Hypoadiponectinemia Is Associated With Prehypertension in Obese Individuals of Multiethnic Origin

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ABSTRACT

Background: Considering that prehypertension is associated with an increase in cardiovascular risk, hypoadiponectinemia seems to be a predictor of hypertension.

Hypothesis: This study investigated whether adiponectin plasma levels are affected in Brazilian obese prehypertensives compared with those in normotensives and hypertensives.

Methods: The study involved 96 multiethnic obese subjects (mean age = 42.8–11.9 years; BMI = 35.7–7.3 kg/m²). Fasting plasma adiponectin and serum insulin were determined by radioimmunoassay. Insulin resistance was estimated by HOMA-IR. Blood pressure was recorded using a calibrated automated sphygmomanometer.

Results: Adiponectin concentrations were significantly lower in prehypertensives compared with those in normotensives, but hypertensives exhibited the lowest adiponectin concentrations of all. Regarding the values of HOMA-IR, both prehypertensives and hypertensives were significantly more insulin resistant when compared with normotensives. When normotensives and prehypertensives were classified according to the 50th percentile of adiponectin ($\leq$ vs $>$ 6.5 mg/mL) a logistic regression was performed to estimate the association of this adipokine with hypertension, the lower the plasma adiponectin values, the greater the association. A multivariate linear regression analysis adjusted for cardiometabolic factors showed that systolic blood pressure increased by 1.612 mm Hg for 1 μ g/mL reduction in adiponectin plasma levels ($P < 0.01$).

Conclusion: Our findings have shown that hypoadiponectinemia is associated with prehypertension in obese individuals of multiethnic origin.

Introduction

The data from the participants in the Framingham Heart Study demonstrate the increased risk seen in people at any blood pressure (BP) level above optimal (below 120/80 mm Hg) to normal (120–129/80–84 mm Hg) to high normal (130–139/85–89 mm Hg).¹ Over a 12-year follow-up, the cumulative incidence of cardiovascular events in the enrolled men rose from 6% in those who started as optimal, to 8% in the normal, and 13% in the high normal. In 2003, the Seventh Report of the Joint National Committee (JNC) identified prehypertension as a new category of BP in adults for those with BP from 120 to 139 mm Hg systolic and/or 80 to 89 mm Hg diastolic, encompassing both the normal and high-normal classifications of prior JNC reports.² A review of recent published data relating prehypertension to cardiovascular damage includes reports showing an increase in coronary heart disease, cardiac procedure, silent myocardial infarction, or ischemic stroke in middle-aged adults followed for an average of 11.6 years,³ and significant progress of coronary atherosclerosis determined by intravascular ultrasound.⁴

The increasing prevalence of hypertension and prehypertension occurred in conjunction with a dramatic increase in the prevalence of overweight and obesity.³ However, the underlying mechanisms of BP elevation associated with excess weight, in particular the pathogenic role of multiple metabolic and neuroendocrine changes frequently associated with obesity, are still partially unclear.⁵ Contemporary research also suggests that the adipocyte-derived hormones, mainly leptin and adiponectin, may be important factors linking obesity and hypertension.⁵

Adiponectin is a major adipocytokine exclusively synthesized by the adipose tissue.⁶ The plasma concentration of adiponectin is decreased in patients with obesity⁷ and hypertension.⁸ In a recent study, prehypertensives exhibited lower adiponectin values as compared with normotensives, but that study included only lean healthy whites.⁹

We decided to evaluate, in a multiethnic population of moderately-to-severely obese Brazilians of multiethnic origin, whether those categorized as prehypertensives had decreased adiponectin plasma levels compared with normotensives. We also estimated the potential risk for hypertension according to adiponectin levels.

