Adiponectin-leptin ratio: A promising index to estimate adipose tissue dysfunction. Relation with obesity-associated cardiometabolic risk

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ABSTRACT

Obesity is currently the most extended metabolic disturbance worldwide favoring the development of cardiometabolic alterations such as type 2 diabetes, hypertension, and dyslipidemia. Obesity and the metabolic syndrome (MS) are characterized by an increase in circulating leptin concentrations, in parallel to a decrease in blood levels of adiponectin. Consequently, the adiponectin/leptin ratio has been suggested as a maker of adipose tissue dysfunction. This emerging biomarker correlates with insulin resistance better than adiponectin or leptin alone, or even HOMA and is decreased with increasing number of metabolic risk factors having been proposed as a predictive marker for the MS. Moreover, the adiponectin/leptin ratio is negatively correlated with markers of low-grade chronic inflammation. In this sense, an increase in this ratio has been related with reduced atherosclerosis risk as well as with a decreased risk of some types of cancer in epidemiological studies. In this commentary we propose new cutoffs to estimate obesity- and MS-associated cardiometabolic risk according to the adiponectin/leptin ratio and discuss different therapeutic strategies to increase this promising biomarker of metabolic risk.

Introduction

Obesity is currently the most extended metabolic disturbance worldwide [1,2]. It has been recently reported that the prevalence of obesity has doubled in more than 70 countries since 1980, with the rate of increase in childhood obesity being, in general, greater than that observed in adults [1]. Obesity favors the development of cardiometabolic alterations such as type 2 diabetes, hypertension, and dyslipidemia, threatening the health improvements achieved in the last decades and leading to an increase in morbidity [3,4]. Growing evidence highlights that obesity is a disorder of the energy homeostasis system, rather than simply resulting from the passive accumulation of excess adiposity [5].

Dysfunctional adipose tissue in obesity

Obesity is defined medically as a condition of abnormal or excessive fat accumulation in adipose tissue, of sufficient extent to produce adverse health consequences [6]. However, the molecular mechanisms involved in the development of obesity and the expansion of adipose tissue are not well understood [7]. Only a couple of decades ago adipose tissue was considered a passive organ for insulation and storage of excess energy in the form of triglycerides [8]. In the last years, however, adipose tissue has emerged as an extremely active endocrine organ, based on its ability to secrete a plethora of biologically active adipokines, such as leptin, adiponectin, tumor necrosis factor-α (TNF-α), or interleukin-6 (IL-6), which are known to be involved in a wide variety of physiological processes [7]. These adipokines play an important role in the pathophysiological link between increased adiposity and cardiometabolic alterations [7,9,10]. Leptin is primarily produced by adipose tissue in proportion to the amount of body fat stores being involved in the regulation of food intake, neuroendocrine function, reproduction, angiogenesis, and blood pressure, among others [11,12]. Circulating leptin levels correlate closely with the total amount of body fat being, therefore, increased in obese individuals [13]. However, obese subjects
exhibit an impaired response to leptin’s anorectic effects, suggestive of leptin resistance [14]. Adiponectin is also secreted almost exclusively by adipose tissue [15]. Adiponectin has cardioprotective functions, protecting against insulin resistance and excessive hepatic lipid accumulation, and exerting also anti-inflammatory effects [16,17]. Adiponectin expression in adipose tissue and serum adiponectin levels are decreased in obese patients. Therefore, obesity-associated alterations in these adipokines, leptin and adiponectin, are playing major contributions in the development of a dysfunctional adipose tissue, characterized by unresolved inflammation, besides to inappropriate extracellular matrix remodeling and impaired angiogenesis [18].

**Adiponectin/Leptin ratio as estimator of dysfunctional adipose tissue**

Obesity, as described above, is characterized by an increase in circulating leptin concentrations, in parallel to a decrease in blood levels of adiponectin, which reflects the obesity-associated alterations in adipose tissue adipokinome. Consequently, the adiponectin/leptin ratio has been suggested as a marker of adipose tissue dysfunction [19]. This emerging biomarker correlates negatively with BMI [20] as can be depicted in Fig. 1. Moreover, it is strongly associated with surrogate measures of insulin resistance such as the homeostatic model assessment (HOMA), the hyperinsulinemic-euglycemic clamp and the quantitative insulin sensitivity check index (QUICKI) in different cohorts [20-23]. Furthermore, it has been stated that the adiponectin/leptin ratio correlates with insulin resistance better than adiponectin or leptin alone, or HOMA even in subjects with hyperglycemia [22,23]. Reportedly, this ratio decreases with increasing number of cardiometabolic risk factors reflecting the functionality of adipose tissue [19]. This promising biomarker is significantly reduced in patients with the metabolic syndrome (MS) [20,24] decreasing with increasing number of metabolic risk factors for MS [19,25,26], having been proposed as a predictive marker for the MS [19]. Moreover, the adiponectin/leptin ratio may constitute also a biomarker of insulin resistance during pregnancy [27] and of the presence of metabolic derangements in polycystic ovary syndrome [28]. Importantly, a recent study has shown that besides fitness and waist circumference the only other variable with an important independent contribution to predict insulin sensitivity in multiple regression models was adipose tissue dysfunction as reflected by the adiponectin/leptin ratio [29].

