The Role of the Novel Adipocyte-Derived Protein Adiponectin in Human Disease: An Update

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Abstract: Adiponectin is a collagen-like protein expressed in adipose tissue. Low serum adiponectin is associated with insulin resistance, atherogenic hyperlipidemia and arterial hypertension. High serum adiponectin predicted a reduced risk of myocardial infarction. Other surveys have shown that high levels of serum adiponectin were a predictor of future cardiovascular disease and mortality. These paradoxical findings might be explained through the concept of the reversal epidemiology in the adiponectin physiology. According to this hypothesis, this protein would behave as an insulin sensitizing and cardioprotective factor in the health state and as a wasting marker in the advanced states of disease.

Keywords: Adiponectin, diabetes, hyperlipidemia, cardiovasacular disease, mortality.

INTRODUCTION

Adiponectin (ACRP30, AdipoQ, apM1 or GBP28), an adipocyte-derived hormone discovered in the mid-1990s by four independent groups [1-4], is a 244 amino acid, 30-kDa, protein, product of the gene *apM1*, that shares structural homology with collagen VIII and X and complement factor C1q. It contains an N-terminal signal sequence, a short variable domain, a collagen-like domain, and a C1q-like globular domain at the C-terminal end [1-4]. Posttranslational hydroxylation and glycosylation give rise to multiples isoforms of adiponectin [5]. In plasma, adiponectin circulates in trimeric, hexameric and high molecular weight (HMW) complexes. The globular domain of adiponectin, a proteolytic cleavage fragment, also circulates and has biological activity [6]. Adiponectin is the most abundant circulating peptide hormone secreted by adipocytes: its serum concentrations are several orders of magnitude higher than that of most of hormones, accounting for about 0.01% of total plasma protein [7].

Adiponectin knockout animals have a tendency to develop glucose intolerance, insulin resistance [8,9], vascular smooth muscle cells proliferation, neointimal thickening [8,10], and a higher expression of tumor necrosis factor-α (TNFα) [9]. Administration of this hormone increases fatty acids oxidation [6] and insulin sensitivity, reduces plasma glucose levels [11,12], and attenuates neointimal proliferation [10] and thrombus formation [13]. These data suggest that adiponectin is a unique adipokine with insulin-sensitizing, antiinflamatory and vasculoprotective properties.

Two adiponectin transmembrane receptors (AdipoR) have been cloned. AdipoR1 is expressed abundantly in skeletal muscle and has a preference for binding to globular adiponectin, while AdipoR2 is distributed mainly in liver and has intermediate affinity for both globular and full-length adiponectin [14,15]. AdipoR1 acts through the adenosine monophosphate-activated protein kinase (AMP kinase) signalling pathway, whereas AdipoR2 is associated with the peroxisome proliferator activator receptor (PPAR)-α pathway [16]. Recent data from experimental investigation suggest that AdipoR1 and AdipoR2 deficiencies give rise to opposite effects on energy expenditure and spontaneous locomotor activity. In fact, AdipoR1$^{-/-}$ mice showed increased adiposity associated with decreased glucose tolerance, spontaneous locomotor activity, and energy expenditure. In contrast, AdipoR2$^{-/-}$ mice were lean and resistant to high-fat diet-induced obesity and showed improved glucose tolerance and reduced plasma cholesterol levels [17]. Whether additional receptors can mediate these or other biological effects of adiponectin is still a matter of debate.

Furthermore, adiponectin may act by the expansion of subcutaneous adipose tissue with decreased levels of macrophage infiltration, similar to the action of PPARγ agonists [18]. Adiponectin is also capable to activate several other signalling pathways such as the production of nitric oxide (NO) through phosphatidylinositol-3-kinase-dependent mechanisms [19].

In the last years a great number of investigations have demonstrated the involvement of adiponectin in different human disease processes (Table **1**). In the present review we have focused on the most recent progresses in our understanding of the role of adiponectin in human disease, with special attention to the relationships of this adipokine with cardiovascular risk factors, cardiovascular disease and mortality.

ADIPONECTIN AND CARDIOVASCULAR RISK FACTORS

Adiponectin and Fat Mass

In contrast to other adipokines obesity is associated to a reduction of adiponectin expression in several animal species. Arita *et al*. [20] showed that adiponectin concentrations

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Table 1. Relationship Between Serum Adiponectin Concentrations and Cardiovascular Risk Factors

