Review Article

Adiponectin, the Controversial Hormone

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Abstract

Adiponectin is an abundant protein hormone that belongs to a family of the so-called adipokines. It is expressed mostly by adipocytes and is an important regulator of lipid, and glucose metabolism. Moreover, adiponectin is an insulin-sensitizing hormone that has anti-diabetic, anti-inflammatory and anti-atherogenic properties. Previous studies have highlighted several controversial aspects of adiponectin; the most striking paradox is that, contrary to all adipose-related proteins, adiponectin decreases with obesity. This 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. This could be related to the development of a feedback inhibition of its production during the development of obesity. Most of the contradictory data regarding 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. Additionally, the lack of a direct relationship between adipose tissue adiponectin expression and plasma concentrations is controversial. Another paradox is that, in general, women show significantly higher adiponectin levels than men, despite having higher body fat content. Moreover, results about the relationship between plasma adiponectin and insulin are contradictory; although adiponectin is supposed to lower hyperinsulinemia. The potential diagnostic usage of Adiponectin was a subject of increasing interest in recent years. More specific research on this hormone will help avoiding all the contradictory data regarding Adiponectin.

Key words: adipokines, hyperinsulinemia, NAFLD, NASH

Structure and Production

Human Adiponectin consists of 244 amino acid residues with a distinct domain structure: it contains both collagen-like and globular C1q-like domains. Collagen-like parts consist of three Adiponectin molecules that interact forming triple coiled structure much alike to that of collagen[1]. C1q-like domains form a "head" of adiponectin globula and share a great degree of structural similarity to complement component C1q. Several oligomeric forms of native circulating Adiponectin have been described in the literature: i) Trimers (low-molecular weight form, LMW), ii) Hexamers (medium molecular weight form, MMW), and iii) Higher order multimers (high molecular weight form, HMW). Three monomers of Adiponectin form a trimer. Trimers linked by disulfide bond forming a hexamer. The exact structure of the HMW form of Adiponectin is not yet known; most

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likely, several combined hexamers and/or trimers constitute high-molecular weight form of Adiponectin. Disulfide bonds as well as some bonds with the participation of modified amino acid residues in the collagen domain of Adiponectin, hold the subunits of the HMW form of Adiponectin together. These oligomeric forms exist in the bloodstream as separate moieties and do not convert into each other[2]. Adiponectin oligomers are capable of binding Ca^{++} ions, which are thought to participate in the maintenance of conformational stability of Adiponectin[3].

Adiponectin receptors
In 2003, Yamauchi and colleagues 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 synthesized in skeletal muscle and liver, respectively, but they are ubiquitously expressed[4]. In fact, Adiponectin receptors have been detected in pancreatic B-cells, macrophages, osteoblast-like cells and others[5]. Experiments of over expression and/or suppression of receptor activity demonstrated that both AdipoR1 and AdipoR2 bind globular and full-length Adiponectin, but with different affinities. AdipoR1 is a high-affinity receptor for globular Adiponectin and a low-affinity receptor for full-length Adiponectin[6]. In contrast, AdipoR2 is an intermediate affinity receptor for both forms[4]. 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) that bind hexamers and high-molecular-weight adiponectin oligomers[7]. The existence of these two distinct natures of adiponectin receptors can be explained by the variety of adiponectin structures (trimers, hexamers, HWM oli-

gomers) which require different receptor conformations to ensure a high binding affinity.

Adiponectin concentration
The concentration of total adiponectin in the blood is about 3-30 μg/ml, whereas the concentration of the closest structural homolog of adiponectin, C1q, is about 80-200 μg/ml. It is therefore of utmost importance that anti-adiponectin antibodies would have no cross-reactivity with human C1q[8]. Some authors describe significant gender differences in adiponectin level in healthy adults which are believed to contribute to the discrepancies in adiponectin concentration reported by various authors. The biologic activity of adiponectin is mediated by its HMW form. The concentration of HMW form or the HMW/total adiponectin serum ratio was suggested to have a stronger correlation–than that of the total adiponectin with insulin resistance and other measures of type 2 diabetes[9].

Functions and Role in Health

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 Immunity
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-α and IL-6, and the formation of foam cells; it also prevents monocytes precursors from differentiating, and monocytes from adhering to vascular walls. It also enhances the production of anti-inflammatory cytokines by monocytes, macrophages and dendritic cells[10]. Additionally, adiponectin was described as a regulator of B-cell proliferation, in a cooperative mechanism as-

sociated with leptin[11]. The physiological action of adiponectin in immunity and inflammation is not as clear as it seems, since it can also exert pro-inflammatory actions. In some cases, adiponectin stimulates the secretion of chemotactic factors and, increases IL-6 production in human adipocytes[10].

