The role of leptin/adiponectin ratio in metabolic syndrome and diabetes

Abstract: The metabolic syndrome comprises a cluster of cardiometabolic risk factors, with insulin resistance and adiposity as its central features. Identifying individuals with metabolic syndrome is important due to its association with an increased risk of coronary heart disease and type 2 diabetes mellitus. Attention has focused on the visceral adipose tissue production of cytokines (adipokines) in metabolic syndrome and type 2 diabetes mellitus, as the levels of the anti-inflammatory adipokine adiponectin are decreased, while proinflammatory cytokines are elevated, creating a proinflammatory state associated with insulin resistance and endothelial dysfunction. In this review, we will give special attention to the role of the leptin/adiponectin ratio. We have previously demonstrated that in individuals with severe coronary artery disease, abdominal obesity was uniquely related to decreased plasma concentrations of adiponectin and increased leptin levels. Leptin/adiponectin imbalance was associated with increased waist circumference and a decreased vascular response to acetylcholine and increased vasoconstriction due to angiotensin II. Leptin and adiponectin have opposite effects on subclinical inflammation and insulin resistance. Leptin upregulates proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6; these are associated with insulin resistance and type 2 diabetes mellitus. In contrast, adiponectin has anti-inflammatory properties and downregulates the expression and release of a number of proinflammatory immune mediators. Therefore, it appears that interactions between angiotensin II and leptin/adiponectin imbalance may be important mediators of the elevated risk of developing type 2 diabetes mellitus and cardiovascular diseases associated with abdominal obesity.

Keywords: adiponectin; angiotensin II; leptin; metabolic syndrome; type 2 diabetes.

Introduction

Metabolic syndrome (MetS) is one of the leading global public health concerns [1]. Its prevalence varies between 15% and 40% internationally [2] and is higher in the populations of developing countries [2, 3]. MetS comprises a cluster of cardiometabolic risk factors, its central features being insulin resistance (IR) and adiposity [1, 4]. The Adult Treatment Panel III (ATPIII) criteria of the National Cholesterol and Education Program (NCEP) for MetS are the presence of three of the following characteristics: dysglycemia, low plasma high-density lipoprotein cholesterol (HDL-C), increased triglycerides (TG), elevated blood pressure, and abdominal obesity (AO) [5]. The diagnosis of MetS has been harmonized internationally using the NCEP ATPIII criteria with the notable exception of cutoffs for AO for waist circumference, which differ by ethnicity, country [5], and region [6]. MetS is of concern due to its association with an increased risk of coronary heart disease (CHD), type 2 diabetes mellitus (DM2), and other cardiometabolic diseases [7, 8]. The concept of MetS is controversial, but the higher prevalence of this cluster of metabolic alterations in Latin America suggests that it is a useful nosographic entity in the context of Latin American medicine. Therefore, it is important that physicians recognize this syndrome in order to identify a particularly high-risk population, often underdiagnosed and undertreated [9]. We will review the possible mechanisms involved in the development of the MetS and DM2, with a particular emphasis on the role of leptin/adiponectin (L/A) ratio and its association with IR and low-degree inflammation.
Abdominal obesity and adipokine imbalance

It is well recognized that AO plays a central role in the development of MetS and contributes significantly to the progression of cardiovascular and metabolic diseases [10]. In a meta-analysis of studies assessing the impact of bodyweight on CHD, a five-unit increase in body mass index (BMI) was associated with a 29% increase in CHD risk [11]. However, it is still uncertain how much of this elevated risk is directly attributable to obesity alone and what the specific mechanisms are by which obesity (particularly AO) causes or accelerates atherogenesis.