Obesity	Insulin resistance	Type 2 diabetes	Hyperlipidemia	Hypertension	Renal disease
Low levels associated to obesity	Low serum concentrations	Low serum concentrations	Relationship between adiponectin and enzymes that regulate lipid metabolism	Low serum concentrations	High serum concentrations
Negative correlation with BMI	Negatively related with fasting insulin	Hypoadiponectinemia increases probability to develop type 2 diabetes	Negative correlation with cholesterol, LDL-cholesterol, triglyceride and apoprotein B	Inverse correlation with systolic and diastolic blood pressures in healthy subjects	Positive correlation with albuminuria in type 2 diabetes
Negative correlation with body fat mass	Negatively related with insulin resistance indices	Hyperadiponectinemia is associated with lower risk of type 2 diabetes	Positive correlation with HDL-cholesterol and apoprotein A-I	Hypoadiponectinemia predicts the development of hypertension	HMW adiponectin positively related with severity of nephropathy in type 2 diabetes
Negative correlation with intra-abdominal fat	Positive correlation with insulin sensitivity	Glimepiride, repaglinide and glitazones increase adiponectin	Ezetimibe does not modify adiponectin	Thiazide diuretics and beta-adrenergic blockers reduce or have no effect on adiponectin	Positive correlation with proteinuria in nephrotic syndrome
Negative correlation with waist to hip ratio	Predicts insulin resistance	Metformin does not modify adiponectin	Nicotinic acid increases adiponectin	Calcium channel blockers increase or lack of effects on adiponectin	Low adiponectin was related with incident cardiovascular events in dialysis
Weight loss increases serum adiponectin	Predicts metabolic syndrome	Insulin therapy does not modify adiponectin	Statins (atorvastatin, pitavastatin and rosuvastatin) increase adiponectin	Angiotensin-converting enzyme inhibitors increase adiponectin	Adiponectin decreases after renal transplantation

BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein; HMW, high molecular weight

in obese subjects were significantly lower than those found in controls, and that females had higher plasma adiponectin than males. Several cross-sectional studies have confirmed the presence of a negative correlation between adiponectin levels and body mass index [20-28], body fat mass [22,29], intra-abdominal fat [23], and waist to hip ratio [23,25,26,30, 31].

Weight loss following lifestyle modification [32], drug therapy [33,34] or anti-obesity surgery [35,36] is accompanied by an increase in adiponectin levels. A 21% reduction in mean body mass index was accompanied by a 46% increase in circulating adiponectin in a study [35]. Weight reduction has been reported to be followed by an increase in both total and HMW adiponectin, and also in the ratio of HMW to total adiponectin [37]. Altogether, these data suggest the existence of a feedback mechanism between adipose mass and adiponectin production in humans.

Adiponectin and Insulin Resistance

Adiponectin concentrations are reduced in subjects with conditions associated to insulin resistance due to either obesity or lipodystrophy, and the administration of this hormone improves metabolic parameters in these conditions [7,21,22,24,38]. Some studies have associated variations in the adiponectin gene with insulin resistance and risk of type 2 diabetes [39,40], and a mutation in adiponectin gene inducing hypoadiponectinemia and insulin resistance have been reported [41].

Serum adiponectin levels are negatively related with fasting insulin and insulin resistance indices, such as HOMA index, in non diabetic subjects [26,42]. In 182 normal subjects a significant relationship between serum adiponectin and insulin sensitivity index, measured by the glucose kinetics minimal model, has been reported [23]. Similar results have been obtained by other investigators [43]. A positive correlation between adiponectin and insulin sensitivity has also been corroborated by using the hyperinsulinemic euglycemic clamp technique [44].

Adiponectin has also been found to be significantly related with the variables of the metabolic syndrome, a clustering of glucose and insulin metabolism derangements in which insulin resistance plays a central role. Low serum adiponectin concentration were significantly correlated with future development of the metabolic syndrome in a prospective cohort study [25] and with a reduction in insulin sensitivity in another survey [45]. In accordance, HMW adi-

ponectin has also been found to be a sensitive marker for the prediction of insulin resistance and the metabolic syndrome [46].

Adiponectin and Type 2 Diabetes

Initial human studies showed that circulating adiponectin levels were clearly lower in patients with type 2 diabetes in relation to nondiabetic subjects [21,32] and that hypoadiponectinemia was more related to the degree of insulin resistance and hyperinsulinemia than to the degree of adiposity or glucose intolerance [21] or the presence of microangiopathy [32]. This inverse relation between adiponectin levels and the presence of diabetes have been confirmed in recent reports [27,28]. Furthermore, prospective cohort studies performed in different populations [25,47,48] have shown that subjects with low serum adiponectin levels have a higher probability to develop type 2 diabetes than subjects with high concentrations of this adipokine, and that this association persisted after adjusting for age, sex, obesity, hypertension, dyslipemia and history of impaired glucose tolerance [25]. A survey of 978 Japanese subjects, followed up for 5 years, showed that subjects in the lower tertile of adiponectin concentrations exhitibed a 9-fold risk for the development of diabetes in comparison with subject in the upper tertile of adiponectin levels [48]. These results, and those of other investigators [25,49-56] strongly suggest that hypoadiponectinemia may be a risk factor for the appearance of type 2 diabetes. In fact, a recent meta-analysis including 13 prospective studies with a total of 14598 participants have demonstrated that higher adiponectin levels were associated with a lower risk of type 2 diabetes in diverse populations. This association was independent of duration of follow-up, proportion of men and women, adiponectin assay and criteria for diabetes diagnosis [57]. In accordance, a reduction in the levels of HMW adiponectin has been also associated with the risk of type 2 diabetes [58,59].

