

## Adiponectin – journey from an adipocyte secretory protein to biomarker of the metabolic syndrome

M. E. TRUJILLO<sup>1</sup> & P. E. SCHERER<sup>1,2,3</sup>

From the Departments of <sup>1</sup>Cell Biology and <sup>2</sup>Medicine; and <sup>3</sup>Diabetes Research and Training Center, Albert Einstein College of Medicine, Bronx, NY, USA

**Abstract.** Trujillo ME, Scherer PE (Albert Einstein College of Medicine, Bronx, NY, USA). Adiponectin – journey from an adipocyte secretory protein to biomarker of the metabolic syndrome (Review). *J Intern Med* 2005; **257**: 167–175.

Adiponectin is an adipocyte-derived hormone that was discovered in 1995. Unlike leptin, which was identified around the same time, the clinical relevance of adiponectin remained obscure for a number of years. However, starting in 2001, several studies were published from different laboratories that highlighted the potential antidiabetic, antiatherosclerotic and anti-inflammatory properties of this protein complex. Methods to measure the protein with high throughput assays in clinical samples were developed shortly thereafter, and as a result hundreds of clinical studies have been published over the past 3 years describing the role of adiponectin in endocrine and metabolic dysfunction.

Furthermore, adiponectin research has expanded to include a role for adiponectin in cancer and other disease areas. Although it is an impossible task to summarize the findings from all these studies in a single review, we aim to demonstrate the utility of circulating adiponectin as a biomarker of the metabolic syndrome. Evidence for this relationship will include how decreased levels of plasma adiponectin ('hypoadiponectinaemia') are associated with increased body mass index (BMI), decreased insulin sensitivity, less favourable plasma lipid profiles, increased levels of inflammatory markers and increased risk for the development of cardiovascular disease. Therefore, adiponectin levels hold great promise for use in clinical application serving as a potent indicator of underlying metabolic complications.

**Keywords:** ACRP30, atherosclerosis, insulin sensitivity, PPAR $\gamma$ .

### Introduction

Adiponectin (also known as: ACRP30, apM1, adiponectin and GBP28) is a hormone produced exclusively by the adipocyte. Initial identification of this protein was made through the isolation of a cDNA using a subtractive hybridization screen designed to identify genes up-regulated during adipocyte differentiation [1]. Adiponectin is dramatically up-regulated during adipogenesis and remains one of the most adipocyte-

specific gene products identified to date. Adiponectin consists of an amino-terminal signal sequence, a variable region and a collagenous domain. Adiponectin protein in its most basic form is a homotrimer of three 30 kDa subunits. Trimers associate through disulphide bonds within the collagenous domains of each monomer to form bouquet-like higher order structures. These higher order structures include low-molecular weight (LMW) hexamers of 180 kDa and high-molecular weight (HMW) 16–18mers of

>400 kDa. Together, these complexes make up approximately 0.01% of total serum protein (circulating at approximately  $10 \mu\text{g mL}^{-1}$ ). Here, we review the current knowledge of the biological function of adiponectin and its relationship to human health and disease.

### Adiponectin complexes and bioactivity

Adipocytes secrete both the LMW and HMW forms of adiponectin *in vivo* and *in vitro*. Thus, the LMW and HMW are the predominant forms in serum whilst smaller complexes such as the trimer are virtually undetectable. Neither the LMW nor HMW interchange with each another after secretion in serum or culture medium [2]. However, studies with recombinant mutant forms of adiponectin that can only generate the trimeric form demonstrate that this trimer possesses increased bioactivity [2]. These findings suggest that circulating pools of LMW and HMW complexes may constitute precursors requiring processing in the form of reduction to trimers at the cell surface of target cells.

To characterize adiponectin action in target tissues, many studies have tested the effects of exogenous adiponectin on murine models both *in vivo* and *in vitro*. Several laboratories describe administration of a bacterially produced, full-length adiponectin or a proteolytic cleavage product thereof (the globular 'head' domain of adiponectin) to mice which results in decreased circulating levels of glucose, free fatty acids and triglycerides [3, 4]. *In vitro*, these changes have been attributed to increased glucose uptake and lipid oxidation in muscle, mediated by activation of AMPK [3, 5]. The decreases in circulating free fatty acids because of increased muscle lipid oxidation are hypothesized to lead to the improvements in insulin signalling in muscle and whole body insulin sensitivity [4, 5].

