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Hypoadiponectinemia is associated with blood pressure increase in obese insulin-resistant individuals

Emilio A. Francischetti[a,*], Bruno M.J. Celoria[a], Stenio Fernando Pimentel Duarte[a,b], Elizabeth Goes da Silva[a], Isabel Jereissati Santos[a], Pedro H. Cabello[c], Virginia A. Genelhu[a]

[a]*Hypertension Clinic, Laboratory of Clinical and Experimental Pathophysiology (CLINEX), School of Medicine, Rio de Janeiro State University, RJ CEP 22221-090, Brazil*
[b]*Service of Human Genetics (SERVGEN), Department of Cellular Biology and Genetics, Roberto Alcântara Gomes Biology Institute, Rio de Janeiro State University, Brazil*
[c]*Human Genetics Laboratory, Oswaldo Cruz Institute, Ministry of Health, Rio de Janeiro, RJ, Brazil*

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Abstract

Adiponectin is a major adipocytokine and has been considered as an independent risk factor for arterial hypertension. Most studies on the subject have been restricted to biracial (white-black) and Asian groups. The present report examined whether adiponectin affects blood pressure in a sample of untreated obese Brazilians of multiethnic origin. Fasting plasma adiponectin and serum insulin were determined by radioimmunoassay. Insulin resistance was estimated by homeostatic model assessment of insulin resistance (HOMA-IR). Blood pressure was recorded using Dinamap 1846 (Critikon, Tampa, FL). Adiponectin was significantly lower in obese hypertensive individuals than in obese normotensive ones. Blood pressure, insulin, and HOMA-IR were significantly higher in obese hypertensive than in obese normotensive individuals. Plasma adiponectin was negatively associated with waist-to-hip ratio, blood pressure, insulin, and HOMA-IR. The comparison of obese individuals who markedly differed in their HOMA-IR (> vs ≤2.71) showed that the association of adiponectin and blood pressure remained significant only in obese insulin-resistant individuals, whose adiponectin showed a positive association with high-density lipoprotein cholesterol. Stepwise regression analysis revealed that HOMA-IR, adiponectin, body mass index, and age independently affected the risk for increased systolic blood pressure, with HOMA-IR the strongest of them all. Finally, when patients were stratified into tertiles of HOMA-IR and further classified according to the 50th percentile of adiponectin (≤ vs >6. 5 μg/mL), a 3 × 2 analysis of variance showed an independent contribution of adiponectin in the variation of mean arterial pressure. These results support the notion that HOMA-IR and adiponectin independently predict blood pressure variation in obese insulin-resistant Brazilians.

1. Introduction

Hypertension is an important public health problem in different regions of the world because of its high prevalence and concomitant risks of cardiovascular and renal diseases [1]. The increasing prevalence of hypertension has occurred in conjunction with a dramatic increase in the prevalence of overweight and obesity. Data from the National Health and Nutrition Examination Survey have shown a strong linear relationship between body mass index (BMI) and systolic and diastolic blood pressures [2]. Furthermore, obese hypertensive (OH) patients have higher triglyceride (TG) levels, insulin resistance, and glucose intolerance as compared with normotensive individuals [3].

Adipose tissue produces and secretes many bioactive substances [4-7]. Dysregulated production of such substances, known as *adipocytokines*, is associated with the pathophysiology of obesity-related disorders, including hypertension [8]. Adiponectin is a major adipocytokine exclusively synthesized by the adipose tissue. The plasma concentration of that protein is decreased in patients with

* Corresponding author. Internal Medicine, Rio de Janeiro State University-UERJ, Laboratory of Clinical and Experimental Pathophysiology-CLINEX, Rio de Janeiro, CEP 22221-090, Brazil. Tel.: +55 21 2587 6836; fax: +55 21 2254 3800.
E-mail address: francischetti@globo.com (E.A. Francischetti).

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obesity [9], type 2 diabetes mellitus [10], and coronary artery disease [11].

