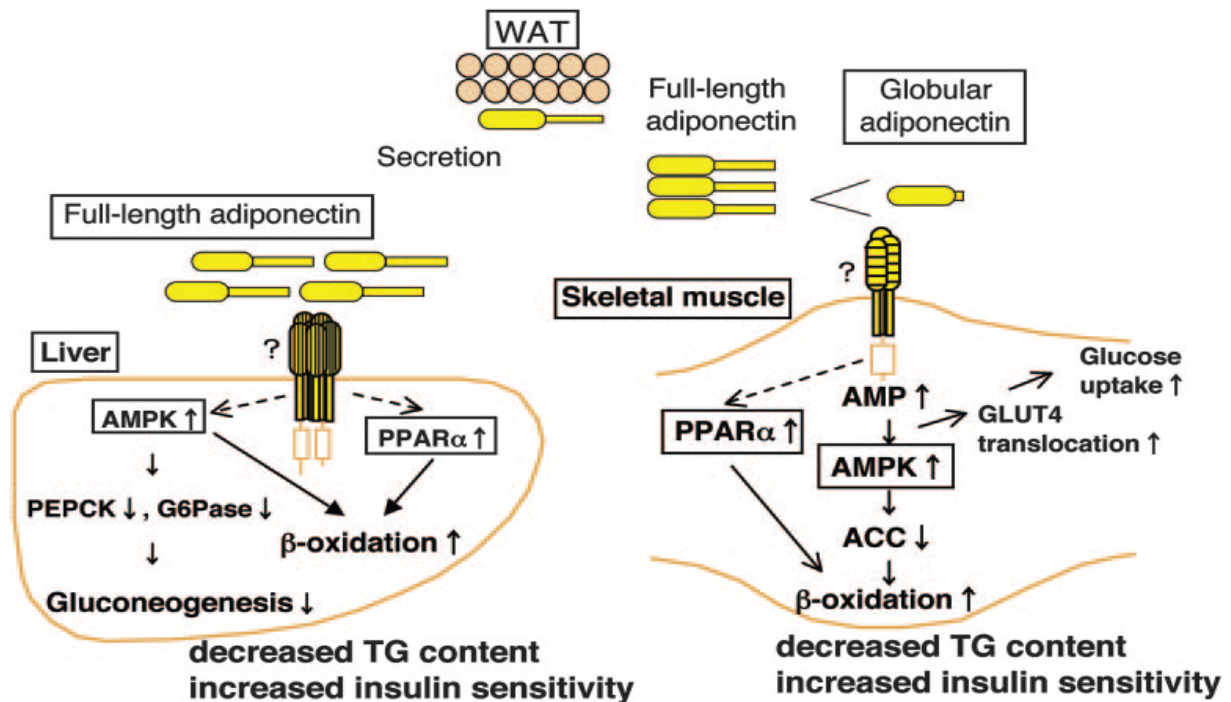


Figure. 5: Adiponectin can activate AMPK and PPAR α in the liver and skeletal muscle. In skeletal muscle, both globular and full-length adiponectin activate AMPK, thereby stimulating phosphorylation of ACC, fatty-acid oxidation, and glucose uptake. Adiponectin activates PPAR α , thereby also stimulating fatty-acid oxidation and decreasing tissue TG content in muscle.

B. Anti obesity action

Obese and Type-2 diabetic patients or animal models exhibit altered profiles of adipokines and energy metabolism and insulin action are markedly impaired in individuals with visceral obesity [50]. Insulin resistance and obesity are both associated with lower plasma adiponectin concentrations. Since insulin resistance and obesity are related, the extent to which the association of adiponectin with insulin resistance is dependent on its relationship with obesity is unclear [51]. To address this issue, fasting plasma adiponectin concentrations were measured in 60 nondiabetic subjects, stratified into four equal groups on the basis of both their degree of adiposity and insulin resistance. Insulin resistance was quantified by determining the steady-state plasma glucose (SSPG) concentration in response to an infusion of octreotide, glucose, and insulin, and degree of adiposity was assessed by BMI [52-54]. Subjects were defined as obese (BMI ≥ 30.0 kg/m 2) or nonobese (<27.0 kg/m 2) and as either insulin sensitive (SSPG <100 mg/dl) or insulin resistant (>190 mg/dl). Insulin-resistant subjects had significantly ($P < 0.001$) lower (mean \pm SD) adiponectin concentrations, whether they were obese (17.1 ± 5.9 μ g/ml) or nonobese (16.3 ± 7.5 μ g/ml) as compared with either obese, insulin-sensitive (34.3 ± 13.1 μ g/ml) or nonobese, insulin-sensitive (29.8 ± 15.3 μ g/ml) subjects [54]. Finally, adiponectin levels in insulin-sensitive subjects varied to a significantly greater degree than in insulin-resistant subjects. These results suggest that adiponectin concentrations are more closely related to differences in insulin-mediated glucose disposal than obesity (55).