The effects of adiponectin on muscle only occur with the bacterially produced full-length or the globular domain of adiponectin. Structurally, the globular form of adiponectin lacks the collagenous domain necessary for multimerization. Because of the differences in mammalian versus bacterial expression systems, the bacterially produced full-length adiponectin is secreted as lower order forms, because bacterial expression systems do not allow for proper folding and orientation of the disulphide bonds within the collagenous domains [6].

Multimerization of adiponectin into higher order complexes is essential for its bioactivity on liver. Therefore, it is uncertain whether the effects observed in muscle are purely pharmacological or whether they are reflective of a physiological aspect of adiponectin function.

Studies conducted in our laboratory using full-length adiponectin produced by mammalian cells suggest that liver and not muscle is the primary site of adiponectin bioactivity [7]. In a mammalian expression system, full-length adiponectin is produced and secreted as LMW and HMW complexes. Administration of mammalian-derived full-length adiponectin to normal and/or obese-diabetic mice results in decreased serum glucose [7]. Pancreatic clamp studies reveal that this decrease in serum glucose was due to decreased hepatic glucose output that was associated with a reduction in the expression of gluconeogenic enzymes [8]. The adiponectin-stimulated decrease in serum glucose was not due to changes in peripheral glucose uptake, glycolysis or glycogen synthesis. *In vitro* studies conducted by Wang *et al.* show that the effect of adiponectin on the liver requires hydroxylation and glycosylation of residues within the collagenous domain of adiponectin [9]. This finding may explain why studies employing the globular form (lacking the collagenous domain) or the bacterially produced full-length form (lacking post-translational modifications in the collagenous domain) do not affect hepatic glucose metabolism or insulin sensitivity.

Together these data suggest adiponectin functions to enhance hepatic insulin sensitivity and that this effect is dependent on the presence of adiponectin in the form of higher order structures (LMW and HMW). In fact, recent data strongly argues that it is not only the absolute levels of LMW and HMW, but rather the relative ratio of these two complexes that serves as a good indicator of systemic insulin sensitivity (discussed further below).

It is important to note that the majority of clinical studies involving adiponectin and human disease only describe the relationship between total circulating levels of adiponectin as assessed via enzyme-linked immunosorbent assay (ELISA) or radioimmunoassay (RIA) and do not account for differences in the complexes of adiponectin present in circulation. Since the relative levels of HMW adiponectin are frequently proportional to total levels and methods for a high throughput assay to measure the

different adiponectin complexes separately have not yet been developed, the use of assays measuring total levels of adiponectin in large clinical studies remains a legitimate approach. However, future studies examining the levels of the LMW and HMW forms of adiponectin are likely to provide better correlations and will further contribute to our understanding of the role of this intriguing protein in human health and the pathogenesis of metabolic disease.

### Adiponectin and body weight

As adiponectin is produced exclusively by the adipocyte, it is not surprising that adiponectin concentrations in the serum are affected by changes in adipose tissue mass. However, unlike most adipose-derived hormones and secreted proteins, adiponectin mRNA and serum levels are decreased in obesity [10, 11]. In addition to obesity, the inverse relationship between adiponectin and body weight is upheld in extremely lean subjects such as those with anorexia nervosa [12, 13]. In support of these findings, cross-sectional studies show an inverse relationship between adiponectin mRNA and/or serum levels and body mass index (BMI) [11, 14]. However, there is an even stronger inverse relationship between adiponectin and fat mass (assessed by bioelectrical impedance or computerized tomography) than there is between adiponectin and BMI [15].

Circulating adiponectin levels and percentage HMW species are higher in females (who have higher levels of body fat for a given BMI) compared with males. Interestingly, the relationship between fat mass and adiponectin does not explain the sexual dimorphism in total adiponectin levels, suggesting that additional factors beyond absolute fat mass are responsible for the regulation of adiponectin [16]. Whatever regulatory mechanisms are in place, it is clear that the circulating levels of adiponectin are tightly controlled and remain relatively constant, despite the relative high circulating levels and rapid turn over of the circulating pool within a few hours.