Methods

We conducted a subgroup analysis of a previous study that evaluated the association between hypertension, insulin resistance, and hypoadiponectinemia. The rationale and design of this study have been presented in detail elsewhere.¹⁰ Patients were recruited from the Hypertension Clinic of the Rio de Janeiro State University. The Rio de Janeiro State University population is peculiar due to its extremely complex multiethnic admixture. It has been the result of 5 centuries of interethnic crosses of European colonizers, African slaves, people from the Middle East, and autochthonous Amerindians, leading to intense genetic flow and homogenization closing to panmixia.¹¹

Normal BP has been defined as systolic BP <120 mm Hg and diastolic BP <80 mm Hg; prehypertension as systolic BP between 120 and 139 mm Hg and/or diastolic BP between 80 and 89 mm Hg; and hypertension as systolic BP $\geq$ 140 mm Hg and/or diastolic BP $\geq$ 90 mm Hg². Weight stability for at least 3 months was required from the participants.

After undergoing routine blood chemistries (plasma concentration of glucose and serum concentrations of creatinine, uric acid, total and high-density lipoprotein cholesterol, and triglycerides), urinalysis, electrocardiography, echocardiography, and duplex-scan of renal arteries, subjects with the following conditions were excluded from the study: type 2 diabetes, secondary forms of hypertension, and any evidence of complication of cardiovascular and renal diseases. The study sample comprised 96 subjects (25 men and 71 women; mean age, 42.8 ± 11.9 yrs; body mass index [BMI] 35.7 ± 7.3 kg/m²), who were instructed to stop any medication that could affect BP levels, insulin sensitivity, and serum lipid concentration at least 2 weeks before entering the study.

All participants followed a diet containing approximately 120 mmol/L of sodium and 75 mmol/L of potassium per day, for at least 1 week before entering the study. Nutrient intake was assessed through 2 self-reporting tools: the semiquantitative food frequency questionnaire and the 3-day dietary record. The study protocol was approved by the Human Research Committee on Ethics of the Pedro Ernesto University Hospital. Written informed consent was obtained from all participants.

Blood pressure was recorded by using a calibrated Dinamap 1846 Critikon automated sphygmomanometer (Tampa, FL), 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, at a constant temperature of 22 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, weight, and waist circumference were measured following

standardized procedures and BMI was calculated as weight in kilograms divided by height in meters squared. Waist-to-hip ratio (WHR) was used as an indicator of central adiposity. Anthropometric measurements were taken twice and mean values were used in all analyses. Blood samples were collected after a 12-hour fasting period and were stored at -80°C for subsequent radioimmunoassay, which was used to determine plasma adiponectin and insulin (double antibody solid-phase enzyme immunoassay; Linco Research, St. Charles, MI). The sensitivity of the insulin radioimmunoassay was 1.1 $\mu\text{U/mL}$ and the intra-assay and interassay coefficients of variation were 4.4% and 6.0%, respectively. The intra-assay and interassay coefficients of variation for adiponectin were 3.9% and 8.5%, respectively. Fasting plasma glucose and serum lipid profile were determined by use of enzymatic methods. The insulin resistance status was assessed by use of the homeostasis model assessment of insulin resistance (HOMA-IR) index.¹²

Statistical Analysis

Data were expressed as mean $\pm$ SD. The statistical tests were 2-sided and the significance level adopted was $P < 0.05$. The values of triglycerides, insulin, adiponectin, and HOMA-IR were log transformed for statistical analysis. Comparison of continuous variables among the 3 groups studied was performed by use of analysis of variance, followed by a post-hoc Student-Newman-Keuls test. Categorical variables were compared across the 3 groups with χ^2 testing. The individuals were classified according to the 50th percentile of adiponectin levels ($\leq$ vs >6.5 $\mu\text{g/mL}$) into lower and higher adiponectin plasma levels, and a logistic regression analysis was performed to estimate the odds ratio (OR) and 95% confidence intervals (CI) of being hypertensive. A multivariate linear regression analysis was performed to evaluate the independent contribution of age, gender, anthropometric measurements, and metabolic risk factors to the variance in systolic BP. Linear relationships among variables were computed by Pearson correlation coefficients. All statistical analyses were performed with SPSS software (version 12.0, SPSS Lead Technologies Station, Chicago, IL).