Treatment with glimepiride [60] and repaglinide [61] has been reported to increased adiponectin levels, but in general insulin secretagogues do not clearly increase plasma adiponectin. No clear effect of chronic metformin or insulin therapy on serum adiponectin has been established [62]. On the contrary, thiazolidinedione treatment enhances adiponectin gene expression in adipose tisue and increases serum adiponectin levels in humans [62-66]. An increase in HMW adiponectin has also been reported [67,68]. Thiazolidinediones stimulate adiponectin gene expression *via* activation of the heterodimer PPARγ/retinoid X receptor, which binds to a PPAR responsive element (PPRE) in the human adiponectin promoter [69].

Adiponectin and Hyperlipidemia

Former studies in nondiabetic subjects showed that serum adiponectin was negatively related to total cholesterol, low-density lipoprotein (LDL)-cholesterol, triglyceride, and apoprotein B concentrations, and positively related to high-density lipoprotein (HDL)-cholesterol and apoprotein A-I concentration [23-25,70]. Similar results were obtained in diabetic patients [32,71] and in patients with coronary artery disease (CAD) [27,28,72]. Treatment of hyperlipidemia with ezetimibe or statins such as simvastatin [73] and pravastatin [74] has been reported not to modify significantly circulating adiponectin. However, recent studies have shown an increase in serum adiponectin using potent statins, such as atorvastatin [75], pitavastatin [76,77] and rosuvastatin [78]. Fenofibrate increased HMW adiponectin levels in subjects with hypertriglyceridemia in one study [79], but this effect has not been confirmed by other authors [80,81]. An increase in total and HMW adiponectin has been reported after therapy with extended-released nicotinic acid [82].

The mechanism that accounts for the relation between adiponectin and serum lipids is not fully understood. Recent research has shown that adiponectin is directly associated with enzymes that regulate lipid metabolism. In nondiabetic subjects, decreased adiponectin concentrations were accompanied by lower lipoprotein lipase activity [83], and and inverse correlation between adiponectin levels and plasma hepatic lipase activity has been reported [84]. These associations were independent of age, sex, body mass index, insulin resistance and systemic inflammation. The hypothesis that adiponectin directly influences the concentration of circulating lipids, especially HDL-cholesterol concentrations is supported by the finding that, in patients with CAD, hypoadiponectinemia was associated with atherogenic dyslipidemia, i.e., hypertriglyceridemia and low HDL-cholesterol levels, regardless of the presence of the main components of the metabolic syndrome [72].

Adiponectin and Hypertension

Prior cross-sectional studies with a limited number of patients found that adiponectin levels were reduced in patients with essential hypertension [85], especially in hypertensive patients with insulin resistance [86]. Young men with high-normal blood pressure were found to have lower serum adiponectin [87], and an inverse correlation between adiponectin levels and systolic and diastolic blood pressure have been repored in healthy population [24]. Other authors reported higher serum adiponectin in patients with hypertension and renal dysfunction in relation to normotensive subjects [88].

In a large case-control study adiponectin concentration was significantly lower in hypertensive men in relation to subjects with normal blood pressure, and was negatively related with blood pressure in normotentive subjects regardless of insulin resistance [89]. In agreement, a recent population-based 5-year prospective study has shown that hypoadiponectinemia behaves as a powerful predictor for the development of hypertension, even after adjustements for sex, age and body mass index [90].

Thiazide diuretics and beta-adrenergic blockers seems to reduce or have no effect on adiponectin levels [91], and calcium channel blockers have been shown to increase or lack of effects on serum adiponectin [91-93]. Treatment with angiotensin-converting enzyme inhibitors or with angiotensin receptor blockers is accompanied by an increase in insulin sensitivity and in serum adiponectin levels [86,91,92,94-97]. It has been suggested that blocking of the renin-angiotensin-aldosterone system increases adiponectin concentrations and that this is followed by an improvement in insulin sensitivity [86]. However, these results have not been confirmed by others [98-101] and need further investigation to be fully clarified.

Adiponectin and Renal Disease

Impaired renal function is associated with higher serum adiponectin concentrations in nondiabetic subjects [102,103], and in type 2 [104,105] and type 1 [106-108] diabetic patients. Serum adiponectin and glomerular filtration rate were inversely associated in subjects with chronic hypertension [88] and in patients with type 1 diabetes [109]. In patients with chronic renal disease and end-stage renal disease (ESRD) serum adiponectin levels are invariably elevated [102,110,111]. In hemodialized patients serum adiponectin levels decrease after renal transplantation [112], thus suggesting that the kidney is involved in the degradation or elimination of adiponectin.

Relationships between serum adiponectin and albuminuria are complex. In patients with type 2 diabetes serum adiponectin concentration was positively related with the urinary albumin to creatinine ratio [105], and serum HMW adiponectin was found to be positively correlated with the severity of nephropathy [113]. Similar resulst have been obtained in patients with type 1 diabetes [108,109]. In patients with nephrotic syndrome, adiponectin and proteinuria were correlated even after accounting for serum creatinine [114]. However, an inverse relationship between serum adiponectin and the degree of proteinuria was recently reported in a group of patients with type 2 diabetes [115]. In accordance, it has been reported that obese subjects with normal renal function had reduced adiponectin levels associated with albuminuria, and that adiponectin deficiency in mice induced fusion of podocyte foof processes in the glomerulus, and urinary albumin excretion. Adiponectin treatment in mice reversed these abnormalities, suggesting that adiponectin is a key regulator of albuminuria and a biomarker for kidney disease [116].

