The Role of Adiponectin in Cardiometabolic Diseases: Effects of Nutritional Interventions

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Abstract
Adiponectin is an adipocyte-derived hormone abundantly present in plasma that exerts its effects through the activation of 3 receptors. Its concentrations are negatively regulated by the accumulation of visceral fat, and clinical studies implicate hypoadiponectinemia in the pathogenesis of diabetes mellitus type 2, coronary artery disease, hypertension, and left ventricular hypertrophy. In contrast, high concentrations of adiponectin are associated with a decreased risk of coronary artery disease, with an improvement in the differentiation of preadipocytes into adipocytes, and with increased endothelial nitric oxide production. Therefore, adiponectin appears to be an important molecule involved in limiting the pathogenesis of obesity-linked disorders, and it may have potential benefits in the treatment and prevention of cardiovascular disease.

Caloric restriction, moderate alcohol consumption, and consuming a Mediterranean diet increase adiponectin concentrations, and current evidence suggests a positive, dose-dependent relation between ω-3 (n–3) fatty acid intake and circulating concentrations of adiponectin. Recently, it was reported that the administration of aged garlic extract and a single food intervention with pistachios can increase adiponectin concentrations in individuals with metabolic syndrome. Moreover, the Mediterranean diet is associated with higher adiponectin concentrations. Additional studies are needed to evaluate the potential benefits of increasing adiponectin by nutritional interventions in the treatment and prevention of cardiometabolic diseases.

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Adiponectin: An Adipocyte-Derived Hormone Implicated in Cardiometabolic Diseases

Adiponectin is an adipocyte-derived hormone abundantly present in human plasma that improves insulin sensitivity in the muscle and liver and has anti-inflammatory effects (1, 2). Adiponectin concentrations in plasma are negatively regulated by accumulation of visceral fat (3) and are therefore lower in more obese individuals (4). Clinical studies implicate hypoadiponectinemia in the pathogenesis of diabetes mellitus type 2 (DM2) (5), coronary artery disease (CAD) (6), hypertension (7), and left ventricular hypertrophy (8). High concentrations of adiponectin decrease the risk of CAD in male diabetic patients (9), decrease cardiovascular disease (CVD) outcomes in patients with end-stage renal failure (10), and decrease the risk of myocardial infarction in healthy men (11).

Several different mechanisms have been proposed to explain the protective role of adiponectin in cardiometabolic diseases. Adiponectin has anti-inflammatory effects, improves insulin sensitivity, increasing cellular glucose uptake and reducing hepatic gluconeogenesis (12), and promotes adipocyte formation (13). In addition, adiponectin increases the production of endothelial NO, a substance with well-documented anti-thrombotic, antiatherogenic and vasodilatory actions (14–16). Therefore, adiponectin appears to be an important molecule involved in limiting the pathogenesis of obesity-linked disorders and may have potential benefits in the treatment and prevention of cardiovascular disease.

Nutritional Interventions to Increase Adiponectin Levels

Caloric restriction and associated weight loss have been shown to increase adiponectin concentrations (17). Moderate alcohol consumption exerts a cardioprotective effect and increases concentrations of adiponectin (18). Current evidence also suggests a positive, dose-dependent relation between ω-3 FA intake and circulating concentrations of adiponectin (19). Moreover, DHA-enriched canola oil increased plasma adiponectin concentrations compared with a control corn and saffron oil treatment (20). In asthmatic patients, a positive significant relation between MUFA intake and adiponectin was observed. In contrast, there was a significant negative relation between adiponectin concentrations and SFA intake (21). Short-term
enteral l-arginine therapy added to the usual enteral nutrition of non-diabetic patients affected by head and neck cancer and surgery was found to improve insulin resistance and increase adiponectin concentrations (22).

A recent meta-analysis that reviewed 17 trials involving 2300 subjects concluded that consumption of a Mediterranean diet increases adiponectin concentrations, decreases inflammation, and improves endothelial function (23). Moreover, a direct association between adiponectin concentrations and the Healthy Eating Index was detected in prediabetic Brazilian adults (64.7% women) (24).

A single food intervention of pistachios led to increased adiponectin concentrations and beneficial effects on the cardiometabolic profile of Asian Indians with metabolic syndrome (25). Grape consumption increased adiponectin concentrations in American adults with metabolic syndrome but without dyslipidemia (26).

Metabolic syndrome is characterized by insulin resistance, and must present at least 3 of the following risk factors: hyperglycemia, low plasma HDL cholesterol, hypertriglyceridemia, hypertension, and abdominal obesity (27). Metabolic syndrome increases the risk of DM2 and CVD (28) and is more common among Hispanic populations (29).

