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Association of Adiponectin with Left Ventricular Mass in African Americans: The Jackson Heart Study

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Abstract

Background—African Americans (AA) have a higher prevalence of left ventricular hypertrophy than whites. Several population-based studies have reported an inverse association between adiponectin and left ventricular mass (LVM). However, the relationship between adiponectin levels and LVM has yet to be defined in AA. The Jackson Heart Study (JHS) cohort provides an opportunity to test the hypothesis that the inverse association between adiponectin and LVM may be modified by risk factors common among AA.

Methods and Results—The study population included 2,649 AA JHS participants; mean age, 51 ± 12 years, 63% women, 51% obese, 54% with hypertension and 16% with diabetes. Multiple linear and spline regression was used to assess the association adjusting for demographic, clinical and behavioral covariates. Among all the participants, there was a statistically significant but modest inverse association between adiponectin and left ventricular mass index (LVMI). Hypertension and insulin resistance emerged as statistically significant effect modifiers of this relationship. The inverse association present among the normotensive participants was explained by obesity measures such as the body mass index. Among participants with both hypertension and insulin resistance there was a significant direct association between adiponectin and LVMI after multivariable adjustment ($\beta = 1.55$, $p = 0.04$; per one standard deviation increments in the adiponectin log-value).

Conclusions—The association between serum adiponectin and LVM among AA in the JHS cohort was dependent on hypertension and insulin resistance status. Normotensive AA exhibited an inverse adiponectin – LVM association, whereas participants with hypertension and insulin resistance had a direct association.

Keywords

adiponectin; biomarkers; epidemiology; left ventricular mass; obesity

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Disclosures
None

Obese individuals, particularly those with visceral fat accumulation, have reduced plasma levels of adiponectin.[1, 2] The associations of adiponectin with cardiac risk factors, such as hypertension, type 2 diabetes and obesity, have been described.[3, 4] In mice, adiponectin inhibits hypertrophic signaling in the myocardium.[5] Several studies have reported an inverse association between adiponectin and left ventricular mass (LVM).[6–12] There are however very few large, community-based studies with adequate adjustment for potential confounders to elucidate this apparent inverse relationship between adiponectin and LVM in greater detail.[13–15] Although African Americans (AA) have a higher prevalence of obesity and left ventricular hypertrophy, the relationship between adiponectin and LVM in this population has yet to be explored. The availability of serum adiponectin measurements on more than 4,000 AA participants in the Jackson Heart Study (JHS) allowed us to quantify the association between serum adiponectin and echocardiography-measured LVM in AA enrolled in the JHS, a large community-based cohort. We queried whether an inverse association adiponectin – LVM is present and whether this association is modified by selected covariates such as hypertension, obesity and insulin resistance known to be particularly prevalent among AA and associated with LVM.

Methods

Study Population

JHS is a single-site, prospective cohort study of the risk factors and causes of cardiovascular disease in adult AA. A probability sample of 5,301 AA, aged 21 – 84 years, residing in the three counties surrounding Jackson, MS, was recruited and examined at baseline (2000–2004) by trained and certified technicians according to standardized protocols. Clinic visits and interviews occurred approximately every three years. Annual follow-up interviews and cohort surveillance are ongoing. Details of the study design are published elsewhere.[16, 17]

After exclusion of individuals with prevalent coronary heart disease (n = 375), undetectable adiponectin levels (n = 93), unreliable ultrasound measurements (n = 879) and mitral or aortic regurgitation (n = 1,305), our final study sample included 2,649 participants.

Written consent was obtained from each participant at the inception of the study, and the study protocol was approved by the Institutional Review Boards of the Morehouse School of Medicine and the University of Mississippi Medical Center.

In all participants, the clinic visit included physical examination, anthropometry, survey of medical history and of cardiovascular risk factors and collection of blood and urine for biological variables. We calculated body mass index (BMI, kg/m^2) as weight in kilograms divided by height in meters squared. Obesity was defined as BMI ≥ 30, and abdominal obesity as a waist circumference ≥88 cm in women and ≥102 cm in men. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive therapy. Diabetes was defined as fasting plasma glucose ≥126 mg/dL or use of insulin or oral hypoglycemic medications. Smoking status was defined as current smoking versus former and never smoking (collapsed). Alcohol drinking was defined as regular drinking in the past 12 months (yes vs. no). A physical activity score was composed with a Baecke-derived questionnaire and used as a continuous variable.

Participants were further subjected to a standardized 2D echocardiographic examination. Left ventricular mass was calculated using the American Society of Echocardiography corrected formula by Devereux.[18] LVM was indexed to height raised to the power 2.7 ($LVMI = LVM/height^{2.7}$) in order to normalize heart size to body size.