Recently, hypoadiponectinemia has been considered as an independent risk factor for arterial hypertension in lean individuals [12] and in young men with high-normal blood pressure [13]. Results from the Bogalusa Heart Study have shown that adiponectin levels have a negative association with insulin resistance and visceral obesity. In that community-based sample, adiponectin levels also decreased significantly with the increasing number of metabolic syndrome risk factors, including hypertension [14].

Most studies investigating the role of adiponectin in insulin resistance, hypertension, and other surrogate end points for atherosclerosis have been conducted in biracial (black-white) and Asian groups [12-14]. Based on this background, we proposed to investigate, in a sample of normotensive and hypertensive obese Brazilians of multiethnic origin, whether adiponectin independently affects blood pressure and to assess its association with the variation in metabolic syndrome components.

2. Methods

A total of 310 individuals aged 18 to 71 years were selected among the patients of the Hypertension Clinic (CLINEX) of the Rio de Janeiro State University from 2002 to 2003 as part of an ongoing study on the mechanistic aspects involved in blood pressure variation in overweight and obese individuals. Ethnicity was categorized as white, African ascent, and mulattos (persons with a known family history of admixture between African-descent and white populations). *Hypertension* was defined as a systolic blood pressure ≥140 mm Hg and/or a diastolic blood pressure ≥90 mm Hg, according to *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)* [15].

After undergoing routine blood chemistries, urinalysis, electrocardiography, echocardiography, duplex Doppler ultrasonography of renal arteries, and endocrine evaluation, the patients with severe and secondary forms of hypertension and those with any evidence of complication of endocrine, metabolic, cardiovascular, cerebrovascular, and renal diseases were excluded.

The patients were instructed to stop using any medication that could affect blood pressure levels or insulin sensitivity at least 2 weeks before entering the study.

Ninety-six individuals (25 men and 71 women; mean age, 42.84 ± 11.95 years; BMI, 37.52 ± 7.36 kg/m^2) formed the study sample, of which 61 were normotensive and 35 were hypertensive. Fifty-one (53.1%) subjects had normal glucose plasma levels, 29 (30.2%) had impaired fasting glucose, and 16 (16.7%) had type 2 diabetes mellitus, according to the guidelines of the American Diabetes Association [16].

They were also put on a diet containing approximately 120 mmol of sodium and 75 mmol of potassium per day for at least 1 week before the study. The nutrient intake was assessed through 2 self-reporting tools: the semiquantitative food frequency questionnaire and the 3-day dietary record. Before the study, written informed consent was obtained from each participant. The study protocol was approved by the Committee on Ethics and Research of the Pedro Ernesto University Hospital.

2.1. Clinical features

Blood pressure was recorded by using a Dinamap 1846 (Critikon, Tampa, FL) automated sphygmomanometer after a resting period of at least 10 minutes in the sitting position. An appropriate arm cuff was used. Blood pressure was measured on the dominant arm, every 3 minutes for 15 minutes, in a room at a constant temperature of 22°C to 24°C. The first value was discarded, and the mean of the last 4 readings was used in the analysis. Mean arterial pressure was calculated as diastolic pressure plus one third of pulse pressure. Height and weight were measured following standardized procedures, and BMI was calculated. Waist-to-hip ratio (WHR) was used as an indicator of central adiposity. Anthropometric measurements were taken twice, and the mean values were used in all analyses. All blood samples were collected after a 12-hour fasting period. Radioimmunoassay was used to determine plasma adiponectin and insulin (double-antibody solid-phase enzyme immunoassay; Linco Research, St Charles, MO). Plasma samples for these assays were stored at −80°C. The sensitivity of the insulin radioimmunoassay was 1.1 mU/mL; and the intra- and interassay coefficients of variation were 4.4% and 6.0%, respectively. The intra- and interassay coefficients of variation for adiponectin were 3.9% and 8.5%, respectively. Fasting plasma glucose was determined by use of the glucose oxidase method. The insulin resistance status was assessed by the homeostasis model assessment of insulin resistance (HOMA-IR) index (ie, serum insulin [in milliunits per milliliter] × plasma glucose [in millimoles per liter]/22.5) [17]. *Insulin resistance* was defined as HOMA-IR ≥2.71, according to the threshold value obtained from a Brazilian population sample of multiethnic origin [18].