There are a number of physiological and metabolic changes associated with obesity that may contribute to an increased risk of cardiovascular diseases (CVD). In recent years, attention has focused on the role of visceral adipose tissue due to the synthesis and release of a number of adipokines from adipocytes [12–14]. In MetS, increased visceral adipose tissue disturbs adipokine secretion and leads to a low-grade chronic inflammatory state mediated by the infiltration of macrophages into adipose tissue [14]. This inflammatory state is found to be associated with IR [15–17] and with atherosclerosis [14]. Visceral adipose tissue functions as a paracrine and an endocrine organ, secreting a number of adipokines, some of which are proinflammatory and atherogenic, such as leptin, tumor necrosis factor-α (TNF-α), resistin, interleukin-6 (IL-6), and fatty acid-binding protein 4, and others, which have anti-inflammatory, protective effects such as adiponectin [12, 13]. In MetS patients, serum adiponectin levels are decreased, while proinflammatory cytokines are elevated [18]. This imbalance in the inflammatory state leads to dysfunction of the endothelial cells, promoting the loss of their vasodilatory, antithrombotic, and antiatherogenic properties [19, 20], apparently a widespread biological response in humans [21]. The relationship between inflammation and MetS is supported by several studies [1, 18, 22], as is the association between increased visceral fat mass and MetS [23].

In this review, we pay particular attention to the interactions between AO and L/A ratio in CHD patients. We have examined these associations using an ex vivo model in which segments of internal mammary arteries were obtained from individuals with severe coronary artery disease (CAD) who subsequently underwent coronary artery bypass grafts. Patients were divided according to the presence of AO and matched by age, sex, glucose and insulin plasma levels, homeostatic model assessment (HOMA) index, lipid profile, tobacco and alcohol consumption, physical activity, and arterial blood pressure. We found that the presence of AO was uniquely related to decreased plasma concentrations of adiponectin and increased leptin levels (Figure 1) and was associated with a decreased vascular response to acetylcholine and an increased vasoconstriction in response to angiotensin II (Ang II). However, in these patients, plasma levels of

**Figure 1** Adiponectin, leptin and leptin/adiponectin ratio in patients with severe coronary artery disease divided by the presence of abdominal obesity.

- AO: Patients without abdominal obesity; +AO: Patients with abdominal obesity. Data presented as mean. Adiponectin: µg/dL; Leptin: ng/dL. Mann-Whitney-Wilcoxon test p<0.05.
other inflammatory markers evaluated, such as C-reactive protein (CRP), IL-6, and TNF-α, did not differ according to the presence or absence of AO [26]. Ang II is produced in adipocytes [25], and plasma levels of angiotensinogen and Ang II are positively associated with BMI [26]. Several studies in obese, insulin-resistant, or hypertensive animals and humans show that treatment with Ang II AT1 receptor antagonists reduces IR [27, 28]. Moreover, blocking the intracellular signals elicited by Ang II produces these effects that oppose the action of insulin on its target organs [29]. It is also proposed that the beneficial effects of AT1 receptor blockers on adipose tissue mass and IR in obesity could be related to the enhancement of adiponectin expression, the reduction of leptin expression, and the concomitant correction of the L/A imbalance [30].

The role of leptin in metabolic syndrome and diabetes

Leptin has an important role in the long-term regulation of body weight. It has also been proposed as an independent risk factor for CVD and as an important link between obesity and cardiovascular risk [31, 32]. Paradoxically, markedly increased plasma leptin levels were found in obese individuals, suggesting a resistance to its effects on target organs when produced excessively [33]. Increased leptin levels were correlated both with BMI and IR in DM2 patients [34–36]. IR was found to indirectly contribute to hyperleptinemia [37], and it has been reported that the hyperinsulinemia that frequently accompanies obesity is likely to result in increased obesogenic gene expression and higher plasma leptin levels [31]. Therefore, the association between leptin and insulin may simply reflect the size of adipose tissue stores [31]. The higher leptin levels generally observed in individuals with increased plasma insulin could be partially explained by a resistance to leptin. Chronically elevated leptin levels in obesity may result in decreased responsiveness of pancreatic β-cell receptors, leading to increased insulin secretion. In turn, the resulting hyperinsulinemia may exacerbate obesity and further increase leptin levels, resulting in a diabetogenic positive feedback loop [36, 37]. In support of this proposal, Uslu et al. [35] found a close relationship between insulin and leptin levels in DM2 patients. Moreover, this group observed that leptin levels were positively correlated with TG, lipoprotein (a) [Lp (a)], Apo-A1, glucose, systolic blood pressure and diastolic blood pressure levels, and negatively with HDL-C levels in DM2 patients. Also, it has been proposed that the increased levels of leptin observed in obesity deregulates blood pressure control and results in hypertension, suggesting that leptin may also be a potential promoter of hypertension [38].