As longitudinal studies in primates suggest that adiponectin decreases with weight gain as animals become obese [17], it is expected that weight loss results in increased adiponectin expression. Indeed, weight loss (>20% of body weight) via bariatric surgery results in significant increases in circulating adiponectin levels within 6–12 months after surgery

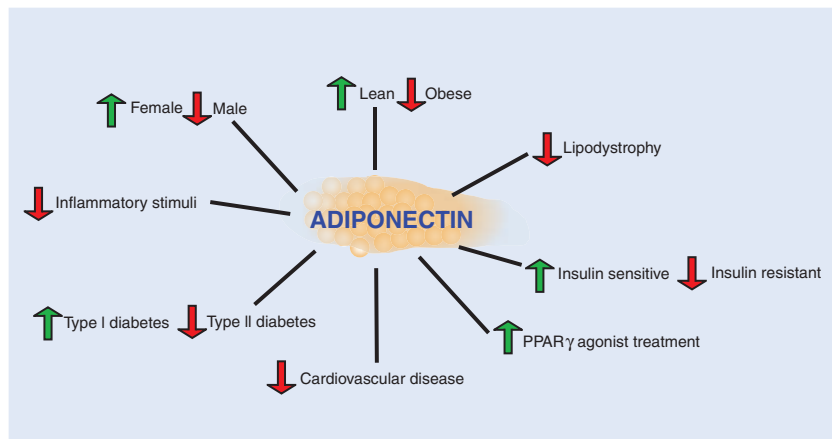
[18–20]. These improvements in adiponectin expression levels are accompanied by increases in insulin sensitivity [18]. Diet-induced weight loss (approximately 20 kg per 24 months) in obese subjects resulted in significant increases in adiponectin plasma and mRNA levels such that the changes in adiponectin levels correlated with improvements in insulin sensitivity [21, 22]. Consistent with these observations in humans, caloric restriction in mice results in significant elevations in circulating adiponectin.

### Adiponectin and distribution of fat mass

In addition to association with fat mass, adiponectin levels differ with body fat distribution. Plasma levels of adiponectin exhibit strong negative correlations with direct (via computerized tomography scan) and indirect (waist-to-hip ratio, waist circumference) measures of intra-abdominal fat (IAF) mass [23, 24]. Another study suggests that IAF was a stronger correlate with adiponectin levels than subcutaneous fat [23]. *Ex vivo* analysis of adipose tissue in lean and obese subjects shows lower adiponectin protein and mRNA levels in omental versus subcutaneous adipose tissue [25, 26]. Thus, it is not only the amount of fat but the distribution of adipose mass which determines adiponectin levels.

In light of the insulin-sensitizing effects of adiponectin on the liver, it is tempting to speculate that decreased production of adiponectin in visceral adipose tissue depots in the obese may explain the association between increased visceral adiposity and insulin resistance. Comparison of adiponectin gene expression in different depots from lean, obese, and obese diabetic subjects shows adiponectin mRNA levels were lower in visceral versus subcutaneous adipose tissue in all groups and adiponectin expression was even lower in visceral adipose tissue from obese subjects with diabetes [22, 26]. However, these results should be interpreted with great caution because mRNA levels are not always a good reflection of circulating protein levels [16].

Adiponectin release from adipocytes undergoes extensive regulation at the post-translational level. The current working hypothesis is that increases in central adiposity results in a down-regulation of adiponectin production by the IAF pads. Because of the rapid down-regulation of adiponectin immediately following primary adipocyte isolation, *in vitro*



**Fig. 1** Summary of the most important factors and disease states that lead to an up-regulation (indicated by a green arrow) or down-regulation (indicated by a red arrow) of adiponectin in adipose tissue.

studies of adiponectin secretion kinetics are technically challenging and the depot differences in the ability to down-regulate adiponectin in obese-diabetics remains unknown.