Several investigators have analysed the relationship between adiponectin and cardiovascular disease in patients with renal failure. In cross-sectional studies, lower adiponectin levels were found to be associated with prevalent cardiovascular disease by some [103,117], although not all authors [111]. In the follow-up study by Zoccali *et al.* [110], lower adiponectin values were significantly related with incident cardiovascular events in patient on hemodialysis. Similar results have been obtained in patients with mild and moderate kidney disease [103] and in patients in peritoneal dialysis [118].

ADIPONECTIN AND CARDIOVASCULAR DISEASE

In human subjects an inverse relationship between serum levels of adiponectin and the intima media thickness of common carotid arteries have been reported [119]. Furthermore, it has been recently shown that adiponectin deficiency is associated with endothelial dysfunction in resistance vessels, thus increasing the risk of cardiovascular events. Adiponectin has been reported to be positively associated with endothelium-dependent vasodilation in healthy subjects [104], diabetic subjects [104,120], and patients with hypertension [121], and also with arterial vasodilation in response to nitroglycerin, a measure of endothelium-independent vasodilation [43].

A relationship between low serum adiponectin levels and CAD was established in the first cross-sectional studies reported [32,122-124]. HMW adiponectin was found to be lower in diabetic patients with CAD in comparison with patients without CAD [125]. Other cross-sectional analyses have confirmed that high serum adiponectin levels are associated with a favourable cardiovascular risk profile [126-128].

Further prospective studies have yielded diverse results. The first reported was the large Health Professionals Follow-up Study, which enrolled 18225 men without cardiovascular disease and who were followed up for 6 year. A nested case-control study involving 266 cases and 532 controls showed that a doubling of adiponectin was associated with an approximately 20-30% decreased risk of incident myocardial infarction, independently of cardiovascular risk factors [129]. A prospective survey involving 1513 community-dwelling men and women from the Rancho Bernardo Study, who were followed for 20 years, showed that higher adiponectin concentrations predicted reduced risk of nonfatal myocardial infarction in men without previous cardiovascular disease [128]. More recent prospective longitudinal studies have confirmed the association of low adiponectin levels with the future development of ischaemic heart disease [52,130-134], and with a predisposition to progressive coronary artery calcification [135].

However, other prospective surveys have not confirmed these results. In the Strong Heart Study, a survey comprising 251 cases and 251 controls [136], and in the British Women's Heart and Health Study, with 167 cases and 334 controls [31], there were no association between adiponectin and CAD. Other authors have reported that adiponectin was not independently associated with future cardiovascular disease [137] or even have reported that adiponectin levels are associated with an increased risk of myocardial infarction or adverse cardiovascular outcome in populations with baseline high risk of CAD [27,138]. In a metaanalysis of seven prospective studies including 1313 CAD cases, the conclusion of the authors was that the association of a single measurement of adiponectin with a combined end point of nonfatal myocardial infarction and CAD death was negligible [139]. Similarly, low HMW adiponectin predicted cardiovascular events in men in some prospective studies [140], but have no predictive value in other surveys [141-144].

In patients with congestive heart failure and cardiac cachexia, serum adiponectin levels have been found to be elevated, and it has been suggested that hypoadiponectinemia may be a sign of physical wasting in these patients [145,146]. In agreement, an association of circulating adiponectin levels with the severity of ventricular dysfunction in congestive heart failure have been reported [147], and a number studies have reported a parallelism between adiponectin and plasma B-type natriuretic peptide (BNP) and the N-terminal of the BNP prohormone (NT-proBNP) levels, prognostic markers of heart failure [18,72,138,145,146,148-156].

When patients with early-stage peripheral arterial disease were compared with patients without peripheral arterial disease, serum adiponectin levels were found to be significantly

lower, and were independently associated with the ankle-brachial index [157,158]. Adiponectin have been reported to be inversely related to the presence of peripheral artery disease by other authors [159], and it has been suggested that serum adiponectin is negatively related with the severity of peripheral arterial disease in its early stages. However, this may not be the case in patients with symptomatic peripheral arterial disease, in whom adiponectin levels were related to disease severity [153].

MECHANISMS LINKING ADIPONECTIN WITH INSULIN RESISTANCE AND CARDIOVASCULAR DISEASE

Epidemiological studies cannot establish a causal relationship between adiponectin and the development of insulin resistance and cardiovascular disease. However, available evidence suggests that this adipokine has a remarkable role in the development of insulin resistance and in inflammatory and atherogenic processes (Table **2**). Adiponectin deficiency may contribute to impair insulin resistance and to favour the development of dyslipemia, hypertension and type 2 diabetes, and also to enhance the deleterious effects of adipokines on glucose and lipid metabolism, inflammatory processes and endothelial dysfunction.