The adiponectin/leptin ratio correlates with BMI also in adolescents as well as with QUICKI, HOMA and insulin levels [30]. Interestingly, the adiponectin/leptin ratio has been reported to have clinical utility in children with diabetes in the discrimination between type 1 and type 2 diabetes [31]. The change in the adiponectin/leptin ratio correlated with the delta in body mass, BMI as well as body fat mass and percentage in adolescents one year after weight loss following a multicomponent therapy for MS [32]. Furthermore, an increase in this ratio has been reported to be an independent predictor of the reduction in carotid intima-media thickness, a marker of subclinical atherosclerosis, in obese adolescents after weight loss [33].

Adipose tissue dysfunction, characterized by proinflammatory macrophage polarization, altered adipokine profile, insulin resistance and hypoxia, has been related with cancer development [34]. In this sense, an elevated adiponectin/leptin ratio as a marker of a reduction in adiposopathy is reportedly associated with the protective effect of intermittent calorie restriction on mammary tumorigenesis in mice [35]. Moreover, an increased adiponectin/leptin ratio has been associated with reduced risk of endometrial cancer as evidenced by a meta-analysis of epidemiologic studies [36].

Our group has recently published a couple of studies suggesting that mice and patients with adipose tissue dysfunction, characterized by a lower secretion of adiponectin in relation to leptin levels, have an increased cardiometabolic risk as reflected by raised systemic oxidative stress.
and inflammation [10,24]. We showed that adiponectin concentrations were decreased in patients with the MS showing a significant negative correlation with markers of systemic inflammation and oxidative stress. Furthermore, the adiponectin/leptin ratio was negatively correlated with systemic inflammation [24].

In the study performed in humans, we aimed to analyze whether the adiponectin/leptin ratio was a good proxy of inflammation and oxidative stress associated with the presence of the MS. Subjects with the MS exhibited increased levels of thiobarbituric acid reactive substances (TBARS), suggesting higher levels of systemic oxidative stress, as compared to individuals without the MS, as well as increased levels of C-reactive protein (CRP), serum amyloid A (SAA) and osteopontin (OPN), well-known markers of obesity-associated inflammation [13,37,38]. Importantly, we observed a negative correlation of the adiponectin/leptin ratio with circulating concentrations of CRP and SAA. We have now extended the number of subjects included in that analysis by adding 31 more additional subjects finding an even stronger negative association of the adiponectin/leptin ratio with the circulating levels of CRP (Fig. 2) This indicates that a dysfunctional adipose tissue, evidenced by a low adiponectin/leptin ratio, is clearly contributing to the low-grade chronic inflammation associated with the MS. Therefore, the adiponectin/leptin ratio may be used as an estimator of obesity- and MS-associated cardiometabolic risk.

**Clinical usefulness of the adiponectin/leptin ratio**

In our study, a low adiponectin/leptin ratio was related with increased levels of markers of inflammation such as CRP and SAA. Accordingly, a dysfunctional adipose tissue as suggested by a low adiponectin/leptin ratio may express a hallmark of obesity and the MS with increased proinflammatory factors as potential mediators in its ethiopathogenesis [24]. Moreover, given that both adipokines, leptin and adiponectin, are involved in the regulation of lipolysis [39], a decrease in the adiponectin/leptin ratio may be also reflecting alterations in this process further contributing to the obesity-associated metabolic disturbances. Furthermore, alterations in adiponectin and leptin levels have been proposed as potential mechanisms to explain the apparently less harmful metabolic profile of metabolically healthy obese subjects as compared to metabolically unhealthy obese individuals [9,40].

Since the adiponectin/leptin ratio reflects the functionality of adipose tissue, this ratio may be clinically useful to identify subjects susceptible to cardiometabolic diseases [19,24,41]. We herein propose tentative cutoff points that may define cardiometabolic risk according to the adiponectin/leptin ratio. Although methodological considerations regarding different levels of leptin and adiponectin depending on the measurement method employed have to be stressed, in particular regarding adiponectin quantification [42], we considered that an adiponectin/leptin ratio over 1.0 (with adiponectin concentrations expressed in μg/mL and leptin levels in ng/mL) should be considered as normal, a ratio between 0.5 and 1.0 may be indicating moderate-medium increased risk, and a ratio below 0.5 suggests a severe increase in cardiometabolic risk. It has to be taken into account that a prolonged fast may decrease leptin concentrations without relevant changes in the amount of body fat [11]. Therefore, these cutoffs should be applied for habitual fasting conditions. Large epidemiological studies will be needed to validate these proposed cutoffs.