Serum lipid profiles, including total cholesterol, TG, and high-density lipoprotein cholesterol (HDL-C), were estimated by enzymatic methods. The other parameters were assessed by routine techniques.

2.2. Statistical analysis

Data were expressed as mean ± SD. A P value < .05 was considered statistically significant and was adjusted for covariates when appropriate. Statistical analysis of the results was performed using the t test when OH and obese normotensive (ON) individuals were compared. Linear relationships among variables were computed by Pearson correlation coefficients. Values of TGs, insulin, adiponectin, and HOMA-IR were log transformed in the analyses to improve normality.

A multiple linear stepwise regression analysis was performed to evaluate the independent contribution of age, sex, BMI, WHR, adiponectin, and HOMA-IR to the variance in systolic, diastolic, and mean arterial pressures. To clarify the additional contribution of adiponectin to changes in blood pressure values in addition to HOMA-IR, the individuals were stratified into HOMA-IR tertiles and further classified on the basis of the 50th percentile of the adiponectin level (≤ vs >6.5 μg/mL). Differences between groups were tested by analysis of variance followed by the Student-Newman-Keuls test. All statistical analyses were performed with SPSS, version 14.0 (SPSS Lead Technologies Station, Chicago, IL), and Prism, version 4.05 (GraphPad Software, San Diego, CA).

3. Results

Plasma adiponectin concentrations were significantly lower in OH patients when compared with those in ON individuals, irrespective of sex and age. In contrast, systolic, diastolic, and mean arterial pressures; BMI; waist circumference; and insulin levels, as well as HOMA-IR were significantly greater in OH (n = 35; 23 women; age, 43.1 ± 11.7 years) than in ON (n = 61; 48 women; age, 42.7 ± 12.2 years) individuals (Table 1). No significant difference in the adiponectin levels was observed among patients with normal glucose levels and those with impaired fasting glucose and type 2 diabetes mellitus.

In the group as a whole, a negative and significant correlation of plasma adiponectin concentration was observed with WHR; systolic, diastolic, and mean arterial pressures; and HOMA-IR. The HOMA-IR was significantly and directly correlated with blood pressure values (Table 2). There was also a negative and significant correlation between plasma adiponectin levels and insulin ($r = -0.24$, $P = .02$). In addition, a significant correlation was observed between insulin and systolic, diastolic, and mean arterial pressures ($r = 0.42$, 0.5, and 0.5, respectively; $P < .0001$). These correlations persisted after adjustments for BMI, waist circumference, age, and sex.

All individuals enrolled in the study were divided into 2 groups: with and without insulin resistance. Ninety-seven percent (n = 34) of the OH patients and 74% (n = 45) of the ON individuals were characterized as insulin resistant (HOMA-IR ≥2.71). The correlation of plasma adiponectin concentration and blood pressure remained significant only in these insulin-resistant individuals, both OH and ON (Fig. 1).

The variables that were significantly different in OH compared with ON individuals were selected as confounding factors. Stepwise linear regression analysis revealed that among the confounding factors, HOMA-IR, BMI, adiponectin, and age independently affected the risk for increased systolic blood pressure, explaining a total of 34.8% of the variance in that measure (Table 3). Fig. 2 shows that although HOMA-IR contributed to changes in mean arterial pressure, adiponectin concentration also had a statistically significant and independent impact on the hemodynamic variable. However, the interaction term between adiponectin values and HOMA-IR regarding their impact on blood pressure values was not significant.