Leptin may also have a role in the immune response via the stimulation of T-helper cell proliferation and production of proinflammatory cytokines as IL-6, which induce liver CRP synthesis. In addition, leptin produced in adipocytes may directly induce IL-6 production, resulting in further upregulation of hepatic CRP production [31]. Thus, serum leptin levels may be used as an integrated marker of adiposity, IR, and vascular dysfunction useful for cardiovascular risk stratification in clinical practice.

The role of adiponectin in metabolic syndrome and cardiometabolic diseases

Adiponectin, also referred to as ACRP30 and AdipoQ [39, 40], is an adipocyte-derived hormone abundantly present in human plasma, ranging between 3 and 30 μg/mL [39]. Adiponectin levels in plasma are negatively regulated by accumulation of visceral fat [41] and are, therefore, lower in more obese individuals [42]. Adiponectin has antiatherogenic, antidiabetic, and anti-inflammatory properties that are directly involved in obesity-related disorders. Moreover, clinical studies implicate hypoadiponectinemia in the pathogenesis of DM2 [43], CAD [44], and hypertension [45]. Hypoadiponectinemia has also been associated with left ventricular hypertrophy, which is accompanied by diastolic dysfunction [46].

Furthermore, adiponectin values may have good prognostic value in terms of CVD. High levels of adiponectin were associated with a decreased risk of CAD in male diabetic patients [47] and with cardiovascular outcomes in patients with end-stage renal failure [48]. A prospective study showed that high plasma adiponectin levels were associated with a lower risk of myocardial infarction in healthy men, independent of CRP level or glycemic status [49]. In addition, in patients with peripheral arterial disease, serum adiponectin was positively correlated with the ankle-brachial pressure index, maximum walking distance, and initial claudication distance [50], and in another study, serum levels were negatively correlated with the Fontaine stage [51].

Different pathophysiological mechanisms are implicated in the protective role of adiponectin against the genesis of cardiometabolic diseases. Adiponectin exerts an anti-inflammatory effect through the activation of its
three receptors (AdipoR1, AdipoR2, and T-cadherin) [52]. The activation of AdipoR1 and R2 results in increased hepatic and skeletal muscle fatty acid oxidation, increased skeletal muscle lactate production, reduced hepatic gluconeogenesis, increased cellular glucose uptake, and inhibition of inflammation and oxidative stress [53]. In vascular endothelial cells, activation of T-cadherin is protective against oxidative stress-induced apoptosis [54]. Several mechanisms have been suggested to explain the anti-inflammatory effects of adiponectin, including direct actions on inflammatory cells, actions on NF-κB, and interactions with TNF-α [52]. It has been demonstrated that adiponectin inhibits the expression of adhesion molecules in endothelial cells and inhibits smooth muscle cell proliferation. It also inhibits the differentiation of monocytes into macrophages and the formation of foam cells and secretion of TNF-α by macrophages [55–57]. Increased adiponectin levels are related to improvement in the differentiation of preadipocytes into adipocytes, a process that is usually impaired in obese subjects [58]. In addition, adiponectin increases endothelial nitric oxide secretion [59, 60]. 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 diseases. However, due to the problematic nature of supplementation of adiponectin, increasing adiponectin production may be a useful approach. The thiazolidinediones, for example, promote an increased secretion of adiponectin by activating PPAR-γ in adipocytes [61, 62]. Caloric restriction has also been shown to increase adiponectin levels and, in turn, confer resistance to myocardial ischemia-reperfusion injury [63]. Recently, a novel nonpharmacological therapeutic intervention, aged garlic extract, was found to increase adiponectin levels in individuals with MetS [64]. However, additional studies are needed to evaluate the potential benefits of increasing adiponectin in the treatment and prevention of cardiovascular and metabolic diseases.

