Adiponectin – a predictor of higher mortality in cardiovascular disease or a factor contributing to longer life?

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REVIEW

Abstract

Adiponectin, a protein secreted by adipocytes, has been recently found to be also secreted by cardiomyocytes. Adiponectin possesses several physiological functions including modulation of glucose metabolism and energy homeostasis. The interactions between adiponectin and metabolic parameters were found. Studies on aging humans revealed that enhanced adiponectin values are a distinctive feature of centenarians. Thus, this parameter may be considered as a prognostic factor of prolonged survival.

However, it has also been demonstrated that high adiponectin levels may predict mortality in patients with cardiovascular disease (CVD). Several mechanisms of adiponectin elevation, both in the process of aging and in pathomechanism of CVD, are discussed in this paper.

INTRODCUTION

Adiponectin is a 244-amino-acid plasma protein secreted by adipocytes that was identified from a gene apM1, specifically expressed in fat tissue (Maeda *et al*. 1996). Moreover, it has been recently shown that adiponectin is also synthesized and secreted by cardiomiocytes (Piñeiroi *et al*. 2005).

It has been assessed that adiponectin operates in conjunction with its two membrane receptors Adipo R_1 and Adipo R_2, that are integral membrane proteins. These receptors differ in expression as Adipo R_1 is present in skeletal muscles and liver whereas Adipo R_2 is mostly found in liver (Kadowaki *et al*. 2008). Furthermore, Adipo R_1 is also expressed in endothelial cells (Motoshima *et al*. 2004), cardiomiocytes (Piñeiroi *et al*. 2005) and pancreatic β cells (Kharroubi *et al*. 2003), and Adipo R_2 is expressed in endothelial cells (Tan *et al*. 2004). Adiponectin mediates its effects through activation of AMP-activated protein kinase (AMPK), the peroxisome proliferators–activated receptor (PPAR)-α and p38 mitogen-activated protein kinase (MAPK) – signaling pathways (Kadowaki *et al*. 2008).

THE ROLE OF ADIPONECTIN IN ENERGY HOMEOSTASIS

Adiponectin has been proposed to be a modulator of glucose and lipid metabolism as it exerts several metabolic actions including stimulation of fatty acid oxidation, reduction of plasma triglycerides and improvement of glucose metabolism by

increasing the insulin sensitivity (Palomer *et al.* 2005). In details, adiponectin enhances insulin sensitivity by stimulation of glucose utilization and fatty acid oxidation through phosphorylation and activation of AMPK in muscles and liver (Tomas *et al.* 2002), (Yamauchi *et al.* 2001).

ADIPONECTIN AND CARDIOVASCULAR SYSTEM

In addition to the metabolic effects, adiponectin reveals direct antiatherogenic and vasoprotective actions (Goldstein & Scalia 2004). Moreover, it has been reported that adiponectin is able to inhibit the inflammatory process, reduce expression of endothelial adhesion molecules (VCAM-1, ICAM-1, E-selectin), decrease macrophage-to foam cell transformation, suppress tumor necrosis factor-alpha (TNF-alpha) expression in macrophages and adipocytes as well as to reduce smooth muscle cell proliferation (Palomer *et al.* 2005; Goldstein & Scalia 2004).

In vitro studies revealed that this peptide possesses ability to induce NO production in aortic endothelial cells through activation of AMPK pathway and to enhance endothelial NO synthase (eNOS) mRNA synthesis (Chen *et al.* 2003; Hattori *et al.* 2003). It is essential to indicate that adiponectin is also a very important endogenous antithrombotic factor (Kato *et al.* 2006). Moreover, it has been demonstrated that adiponectin is able to protect the myocardium from ischemia-reperfusion injury through AMPK-mediated antiapoptotic effects and COX-2 mediated anti-inflammatory actions (Shibata *et al.* 2004).

Thus, adiponectin has protective properties against the initiation and progression of atherosclerosis (Szmitko *et al.* 2007; Shimada *et al.* 2004) as it protects from development of all stage atherosclerotic plaque. In addition, adiponectin protects against plaque rupture and thrombosis (Szmitko *et al.* 2007).