The relative frequencies of subjects of white ascent, African ascent, and mulattos were 35.4%, 7.3%, and 51.3%, respectively. Ethnicity could not be determined in 6% of the individuals. Despite these differences, ethnicity did not seem to have influenced the results of the present

Table 1
Clinical characteristics of hypertensive and normotensive subjects

Clinical characteristics	Normotensive (n = 61)	Hypertensive (n = 35)
BMI (kg/m^2)	36.6 ± 5.7	39.2 ± 9.2
WHR	0.91 ± 0.1	0.93 ± 0.1
Waist circumference (cm)	108.2 ± 11.4	113.4 ± 16.6
Glucose (mg/dL)	103.5 ± 30.2	105.3 ± 19.8
TGs (mg/dL)	144.3 ± 86.9	164.2 ± 90.9
Total cholesterol (mg/dL)	198.3 ± 49.2	198.7 ± 37.1
HDL-C (mg/dL)	46.7 ± 11.1	42.7 ± 9.4
LDL-C (mg/dL)	122.7 ± 39	123.2 ± 34.8
Creatinine (mg/dL)	0.80 ± 0.14	0.83 ± 0.26
Systolic blood pressure (mm Hg)	119.3 ± 10	146.6 ± 11.3 *
Diastolic blood pressure (mm Hg)	76.3 ± 8.5	92.6 ± 8.1 *
Mean arterial pressure (mm Hg)	90.9 ± 8.3	109.7 ± 7.7 *
Insulin (mU/L)	18.2 ± 8.6	28.1 ± 12.6 *
Adiponectin (μg/mL)	7.4 ± 3.2	5.5 ± 2.7 **
HOMA-IR	4.7 ± 3.2	7.3 ± 4.1 **

Results are expressed as mean ± SD. All variables were adjusted for sex and age. LDL indicates low-density lipoprotein.

* $P < .0001$.

** $P < .01$.

Table 2
Pearson correlation coefficients between risk factor variables and adiponectin and HOMA-IR

Variables	Adiponectin		HOMA-IR	
	Total sample (n = 96)	Insulin resistant (n = 79)	Total sample (n = 96)	Insulin resistant (n = 79)
BMI (kg/m^2)	0.09	0.07	0.29 *	0.25 **
WHR	−0.20 **	−0.07	0.26 *	0.31 *
Mean arterial pressure (mm Hg)	−0.29 *	−0.28 *	0.45 ***	0.33 *
Systolic blood pressure (mm Hg)	−0.32 *	−0.31 *	0.40 ***	0.24 **
Diastolic blood pressure (mm Hg)	−0.23 **	−0.22 **	0.44 ***	0.36 *
HDL-C (mg/dL)	0.18	0.26 **	−0.23 **	−0.25 **
HOMA-IR	−0.20 **	−0.24 **	–	–
Glucose (mg/dL)	0.08	0.11	0.52 ***	0.52 ***

Adjusted for sex and age.

* $P < .01$.

