

# Adiponectin, the controversial hormone

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## Abstract

*Objective:* To discuss present knowledge about adiponectin hormone.

*Design:* Review of existing literature.

*Setting and results:* Adiponectin is one of the most interesting cytokines associated with obesity, although its physiological role remains to be fully clarified. Adiponectin is a 247-amino acid protein that contains four differentiable domains. Contrary to most adipose-related cytokines, adiponectin levels are surprisingly lower in obese than in lean humans. Women have been found to have significantly higher adiponectin plasma concentrations than men. Further research is needed in order to identify new polymorphisms which contribute to explain the potential role of adiponectin in obesity and related pathologies.

Considering the anti-inflammatory properties of adiponectin and the fact that it is negatively associated with adiposity, this cytokine could be one of the links between obesity and inflammation. The main mechanisms of action of adiponectin are directed to a protective role against atherogenic and insulin resistance processes. Research has revealed interesting new functions far beyond metabolism, such as immunity, cancer and bone formation.

Contrary to all adipose-related proteins, adiponectin decreases with obesity. Most of the contradictory data surrounding adiponectin are related to plasma values and their relationship with body fat, gender differences and insulin resistance. There are important confounding results regarding the mechanisms of action and functions of adiponectin, especially in relation to insulin resistance and inflammation.

**Keywords**  
Adiponectin  
Cytokines  
Obesity  
Inflammation  
Adipose tissue

Only in the last decade, more than 2000 scientific articles have been published about one of the most interesting cytokines associated with obesity: Adiponectin. Its interest is mainly based on the novelty of this hormone, on its high production in the adipose tissue (adiponectin is also called ApM1, i.e., adipose most abundant gene transcript 1) and on its protective role in the different alterations associated with obesity, such as insulin resistance and inflammation<sup>1</sup>. This cytokine in a certain way can be considered as the 'guardian angel' against the pathophysiology of obesity.

However, the physiological role of adiponectin remains to be fully clarified, since many of the results obtained are contradictory. Furthermore, some crucial points must be considered when investigating this hormone. First of all, it is important to take into account the different configurations circulating in plasma, and the fact that depending on the analytic method used, we may be detecting one of these configurations, and not total adiponectin. On the other

hand, there are still remaining questions about the nature, specificity and actions of the receptors for adiponectin.

In the present review, all these topics will be commented, beginning with the name and the structural and biochemical characteristics of adiponectin; later, we will describe its relationship with obesity, insulin resistance and other alterations such as inflammation and atherosclerosis; finally, we will introduce the recently discovered functions of adiponectin and focus on the controversial aspects of this surprising hormone.

## The name

In the same way the name of a person can provide information about them, so also with hormones. Some of the most characteristic features of a protein lie behind its name. Who has selected it and for what reasons? What is implicit in the name?

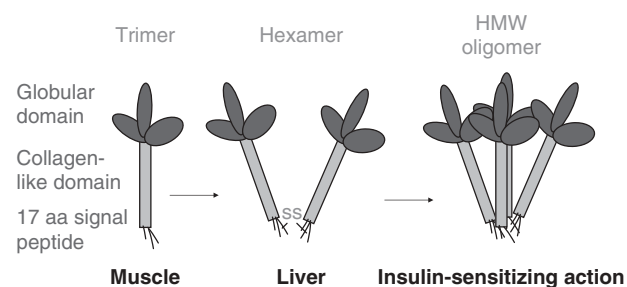
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In the case of adiponectin, the name has varied with time, among different research groups, or because of the species in which the protein was found. Adiponectin was discovered almost simultaneously by four different research groups. In 1995, Scherer *et al.*<sup>2</sup> identified the protein by cDNA cloning from the mouse adipocyte cell line 3T3-L1 and named it Acrp30, which means 'adipose complement-related protein of 30 kDa', because of its high similarity to the complement protein family. Practically, at the same time, Hu *et al.*<sup>3</sup>, using the 3T3-F442A adipocyte cell line, also isolated the protein, and called it AdipoQ. Both names are still used when referring to this protein in mice<sup>4</sup>.