### Adiponectin and lipodystrophy

Lipodystrophy, is characterized by adipose loss or remodelling coupled with metabolic abnormalities including insulin resistance, diabetes, dyslipidaemia and liver steatosis. Because the change in adipose tissue mass or distribution is strongly associated with aspects of the metabolic syndrome, recent studies have examined the role of adipokines (including adiponectin) in the pathogenesis of lipodystrophy. Several clinical studies have shown that both congenital and HIV-related lipodystrophies are associated with hypoadiponectinaemia. In congenital lipodystrophy, the reduction in serum adiponectin levels is in proportion to body fat reduction [27]. In HIV-associated lipodystrophy syndrome (HALS) serum adiponectin levels are proportional to body fat redistribution (from peripheral to central adipose depots) [28]. These studies also show that markers of the metabolic syndrome such as insulin resistance and fatty liver exhibit strong inverse correlations with adiponectin levels suggesting a role for this hormone in the metabolic complications of both congenital lipodystrophy and HALS.

The HIV-positive patients on highly active anti-retroviral therapy (HAART) are at increased risk of developing HALS [29], suggesting HAART contributes to the development of HALS, perhaps through a reduction in adiponectin levels. In support of this hypothesis, several studies show HAART lowers

adiponectin levels in HIV-positive subjects and in HIV-negative subjects [30, 31]. Another study showed that in subjects on HAART, adiponectin levels are lower in subjects with lipodystrophy compared to those without [32]. Together these findings suggest HAART may decrease adiponectin levels and thereby promote the development of HALS, but it is unclear whether HAART has a direct affect on adiponectin in HIV-positive patients. In contrast to the effects of HAART, treatment of HIV-positive or -negative males with HIV protease inhibitors increases adiponectin levels [31]. However, similar to the situation in HAART, the relationships between protease inhibitors and circulating adiponectin levels are poorly understood.

### Adiponectin and insulin resistance

Several studies in rodent models support the hypothesis that adiponectin functions as an insulin sensitizer by decreasing hepatic glucose output and thereby contributing to the regulation of whole-body glucose homeostasis. These data are supported by studies in humans where adiponectin levels correlate with basal and insulin-suppressed endogenous glucose production [33]. Therefore, it is not surprising that hypoadiponectinaemia is associated with insulin resistance in humans [14, 15], or that a relationship between hypoadiponectinaemia and insulin resistance has been established in gestational diabetes [34], diabetes associated with lipodystrophy [35] and type II diabetes [36]. Interestingly, adiponectin levels are low in insulin-resistant subjects regardless of whether they are obese [37]. These findings suggest that hypoadiponectinaemia may

directly contribute towards changes in the regulation of glucose homeostasis and decreased hepatic insulin sensitivity observed with diabetes.

The strong inverse relationship between adiponectin and diabetes is further supported through genetic studies where identification of genetic polymorphisms resulting in hypoadiponectinaemia are associated with insulin resistance, and linkage analysis has identified a locus on chromosome 3 (3q27, encoding the gene for adiponectin) as a susceptibility locus for the metabolic syndrome and diabetes [38]. Furthermore, recent studies show low adiponectin levels predict the risk of the development of type II diabetes, even in the absence of any other indicators of insulin resistance [39, 40]. Thus, these results from genetic studies highlight the importance of adiponectin as a physiological regulator of glucose homeostasis and insulin sensitivity.

One potential reason for the relationship between adiponectin and insulin sensitivity may be a direct effect of insulin on adiponectin levels. Insulin decreases adiponectin levels in humans and rodents *in vivo* [8, 41] and *in vitro* [42–44]. In addition, adiponectin levels are elevated in type I diabetics compared with healthy controls [45]. Together these findings suggest hyperinsulinaemia may have a negative impact on circulating adiponectin levels causing insulin resistance. However, because hyperinsulinaemia is accompanied by insulin resistance *in vivo*, it is difficult to discern cause and effect relationships based on correlation alone. Furthermore, studies performed in Rhesus monkeys clearly indicate that the drop in adiponectin levels precedes the development of hyperinsulinaemia [17, 46], suggesting that low adiponectin levels may be a cause and not a consequence of hyperinsulinaemia.

