Relationships between adiponectin levels, the metabolic syndrome, and type 2 diabetes: a literature review

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ABSTRACT

Elevated hepatic glucose production, impaired insulin secretion, and insulin resistance – abnormalities of glucose metabolism typically found in subjects with obesity – are major factors underlying the pathogenesis of type 2 diabetes (DM2) and the metabolic syndrome (MS). Adiponectin is a major regulator of glucose and lipid homeostasis via its insulin-sensitizing properties, and lower levels seems to be associated with the development of DM2 and MS. The purpose of this review is to clarify the mechanisms whereby adiponectin relates to the development of DM2 and MS and the association between polymorphisms of the adiponectin gene, circulating levels of the hormone, and its relationships with DM2. In addition, the impact of dietary lipids in the circulating levels of adiponectin will be addressed. According to the literature, circulating adiponectin levels seem to decrease as the number of MS components increases. Lower adiponectin concentrations are associated with higher intra-abdominal fat content. Therefore, adiponectin could link intra-abdominal fat with insulin resistance and development of MS. Therapeutic strategies that target the MS and its components, such as lifestyle modification through physical activity and weight loss, have been shown to increase adiponectin concentrations. Possible roles of diets containing either low or high amounts of fat, or different types of fat, have been analyzed in several studies, with heterogeneous results. Supplementation with n-3 PUFA modestly increases adiponectin levels, whereas conjugated linoleic acid supplementation appears to reduce concentrations when compared with unsaturated fatty acid supplementation used as an active placebo. Arch Endocrinol Metab. 2017;61(6):614-22

Keywords
Adiponectin; metabolic syndrome; type 2 diabetes

INTRODUCTION

The prevalence of the metabolic syndrome (MS) and diabetes mellitus type 2 (DM2) in the North American population is 22.9% and 9.3%, respectively, according to NHANES and CDC data (1,2). Very similar prevalence figures have been reported in Brazil (3). In a recent systematic review of cross-sectional studies, the weighted average prevalence of MS was 29.8%, 20.1%, and 41.5% in the adult Brazilian population in urban, rural, and indigenous areas, respectively (3). According to the results of a study conducted with fixed-shift industry workers in the state of Rio Grande do Sul, being female, being older, and having sleep deprivation proved to be potential risk factors for MS, while having a higher education and eating a greater number of meals per day were considered protective factors against MS (4). Regarding DM2, the Multicenter Study on the Prevalence of Diabetes in Brazil estimated its prevalence the adult population at 7.6%

in the late 1980s (5). According to 2012 data, 7.4% of respondents to a telephone survey representative of the entire adult population of all 26 state capitals and the Federal District reported a medical diagnosis of DM2 (6). Complications from DM2 result in high morbidity and mortality and an average 6-year reduction in average life expectancy when the disease is diagnosed at age 50 (7). The direct and indirect costs of DM2 amount to US$ 245 billion a year in the United States alone. Health expenditures on individuals with DM2 are increased twofold when compared to spending on individuals without the disease (1). In Brazil, DM is also considered a major public health problem. Its estimated cost per capita is US$ 1527.6/year; considering that an estimated 11.6 million Brazilians aged 20 to 79 have DM2, direct expenses related to this condition amount to approximately US$ 17 billion a year (8).

Obesity is associated with development of the MS, which is characterized by a cluster of risk factors for

cardiovascular disease and DM2, such as hyperglycemia, elevated blood pressure, elevated triglycerides, low HDL cholesterol, and central obesity (9). Moreover, obesity and abdominal fat deposition cause a number of metabolic abnormalities that result in increased hepatic glucose output and decreased insulin sensitivity in skeletal muscle, liver, and adipose tissue – processes that are closely related to the pathogenesis of DM2 (10).

In view of the foregoing, the present review sought to clarify the mechanisms whereby the hormone adiponectin relates to the development of MS and DM2. The association between polymorphisms of the adiponectin gene, circulating levels of the hormone it encodes, and its relationships with DM2 will also be explored. In addition, the impact of diets with different levels and types of lipids on circulating levels of adiponectin will be addressed.