In humans, a group of Japanese researchers described an adipose-specific gene from a cDNA library, which was curiously the most abundant transcript found in human adipose tissue, so they named it ApM1 ('adipose most abundant gene transcript 1'). Nakano *et al.*<sup>5</sup> isolated the protein as well, by high-affinity chromatography, and named it GBP-28 (gelatin-binding protein of 28 kDa). The gene product was predicted to be a kind of matrix protein synthesised by adipose tissue, so in 1999 Arita *et al.*<sup>6</sup> decided to call it adiponectin<sup>4</sup>. The use of these five different names (Acrp 30, adipoQ, ApM1, GBP28 and adiponectin) makes it highly confusing to obtain information about this protein. Nowadays, 'adiponectin' is the most commonly accepted name and therefore we will use it throughout this review.

### The protein and its activity

Adiponectin is a 247-amino acid protein, which contains four differentiable domains: an amino-terminal signal sequence and a variable region, with no homology to any other known protein, a collagenous domain, and a carboxy-terminal globular domain. The monomeric (30 kDa) form of adiponectin is thought to appear only in the adipocyte, since it has not yet been detected in the circulation. The most abundant configuration of adiponectin is the trimer, formed by a strong association between three monomers at their globular domains (Fig. 1). Trimers themselves associate through their collagenous domains, in groups of four to six, resulting in higher molecular weight oligomers<sup>4</sup>. There is still a fourth possible configuration for adiponectin, the globular one. It is



**Fig. 1** Different configurations of adiponectin

the result of a cleavage of the adiponectin monomer, and maintains the ability of trimerising, although higher order structures cannot be formed<sup>4</sup>. The globular portion of adiponectin appears to be as efficient as full-length adiponectin at lowering serum glucose and free fatty acid levels, at least in mice<sup>7</sup>. Regarding oligomers, the interactions among globular and collagenous domains seem to confer stability and to determine their activity, even though the precise molecular mechanisms underlying these associations of adiponectin trimers are not known.

In plasma, the protein circulates mainly in two forms: hexamers of relatively low molecular weight (LMW) and larger multimeric structures of high molecular weight (HMW). It is likely for them to have different properties and actions, but it has been suggested that it is the ratio between them (HMW/LMW), rather than their respective concentrations, which determines adiponectin physiological activity<sup>8</sup>.

### Plasma values

Adiponectin is really abundant in plasma, at concentrations ranging from 5 to 30  $\mu\text{g ml}^{-1}$ , thus accounting for 0.01% of total plasma proteins<sup>1</sup>. This concentration is higher than that of most hormones; indeed, leptin and cortisol values are a thousand times lower, in the order of  $\text{ng ml}^{-1}$ , while tumour necrosis factor alpha (TNF- $\alpha$ ) or interleukin (IL)-6 are measured in  $\text{pg ml}^{-1}$  ( $10^{-6}$  times lower than adiponectin).

Contrary to most adipose-related cytokines (leptin, adipsin, resistin, IL-6, etc.), adiponectin levels are surprisingly lower in obese than in lean humans. It has been generally accepted that adiponectin decreases with obesity<sup>9</sup>, although there are still studies that find no significant associations between body mass index and adiponectin plasma values<sup>10,11</sup>. In addition, it is interesting to highlight that women have been found to have significantly higher adiponectin plasma concentrations than men<sup>4</sup>. These data are surprising considering that women have a higher body fat content than men and, as it has been already commented, adiponectin is negatively associated with body fat percentage. Adiponectin plasma levels appear to depend on body fat distribution<sup>12</sup>, which in turn is strongly affected by sex hormones; thus, the involvement of sex steroids could be a possible explanation of this paradoxical relationship between adiponectin plasma values and gender. In this way, some studies have shown an inverse relationship between androgens and adiponectin plasma values. Furthermore, our own research group has observed a dehydroepiandrosterone and its sulphate (DHEAS)-induced up-regulation of adiponectin gene expression in adipocytes<sup>11</sup>.

### The gene and its expression

To fully understand a protein, it is important to have a deep knowledge of its gene, the characteristics, the

expression and the different polymorphisms that may affect the function of the protein.