Metabolic Effects of Adiponectin

Data from basic investigation indicate that the administration of adiponectin reverses insulin resistance in rodent models of obesity and type 2 diabetes [12], and that transgenic mice overexpressing adiponectin exhibit amelioration of insulin resistance [14]. The mechanism of this amelioration of insulin resistance seems to be in relation with the metabolic actions of adiponectin. Adiponectin induces AMP kinase and inhibition of acetyl coenzyme A carboxylase, resulting in the stimulation of glucose uptake in muscle, fatty acid oxidation in muscle and liver, and the inhibition of hepatic glucose production, cholesterol and triglyceride synthesis, and lipogenesis [160,161].

These effects are followed by a decrease in circulating free fatty acids and a reduction in triglyceride muscle content [6,12]. Increased free fatty acid oxidation in muscle is also mediated by increased expression of genes encoding CD36, acyl CoA oxidase, and UCP2, which enhance free fatty acid oxidation, fat combustion, and dissipation, respectively [12]. Free fatty acid liver uptake also decreases and this might lead to decreased hepatic triglyceride content, which improves hepatic insulin sensitivity and reduces glucose output.

Anti-Inflammatory Properties

In addition to its metabolic effects, adiponectin exerts noteworthy anti-inflammatory properties. This protein suppresses leukocyte colony formation, reduces phagocytic activity and decreases TNFα production from macrophages [162,163]. Furthermore, it inhibits TNFα-induced expression of several adhesion molecules on the surface of endothelial cells, including vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and intercellular adhesion molecule-1, and decreases the effect of TNFα to induce the adhesion of monocytes to endothelial cells [122,162,163]. Adiponectin also suppresses TNFα-induced inflammatory changes in endothelial cells by blocking inhibitory nuclear factor-κB phosphorylation and nuclear factor-κB activation without affecting TNFα-mediated activation of c-Jun N-terminal kinase, p38 and Akt [164]. Within the vascular wall adiponectin inhibits monocyte adhesion, expression of adhesion molecules and macrophage transformation into foam cells [104,122].

Antiatherogenic Properties

Adiponectin attenuates proliferation of vascular smooth muscle cells in response to a variety of growth factors and migration induced by heparin-binding-epidermal growth factor or platelet-derived growth factor-BB [10,165]. Interestingly, in mouse models adiponectin exerts inhibitory effects on thrombus formation and platelet aggregation [13], and attenuates cardiac myocyte hypertrophy in response to pressure overload [166]. Besides, adiponectin may play a

Table 2. Summary of the Effects of Adiponectin on Glucose and Lipid Metabolism, and its Anti-Inflammatory and Antiatherogenic Properties

Metabolic effects	Anti-inflammatory effects	Vascular effects
Activation of the AMP-activated protein kinase	Reduction of the expression of TNFα mRNA	Suppression of proliferation and migration of vascular smooth muscle cells
Inhibition of acetyl coenzyme A carboxylase	Reduction of TNFα levels	Inhibition of lipid accumulation in human monocyte-derived macrophages
Stimulation of fatty acid oxidation in liver and muscle	Supression of leukocyte colony formation and inhibition of fagocytic activity	Stimulation of the production of NO in vascular endothelial cells in vitro
Reduction of circulating free fatty acids	Inhibition of TNFα induction of nuclear factor-κB	Protection against development of atherosclerosis in susceptible mice
Stimulation of glucose uptake in muscle	Inhibition of endothelial nuclear factor-κB signaling	Suppression of class A scavenger receptor expression in macrophages
Suppression of glucose hepatic output	Reduction of the expression of the vascular cell adhesion molecule-1, E-selectin, and intracellular adhesion molecule-1	Supression of the expression of growth factors in endothelial cells
Decrease in blood glucose	Inhibition of monocyte adhesion to endothelial cells	Inhibition of thrombus formation and platelet aggregation
Improvement in insulin resistance	Inhibition of foam cell transformation of human monocyte-derived macrophages	
Stimulation of insulin secretion		
Stimulation of glucose uptake in adipocytes		
Reduced triglyceride content in liver and skeletal muscle		

AMP, adenosine monophosphate; TNFα, tumor necrosis factor-α; NO, nitric oxide.

beneficial role as a scaffold of newly formed collagen in myocardial remodeling after ischemic injury [167]. In *in vivo* studies, adiponectin has been reported to accumulate in the injured vessel wall and suppress the development of atherosclerosis in apolipoprotein E-deficient susceptible mice [168]. This effect was associated with suppression of the expression of VCAM-1 and class A scavenger receptors [168].

Other putative mechanism of the beneficial effect of adiponectin on the vasculature relates to the endothelial NO generation. Concentrations of adiponectin similar to those found in serum have been shown to enhance NO production in cultured aortic endothelial cells [19,104]. In endothelial cells treated with oxidized LDL, adiponectin inhibited cell proliferation as well as basal and oxidized LDL-induced release of superoxide, and increased NO production by ameliorating the suppression of eNOS activity by oxidized LDL [169].