** $P < .05$.

*** $P < .0001$.

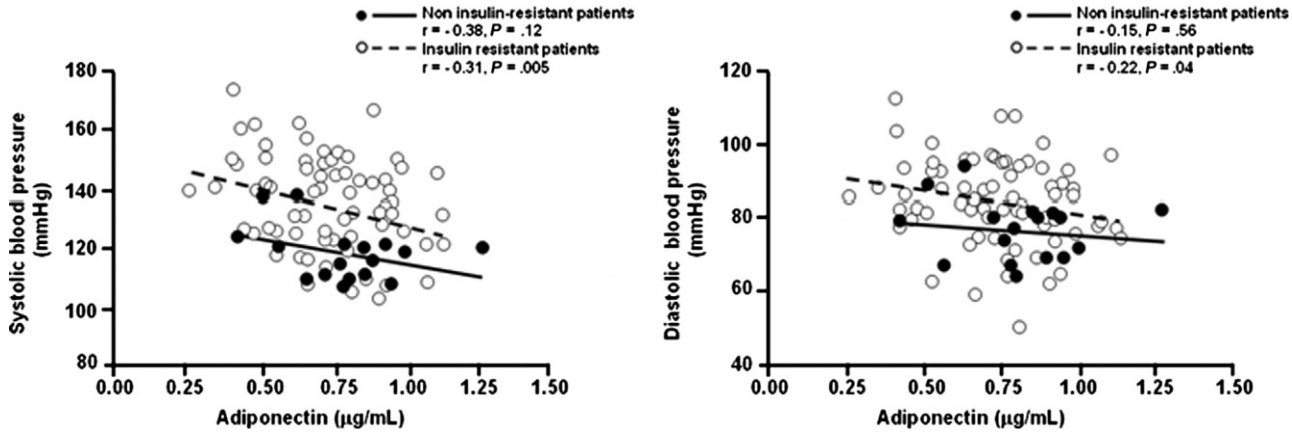

Fig. 1. Correlation between adiponectin concentration and systolic and diastolic blood pressures in ON and OH patients. ○ indicates subjects with insulin resistance (n = 79); ● indicates subjects without insulin resistance (n = 17).

study because concordant findings were obtained in all ethnic groups.

4. Discussion

We demonstrated in this cross-sectional and observational study that the increased blood pressure that was associated with low adiponectin was significant only among those obese individuals who were insulin resistant. In addition, HOMA-IR, adiponectin, BMI, and age were independent determinants for systolic blood pressure.

Such results are in accordance with those of studies previously conducted in normal-weight and moderately overweight hypertensive and prehypertensive patients [12-14,19]. Although the mechanisms of hypoadiponectinemia in hypertension and in obesity-related hypertension remain to be fully elucidated, the main possible reasons for the negative association between adiponectinemia and blood pressure may be related to the following: an increase in the sympathetic nervous activity, which may inhibit adiponectin gene expression via β-adrenergic stimulation [20], and the induced activation of the renin-angiotensin system in the adipose tissue by hypoadiponectinemia [21].

The results of our study also demonstrate that fasting insulin and HOMA-IR were significantly higher in OH individuals as compared with those in ON individuals. These variables also correlated with blood pressure values. Furthermore, there was a negative and significant association of adiponectin concentration with insulin resistance index that persisted after adjustments for BMI, age, and sex. The cause-effect relationship among hypoadiponectinemia, insulin resistance, and hypertension has not been completely clarified. Recently, Iwashima et al [12] reported that adiponectin decreased with increases in blood pressure, even in young and normal-weight individuals without insulin resistance. In contrast, Furuhashi et al [22] reported that only hypertensive patients with insulin resistance exhibited a decreased adiponectin concentration. As a particular characteristic of the present report, all patients enrolled in the study were obese; and 74% and 97% of the ON and OH individuals, respectively, showed an insulin-resistant status.

Table 3
Stepwise regression analysis for hypertension

Term	β	Partial R^2	P
HOMA-IR	.291	20%	.002
Adiponectin	−.336	6.0%	<.0001
Age	.254	4.1%	.005
BMI	.231	4.7%	.012

Model R^2 = 34.8% (n = 96).