One of the most significant characteristics of human adiponectin gene is its localisation: it spans 17 kb on chromosome 3, locus 3q27. This locus is of special interest, since it is associated with the susceptibility to type 2 diabetes and cardiovascular disease, two alterations highly interrelated with adiponectin protective role<sup>13</sup>. Analysis of the gene structure has been extensively described by Takahashi *et al.*<sup>14</sup> in 2000. It consists of three exons and two introns, which coincides with the gene structure of the anti-obesity protein par excellence, leptin.

During the last years, it has been defended that the expression of adiponectin is confined to adipose tissue. Recently, some studies have demonstrated that other tissues such as bone, mammary glands, salivary glands, etc. are able to express adiponectin, although in a minimum quantity<sup>15–17</sup>.

Perhaps one of the most exciting subjects in protein research is the identification of different polymorphisms on its gene. Indeed, many studies support that polymorphisms are associated with alterations of the protein function or even with important related diseases. In the case of adiponectin, 16 polymorphisms have been described in its gene, although only a reduced part has clinical implications. In the study of Takahashi *et al.*<sup>14</sup>, two polymorphisms, one occurring in exon 2 and the other being a missense mutation in exon 3, were associated to markedly low plasma adiponectin concentrations. Menzaghi *et al.*<sup>18</sup> have also found two single-nucleotide polymorphisms (SNP) associated with high risk of type 2 diabetes. Another SNP, which cause no change in the protein, is associated with obesity, insulin resistance and dyslipidaemia<sup>19</sup>. Further research is needed in order to identify new polymorphisms, which contribute to explain the potential role of adiponectin in obesity and related pathologies.

### The adiponectin receptors

Since adiponectin was first described in 1995, a receptor-mediated activity was postulated. Paradoxically, the mechanism of action of the hormone was described previously to receptor identification<sup>20</sup>.

In 2003, Yamauchi *et al.*<sup>21</sup> isolated and described for the first time human and mouse adiponectin receptors, transforming the understanding of several actions of this hormone. The two receptors, designated AdipoR1 and AdipoR2, are abundantly synthesised in skeletal muscle and liver, respectively, but they are ubiquitously expressed. In fact, adiponectin receptors have been detected in pancreatic  $\beta$ -cells, macrophages, osteoblast-like cells and others<sup>22,23</sup>. Experiments of overexpression and/or suppression of receptor activity demonstrated that both AdipoR1 and AdipoR2 bind globular and full-length

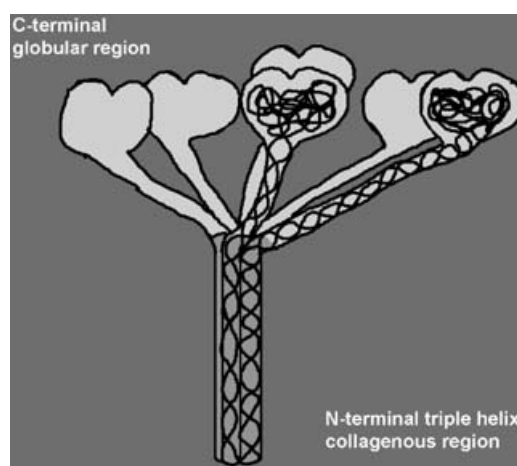
adiponectin, but with different affinities. Nowadays, we know that AdipoR1 is a high-affinity receptor for globular adiponectin and a low-affinity receptor for full-length adiponectin. In contrast, AdipoR2 is an intermediate-affinity receptor for both forms<sup>21</sup>. In 2004, a third receptor for adiponectin was proposed: T-cadherin, a member of the cadherin superfamily, a group of proteins involved in cell adhesion and signalling. It is thought to bind hexamers and high-molecular-weight adiponectin oligomers<sup>24</sup>.

The existence of these two distinct natures of adiponectin receptors can be explained by the variety of adiponectin structures – trimers, hexamers, HWM oligomers – which require different receptor conformations to ensure a high binding affinity, and by the wide tissue distribution of adiponectin actions.