Adiponectin-induced AMP kinase activation may be a potential link between adiponectin and vascular effects of this adipokine [19,170]. In fact, AMP kinase activates eNOS in endothelial cells and also ameliorates the increased apoptosis observed in endothelial cells exposed to high glucose, suggesting that this enzyme may mediate endothelial cell growth and differentiation responses [171].

Other potential signalling pathways for adiponectin actions in endothelial cells include the activation of Akt, which is linked upstream to phosphatidylinositol 3'-kinase (PI-3K) signaling [19,170]. Recently, a stimulating effect of adiponectin on angiogenesis by promoting cross-talk between AMP kinase and Akt signaling has been reported in endothelial cells [170].

ADIPONECTIN AND MORTALITY

Taking into account the above summarised evidence a positive association between hypoadiponectinemia and mortality could be anticipated. However, paradoxical results have been obtained in studies assessing the relationship between serum adiponectin and the risk of all-cause and cardiovascular mortality in diverse clinical settings.

Congestive Heart Failure

The prospective study by Kistorp *et al.* [148], in 195 patients with congestive heart failure, followed-up for a median of 2.6 years, found that high, rather than low levels of serum adiponectin, were a predictor of mortality, independent of risk markers of heart failure severity. Other series have corroborated this finding [149,150,172], particularly in patients with ischemic congestive heart failure [145], and with acute destabilized heart failure [155], thus suggesting that high adiponectin may be a marker of wasting process in subjects with increased risk of death.

Coronary Artery Disease

Some other studies support the hypothesis that adiponectin might be a marker of poor prognosis in high risk patients. In a high risk cohort of 325 male patients with stable angina, unstable angina and non-ST-segment elevation myocardial infarction, referred for coronary angiography and followed-up for 24 months, subjects with adiponectin levels in the upper tertile exhibited a lower survival in comparison with patients in the lower and middle tertiles [27]. Another prospective survey showed that higher concentrations of serum adiponectin predicted total and cardiovascular mortality in a cohort of 2473 persons with angiography confirmed coronary artery disease, independently of classic and emerging risk factors. However, there was no significant and independent association between adiponectin and the risk of death in a group of 673 individuals without angiographic CAD [28]. The Rancho Bernardo Study showed that adiponectin was not associated with fatal incident CAD events or 20-year CAD mortality in either sex. When analysing subjects by quintiles of adiponectin concentrations, the risks of cardiovascular and all-cause mortality were similar for the first four quintiles of adiponectin levels, but were only elevated for the top quintile [128]. A further prospective study in a cohort of high-risk CAD patients showed that cardiovascular mortality rate were higher in subjects with adiponectin levels above the median [173].

Cerebrovascular and Peripheral Artery Disease

Lower serum adiponectin has been found to be associated with increased risk of ischemic stroke and increased mortality after first stroke event in some surveys [174,175], but not in others [176-178]. On the contrary, high plasma adiponectin levels were independently associated with an increased risk of death in patients with severe peripheral arterial disease who underwent a bypass operation [179]. These results have been recently confirmed in a prospective study of a cohort of 487 patients with symptomatic peripheral artery disease [156]. In this survey increased adiponectin concentrations predicted 5-year mortality, independently of several established and emerging risk factors, with the exception of NT-proBNP.

Elderly

In a prospective study performed in 4046 elderly men, followed-up for a mean of 6 years, elevated adiponectin levels were also associated with increased risk of mortality from noncardiovascular causes in elderly men without cardiovascular disease or heart failure [172]. A case-control study has also reported that the risk of noncardiovascular noncancer risk is higher in subjects with higher adiponectin levels in comparison with those with lower levels [180].

Chronic Kidney Disease

No relationship between adiponectin levels and mortality was found in the first prospective study performed in patients with ESRD undergoing hemodyalisis [110]. On the contrary, a direct relationship between adiponectin and all-cause and cardiovascular mortality, independent of metabolic risk factors and prevalent cardiovascular disease, has been reported in a cohort of patients with chronic kidney disease stages 3 to 4, in the MDRD study [181]. In a group of 74 hemodialysis patients serum adiponectin was a significant determinant of mortality, but this relationship was lost after adjustment for nutritional and inflammatory markers or when malnourished patients were excluded [182]. Hemodialysis patients with plasma adiponectin in the lowest tertile were characterized by a shorter survival time compared to

patients with highest tertile subgroups in a study [183]. In type 1 diabetic patients with overt nephropathy serum adiponectin levels predicted end-stage renal disease and all-cause mortality, however they were not associated with cardiovascular events [184].