ADIPONECTIN AND GLUCOSE METABOLISM

Adiponectin, a hormone present mainly in adipose tissue, is encoded by the *APM1* gene (chromosome 3q27). In humans, adiponectin plasma levels range from 3 to 30 μg/mL, which is among the highest plasma concentrations of a circulating protein. The adiponectin molecule is a 247-amino acid polypeptide and is secreted into circulation in three oligomeric isoforms: a low-molecular-weight trimer, an intermediate-molecular-weight hexamer and a high-molecular-weight complex (11). Some studies suggest that the high-molecular-weight isoform is most biologically active, and that lower levels of this form are associated with DM and coronary artery disease (12-14). Adiponectin acts through two receptors, AdipoR1 and AdipoR2; the former is expressed at higher levels in muscle tissue, and the latter, in liver tissue. Studies have demonstrated that the AdipoR1 receptor is also present in endothelial cells (15), cardiomyocytes (16), and pancreatic beta cells (17), while AdipoR2 is present in endothelial cells (18), and both receptors are present in the hypothalamus (19). Resistance to the action of insulin resulting from obesity causes downregulation of adiponectin receptors in muscle and liver (20). Furthermore, adiponectin expression blunts increases in insulin, TNF-α, endothelin-1, and glucocorticoids, factors implicated in the pathogenesis of insulin resistance, subclinical inflammation, endothelial dysfunction, and regulation of energy metabolism, and closely related to the development of MS, DM2, and cardiovascular

disease (21). Accordingly, extensive research has shown that adiponectin levels are reduced in obesity (22,23), DM2 (22,24), and coronary artery disease (25-27).

To test the *in vivo* effect of adiponectin on insulin sensitivity, a lipoatrophy mouse model with adiponectin deficiency was developed. In these animals, replacement of physiological doses of adiponectin improved insulin resistance (28). Adiponectin stimulated fatty acid oxidation in muscle by increasing the expression of molecules involved in the transport of fatty acids (CD36), their combustion (acetyl coenzyme A oxidase), and dissipation of energy through increased expression of type 2 uncoupling protein (UCP-2) (28). Adiponectin replacement in these animals increased PPAR-alpha expression, fatty acid oxidation, and energy consumption, causing a reduction of triglyceride levels in muscle and liver tissue (28). The reduction in triglyceride content in skeletal muscle was associated with increased translocation of GLUT-4, which led to improved insulin sensitivity (28). In another study by the same group, acute treatment (up to 6 hours) of C2C12 myoblasts with adiponectin increased the oxidation of fatty acids and stimulated glucose uptake via activation of AMPK (29), leading to a reduction in levels of enzymes that indicate hepatic gluconeogenesis. Furthermore, wild-type mice that received a diet rich in total lipids had a reduction in adiponectin levels compared to a diet rich in carbohydrates. Adiponectin replacement in these animals also improved insulin resistance and hypertriglyceridemia induced specifically by the high-fat diet (28). Additionally, studies demonstrated in wild-type and *ob/ob* or streptozotocin-induced DM1 mouse models that an acute increase in circulating levels of adiponectin leads to a transient decrease in baseline glucose level by inhibiting enzymes involved in hepatic gluconeogenesis and hepatic glucose production rate (30,31). Based on these studies, it was demonstrated that stimulation of fatty acid oxidation in muscle and liver, increasing glucose uptake in skeletal muscle and suppressing hepatic gluconeogenesis, are potential routes through which adiponectin regulates insulin sensitivity (28,30,31). These data suggest that insulin resistance associated with a high-fat diet and obesity are partly related to a reduction in circulating adiponectin levels and that an increase of these levels would protect against the development of different components of MS, especially those related to the modulation of insulin sensitivity, body fat distribution, and lipoprotein metabolism (28).