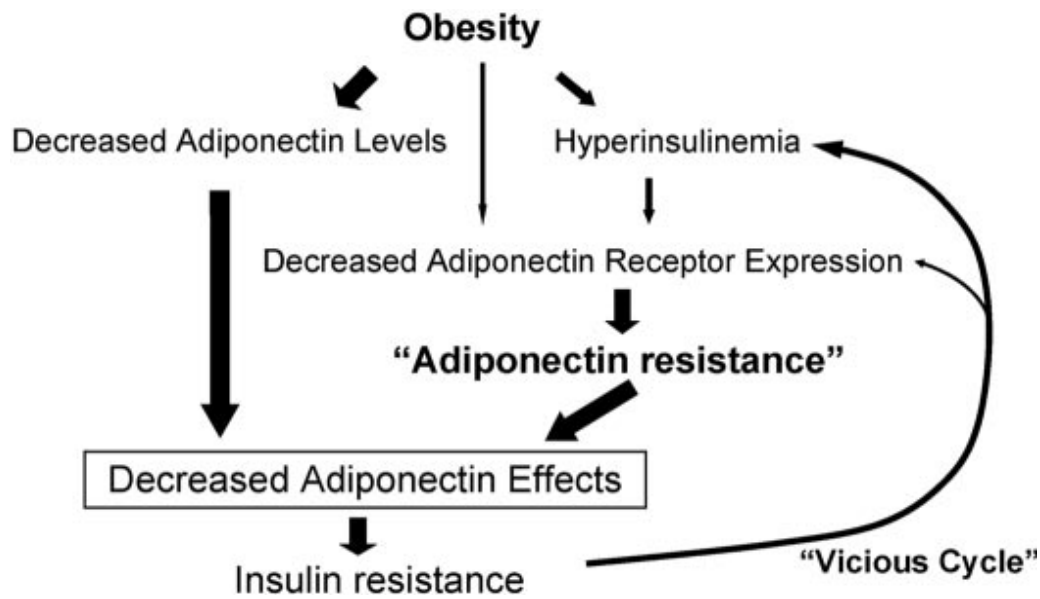


Figure 6: Obesity, adiponectin resistance, and insulin resistance. Plasma adiponectin levels were decreased in obesity, which may play causal roles in the development of insulin resistance.

C. Antiatherosclerotic actions

Some recent studies shows that adiponectin level is reduced in atherosclerosis and there is great increase in various markers like cytokine TNF-alpha also present. The Adenovirus-expressed adiponectin reduces atherosclerotic lesions in a mouse model of atherosclerosis, and adiponectin-deficient mice exhibit an excessive vascular remodeling response to injury. Clinically, hypoadiponectinemia is closely associated with increased levels of inflammatory markers such as C-reactive protein and interleukin-6 [56].