Adiponectin and Insulin
Results about the relationship between plasma adiponectin and insulin are contradictory; although Adiponectin is supposed to lower hyperinsulinemia[12], there are works in which no significant correlations have been found between both hormones. Previously, no relationship between Adiponectin and insulin was found in obese women. However, when patients were divided based on body fat distribution, an inverse correlation was found between adiponectin and insulin only in women with a gluteo-femoral fat distribution[13].

Adiponectin and bone formation
Although adiponectin can clearly act on bone metabolism, the precise mechanism of action remains unclear. A link between adiponectin and bone homeostasis was first described by Berner et al[14]. They observed that both adiponectin and its receptors, AdipoR1 and AdipoR2, were expressed and secreted in bone-forming cells. They also demonstrated that adding adiponectin to osteoblast cultures, stimulated cell proliferation. Conversely, Shinoda et al., have shown that the addition of adiponectin suppressed osteogenesis in cell cultures[15].

Adiponectin and endometrium
Adiponectin receptors have been also detected in the endometrium, where it decreases interleukin and chemoattractant production from endometrial stromal cells. Furthermore, patients with endometrial cancer have significantly lower serum adiponectin levels[16].

Adiponectin and cancer prevention
The association between low levels of adiponectin and cancer has been observed in patients with breast and prostate cancers[17]. In vitro, adiponectin inhibits tumor growth in mice, probably through the suppression of neo-vascularisation, a key process for tumourigenesis[18].

Adiponectin and adipose tissue
Adipose tissue itself is a target for adiponectin activity. Overexpression of Adiponectin gene in 3T3-L1 c ells has been shown to stimulate cell proliferation and differentiation[19].

Adiponectin and liver
In the liver, adiponectin activates adenosine monophosphate protein kinase and peroxisome proliferator-activated receptor alpha (PPARα), leading to an increase in fatty acid oxidation and the suppression of fatty acid synthesis[20]. Moreover, Adiponectin increases insulin sensitivity in isolated primary hepatocytes, resulting in decreased glucose production[21]. A negative association between serum levels of adiponectin and liver enzyme has been shown in healthy subjects[22].

Adiponectin and platelets
Adiponectin has been associated with platelet activity[23].

Role of Adiponectin in Disease

Adiponectin and obesity
There are 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[24]. On the other hand, Adiponectin has been called the '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[24].

Adiponectin and diabetes/heart disease

In patients with type 2 diabetes mellitus, plasma adiponectin concentrations are inversely related to hepatic fat content[25]. Moreover, decreased serum adiponectin concentration indicates insulin resistance[26].

Adiponectin and heart disease

Hypoadiponectinemia was shown to be associated with coronary artery disease[27]. Several authors had pointed out that high level of circulating adiponectin reduced risk of coronary heart disease among type 2 diabetes patients[28] and was associated with reduced risk of myocardial infarction in apparently healthy men[29]. Since adiponectin inhibits triglyceride accumulation in the hepatocytes by reducing their free fatty acids production and increasing beta-oxidation[30], a growing interest is directed to use adiponectin to diagnose insulin resistance and predicts cardiovascular complications in type 2 diabetes patients.

Adiponectin and inflammation

Adiponectin directly affects the inflammatory response by regulating both the production and activity of cytokines[31], and acting as an antiapoptotic agent in a variety of cell types[32]. The anti-inflammatory effects of adiponectin could protect the liver from the development of inflammation and cell injury[31]. In both alcoholic and non-alcoholic fatty liver, adiponectin administration suppresses hepatic production and the circulating levels of TNF-α and ameliorates hepatic steatosis[33].

Adiponectin and liver diseases

The association between low circulating adiponectin levels and liver disease is well documented, and a protective effect of adiponectin against fatty liver disease was suggested (i.e. reduced levels of circulating adiponectin were reported in a rodent model of fatty liver disease)[34]. Reduced serum adiponectin was also observed in patients suffering from chronic hepatitis with liver steatosis[35]. Moreover, serum adiponectin levels negatively correlated with steatosis grade. Genetic variations in the adiponectin and AdipoR2 genes were found to be associated with the progression of liver fibrosis and liver fat content, respectively[36,37].