### The family and the functions

Knowing the characteristics of a family usually helps to understand the individual. Concerning adiponectin, its three-dimensional structure reminds of that from other proteins and cytokines, throwing a little light on the actions and characteristics of this hormone (Fig. 2).

What is of interest in adiponectin structure is its collagen-like domain, responsible for oligomerisation, and the globular domain with high homology to some factors from the alternate pathway of the complement system. The complement system is a complex protein activation cascade that participates in immune defense, and the alternate pathway is related to natural immunity, which acts through direct interaction between macrophages and pathogens, without the involvement of antibodies. On the basis of both its primary amino acid sequence and its C-terminal domain structure, adiponectin is most similar to complement protein C1q. However, X-ray



**Fig. 2** Adiponectin structure (by courtesy of 10-year-old Olga Albasini-Garaulet)

crystallography of the globular fragment of adiponectin also reveals a striking structural homology to TNF- $\alpha$ <sup>4</sup>.

Taking into account this similarity between adiponectin and immune-related proteins, the question arose as to whether it would play a role in immunity. Further studies have shown that the globular domain confers interesting immune actions to this protein<sup>24</sup>.

### **The guardian angel**

Adiponectin is capable, like the proteins of the complement system, of interacting with immune cells, such as macrophages and monocytes. In macrophages, it suppresses the production and secretion of TNF- $\alpha$  and IL-6, and the formation of foam cells; it also prevents monocytes precursors from differentiating, and monocytes themselves from adhering to vascular walls; and enhances the production of anti-inflammatory cytokines by monocytes, macrophages and dendritic cells<sup>24</sup>. There is a growing number of studies considering obesity as a state of low-grade but chronic inflammation. Considering the anti-inflammatory properties of adiponectin and the fact that it is negatively associated with adiposity, this cytokine could be one of the links between obesity and inflammation.

On the other hand, adiponectin has been called 'fat-burning molecule', because it is able to redirect fatty acids to the muscle for their oxidation. This special capability is of great interest, because the influx of fatty acids to the liver decreases, and so does total triglyceride content, leading to a higher insulin-sensitivity state.

The main mechanisms of action of adiponectin are all directed to the same finality, a protective role against atherogenic and insulin resistance processes, one of the reasons why adiponectin is considered as a 'guardian angel' in the metabolic syndrome.

### **New discoveries in adiponectin**

After the discovery of adiponectin in 1995, research has revealed interesting new functions far beyond metabolism, such as immunity, cancer and bone formation.

#### ***Adiponectin and bone formation***

A link between adiponectin and bone homeostasis was first described by Berner *et al.*<sup>15</sup>. These authors observed that both adiponectin and its receptors, AdipoR1 and AdipoR2, were expressed and secreted in bone-forming cells. They also demonstrated that adiponectin addition to osteoblast cultures stimulated cell proliferation. Conversely, a recent study of Shinoda *et al.*<sup>25</sup> has shown the opposite effect. In this work, the addition of adiponectin suppressed osteogenesis. In consequence, although adiponectin clearly acts on bone metabolism, the precise mechanism of action remains unclear.

#### ***Adiponectin and endometrium***

Adiponectin receptors have been also detected in the endometrium<sup>26</sup>, where it decreases interleukin and chemo-attractant production from endometrial stromal cells. Furthermore, patients with endometrial cancer show serum adiponectin levels significantly lower than controls<sup>27</sup>.

#### ***Adiponectin and cancer***

The association between low levels of adiponectin and cancer has been once again observed in patients with breast and prostate cancer<sup>28</sup>. *In vitro*, adiponectin inhibits tumour growth in mice, probably through suppression of neo-vascularisation, a key process for tumourigenesis<sup>29</sup>.

#### ***Adiponectin and adipose tissue***

Adipose tissue itself is a target for adiponectin activity. Overexpression of adiponectin gene in 3T3-L1 cells has been shown to stimulate cell proliferation and differentiation<sup>30</sup>.

#### ***The actions of adiponectin span other tissues***

Adiponectin has been associated with platelet activity<sup>31</sup>, and it has been even proposed as a regulator of  $\beta$ -cell proliferation, in a cooperative mechanism associated with leptin<sup>32</sup>. There is no doubt that innovative research is necessary to provide and identify the different and tissue-specific actions of this pleiotropic hormone.