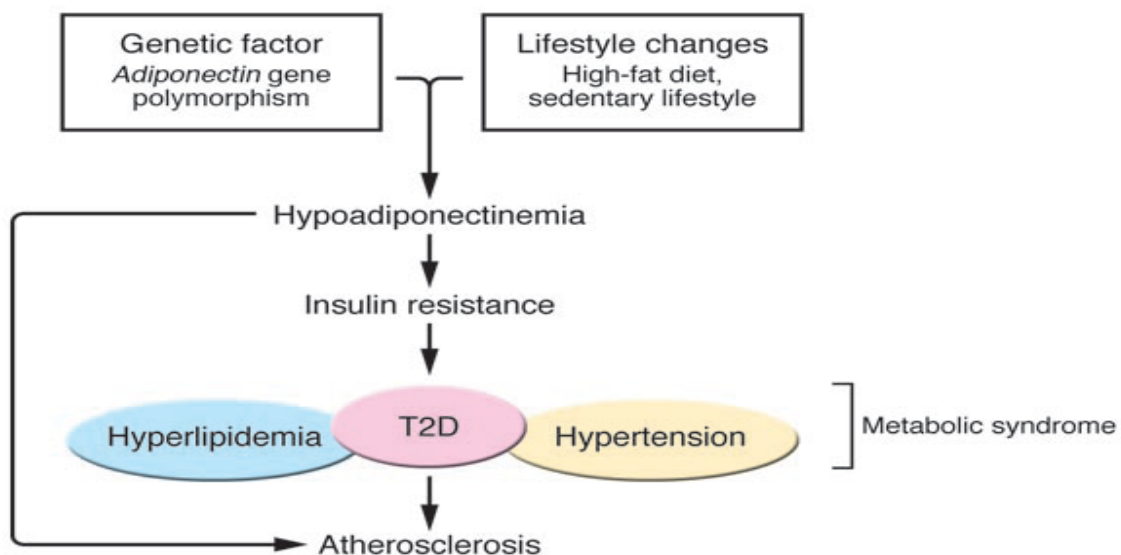


Figure 7: Reduced adiponectin levels also directly play a causal role in the development of atherosclerosis.

D. Anti Asthmatic actions

Adiponectin, a 30-kDa adipocyte complement-related protein that is exclusively secreted from adipose tissue, is a potent regulator of the immune response. Adiponectin inhibits inflammatory gene expression such as IL-6 in a variety of cell types via the modulating nuclear factor kB (NF-kB) and extracellular signal-regulated kinase activation and enhances expression of anti-inflammatory genes, including the IL-10 and IL-1 receptor antagonist genes [57]. Alteration of adiponectin concentrations may influence various diseases related to the development of asthma and atopy. Thus, the balance between adiponectin and leptin may be one of the factors contributing to development of asthma and subphenotypes [58]. Recently, Komakula et al. observed that the ratio of leptin to adiponectin was associated with exhaled NO as a marker of airway oxidative stress in moderately persistent asthma. However, they found no difference in the ratio of leptin to adiponectin in asthmatics compared to normal control subjects. However, as the authors mentioned, there were some limitations of the study including the severity of asthma, overweight or obese study subjects, gender, and medications used to control the symptoms in the subjects. Thus, we reanalyzed the serum leptin and adiponectin levels in age and gender-matched, unmedicated, non-obese mild asthmatics to determine whether the relative concentrations of adiponectin and leptin are associated with asthma and asthma sub-phenotypes [59].

Conclusion

An association between adipokines and insulin resistance has been noted in both diabetic and nondiabetic states. In the recent some studies shows that adiponectin may play a direct role in determining insulin-mediated glucose uptake. However, since adiponectin is the major adipokine secreted by fat cells and is closely linked to obesity, it is unclear to what extent the association of adiponectin with insulin resistance is independent of its relationship with obesity. Understanding this association is of importance because it may clarify mechanisms of insulin resistance and influence our understanding and use of therapeutic modalities, such as weight loss or exercise to enhance insulin sensitivity. Studies have documented that adiponectin concentrations are significantly related to various measures of body fat and that significant weight loss leads to a rise in adiponectin levels. One way to determine whether insulin resistance is associated with adiponectin independently of obesity is to take advantage of the fact that both obese and nonobese individuals can be insulin sensitive as well as insulin resistant. We have used this approach in this study and have compared plasma adiponectin levels in nonobese and obese individuals, stratified at baseline into insulin-sensitive and insulin-resistant groups. To conclude this review we can say that adiponectin receptors will be a potential target for anti-diabetic, anti-obesity, anti-asthmatic and anti-hyperlipidemic drugs.

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