Studies have suggested a relationship between adipokines, such as letptin and resistin, and DM-related vascular complications (32,33). Chronic kidney disease is considered a long-term complication of DM, and its development has been associated with higher levels of these adipokines (34). According to an experimental study, adipokines can lead to kidney injury by regulation of endothelial dysfunction, oxidative stress, and inflammatory processes (35). A longitudinal study of 161 subjects with diabetes followed from 2002 to 2013 demonstrated that plasma adiponectin increased in patients with renal insufficiency, and that its levels were positively associated with albuminuria (36). It is interesting to highlight that, in the context of chronic kidney disease, higher levels of adiponectin have been found to predict progression to end-stage renal disease (ESRD), cardiovascular mortality, and total mortality (37,38). Adiponectin levels are known to increase with decreasing glomerular filtration rate in chronic kidney disease, as a reflection of decreased renal clearance (39). As a result, ESRD features increased adiponectin levels and AdipoR1 expression (40). Both mechanisms may explain the association between higher adiponectin levels and total and cardiovascular mortality in this scenario.

ASSOCIATION BETWEEN ADIPONECTIN GENE POLYMORPHISMS, CIRCULATING ADIPONECTIN LEVELS, AND DM2

Epidemiological studies have shown that DM2 clusters in families, suggesting a genetic contribution to its development. The cumulative risk of DM2 at age 65 was 14.8% for individuals with no family history of DM2, 22% for individuals with only one parent with DM2, and 41% for individuals whose parents are both affected by the disease (41).

Recent studies have shown that a number of genetic polymorphisms are associated with the development of obesity and DM2 (42,43). Genes that modulate the metabolism of adipose tissue and, consequently, are involved in the fatty acid synthesis and metabolism pathways are important determinants of body fat distribution and insulin sensitivity, which, in turn, are also related to abnormalities in glucose metabolism and development of DM2. Genetic variants of the adiponectin gene have also been associated with resistance to insulin action and DM2 (44).

It is estimated that 39-46% of the variability of circulating adiponectin levels is due to genetic factors (45,46). In this regard, a recent systematic review and meta-analysis compiled data from seven studies that explored the association between three single-nucleotide polymorphisms (SNPs), -11391G→A, +45T→G, and +276G→T, and plasma level of adiponectin (25). The -11391G→A SNP was associated with higher levels of circulating adiponectin in subjects carrying the A allele compared to subjects carrying only the G allele. No association was found between the +45T→G SNP and adiponectin levels. Regarding the SNP +276G→T, adiponectin levels showed a progressive increase in homozygotes for the G allele when compared to heterozygotes and homozygotes for the T allele (25).

Associations between adiponectin gene polymorphisms and risk of DM2 have also been widely explored in the literature. Among the nine chromosomal regions related to DM2, three (3q, 15q, and 20q) are found in various ethnic groups, such as the Japanese, German, and French (47). Interestingly, the 3q27 region containing the adiponectin gene once again suggests a role of adiponectin as a determinant of susceptibility to DM2. The 276 SNP in intron 2 (G vs. T) has been associated with distinct phenotypes of adiponectin levels, insulin resistance, and susceptibility to DM2. Individuals with the G/G genotype at position 267 had lower adiponectin levels and increased DM2 risk compared with T/T genotype carriers (24). Similar associations between the adiponectin gene and susceptibility to DM2 have also been demonstrated in German and French populations (48,49).

Given the large number of studies that have sought associations between different polymorphisms of the adiponectin gene and DM2, a recent systematic review and meta-analysis pooled the results of more than 2,000 individuals with DM2 vs. controls for four SNPs: -11391G→A, -11377C→G, +45T→G, and +276G>T (25). No association was demonstrated between the evaluated SNPs and risk of DM2. Subsequently, another systematic review and meta-analysis of 45 studies (9,986 individuals with DM2 vs. 16,222 control subjects) only assessed polymorphism +45T→G and, through a subgroup analysis, found an association between +45T→G and risk of DM2 in studies involving Asians. However, there was no such association in studies involving Caucasians (50). Regarding insulin resistance, an association between the +276G→T SNP and insulin resistance estimated

by HOMA-IR has been observed. Resistance to insulin action was higher in individuals homozygous for the G allele compared to heterozygotes and those homozygous for the T allele, indicating higher insulin sensitivity in individuals carrying the T allele – the same allele that showed a trend toward association with higher levels of adiponectin (25).