Garlic (*Allium sativum* L.) is known to be associated with a lower risk of hypertension and hypercholesterolemia. Despite these positive properties, consumption of fresh garlic as a usual component of the diet is limited by its negative properties that cause indigestion and because of its pungent odor. (30). The process of aging garlic has been demonstrated to eliminate the odor and maintain the antioxidant components of garlic (31).

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4 Abbreviations used: AdipoR1, adiponectin receptor 1; AdipoR2, adiponectin receptor 2; AdipoRon, adiponectin receptor agonist; CAD, coronary artery disease; CVD, cardiovascular disease; DM2, diabetes mellitus type 2; SNP, single-nucleotide polymorphism.

Aged garlic extract administered for 12 wk produced an increase in adiponectin concentrations in Colombian individuals with metabolic syndrome (32). One of the components of garlic, 1,2-vinyldithiin (1,2-DT), has anti-inflammatory properties in human preadipocytes (33). To explain these results, it has been proposed that there is a tight relationship between adiponectin and NO (14, 15), as adiponectin increases NO production (34), and NO up-regulates adiponectin production (35). Moreover, aged garlic extract restores NO bioavailability in cultured human endothelial cells (36).

Because the majority of the studies evaluating the role of nutritional intervention in concentrations of adiponectin are observational or small clinical trials, additional studies are needed to confirm the potential benefits of increasing adiponectin by nutritional interventions in the treatment and prevention of cardiovascular and metabolic diseases.

**Differences in Plasma Adiponectin Concentrations in Subjects with Metabolic Syndrome**

Although in the developed world the incidence of CVD is stabilizing or decreasing and prognosis is improving, the incidence of CVD is increasing in the developing world. These differences in the global epidemiologic profile of CVD may be due to diverse geographic, environmental, demographic, socioeconomic, and ethnic characteristics (37-40).

Ethnic differences in insulin resistance and cardiometabolic disease risk have been described and it has been proposed that these may be the result of differences in circulating adipokines and inflammatory markers associated with ethnic variations in obesity and body fat distribution (41). A study conducted in the United States demonstrated significant ethnic differences in adiponectin, showing that, compared with those in white Americans, adiponectin concentrations in African-American men and women, Japanese-American women, and native Hawaiian women were significantly lower. When adjusted for BMI at cohort entry, the differences between the lowest and highest values across ethnic groups decreased for all biomarkers except adiponectin in men, indicating that ethnic differences were only partially due to weight status (41). Another study conducted in healthy Canadian Aboriginal, Chinese, European, and South Asian adults found that South Asians had the greatest insulin resistance, followed by Aboriginals, Chinese, and Europeans. Plasma adiponectin concentrations were lower in Chinese and South Asians than in Aboriginals and Europeans, and adiponectin was inversely associated with insulin resistance. The authors concluded that ethnic-specific differences in adiponectin may account for the differences in insulin resistance (42).

It was observed that plasma adiponectin concentrations were lower for both Greenlandic Inuit boys and girls, who have a more adverse metabolic profile, than for Danish children. The differences remained after adjustment for body fat percentage, aerobic fitness, age, and puberty (43).

However, in a large study conducted in the United States that included 994 schoolchildren (47% boys and 53% girls; 12% African-American, 14% East Asian, 13% South Asian, 9% Caucasian, 45% Hispanic, and 7% other), there were no significant racial or ethnic differences in circulating concentrations of adiponectin, even when adjusted for age, sex, and body composition (44). This result contrasts with a previous study in adults that reported that circulating concentrations of Adiponectin and cardiometabolic diseases 423S
adiponectin were lower in South Asians even after adjusting for age, sex, and BMI (45).

To explain these contrasting results, it is interesting to consider the proposal that fetal undernutrition produces poor development of structural units such as nephrons, cardiomyocytes, and β pancreatic cells (46, 47). These adaptations during fetal programming produce a negative effect in adulthood if food is more abundant in the postnatal period. To support this proposal, it has been reported that individuals conceived during the period of hunger in Europe after World War II showed higher rates of obesity, dysglycemia, and CAD at age 50 y (48–50). Nutritional deficiencies during fetal programming through epigenetic mechanisms could affect the expression of genes that result in decreased synthesis of adiponectin (51).