Adiponectin and NASH/NAFLD

Epidemiological investigations in different ethnic groups have identified lower adiponectin level as an independent risk factor for nonalcoholic fatty liver diseases (NAFLD) and liver dysfunctions[38]. Compared with healthy controls, Adiponectin levels are lower by more than 50% in nonalcoholic steatohepatitis (NASH) patients[39]. In contrast to leptin and TNF-α, adiponectin is more closely implicated in the pathogenesis of NAFLD/NASH[40]. Adiponectin expression is decreased by 20-40% during the development of NAFLD, from simple steatosis to NASH[41]. Moreover, NASH patients with lower levels of adiponectin showed higher grades of inflammation, suggesting that adiponectin deficiency is an important risk factor for the development of fatty liver, steatohepatitis and other forms of liver injuries[42,43]. A direct

relationship between hypo adiponectinemia and NASH independent of insulin resistance was reported[39]. Animal-based studies have demonstrated that adiponectin possesses potent protective activities against various forms of liver injuries, including those induced by carbon tetrachloride, lipopolysaccharide (LPS)/D-galactosamine, pharmacological compounds, bile duct ligations and methionine deficient diet etc.[44,45]. In animal model studies of both alcoholic and nonalcoholic steatohepatitis, exogenous adiponectin reduces hepatomegaly, depletes lipid accumulation, quenches hepatic inflammation, and decreases hepatic expression and plasma concentrations of TNF-α[33]. Adiponectin knockout mice exhibit an enhanced pattern of hepatic fibrosis induced by carbon tetrachloride[46]. Moreover, the lack of adiponectin expression could accelerate hepatic tumor formation in a NASH model in mice[47].

Adiponectin and Alcoholic Fatty Liver Diseases
Xu and colleagues have shown that decreased expression of adiponectin might be partially responsible for alcohol induced liver injury in mice[33]. The alcohol induced reduction of adiponectin expression could be due to the elevated levels of TNF-α, which suppress adiponectin expression in adipose tissue through a paracrine or endocrine mechanism. Both circulating concentrations of TNF-α and local production of TNF-α in adipose tissue are increased at the early stage of alcoholic liver injury[33]. Incubation of adipocytes with TNF-α markedly decreased the expression of adiponectin[48]. In addition, it is possible that alcohol may act directly on adipocytes and suppress adiponectin expression. Chronic consumption of alcohol in rats has been shown to increase the relative expression of heterotrimeric guanosine tri-

phosphate binding protein stimulatory α subunit ($G_s\alpha$) to the inhibitory α subunit ($G_i\alpha$) in adipocyte membranes and to induce activation of the protein kinase A (PKA) pathway. PKA activation can dramatically decrease adiponectin expression in vivo as well as in vitro[49,50].

Adiponectin and Liver cirrhosis
A significant elevation in the plasma levels of adiponectin was reported in cirrhosis; this elevation correlated exclusively with reduced liver function and altered hepatic hemodynamics[51, 52]. Kaser and co-workers reported that circulating adiponectin was increased in liver cirrhosis independent of the etiology of liver disease. They suggested that high adiponectin levels in chronic liver disease might reflect one of the body's anti-inflammatory mechanisms[53].

Adiponectin and Chronic HBV infection
Little is known about the role of adiponectin in hepatitis B related liver diseases[54]. Hui and co-workers reported that serum adiponectin was increased in HBV-related advanced liver fibrosis and declined with post-treatment reduction in fibrosis. They thus concluded that serum adiponectin might have a role in fibrosis progression in chronic HBV infection[55]. In the meantime, Liu et al. suggested a correlation between serum adiponectin and the progression of HBV-related liver diseases however, HBV infection itself might not affect adiponectin levels[56].

Adiponectin in HCV infection
Significant hypoadiponectinemia was found in patients with chronic hepatitis C (CHC) and metabolic syndrome[7,57]. Petit et al., found no correlation between adiponectin levels and BMI in CHC patients[58]. However, others reported a significant inverse correlation between Adiponectin levels and BMI in those patients[59,60]. In chronic HCV infection, hypoadiponectinae-

mia was significantly associated with the development of liver steatosis[58]. Additionally, the degree of insulin resistance and steatosis correlated directly with the degree of fibrosis in patients with hepatitis C[39]. The fact that the plasma levels of adiponectin inversely correlate with steatosis in HCV infected subjects suggests that hypoadiponectine-mia may contribute to hepatic steatosis progression and liver injury in this population[58]. According to Meng et al., the decreased serum adiponectin on patients with CHC was associated with male gender, elevated γ-GT, albumin, and TNF-α, and steatosis[61]. Moreover, serum adiponectin correlated with viral factors (i.e. HCV genotype and viral load)[62]. A higher level of serum adiponectin was demonstrated in patients infected with HCV genotype 2a compared to patients with genotype 1b[61]. Thus, HCV genotype 2 might be directly involved in the development of hepatic steatosis[63]. Meng et al. suggested that the significant differences regarding viral genotype seemed to occur only in male patients with CHC but not in female patients[61]. According to Hsu et al. Insulin resistance was higher in HCV genotype 1 patients compared to genotype 2 patients. In sharp contrast, there was a trend towards lower serum Adiponectin levels in patients with genotype 1 infection. Thus, insulin resistance and adiponectin appeared to play opposite roles in this genotype-specific difference. This kind of correlation remained unchanged, even after adjustment for age, gender, BMI, and ALT levels. They also found a positive association of serum adiponectin level with HCV titer, independent of insulin resistance[64]. Zografos et al. suggested that HCV genotype 3 may directly affect adiponectin. This was further supported by the significant increase in adiponectin at the end of treatment only in HCV genotype 3 patients[65]. In HCV geno-

type 4, the total adiponectin level increases with progression of hepatic fibrosis regardless of insulin resistance or, viral load. However, no cut off level have shown reasonable sensitivity/specificity for predicting hepatic fibrosis stage in those patients[66]. These findings support a role of HCV genotype on insulin resistance and adiponectin levels which could be related to the existence of HCV specific differences in AdipoR1 and AdipoR2 gene expression[62,64].