It has been proposed that adiponectin may have antiatherogenic, anti-inflammatory, cardioprotective and insulin-sensiting properties (Szmitko *et al.* 2007). Remarkably, adiponectin levels were found to be decreased in patients with obesity, type 2 diabetes, hypertension, coronary disease as well as in patients with ischemic cerebrovascular disease (Daimon *et al.* 2003; Iwashima *et al.* 2004; Chen *et al.* 2005; Sakuta *et al.* 2005; Rabin *et al.* 2005; Adamczak *et al.* 2003).

Adiponectin links the metabolic syndrome and its cardiovascular consequences (Rabin *et al.* 2005) as hypoadiponectinemia is known to contribute not only to insulin resistance but also to the endothelial vascular dysfunction (Goldstein & Scalia 2004). Besides, low adiponectin concentrations are significantly associated with hypertension and, on the other hand, hypoadiponectinemia is an independent risk factor for hypertension (Iwashima *et al.* 2004). Furthermore, some factors may be involved in the mechanism of hypoadiponectinemia in hypertensive patients. In details, an increase in the sympathetic nerve activity may inhibit adiponectin gene expression via β-adrenergic stimulation. Moreover, the association between adiponectin and high sensitive C-reactive protein may suggest that low adiponectin levels might enhance predisposition to hypertension via vascular injury. Finally, activation of the angiotensin system by hypoadiponectinemia may result in an increase in fat mass and blood pressure (Iwashima *et al.* 2004). On the other hand, hypoadiponectinemia has been associated with endothelial dysfunction, increased carotid intima-media thickness and coronary artery disease. In addition, high adiponectin values are thought to be connected with lower prevalence of acute coronary disease (Sakuta *et al.* 2005; Wolk *et al.* 2007).

THE CONTROVERSIAL OPINIONS ON THE INFLUENCE OF ADIPONECTIN ON CARDIOVASCULAR DISEASE

The recent prospective studies concerning correlation between adiponectin and cardiovascular disease (CVD) and mortality demonstrated controversial results.

Some authors reported that adiponectin was not independently associated with future development of CVD (Lawlor *et al.* 2005; Sattar *et al.* 2006; Koenig *et al.* 2006) whereas others showed that high adiponectin levels were correlated with an increased risk of CVD and/or mortality (Cavusoglu *et al.* 2006; Laughlin *et al.* 2007), (Kistorp *et al.* 2005; George *et al.* 2006).

Dekker *et al.* (Dekker *et al.* 2008) reported that elevated values of adiponectin predict mortality in patients with prevalent CVD. These authors suggested that adiponectin may protect against metabolic and vascular disease but in patients with CVD its levels are compensatory upregulated.

It has been shown that in some risk groups an increase in adiponectin levels predict higher mortality rate (Kistorp *et al.* 2005; Pilz *et al.* 2006). The patients with chronic heart failure, coronary artery disease and chronic kidney disease are amongst them.

Maiolino *et al.* (Maiolino *et al.* 2008) demonstrated that enhanced adiponectin values in a group of high-risk coronary artery disease patients result in a higher risk of cardiovascular death. Moreover, the findings of Kizer *et al.* (Kizer *et al.* 2008) showed that in older adults elevated concentrations of adiponectin are associated with increased risk of incident of coronary disease. In addition, Laughlin *et al.* (Laughlin *et al.* 2007) considered whether serum adiponectin level is an independent risk factor for coronary heart disease or is simply a risk marker. However, these authors have indicated that use of adiponectin estimation for cardiovascular disease risk stratification may be premature.

ADIPONECTIN AND THE PROCESS OF AGING

It has been commonly accepted that obesity, hypertension and hyperlipidemia, collectively named as metabolic syndrome, result in substantial morbidity and mortality (Rabin *et al.* 2005). Moreover, the prevalence of hypertension, insulin resistance and diabetes increases with age.

Interestingly, it has been demonstrated that adiponectin levels may be elevated in elderly (Isobe *et al.* 2005).

A decline of renal function with aging contributes independently to the rise of adiponectin level. Thus, a decrease in adiponectin clearance due to a slight impairment of renal function with aging may cause increase in serum adiponectin (Isobe *et al.* 2005). Besides, it has been shown that there is a relationship between adiponectin and creatinin clearance in essential hypertension that was confirmed by findings of increased adiponectin levels in hypertensive patients with decline of renal function (Mallamaci *et al.* 2002).