Results

Hypertensives had greater values of BMI, waist circumference, and WHR, but only WHR reached statistical significance (Table 1). Prehypertensives had higher values of uric acid as compared with normotensives. The triglyceride levels were significantly higher in prehypertensives and hypertensives compared with normotensives. The adiponectin concentrations were significantly lower in prehypertensives as compared with those in normotensives, but hypertensives exhibited the lowest concentrations of

Table 1. Comparison of Cardiovascular Risk Factors in Obese Individuals According to the VII JNC Classification of Hypertension

Risk Factors	Normotensive (n = 29)	Prehypertensive (n = 32)	Hypertensive (n = 35)	P Value
Demographic Characteristic				
Race/ethnicity, n (%)				0.78
Mulattos ^a	19 (58.9%)	17 (58.6%)	20 (57.1%)	
European ancestry	10 (33.3%)	8 (27.5%)	10 (28.5%)	
African descent	2 (6.25%)	3 (10.3%)	3 (8.57%)	
Others	1 (1.55%)	1 (3.55%)	2 (5.3%)	
Age (yrs)	40.2 ± 11.5	44.4 ± 12.3	43.3 ± 11.8	0.38
Anthropometric Measures				
Body mass index (kg/m ²)	105.6 ± 9.9	110.4 ± 12.2	113.4 ± 16.6 ^d	0.07
Waist circumference (cm)	0.87 ± 0.1	0.95 ± 0.1 ^b	0.93 ± 0.1 ^d	0.01
Waist-to-hip ratio				
Laboratory Assessments	192.4 ± 37.7	203.6 ± 57.8	198.7 ± 37.1	0.63
Total cholesterol (mg/dL)				
HDL cholesterol (mg/dL)	47.2 ± 11.5	46.2 ± 10.8	42.7 ± 9.4	0.19
Triglycerides (mg/dL)	127.9 ± 88.6	159.1 ± 83.9	164.2 ± 90.9	0.04
Fasting plasma glucose (mg/dL)	99.1 ± 25.8	107.6 ± 33.5	105.3 ± 19.8	0.44
Uric acid (mg/dL)	4.5 ± 1.1	5.3 ± 1.5 ^b	5.8 ± 1.5 ^d	0.01
Hemodynamic Variables				
Systolic blood pressure (mm Hg)	111.3 ± 6.1	126.5 ± 6.4 ^b	146.6 ± 11.3 ^{c,d}	<0.0001
Diastolic blood pressure (mm Hg)	70.2 ± 7.6	81.6 ± 5.1 ^b	92.6 ± 8.1 ^{c,d}	<0.0001
Mean arterial pressure (mm Hg)	89.5 ± 6.7	96.8 ± 4.3 ^b	109.7 ± 7.7 ^{c,d}	<0.0001
Adiponectin, insulin, and HOMA-IR				
Plasma adiponectin (μg/mL)	7.9 ± 3.3	6.9 ± 3.0 ^b	5.5 ± 2.7 ^{c,d}	0.01
HOMA-IR	3.7 ± 2.1	5.6 ± 3.7 ^b	7.3 ± 4.1 ^{c,d}	<0.0001
Serum insulin (μm/L)	15.1 ± 6.4	21 ± 9.4 ^b	28.1 ± 12.6 ^{c,d}	<0.0001
HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance.				
^a Mulattos are persons with a known family history of admixture between African descent and white populations.				
^b P < 0.05 for prehypertension vs normotension.				
^c P < 0.05 for hypertension vs prehypertension.				
^d P < 0.05 for hypertension vs normotension.				

adiponectin of all. In regard to HOMA-IR values, both prehypertensives and hypertensives were significantly more insulin-resistant than normotensives (Table 1).

To estimate the association of hypertension with the adiponectin levels, a logistic regression analysis was performed, and normotensives and prehypertensives were classified according to the 50th percentile of adiponectin

(≤ vs >6.5 μg/mL). The lower the plasma adiponectin values, the greater the association of this adipokine with hypertension (OR: 4.2, 95% CI: 1.6–10.7). A total of 46% of prehypertensives had lower plasma adiponectin values in contrast to 27.5% of normotensives (*P* < 0.01).