Regardless of the underlying reasons for hypoadiponectinaemia, treatment of both humans and rodents with thiazolidinediones (TZDs) that are potent PPAR $\gamma$  agonists raises circulating adiponectin levels [47]. This effect on adiponectin production is specific to PPAR $\gamma$  agonists, as metformin and PPAR $\alpha$  agonists have no effect on adiponectin levels [47]. Furthermore, exposure of 3T3-L1 cells to TZDs increases adiponectin expression, suggesting the effects of TZDs on adiponectin are direct [48]. However, it is not clear whether this is merely a reflection of increased adipocyte differentiation [16], or the result of specific binding of PPAR $\gamma$  to a recently identified PPAR $\gamma$  response element (PPRE)

within the adiponectin promoter [49]. Although these data suggest that adiponectin may mediate some of the effects of this class of antidiabetic drugs, it is unlikely that all of the effects of PPAR $\gamma$ -agonists could be explained through the action of a single mediator. In support of this hypothesis, 'fat-less' A/ZIP mice with little to no circulating adiponectin exhibit improved insulin-stimulated glucose uptake in muscle upon TZD administration [50]. Yet, in spite of improvements in muscle insulin sensitivity, treatment of A/ZIP mice with TZDs exaggerates hepatic insulin resistance resulting in no net antidiabetic effect. Future studies designed to examine the effects of TZDs on insulin sensitivity in the absence of adiponectin will greatly improve our understanding of adiponectin-mediated TZD action.

Although TZDs are a widely used class of antidiabetic drugs, a significant proportion of all patients fail to demonstrate improvements in insulin sensitivity [51]. However, adiponectin increases in the majority of patients on TZDs, suggesting disconnect between the induction of adiponectin and improvements in insulin sensitivity. We have recently proposed an alternative method of measuring the relationship between adiponectin induction and TZD-mediated improvements and obtained vastly improved correlations. We defined a new index that takes the different circulating forms of adiponectin into account and called this index the adiponectin sensitivity index ( $S_A$ ), defined as the percentage of the HMW form/total circulating adiponectin. The distribution of adiponectin complexes was measured in samples from a number of different clinical studies before and after treatment with TZDs, changes in  $S_A$  were measured and correlated with changes in insulin sensitivity. This type of analysis gave remarkably tight correlations in all patient samples studied [52]. More importantly, this was particularly relevant for improvements in hepatic insulin sensitivity and less relevant for improvements seen in muscle insulin sensitivity. An accompanying *in vitro* study in 3T3-L1 adipocytes showed TZD-induced increases in  $S_A$  are due at least in part to increased secretion of the HMW form of adiponectin [52]. Thus, it appears the HMW form of adiponectin may be responsible for the insulin-sensitizing effects of TZDs, whereas the LMW form may even act as an antagonist. The mechanism through which TZDs stimulate an increase in HMW adiponectin levels is not known, but the secretory pathway of adipocytes

appears to be the main site of action. Studies that focus on the usefulness of the  $S_A$  as a parameter for systemic insulin sensitivity under other conditions are currently underway. The hope is that  $S_A$  will be a clinically useful indicator that could be applied in combination with other parameters (such as oral glucose tolerance tests and the measurement of inflammatory cytokines) to provide an integrated assessment of a patient's insulin sensitivity.

### Adiponectin and atherosclerosis

A growing body of evidence from animal and *in vitro* studies suggests adiponectin is protective against the development of atherosclerosis. For example, mice lacking adiponectin are reported to have a significant trend towards increased neointimal formation in response to external vascular cuff injury. Furthermore, mice overexpressing globular adiponectin in the pro-atherogenic background of the apoE<sup>-/-</sup> mice display a reduced development of atherosclerotic lesions [53, 54]. *In vitro* studies have attributed the protective effects of adiponectin to its ability to down-regulate vascular adhesion factors in endothelial cells [55], inhibit foam cell formation and smooth muscle migration [54, 56] and exert anti-inflammatory effects on macrophages [57]. However, because the majority of these studies employed the use of the globular form of adiponectin, it is uncertain whether full-length adiponectin exerts such direct effects on vascular cell function.