Our previous studies (Baranowska *et al.* 2006; Bik *et al.* 2006) have demonstrated higher adiponectin levels in centenarians as compared with young subjects and patients aged below 70 yrs old. In addition, centenarians showed the lower incidence of hypertension, diabetes and dyslipidemia. We also found that adiponectin correlated negatively with index of insulin resistance (HOMA). Our findings are in accordance with study by Arai *et al.* (Arai *et al.* 2006) who also observed that high plasma adiponectin concentration in centenarians was associated with favorable metabolic indicators and with lower levels of C-reactive protein and E-selectin. Both Arai and ours data suggest that hyperadiponectinemia may contribute to longevity. The study conducted by Atzmon *et al.* not only confirmed elevated adiponectin levels in the oldest-old subjects but also revealed higher values of this particular peptide in the centenarians offsprings (Atzmon *et al.* 2008). The studies concerning adiponectin activity in hundred-year-old strongly confirm the beneficial role of adiponectin in prolonged survival.

LINKING ADIPONECTIN TO CVD RISK

It is an open question why an increase in adiponectin, that is an antiatherogenic and cardioprotective peptide, is associated with higher mortality in patients with cardiovascular disease. How it could be explained that there is a discrepancy in findings that hyperadiponectinemia correlates with longevity and on the other hand is associated with higher mortality in some diseases?

Dekker *et al.* (Dekker *et al.* 2008) indicated that adiponectin protects against metabolic and vascular diseases but in patients with CVD adiponectin is compensatory upregulated and therefore is associated with higher mortality risk. Some possible factors leading to hyperadiponectinemia in CVD may be considered, amongst them weight loss, adiponectin resistance due to down regulation of adiponectin receptors and reduced renal clearance (Dekker *et al.* 2008; Sattar & Nelson 2008).

Although the mechanisms in which adiponectin is metabolized and in which exerts its action are not known in details, it is reasonable to speculate that production and degradation of adiponectin may be altered in CVD. It has been suggested that in patients suffering from CVD the secretion of adiponectin by cardiomyocytes is increased and may be stimulated by atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) (Piñeiro *et al.* 2005; Tsutamoto *et al.* 2007). This theory may be confirmed by findings of significant correlation between adiponectin and ANP and BNP in patients with heart failure or in subjects with coronary heart disease (von Eynatten *et al.* 2006). In addition, recent study by Ohara *et al.* suggests that plasma adiponectin levels indicate the status of heart function as in healthy subjects increase in adiponectin concentration was associated with elevation in BNP values (Ohara *et al.* 2008).

Adiponectin synthesis may be also stimulated in response to vascular inflammation which is characteristic for atherosclerotic process (Sattar & Nelson 2008). A rise in adiponectin concentration may be a result of acute or chronic compensatory mechanisms that counteract the metabolic and vascular stress.

Differences in activity of adiponectin complexes have also been considered. It has been found that there are three major complexes of adiponectin: LMW, a low molecular weight (trimer), a MMW, middle molecular weight (hexamer) and HMW, high molecular weight (12- to 18-mer) (Szmitko *et al.* 2007; Pajvani *et al.* 2003). Some data demonstrated that HMW multimers have more potent insulin-sensitizing effects than trimers (LMW) or hexamers (MMW) (Kadowaki *et al.* 2006).

Although elevated adiponectin levels may predict higher risk for cardiovascular disease mortality in the general populations, it could be speculated that in CVD patients alterations in the process of adiponectin multimerization may lead to the deficiency of cardioprotective isoforms of adiponectin. Studies on chronic heart failure indicate that evaluation of total adiponectin concentration is more useful to assess mortality risk than HMW adiponectin (Tsutamoto *et al.* 2007). Thus, it could be stated that not all isoforms of adiponectin protect against CVD (Sattar *et al.* 2008). Moreover, an increased in total adiponectin values might reflect the severity of chronic heart failure (Tsutamoto *et al.* 2007).

It could be considered that determination of all adiponectin isoform levels in plasma of CVD patients as well as in centenarians may help to explain these intriguing and controversial opinions and conflicting findings.

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