During interferon-α (IFN-α) therapy in patients with chronic hepatitis B and C infections, IFN-α resulted in a decrease of serum adiponectin levels but an improvement of insulin resistance was observed among responders. The result contradicts the previous concept of the relationship between insulin resistance and adiponectin levels. The decrease of adiponectin levels was suggested to be the result of the augmented immune response due to the disappearance or the profound down-regulation of the virus or viral antigens in responders to IFN-α treatment[54]. Unlike serum TNF-α, that was identified as an independent predictor of liver steatosis; serum adiponectin appears to be an independent predictor of both liver steatosis and end-of-treatment virological response in HCV patients[65].

Potential therapeutic role of Adiponectin

To date, there have been very few effective drug treatments for NAFLD and NASH. Early diagnosis and management of the underlying condition remains the mainstay of treatment. The present "gold standard" for treatment of NAFLD is weight reduction or a reduction of central obesity[67]. These "life style adjustment" or anti-obesity measures impressively reduce liver cell injury, inflammation and hepatic fibrosis, as well as steatosis[68, 69]. Strategies to block oxidative stress are of great interest[70]. Among the known adipokines, adiponectin

may be used as a promising drug candidate for the treatment of liver diseases[71]. Adiponectin and its agonists might represent emerging therapeutic agents for the treatment and/or prevention of liver dysfunctions. Adiponectin replacement therapy is not yet available as a treatment option. Pharmacological intervention aimed at elevating adiponectin production might hold promise for the treatment and/or prevention of NAFLD. Xu et al. have reported the identification of two structurally related natural compounds (astragaloside II and isoastragaloside I) from the medicinal herb Radix Astragali that possess such an activity[72]. Astragaloside II and isoastragaloside I selectively increase adiponectin secretion in primary adipocytes without any obvious effects on a panel of other adipokines. Furthermore, an additive effect on induction of adiponectin production has been observed between these two compounds and rosiglitazone. Chronic administration of astragaloside II and isoastragaloside I in both dietary and genetic obese mice significantly elevated serum levels of total adiponectin and selectively increased the composition of its high molecular weight oligomeric complex. These changes were associated with an alleviation of hyperglycemia, glucose intolerance, and insulin resistance. The two natural compounds might also provide the lead as a novel class of therapeutics for obesity related diseases, such as NAFLD[71].

The controversial hormone
Several controversial aspects of adiponectin, which affect it structure, receptors, plasma values, and in consequence, the main functions exerted by the hormone were observed[10]. The most striking paradox is that, contrary to all adipose-related proteins, adiponectin decreases with obesity despite being the most secreted protein in adipose tissue. One pos-

sible explanation is that although Adiponectin expression is activated during adipogenesis, a feedback inhibition of its production may occur during the development of obesity. Most of the paradoxical data regarding adiponectin are related to its plasma levels and their relationship with body fat, gender, and insulin resistance. Additionally, there are important confounding results regarding the mechanisms of action of adiponectin in relation to insulin resistance and inflammation. Moreover, the lack of a direct relationship between adipose tissue adiponectin expression and plasma concentrations is controversial[13,73]. Another paradox is that, in general, women show significantly higher adiponectin levels than men, despite having higher body fat content. Regarding Adiponectin actions, both globular and full-length Adiponectin are efficient in ameliorating hyperinsulinemia and hyperglycaemia[12]. However, this affirmation is in disagreement with the observations of Berg et al. 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[21].

Explanation of the paradoxical results of adiponectin
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 sensitizing action of Adiponectin in skeletal muscle, while hexamers would be acting in the liver. In addition, it has been suggested that the HMW form of adiponectin is responsible for its pro-inflammatory actions, while the LMW form would be the anti-inflammatory one[10]. 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[24].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 different analytic techniques[24].

Conclusion

Innovative researches are necessary to identify the different and tissue specific actions of this pleiotropic hormone. Technical handicaps are obstructing the comprehension and interpretation of adiponectin functions and mechanisms of action. Perhaps, in the future, scientists will be able to measure the different adiponectin structures depending on the function to be studied. Specific researches on adiponectin will help avoiding all the contradictory data regarding this hormone.

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