However, in the HEMO study [185], performed in a cohort of 182 HD patients, baseline low levels of adiponectin predicted cardiovascular and mortality outcomes. We analysed the relationships of serum adiponectin levels, measured in two occasions, 1 year apart, with all-cause and cardiovascular mortality in a group of stable hemodialysis and peritoneal dialysis patients [186]. We found that patients with high mean adiponectin levels had a better survival rate, independently or residual renal function and prior cardiovascular risk factors. In a recent report, longitudinal increases in adiponectin levels were related to higher risks of cardiovascular events and mortality in a cohort of diabetic hemodialysis [187] patients. In this study the increase in adiponectin was correlated to an increase in NT-proBNP, a risk factor for adverse outcome in dialysis patients, and adjustments for NT-proBNP and its changes resulted in lower effect estimates. These findings suggest that increasing adiponectin in the dialysis population is a reflection of the impairment of disease condition.

ADIPONECTIN AND THE REVERSE EPIDEMIOLOGY

The variable and paradoxical results observed in the above mentioned mortality studies may be accounted for by the differences in demographic features of the studied populations, sample sizes, time of follow-up, disease conditions, severity of patients, and confounding influences of covariates included in the analysis. Discrepancies may also be affected by the diverse methods for adiponectin assay and the disparate quantification of the isoforms of adiponectin. Most studies on mortality measured total adiponectin and not HMW adiponectin concentrations. Nevertheless, this do not invalidate their results, since HMW adiponectin levels are closely correlated with conventional total adiponectin levels [188]. Furthermore, recent studies have found no association between HMW adiponectin levels with incident cardiovascular events [143,144].

It is possible that one baseline measurement of adiponectin may fail to capture the complexity of the compensatory mechanisms involved in regulating adiponectin concentrations prior to death. Therefore, it has been suggested that multiple measurements of adiponectin, as opposed to a single assessment, would provide more reliable results [185,186].

On the whole, previous condition of the patients seems to be the most important factor conditioning the relationship between adiponectin and mortality. Prognostic value of serum adiponectin is different in high risk patients than in healthy population or low risk patients. In groups with elevated risk, including those with chronic heart failure [148,155], CAD [27,28,138,173], severe peripheral arterial disease [156,179] or chronic kidney disease [181,187], high levels of adiponectin have been shown to predict mortality. Accordingly, some investigators have found that high levels of adiponectin predicted mortality in subjects already afflicted with cardiovascular disease and that this association was clearly less pronounced in patients without prevalent cardiovascular disease [189]. In patients with acute coronary syndrome, progression of disease, as measure by BNP levels, was accompanied by an increase in serum adiponectin and in the risk of an adverse outcome [154]. Recent data also suggest that, in dialysis patients, adiponectin is related with mortality mainly in patients with poor nutritional state and vulnerability to the wasting processes and behaves as a protective factor in stable and good prognosis patients [182,186].

These paradoxical findings may be accounted for by the fact that a compensatory up-regulation in adiponectin production might occur in patients with advanced disease in an attempt to compensate the cardiovascular alterations and the pro-inflammatory state associated with cardiovascular disease [189]. In other words, at the same time that adiponectin levels protects against the development of insulin resistance, diabetes and vascular disease, it is possible that elevated adiponectin levels also signal higher all-cause and cardiovascular mortality in subjects at elevated risk (Fig. **1**). This elevation of adiponectin production would result from a compensatory mechanism to counteract metabolic and vascular stress, systemic inflammation and wasting [190,191]. This risk factor reversal, named *reverse epidemiology* [192,193], has been previously described for the obesity paradox, when body mass index can result in a reverse beneficial association with outcome as seen in advanced kidney disease and congestive heart failure [194].

Alternatively, the increased levels may be a consequence of resistance at the level of the adiponectin receptor. This might be a consequence of down-regulation of the adiponectin receptors as reported in obesity and insulin resistance [16]. It is known that four lysine residues in the collagenous domain of the adiponectin molecule can be both hydroxylated and glycosylated [195]. These post-translational modifications in the adiponectin molecule may be potentiated in disease states and lead to a changed three-dimensional structure, with subsequent modifications in receptor affinity and resulting in adiponectin resistance [196]. As stated above, recent data have suggested that AdipoR1 and AdipoR2 are yin yang receptors, at least in the regulation of energy metabolism [17]. One possibility would be that as the disease process progresses, there may be changes in the affinity of adiponectin for AdipoR1 and AdipoR2 receptors, with subsequent changes in the final biological effects, although this is a merely speculative hypothesis.

Another possibility is that under certain circumstances higher adiponectin levels may actually be damaging to the vasculature, although this hypothesis has not been explored. It has been speculated that, in advanced stages of disease, the compensatory increase in adiponectin production might increase energy expenditure and decrease body weight through a direct effect on the brain, and consequently adversely affect the outcome of cardiovascular disease [16,192,197]. Furthermore, not all adiponectin circulating isoforms may be protective for the cardiovascular system. HMW form seems to be the most active and clinically relevant form for the metabolic and vasculoprotective effects of adiponectin