In summary, studies have suggested that genetic factors modulate circulating adiponectin levels (27). Additionally, adiponectin gene variants have been associated with higher risk of developing DM2 and MS, especially in phenotypes associated with insulin resistance (51). However, this finding remains controversial.

ADIPONECTIN AND THE METABOLIC SYNDROME

Studies have suggested that expression of the *APM1* gene in visceral abdominal fat is lower than in subcutaneous abdominal fat (52,53). This gene expression in adipose tissue correlates significantly with plasma levels, being higher in lean individuals and those with higher sensitivity to insulin action (23). Furthermore, the lowest concentration of adiponectin is associated more strongly with quantification of visceral abdominal fat than with subcutaneous abdominal fat, suggesting a possible relationship with MS (54).

The inverse relation between adiponectin levels and criteria for MS has been described in the literature (47,55-58). It is well demonstrated that overweight individuals have lower levels of adiponectin compared to lean individuals, and that levels of this hormone decrease as BMI increases in men and women (55). In addition, higher levels of adiponectin were associated with a lower incidence of DM2 in a Japanese cohort followed for 5 years in order to better understand the factors related to development of DM. Individuals in the lowest tertile of adiponectin levels developed approximately nine times more DM2 than those individuals belonging to the highest tertile (56). Additionally, individuals with lower plasma levels of adiponectin have LDL-cholesterol molecules of smaller size, lower lipoprotein lipase activity, lower HDL-cholesterol levels, and higher triglyceride levels (47,58). Regarding blood pressure, lower levels of circulating adiponectin were observed in hypertensive compared to non-hypertensive patients, even after adjusting for obesity, insulin resistance, and DM2 (57). Studies have suggested an effect of adiponectin on blood pressure homeostasis. An increase in collagen deposition promoted by increased

serum levels of procollagen type I carboxy-terminal propeptide (PICP) is associated with an acceleration of the arterial stiffening process, a phenomenon closely related to the development of hypertension (59) and MS (60). A cross-sectional study of 188 hypertensive patients without DM2 showed that higher adiponectin levels were associated with lower circulating levels of PICP (61). Reinforcing this hypothesis, lower levels of adiponectin were associated with increased arterial wall stiffness in a cohort of elderly individuals (62). An effect of adiponectin on endothelial function has also been demonstrated. Adiponectin increases gene expression and activates endothelial nitric oxide synthase through activation of AMPK (63), stimulating the synthesis of nitric oxide, an important endothelial factor and potent vasodilator (64). Additionally, it is known that the renin-angiotensin system plays an important role in regulating blood pressure and that, when activated, it perpetuates the inflammatory process in the arterial wall, increasing oxidative stress and fostering development of atherosclerosis (65,66). Through its antioxidant and anti-inflammatory effects, adiponectin inhibits the deleterious vascular effect of renin-angiotensin system activation and is closely related to dysregulation of blood pressure homeostasis in MS (67). Figure 1 shows the different mechanisms involved in the pathogenesis of MS related to hypoadiponectinemia.