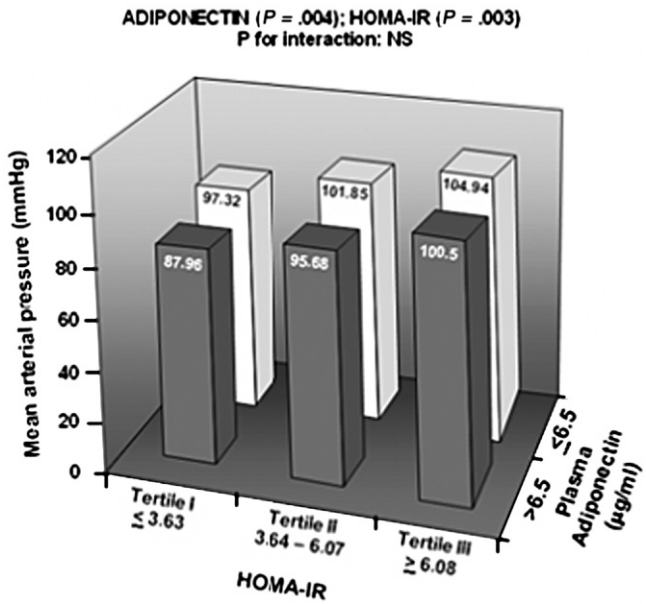

Fig. 2. Contribution of adiponectin concentration and HOMA-IR to the variance in mean blood pressure. NS indicates not significant.

In this regard, the negative relationship between adiponectin and blood pressure observed in the whole group of obese patients remained statistically significant exclusively in insulin-resistant individuals when the total sample was divided into insulin-resistant and non–insulin-resistant individuals. To further document this issue, multivariate analysis showed that the direct association of HOMA-IR and blood pressure was the strongest in regard to the variance in systolic blood pressure; plasma adiponectin concentration correlated negatively, but less strongly. In this regard, mechanistic studies had already reported that hyperinsulinemia induces sympathoactivation in different tissues [23], including the kidney [24], and may cause an increase in renal tubular sodium reabsorption [25,26] and activation of the tissue renin-angiotensin system [26]. Volume expansion and overactivity of the sympathetic nervous system are major features in causing obesity-hypertension in human and animal models [27].

In young and nonobese individuals, hypoadiponectinemia may contribute to the pathogenesis of hypertension at a very early stage, without involving insulin resistance. Contrariwise, our results support the notion that in individuals with weight excess, in whom visceral adiposity prevails, hypoadiponectinemia may be partially attributable to insulin resistance. Insulin infusion during a glucose clamp study has been reported to lead to a decrease in adiponectin concentration [28], suggesting that chronic hyperinsulinemia associated with insulin-resistant states may decrease adiponectin levels. Previously, Weyer et al [29] had also demonstrated a close association of hypoadiponectinemia with insulin resistance and hyperinsulinemia in obese patients with type 2 diabetes mellitus. It is worth noting that data from the Bogalusa Heart Study have also shown a significant interaction effect between insulin resistance and visceral adiposity on adiponectin concentration [14]. Thus, considering the significant relationship between adiponectin concentration, insulin plasma levels, and blood pressure, hyperinsulinemia might be responsible, at least in part, for the link between adiponectin and blood pressure.

In addition to blood pressure and insulin resistance, HDL-C was correlated with adiponectin only in obese insulin-resistant individuals. Several reports have shown that adiponectin is independently associated with HDL-C [30,31]. This has been attributed to the activation of the transcription factor peroxisome proliferator–activated receptor α, which decreases TGs and increases HDL-C by increasing the expression of genes involved in the metabolic process of lipids and apolipoproteins [32].

The present study has certain limitations. It was designed to be a cross-sectional study. Evaluation of the cause-effect relationship between hypoadiponectinemia and obesity-hypertension would require a prospective study design with a cohort base and larger casuistics. Therefore, we cannot prove causality or predictive ability, but only discern associations. Furthermore, the study lacks direct assessment of body mass fat and distribution and in vivo insulin action used in etiologic studies. We tried to overcome these biases by using well-established simple surrogate measures that are applicable to population studies.

In conclusion, our findings suggest that plasma adiponectin concentration is significantly associated with blood pressure in a sample of adult obese Brazilians of multiethnic origin with insulin resistance. Although adiponectin predicts systolic blood pressure like other variables, such as HOMA-IR and BMI, the direct association of HOMA-IR with blood pressure was the strongest regarding the variance in systolic blood pressure, thus supporting the participation of both variables in blood pressure regulation.

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