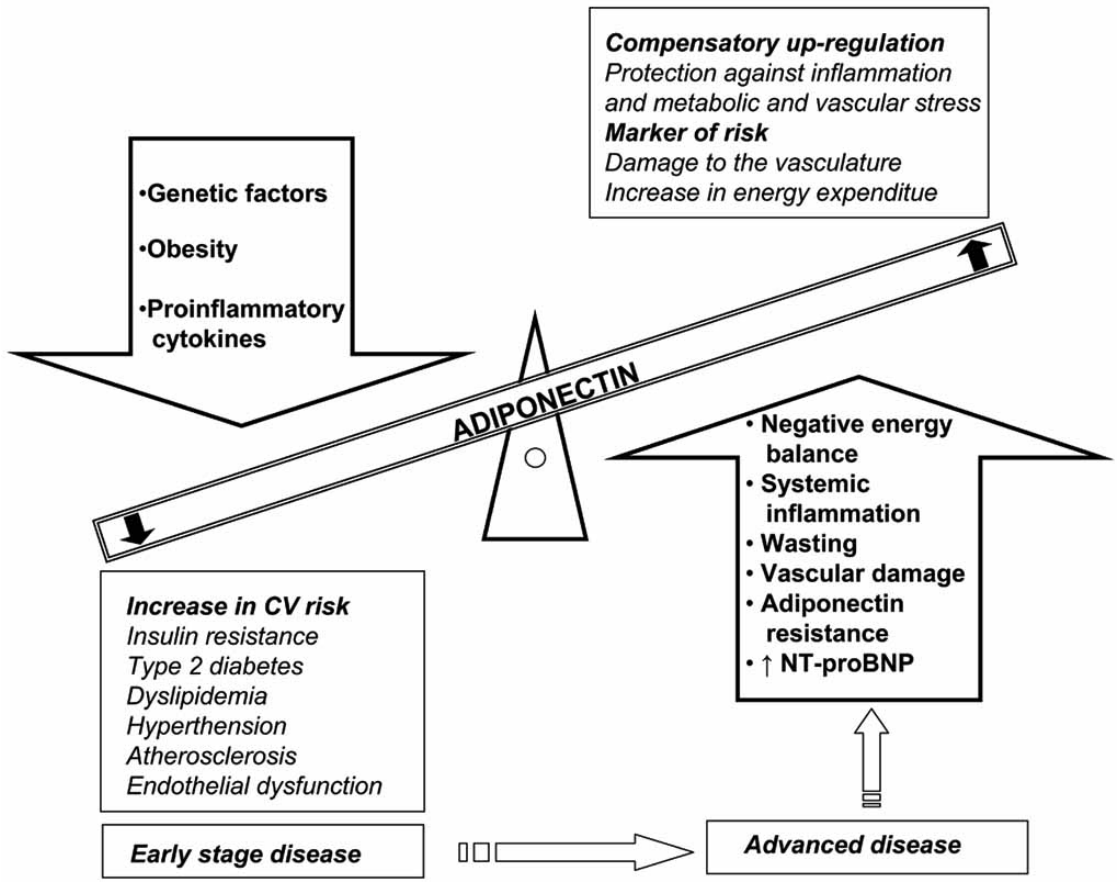

Fig. (1). Schematic diagram depicting the reverse epidemiology of the adiponectin physiology. A decrease in adiponectin levels may be conditioned by genetic factors, obesity and pro-inflammatory cytokines. Hypoadiponectinemia increases the risk of cardiovascular disease and favours the development or progression of disease. When disease reaches an advanced state, diverse mechanisms such as wasting, vascular damage and the increase of mediators of poor prognosis promote a compensatory up-regulation of serum adiponectin. This increase in circulating adiponectin may be understood as a compensatory mechanism to counteract metabolic and vascular derangements of advanced disease process or as a marker of risk in high risk conditions.

NT-proBNP: N-terminal of the B-type natriuretic peptide prohormone.

[125,198], but globular adiponectin has been reported to enhance angiotensin II-induced proliferation in cardiac fibroblasts and may contribute to myocardial hypertrophy [199].

CONCLUSION

In few words, adiponectin exerts remarkable effects on glucose and lipid metabolism. In the liver, it enhances insulin sensitivity, reduces hepatic glucose output and increases fatty acid oxidation. Glucose use and fatty acid oxidation is also stimulated in the muscle. In addition, adiponectin blunts several crucial steps for the atherogenic process. Within the vascular wall adiponectin inhibits monocyte adhesion, expression of adhesion molecules, macrophage transformation into foam cells, and proliferation of migrating smooth muscle cells in response to growth factors. The stimulation of NO production in the endothelium and angiogenesis are other contributors to the beneficial vascular effects of adiponectin.

A large body of experimental evidence and a number of epidemiological studies support the thesis that adiponectin is a protective factor for the cardiovascular system. Nevertheless, the finding of the association of high adiponectin levels with increased risk of death in some populations has been surprising and paradoxical. Conceivably, this paradoxical effect is only a reflection of the two different faces that shows this intriguing hormone, one for the health state and early phase of disease (cardioprotective factor) and the other for advanced state of disease and high risk conditions (wasting marker).

DECLARATION OF INTEREST

The authors declare that there is no conflict of interests that could be perceived as prejudicing the impartiality of the research reported. This research did not receive any grant from any funding agency in the public, commercial or non-for-profit sector.

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