### **The controversial hormone**

Throughout the present review we have highlighted several controversial aspects of adiponectin, which affect the protein structure, its receptors and plasma values, and in consequence, the main functions exerted by the hormone.

Perhaps the most striking paradox related to this protein is that, contrary to all adipose-related proteins, adiponectin decreases with obesity. This fact is even more surprising when considering the fact that adiponectin is the most secreted protein in adipose tissue, so it would be expected to increase proportionally to body fat. One possible explanation is that although adiponectin expression is activated during adipogenesis, a feedback inhibition on its production may occur during the development of obesity. For example, adiponectin expression and secretion in adipocytes has been shown to be reduced by TNF- $\alpha$ <sup>24</sup>. Therefore, the adipocytokines that are increased in obesity could be contributing to the decreased adiponectin production.

Most of the contradictory data surrounding adiponectin are related to plasma values and their relationship with body fat, gender differences and insulin resistance. Additionally, there are important confounding results regarding the mechanisms of action and functions of

adiponectin, especially in relation to insulin resistance and inflammation.

The lack of a direct relationship between adipose tissue adiponectin expression and plasma concentrations as observed by some authors<sup>11,33</sup> is controversial. Another paradox is that, in general, women show significantly higher adiponectin levels than men, despite having higher body fat content. In addition, results about the relationship between plasma adiponectin and insulin are contradictory; although adiponectin is supposed to lower hyperinsulinemia<sup>1</sup>, there are works in which no significant correlations have been found between both hormones. Indeed, in a work performed by our own group in obese women, we did not observe any relationship between both hormones in the total population. However, when we divided our subjects attending to body fat distribution, an inverse correlation was found between adiponectin and insulin only in women with a gluteo-femoral fat distribution<sup>33</sup>.

Regarding adiponectin actions, we have already mentioned in the present review that both globular and full-length adiponectin are efficient in ameliorating hyperinsulinemia and hyperglycaemia<sup>1</sup>. However, this affirmation is in disagreement with the observations of Berg *et al.*<sup>7</sup>, whereby injection of bacterially produced globular adiponectin into mouse models of diabetes did not induce a decrease in serum glucose, even though the full-length form did.

In addition, the physiological action of adiponectin in immunity and inflammation is not, to our surprise, as clear as it seems, since it can also exert proinflammatory actions. In some cases, adiponectin stimulates the secretion of chemotactic factors and, even more remarkable, it increases IL-6 production in human adipocytes<sup>24</sup>.

### Is there an explanation for these paradoxical results?

It has been postulated that the different adiponectin conformations exert diverse effects in various tissues. For instance, trimers seem to be responsible for the insulin-sensitising action of adiponectin in skeletal muscle, while hexamers would be acting in the liver. In addition, it has been suggested that the high-molecular-weight form of adiponectin is responsible for its proinflammatory actions, while the low-molecular-weight form would be the anti-inflammatory one<sup>24</sup>. These findings highlight the importance of considering adiponectin oligomerisation when studying its properties and functions.

On the other hand, not only the different adiponectin forms determine its action but also the participation of the different receptors is of high relevance. More information is needed regarding their types and structures, their tissue distribution and, above all, the particular affinities of these receptors for the various adiponectin configurations, i.e., trimers, hexamers and HMW oligomers.

Perhaps the main problem in the interpretation of data regarding the relationships between adiponectin concentrations, obesity, insulin resistance and inflammation, is the fact that we really do not know what we are actually measuring in plasma when using standardised analytic techniques such as enzyme-linked immunosorbent assay (ELISA) or radioimmunoassay (RIA). The key point is to know if we are detecting the trimer, the hexamer, larger multimeric structures or total adiponectin. But first of all, we must determine what we are really looking for. In the near future, we will be able to measure the distinct adiponectin structures in plasma depending on the function to be studied. In our opinion, these technical handicaps are obstructing the comprehension and interpretation of adiponectin functions and mechanisms of action. A most specific research on this hormone will allow us to avoid all these contradictory data surrounding adiponectin.

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