In addition to the potential effects of adiponectin on the vasculature, adiponectin may exert additional antiatherogenic effects through the modulation of lipid metabolism. Several clinical studies show adiponectin levels are negatively correlated with serum triglycerides and small dense low-density lipoprotein (LDL), and positively correlated with high-density lipoprotein (HDL) [36, 58, 59]. Cross-sectional and intervention studies show that the relationship between adiponectin and plasma lipids is independent of age, gender, BMI and insulin sensitivity [23, 60, 61]. Although it is tempting to speculate that adiponectin may modulate serum lipids through direct effects on the liver and/or adipose tissue, the mechanisms mediating the relationship between adiponectin and lipid metabolism are unknown.

Beyond a possible direct involvement of adiponectin in lipid metabolism, a number of recent studies

have described inverse associations between circulating adiponectin levels and measures of cardiovascular disease [36, 62–64]. Cross-sectional studies report that the relationship between hypoadiponectinaemia and cardiovascular disease remains intact after adjustment for cardiovascular risk factors such as diabetes, dyslipidaemia, hypertension, smoking and BMI [63, 64]. In fact, hypoadiponectinaemia may explain in part why ethnic groups where lower levels of adiponectin have been reported such as African-Americans and people of South Asian descent [65, 66], have an increased risk of type 2 diabetes mellitus and coronary artery disease compared with other ethnic groups [67]. More impressively, a large case-control study conducted by Pischon *et al.* demonstrated high circulating levels of adiponectin are associated with decreased risk of myocardial infarction in men [62]. This association was independent of inflammation or glycaemic status, and was only partially explained by serum lipid profile. Together these findings suggest that cardiovascular risk factors such as dyslipidaemia and vascular inflammation may contribute to the relationship between hypoadiponectinaemia and cardiovascular disease, but that the mechanisms that underlie the relationship between adiponectin and cardiovascular disease have yet to be elucidated.

### Adiponectin receptors

The biology of adiponectin as described is both complex and diverse with effects ranging from alterations of hepatic gene expression to modulation of immune cell function. These effects have spurred intense search for the receptor(s) through which adiponectin acts. Thus far, three putative adiponectin receptors have been isolated. The first set of receptors was identified using the globular and bacterially produced full-length forms of adiponectin [68]. These receptors exist in two isoforms, AdipoR1 and AdipoR2. In the mouse, AdipoR1 is expressed ubiquitously with highest expression levels in skeletal muscle and AdipoR2 is expressed most abundantly in the liver [68]. A recent study in humans suggests these two forms take on different expression patterns where mRNA for AdipoR1 and AdipoR2 are both expressed in skeletal muscle [69]. Although clinical studies have been published on mRNA levels of these receptors under different disease states, the relevance of these receptors *in vivo*

has yet to be determined. In addition to AdipoR1 and AdipoR2 that bind globular and bacterially produced adiponectin, full-length adiponectin produced in human embryonic kidney cells has been shown to bind T-cadherin [70]. T-cadherin is a GPI-anchored extracellular protein expressed in smooth muscle and endothelial cells. Both the LMW and HMW forms but not the globular form of adiponectin has been shown to bind T-cadherin; however, the functional implications of adiponectin binding to T-cadherin remains to be demonstrated.

## Conclusion

Adiponectin is a hormone produced exclusively by the adipocyte. Adiponectin circulates as either LMW or HMW forms. Unlike most other adipose-derived hormones, adiponectin is down-regulated in obesity and the lack of adiponectin has been associated with the metabolic syndrome. The correlations between hypoadiponectinaemia and lipodystrophy, insulin resistance, dyslipidaemia and cardiovascular disease are very well established (summarized in Figure 1). Future studies that focus on the relative distribution of the different adiponectin complexes may provide even stronger correlations. Adiponectin has the potential to become a clinically relevant parameter to be measured routinely in the diabetes clinic of the future. However, more work is required to establish and standardize the methods by which the levels of this protein are measured, and additional parameters will have to be considered to help interpret the adiponectin data in the context of insulin resistance and the metabolic syndrome.

## Conflict of interest statement

No conflict of interest was declared.

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*Correspondence:* Philipp E. Scherer, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461, USA. (fax: (718)-430-8574; e-mail: scherer@aecom.yu.edu).