More recently, several reports have contributed to supporting the view that subjects with metabolic syndrome had deficient maternal nutrition during fetal life (52–54). Also, it has been proposed that there are transgenerational effects of epigenetic changes experienced by the parents and/or grandparents (51). We have suggested that the populations of developing countries are more prone to developing cardiovascular and metabolic diseases at lower levels of abdominal obesity as a result of shorter exposure times to the new lifestyles associated with modernization (40, 55). The shorter the exposure time, the less adapted the population is, and the greater the risk of an inflammatory imbalance at lower levels of abdominal obesity. This phenomenon may be explained by epigenetic modifications in the visceral adipose tissue and, in consequence, a larger reduction in adiponectin concentrations in individuals in developing countries, which in turn increases their risk of DM2 and CVD. Although it is difficult to establish consistent regional differences, there appear to be considerable differences between developed and developing countries. In Latin America, a Brazilian study reported adiponectin values of 7.11 μg/mL (56), and we reported concentrations of 5.93 μg/mL in Colombia (32). In Australian women with metabolic syndrome, however, the values were 13.7 μg/mL (57), whereas in Indonesian women with metabolic syndrome, the values were much lower, at 4.9 μg/mL (58).

In the United States, a higher incidence of insulin resistance and DM2 has been reported in Latinos than in non-Latino whites (59, 60). Although this observation has been attributed, at least in part, to a higher rate of obesity in Latinos, insulin resistance and DM2 are more prevalent in Latinos than in whites, even after controlling for weight differences (61). Moreover, decreased adiponectin concentrations were found in Latino compared with non-Latino white patients with CVD risk (62). Lower adiponectin concentrations in the Latino group were independent of BMI and other factors known to affect adiponectin and seemed to account for the increased insulin resistance observed in this group (63). These findings in Latinos are similar to those from studies of adiponectin in other minority ethnic/racial groups in that adiponectin is lower in minority groups than in white populations (61).

Genetic Control of Metabolic Syndrome and Adiponectin

The familial nature of metabolic syndrome, the marked difference in the prevalence among various racial groups, and the differences in concordance rates between monozygotic twins clearly suggest that metabolic syndrome is under genetic control (64). A number of studies have reported that polymorphisms in the gene encoding adiponectin are associated with metabolic syndrome (65). A 2009 meta-analysis demonstrated that the adiponectin gene is a pleiotropic locus for metabolic syndrome and its components, potentially serving as an important pharmacologic target in the prevention and treatment of metabolic syndrome (66). The common single-nucleotide polymorphism (SNP) -11377 C.G (rs266729) has consequences on adiponectin gene expression (67), and has been associated with low concentrations of adiponectin in diverse ethnic groups (68) and higher prevalence of DM2 and coronary disease (69, 70).

In a multiethnic population in Canada (71), adiponectin concentrations were positively associated with HDL cholesterol and negatively associated with BMI, waist-to-hip ratio, TGs, glucose, insulin, and systolic and diastolic blood pressure. The rs266729 minor G allele was associated with lower adiponectin and higher HOMA-IR, but lost significance when adjusted for adiponectin concentration. The rs266729 SNP was associated with HOMA-IR to an extent that exceeded its effect on adiponectin concentration and it was not observed an interaction between the rs266729 SNP and ethnicity on adiponectin or HOMA-IR. In contrast, the SNP rs1260326 in Glucokinase Regulatory Protein was associated with HOMA-IR but not with adiponectin concentration. These results suggest that the association between rs266729 and lower serum adiponectin and increased insulin resistance may be causal. Moreover, in a recent report of eutrophic and obese Mexican children, it was found that adiponectin concentrations and metabolic syndrome components were inversely related, supporting the idea that this hormone could be a biomarker for identifying individuals with the risk of developing metabolic syndrome (72).

Potential Pathways to Increase Adiponectin

Recently, it was reported that an orally active small molecule that binds to and activates adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2) could ameliorate obesity-related diseases such as DM2 (73). This compound, named adiponectin receptor agonist (AdipoRon), bound to both AdipoR1 and AdipoR2 in vitro and showed very similar effects to adiponectin in muscle and liver, such as the activation of protein kinase ASM-activated and PPARΑ pathways, amelioration of insulin resistance, and glucose intolerance in mice fed a high-fat diet. These effects were completely obliterated in AdipoR1 and AdipoR2 double-knockout mice. Moreover, AdipoRon ameliorated diabetes in genetically obese rodent model db/db mice and prolonged the shortened lifespan of db/db mice on a high-fat diet (73). Thus, orally active agonists such as AdipoRon are a promising therapeutic approach for the treatment of obesity-related diseases such as metabolic syndrome and DM2.

Conclusions

Adiponectin appears to be an important molecule that is involved in limiting the pathogenesis of obesity-linked disorders and may have potential benefits in the treatment and prevention of CVD. Regional differences in adiponectin values may have an important role in the susceptibility of certain populations to CVD. However, there is a paucity of data to support this, and more research is required. Future research should investigate potential pathways to increase adiponectin concentrations in subjects at elevated cardiometabolic risk. In this context, the importance of the observation that nutritional interventions such as aged garlic extract can increase adiponectin and thus...