**Leptin/adiponectin ratio in metabolic syndrome and diabetes**

As reviewed above, leptin and adiponectin have opposing effects on subclinical inflammation. Leptin upregulates cytokines such as TNF-α and IL-6 that are associated with IR in DM2 and is therefore considered as a proinflammatory cytokine. In contrast, adiponectin downregulates the expression and release of many proinflammatory immune mediators and exerts anti-inflammatory properties. Thorand et al. [37] suggested that leptin and adiponectin interact with each other in the modulation of DM2 risk, but that adiponectin is likely to have a stronger association with DM2 risk. Other groups also found an inverse relationship between leptin and adiponectin in DM2 patients [36] and in patients with obesity and CAD [24]. Although leptin or adiponectin were separately associated with the risk of MetS, DM2, and CAD, the association of DM2 risk with the L/A ratio was stronger than with leptin or adiponectin alone [24, 65]. These results suggest that the L/A ratio may be a useful index for IR in clinical practice and a good indicator for assessing the effectiveness of antidiabetic therapy. Indeed, it has been reported that both the calculated HOMA-IR index and the L/A ratio can be used to identify IR.

**Regional differences in plasma adiponectin levels in subjects with metabolic syndrome**

While in the developed world the incidence of CVD is stabilizing or decreasing [3, 66, 67] and prognosis is improving [3, 68], incidence is increasing in the developing world. These differences in the global epidemiological profile of CVD may be due to diverse geographical, environmental, demographic, socioeconomic, and ethnic characteristics [3]. We suggest that one of the explanations for these differences is that the populations of developing countries are more prone to develop cardiovascular and metabolic diseases at lower levels of AO as a result of shorter exposure times to the new lifestyles associated with modernization [69]. The shorter the exposure time, the less adapted the population and the greater the risk of an inflammatory imbalance at lower levels of AO. We propose that this phenomenon may produce epigenetic modifications in the visceral adipose tissue and, in consequence, a larger reduction in adiponectin levels in individuals in developing countries, in turn, increasing their risk of DM2 and CVD.

To evaluate this hypothesis, we reviewed studies that assessed adiponectin plasma values in subjects with MetS and then examined potential regional differences. We reviewed only English and Spanish language articles related to the association between adiponectin and MetS published since January 2002 in the Medline database. Our initial search terms were *metabolic syndrome* and *adiponectin*; we then conducted the same search as MESH terms.
We included cross sectional and cohort studies that reported adiponectin values in adults (≥18 years) with MetS. We included abstracts only when they presented unique data not already included in our review from published studies. We only included studies in which adiponectin levels were determined by ELISA and RIA. Studies were excluded from our review if they were clinical trials or case-control studies, as these types of research studies did not account for representative samples of the general population. Moreover, if the studies included postpartum women or patients with any additional condition, such as bipolar affective disorder, rheumatoid arthritis, chronic hepatitis, and chronic obstructive pulmonary disease, they were also excluded. Articles that we could not get access to were also excluded. One hundred fifty-eight articles were identified with the general search and 195 using the MESH terms, 23 of which met our inclusion criteria. Two investigators independently reviewed titles, abstracts, and full articles to determine whether studies met the inclusion criteria. Moreover, the two investigators independently abstracted data on study design; numbers of patients assessed, evaluated population, method of adiponectin quantification, and reported levels of plasma adiponectin (Table 1). Conflicting assessment between reviewers were resolved through discussion and review.