Therapeutic strategies aimed at increasing the adiponectin/leptin ratio have been proposed, in particular in the context of the prevention of some types of cancer [41]. Four possible approaches may be used to try to increase the adiponectin/leptin ratio. The first strategy is weight loss. It is well known that dietary restriction and weight loss increase adiponectin levels and reduce leptin concentrations, which render an increase in the adiponectin/leptin ratio [43]. The weight-loss induced increase

![Figure 2. Scatter diagram showing the negative correlation found between the adiponectin/leptin ratio and the circulating concentrations of the proinflammatory marker CRP. Pearson’s correlation coefficient and P value are indicated. CRP was logarithmically transformed due to its non-normal distribution. Data correspond to the same 140 subjects included in reference [24] plus 31 additional individuals.](image-url)
in the adiponectin/leptin ratio has been related, as commented above, with reduced atherosclerosis risk in obese adolescents [33]. The second strategy is physical activity. Exercise has been reported to increase and reduce adiponectin and leptin concentrations, respectively, although a different impact may be produced depending on the type of exercise (endurance vs resistance exercise) [44]. The elicited changes will produce an increase in the adiponectin/leptin ratio that might, for example, decrease the risk for postmenopausal breast cancer [45]. The third approach is to change diet composition. Daily intake of fish or omega-3 supplementation, as well as fiber supplementation increase adiponectin concentrations [46]. Likewise, diets rich in fish and omega-3 polyunsaturated fatty acids are associated with lower plasma leptin levels [47]. Therefore, changes in diet composition may be used to increase the adiponectin/leptin ratio. Finally, the adiponectin/leptin ratio may be raised by pharmacotherapy. Regarding leptin, pharmacological interventions may be more focused on restoring leptin sensitivity as a therapeutic approach [48], which in the long term will translate into a reduction in obesity and, therefore, a decrease in leptin levels, although some drugs such as metformin or peroxisome proliferator-activated receptor-γ (PPARγ) agonists (thiazolidinediones) and PPARα agonists (fibrates) may reduce leptin levels [47]. Circulating adiponectin concentrations may be increased by several drugs, such as statins, angiotensin converting enzyme inhibitors, as well as PPARγ and PPARα agonists [49]. Statins, for example, may increase the adiponectin/leptin ratio exerting protective effects against the development of Alzheimer’s disease in mice [50].

Concluding remarks

Obesity and MS are characterized by increased and decreased levels of leptin and adiponectin, respectively. This translates in a reduction in the adiponectin/leptin ratio which is indicative of a dysfunctional adipose tissue. This ratio is highly and negatively correlated with markers of low-grade chronic inflammation emerging as an interesting and useful estimator of obesity- and MS-associated cardiometabolic risk. Therapeutic strategies aimed at improving this dysfunctional adipokine secretion profile in adipose tissue, denoted by a low adiponectin/leptin ratio, may render a lower proinflammatory profile and, consequently, a lower cardiometabolic risk.

Abbreviations

| Acronym | Definition                                |
|---------|-------------------------------------------|
| BMI     | body mass index                           |
| CRP     | C-reactive protein                        |
| HOMA    | homeostatic model assessment              |
| IL-6    | interleukin-6                             |
| MS      | metabolic syndrome                        |
| OPN     | osteopontin                               |
| PPARγ   | peroxisome proliferator-activated receptor-γ |
| PPARα   | peroxisome proliferator-activated receptor-α |
| QUICKI  | quantitative insulin sensitivity check index |
| SAA     | serum amyloid A                           |
| TBARS   | thiobarbituric acid reactive substances    |
| TNF-α   | tumor necrosis factor-α                    |

Disclosure of potential conflict of interest

No potential conflicts of interest were disclosed.

Acknowledgements

This work was supported by the project grants PI14/00950 and PI16/01217 integrated in the Plan Estatal I+D+i 2013–16 from the Spanish Instituto de Salud Carlos III–Subdirección General de Evaluación y Fomento de la investigación–FEDER and by Centro de Investigación Biomédica en Red Fisiopatología de la Obesidad y Nutrición, CIBEROBN, ISCIII, Spain.

Funding

Instituto de Salud Carlos III, Spain ID: PI14/00950
Instituto de Salud Carlos III, Spain ID: CIBEROBN
Instituto de Salud Carlos III, Spain ID: PI16/01217

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