Cross-sectional studies have evaluated the associations between the different MS components and adiponectin levels in populations with different metabolic profiles (68-70). The results of a cross-sectional study conducted in the elderly U.S. Rancho Bernardo cohort demonstrated that individuals with MS had lower circulating levels of adiponectin compared to individuals without MS (68). Furthermore, the presence of each of the MS components was associated with lower levels of adiponectin (68). Koh and cols. included only Asian individuals over the age of 40, and found that lower adiponectin levels were associated with greater waist circumference and increased levels of triglycerides, CRP, fasting glucose, and insulin. Furthermore, individuals with higher circulating adiponectin had higher HDL-cholesterol levels (69). In a study conducted by von Frankenberg and cols. in Brazil, individuals were referred to a tertiary care hospital (*Hospital de Clínicas de Porto Alegre*, state of Rio Grande do Sul) for screening and evaluation of glucose metabolism abnormalities and MS. A replication analysis was performed in subjects
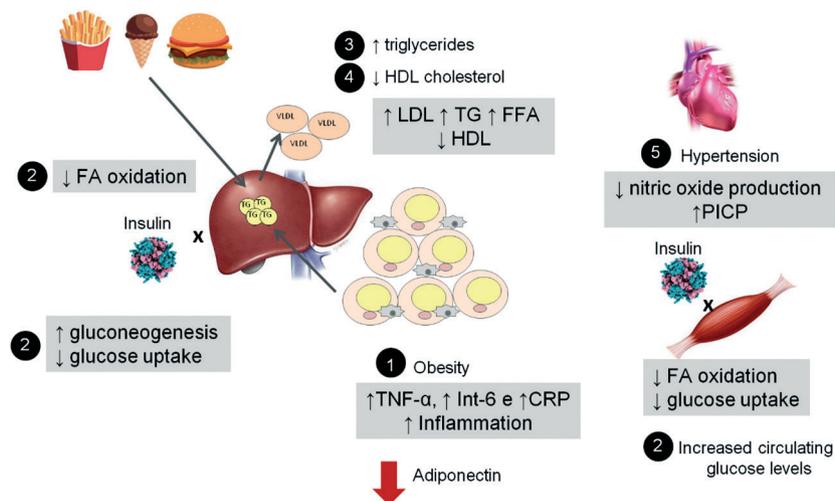
Figure 1. Mechanisms whereby a reduction in adiponectin levels is associated with the development of MS. **1:** Accumulation of visceral fat reduces production of adiponectin. Tissue inflammation increases levels of C-reactive protein (CRP) and inflammatory cytokines (TNF-α and interleukin-6), activating hepatic gluconeogenesis. **2:** Hepatic gluconeogenesis is activated and insulin sensitivity in muscle and liver is further reduced, resulting in increased circulating glucose levels. **3** and **4:** Reduction of triglyceride oxidation from adipose tissue and dietary lipids by the liver increases levels of free fatty acids (FFA) and production of VLDL, generating an imbalance in lipid profile (increased LDL cholesterol, triglycerides [TG], and reduced HDL cholesterol). **5:** Increased serum level of procollagen type I carboxy-terminal propeptide (PICP) intensifies arterial stiffness, and reduced nitric oxide production contributes to reduced vasodilation. These mechanisms, along with the pro-inflammatory environment, promote changes in blood pressure homeostasis, which contribute to the development of systemic arterial hypertension.

undergoing cardiac catheterization at another tertiary referral center (*Hospital São Paulo*, in the city of São Paulo). This study demonstrated that levels of total and high-molecular-weight adiponectin were lower in the presence of MS, and were reduced with each increase in the number of components of MS. Adiponectin levels were mainly determined by their relation with HDL cholesterol, triglycerides, and waist circumference. In addition, blood glucose, subclinical inflammation, and insulin resistance partially explained why adiponectin levels were lower in individuals with compared to individuals without MS (70).

EFFECT OF DIETARY LIPIDS ON CIRCULATING ADIPONECTIN LEVELS

Intervention studies have shown that adiponectin levels can be partly determined by different types of diet. Given the important role of adiponectin in carbohydrate and lipid metabolism, including improving insulin sensitivity and increasing fatty acid oxidation, diets that modify the quantity and quality of lipids ingested can have an impact on the metabolism and plasma levels of adiponectin (71,72). Several studies conducted in humans aimed to show the effect of diets with high or low levels of total lipids in the regulation of adiponectin