In the group as a whole, that included the normotensive, prehypertensive, and hypertensive subjects, a multivariate

linear regression analysis, adjusted for BMI, WHR, adiponectin, total cholesterol, triglycerides, high-density lipoprotein cholesterol, and HOMA-IR showed that systolic BP increased by 1.612 mm Hg for 1 $\mu\text{g/mL}$ reduction in adiponectin plasma levels ($P < 0.01$). Also in the same population, a negative and significant correlation was observed between systolic and mean BP and plasma adiponectin. These correlations remained significant after adjustment for sex, gender, total cholesterol, high-density lipoprotein cholesterol, triglycerides, BMI, waist circumference, and HOMA-IR (Figure 1).

Discussion

This cross-sectional analysis demonstrates that compared with obese normotensive subjects, prehypertensive, and more so, hypertensive subjects showed reduced adiponectin levels. Almost 50% of our prehypertensive patients exhibited adiponectin levels below the 50th percentile of adiponectin concentration. In addition to being significantly more insulin-resistant, prehypertensives also exhibited a potential higher risk for being hypertensives.

The relation between hypoadiponectinemia and the risk for hypertension is well-known.¹³ Several cross-sectional

studies had previously shown an inverse relation between adiponectin levels and BP.^{14,15} Recently, Chow et al⁶ added another important observation to the relationship between adipose tissue and high BP by demonstrating for the first time an inverse relation between plasma adiponectin concentration and the future development of hypertension. In this case, the control study, which was carried out in a population-based prospective investigation of Chinese subjects, 70 normotensive, nondiabetic subjects who will develop hypertension within the next 5 years were compared with 140 age-matched and sex-matched individuals who remained normotensive at year 5. A low serum adiponectin at baseline was a powerful predictor of future hypertension.

Information regarding the relationship of adiponectin and prehypertension is scarce. Papadopoulos et al⁹ have shown that lean healthy white prehypertensives had lower plasma adiponectin values and higher plasma resistin values as compared with those of normotensives. Our study confirmed and extended their findings to a group of prehypertensive multiethnic obese subjects.

The mechanisms of hypoadiponectinemia in prehypertension remain to be elucidated. In nonobese individuals,

Figure 1. Correlation between systolic blood pressure, mean arterial pressure, and plasma adiponectin before (A) and after adjustment (B) for cardiovascular risk factors: BMI, waist circumference, triglycerides, total cholesterol, high-density lipoprotein cholesterol, HOMA-IR, gender, and age. Abbreviations: BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance. Legends: A = before adjustment for cardiovascular risk factors. B after adjustment for cardiovascular risk factors.

hypo adiponectinemia may contribute to the pathogenesis of prehypertension at a very early stage, without involving insulin resistance.⁹ The present results, however, support the notion that in our obese prehypertensives hypo adiponectinemia could be partially attributable to insulin resistance, as these individuals exhibited significantly higher levels of insulin and HOMA-IR, compared with the normotensives. Insulin infusion during a glucose clamp study has been reported to lead to a decrease in adiponectin concentration,¹⁶ suggesting that chronic hyperinsulinemia associated with insulin-resistant states may decrease adiponectin levels. Mechanistic studies had already reported that hyperinsulinemia induces sympathoactivation in different tissues,¹⁷ including the kidney,¹⁸ and may cause an increase in renal tubular sodium reabsorption.¹⁹ The overactivity of the sympathetic nervous system may also inhibit adiponectin gene expression in adipose tissue via β -adrenergic stimulation.²⁰ In addition, hypo adiponectinemia may induce activation of the adipose-renin-angiotensin system in the adipose tissue.²¹

There are several limitations to our study. First, it was designed to be a cross-sectional study. Evaluation of the cause-effect relationship between hypo adiponectinemia and prehypertension 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. Second, 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. Third, we did not evaluate other previously proposed predictors of progression from prehypertension and hypertension such as the plasma level of high sensitivity C-reactive protein, a marker of inflammation²² and the brachial-ankle pulse wave velocity, a marker of arterial stiffness.²³ Finally, our sample was limited to obese multiethnic subjects originated from a university reference center, most of them clustering several cardiometabolic risk factors. Thus, we do not know if the findings can be extended to populations including apparently healthier obese individuals or different ethnic mixtures.

In conclusion, our findings have shown that hypo adiponectinemia, in addition to being a potential risk for obesity-hypertension, is also commonly present in obese prehypertensives.

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