We found evidence of worldwide differences in adiponectin levels in subjects with MetS. While it is difficult to establish consistent regional differences (Table 1), there appears to be considerable differences between developed and developing countries within the same region. In Latin America, a Brazilian study reported adiponectin values of 7.11 µg/mL [70], and we observed levels of 5.93 µg/mL in Colombia [64], but in Australian women with MetS, the values were 13.7 µg/mL [71], while in Indonesian MetS women, the values were much lower, 4.9 µg/mL [72]. Moreover, important differences between genders were found: women showing higher levels of adiponectin than men when compared within the same country. In the United States, a higher incidence of IR and DM2 has been reported in Latinos, compared to non-Latino whites [73, 74]. Although this observation has been attributed, at least in part, to a higher rate of obesity in Latinos [73], IR and DM2 are more prevalent in Latinos compared to whites even after controlling for weight differences [74, 75]. Moreover, decreased adiponectin levels were found in Latino compared to non-Latino White patients with CVD risk. Lower adiponectin levels in the Latino group were independent of BMI and other factors known to affect adiponectin and seemed to account for the increased IR observed in this group [76]. 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 White populations [77]. Ethnic and racial minority groups (including Latinos) participating in the Diabetes Prevention Program study were also reported to have lower baseline adiponectin levels than non-Latino White participants [75].

In this review, we are not able to neither establish a causative association between low adiponectin and the progression of cardiovascular and metabolic diseases nor conclusively demonstrate regional differences in adiponectin levels. Our review, however, does appear to suggest a developed vs. developing country patterning of adiponectin levels. We are not able to ascertain whether the lower adiponectin values observed in subjects with MetS from developing countries were related to genetic and or environmental factors. Moreover, it is noteworthy that values of different parameters can differ from one laboratory to another; therefore, a possible bias can be present. Furthermore, the contribution of adiponectin to regional differences in cardiometabolic disease incidence has not been evaluated.

**Expert opinion**

The MetS, with IR and adiposity as its central features, is associated with an increased risk of CHD, DM2, and other cardiometabolic diseases. While there are a number of adipokines involved in the proinflammatory state caused by AO, interactions between Ang II and L/A imbalance, in particular, appear to have an important role in the metabolic alterations related to visceral adiposity and in the increased risk of developing DM2 and CVD associated with AO. Leptin and adiponectin have opposing effects on subclinical inflammation and IR. Leptin upregulates proinflammatory cytokines, while adiponectin has anti-inflammatory properties. Moreover, L/A imbalance is associated with increased vasoconstriction due to Ang II. To date, there are few therapeutic options to improve the L/A imbalance, and more research is warranted.

**Outlook**

We anticipate an increasing interest in producing epigenetic modifications of visceral adipose tissue, either by pharmacological therapy or dietary interventions, with the purpose of improving the L/A imbalance in patients at elevated cardiometabolic risk. Moreover, pharmacological interventions using adiponectin supplements or analogs...
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<tr>
<th>Author</th>
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Adiponectin values evaluated by ELISA.
to examine the potential benefits of this adipokine in the treatment and prevention of cardiovascular and metabolic diseases may be conducted. The increasing burden of noncommunicable diseases in the developing world, such as in Latin America and South Asian countries and the higher sensitivity of these populations to CVD at lower levels of AO, will stimulate a particular interest in studying interactions and interventions in these populations.

**Highlights**

- In patients with CAD, AO is associated with decreased plasma concentrations of adiponectin and increased leptin levels and with a decreased vascular response to acetylcholine and an increased vasoconstrictor in response to Ang II.
- The 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, and more research is required.
- Future research should investigate potential pathways to improve the L/A ratio, especially by increasing adiponectin levels in subjects at elevated cardiometabolic risk.
- Epigenetic modifications of the visceral adipose tissue could become an important mechanism for improving the L/A ratio.

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