(73-75). In a randomized clinical trial comparing a fat-restricted hypocaloric diet (27% fat, 52% carbohydrates, and 21% protein) vs. a high-fat diet (41% fat, 39% carbohydrates, and 20% protein), there were no changes in adiponectin levels observed at the end of 10 weeks of intervention (73). However, another study that compared a normal-lipid hypocaloric diet (30% fat) vs. a high-lipid (61% fat) diet showed 30% and 18% increases in adiponectin levels after 52 weeks of intervention respectively (75). However, providing isocaloric diets for weight maintenance with high fat (55% fat, 27% carbohydrates, 18% protein) or low fat (20% fat, 62% carbohydrates, 18 % protein) was not associated with differences in adiponectin levels after 4 weeks of intervention (74). These results suggest there is no consensus about the effect of total dietary lipid intake (low fat vs. high fat) on adiponectin levels in interventional studies conducted in humans.

Greater adherence to the Mediterranean style diet, which is rich in unsaturated fats, has been associated with higher adiponectin levels (76). This relationship is possibly attributable not only to the low glycemic load and moderate alcohol consumption characteristic of this diet, but also to its high content of oilseeds and olive and fish oil, which are dietary sources of polyunsaturated fatty acids (71). The mechanisms

through which the Mediterranean diet has impacts on circulating levels of adiponectin is still unknown, but several hypotheses have been raised. The omega-3 type polyunsaturated fatty acids (n-3 PUFA) found in this diet can modulate adiponectin levels by interacting with the peroxisome proliferator-activated receptors alpha (PPAR-α) and gamma (PPAR-γ) (77). Activation of PPAR-α stimulated by consumption of n-3 PUFA increases expression of AdipoR1 and AdipoR2 in muscle and liver, improving sensitivity to this hormone in these tissues (78). Adiponectin then acts by reducing inflammation and oxidative stress, which ultimately leads to improved insulin sensitivity (79). Moreover, n-3 PUFAs activate PPAR-γ, thus increasing adiponectin levels through a second route. In an experimental study, consumption of n-3 PUFAs was associated with a twofold increase in expression of the adiponectin gene, which occurred parallel to a twofold to threefold increase in expression of the gene which encodes PPAR-γ (77). Thus, the activation of PPAR-α and PPAR-γ promoted by n-3 PUFAs increases adiponectin levels and activity, which results in improvement in obesity-induced inflammation and insulin resistance (78).

In addition to the n-3 PUFAs, other types of lipids have shown effectiveness in the regulation of adiponectin, among which conjugated linoleic acid (CLA) stands out. CLA can cause resistance to insulin action by reducing plasma levels of adiponectin (80). The mRNA levels of adiponectin were reduced after CLA supplementation in rats (81) and in cultured human adipocyte cells (82). Since the adiponectin gene is modulated by activation of PPAR-γ, suppression of the adiponectin gene can be partly attributed to the antagonistic effect of the trans-10, cis-12 CLA on PPAR-γ (83).

Analysis of the results of clinical trials conducted across different ethnic groups, genders, metabolic profiles, and diseases provides an understanding of the effects of lipid intake on circulating levels of adiponectin. In this regard, a recent systematic review and meta-analysis performed by our group showed that, in intervention studies comparing low-fat vs. high-fat diets, there was no association of total amount of fat with circulating levels of adiponectin (72). Omega-3 PUFA supplementation modestly increased circulating concentrations of adiponectin; however, these findings should be interpreted with caution, since publication bias was identified in this meta-analysis (72).

However, CLA supplementation reduced adiponectin concentrations as compared with unsaturated fatty acid supplementation as active placebo (72).

CONCLUSIONS

Circulating levels of adiponectin are reduced in the presence of the MS, cardiovascular disease, and DM2, and also decrease as the number of MS components increases. The association of adiponectin with HDL cholesterol, triglycerides, and abdominal fat may partly explain the lower levels of adiponectin found in individuals with MS. Among dietary interventions, diets low in total lipids have shown no effect on circulating adiponectin. Supplementation with n-3 polyunsaturated fatty acids, however, was associated with a moderate increase in adiponectin. In contrast, conjugated linoleic acid appears to reduce adiponectin levels when compared to unsaturated fat supplementation.

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