Lipid variables, fasting plasma glucose and fasting insulin were measured using standard laboratory techniques. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as [insulin (microunits per milliliter) × fasting blood glucose (millimoles per liter)]/22.5. Insulin resistance status was defined as a HOMA-IR in the highest quartile of its distribution.[19, 20]

Adiponectin measurement

Venous blood samples were withdrawn from each subject at baseline examination after more than 8 hours of fasting as described elsewhere.[16] Serum concentration of adiponectin was measured as total adiponectin at the JHS central laboratory in Minneapolis, MN, by an ELISA system (R&D Systems; Minneapolis, MN) using baseline serum specimens stored at −80°C until assayed. The inter-assay coefficient of variation was 8.8%. No biological degradation has been described using stored specimens, indicating a high validity for our measurements.[21]

Statistical Analyses

Because the distributions of adiponectin and HOMA-IR were skewed, log-transformed values were used for the analyses to approximately normalize the distribution.

The cross-sectional association between adiponectin and LVMI was assessed with Spearman correlation coefficients and multiple linear regression. Using full-models, we assessed the individual effect measure modification for a series of covariates (age, sex, hypertension, obesity and abdominal obesity, diabetes and insulin resistance status) known to be associated with both adiponectin [22] and left ventricular mass.[23, 24] Models including hypertension and insulin resistance were used to also test the three-way interaction between adiponectin and hypertension, insulin resistance on LVMI. These models were constructed by including within the models adjusted for age and sex the three-variable interaction term adiponectin by hypertension by insulin resistance as well as all the two-variable interaction terms adiponectin by hypertension and adiponectin by insulin resistance. The multivariable regression full models were adjusted for age, sex, BMI, alcohol drinking, triglycerides, high-density lipoprotein cholesterol (HDL-cholesterol), hypertension status and HOMA-IR. We also modeled continuous LVM as a nonlinear predictor of adiponectin concentrations using generalized additive model (GAM). In GAM, we used penalized splines smoothing function to fit a curve that describes the relationship between adiponectin and LVM without assuming a linear relationship. For all the analyses, the nominal p-value was set at 0.05 for the main and the interactive effects.

Analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, 2005).

Additional Analyses

Because hypertension medication directly influences blood pressure values, a direct determinant of LVM, we also run the same analyses after excluding 1,118 subjects who had been on medical treatment for hypertension. We also assessed the effects of the use of medications that inhibit the renin-angiotensin-aldosterone system (such as angiotensin-converting enzyme inhibitors, ACE inhibitors, and angiotensin receptor blockers, ARB) and of statins, all reported to increase adiponectin levels.

Results

The overall characteristics of the JHS study sample (mean age ± SD, 51 ± 12 years; 63% women) are as follows. BMI had a mean (standard deviation) of 31.3 (6.9) kg/m^2. Obesity had a prevalence of 51% and that of abdominal obesity 60.5%. Systolic blood pressure

(SBP) ranged from 73 to 210 mm Hg, and the mean was 124 mm Hg. Hypertension was present in 54% of participants. The prevalence of diabetes was 15.7%. Serum adiponectin level ranged from 0.4 to 41.4 μg/mL, and the mean was 5.1 μg/mL. LVM ranged from 66.4 g to 379.9 g, and the mean was 144.0 g. The characteristics of the participants across adiponectin quartiles are presented in Table 1. Age, sex, BMI, alcohol drinking, hypertension status, HDL-cholesterol, triglycerides and HOMA-IR emerged as the main variables that varied statistically significant across quartiles.

In accordance with previous observations, serum adiponectin levels had a positive and statistically significant correlation with HDL-cholesterol (Spearman r = 0.43) and a negative correlation with HOMA-IR (r = − 0.36), triglycerides (r = − 0.29), waist circumference (r = − 0.24) and BMI (r = − 0.15); all p-values < 0.0001. There was no statistically significant correlation between adiponectin and systolic blood pressure (r = 0.02; p-value = 0.21). In the overall sample, we observed a statistically significant negative correlation between adiponectin levels and LVM (r = − 0.19; p-value = 0.0001) and between adiponectin and LVMI (r = − 0.04; p-value = 0.047).

Several effect modifiers emerged as statistically significant: hypertension (p = 0.03), insulin resistance (p = 0.01) and hypertension in conjunction with insulin resistance (p = 0.04). Sex and obesity did not appear to affect the adiponectin – LVMI relationship as effect modifiers. Based on the finding that hypertension and insulin resistance were significant effect modifiers, the subsequent analyses were performed based on sub-stratification by these variables. Among the normotensive participants (N = 1,206), the significant inverse association adiponectin – LVMI present in the crude model appeared mediated by measures of obesity such as BMI and by insulin resistance (Table 2). It is notable that there was no significant association between adiponectin and LVMI among participants with hypertension, and that this association became statistically significant when adjusted for BMI or insulin resistance (Table 2). The variance explained in the fully-adjusted models was 22%.

To further define the interaction of hypertension and insulin resistance on the adiponectin – LVMI relationship, the entire sample was sub-stratified by both variables, as shown in Table 3. The inverse association between adiponectin and LVM that was found among participants without hypertension or insulin resistance (N = 998) was explained by BMI (Table 3). Among those with hypertension and insulin resistance (N = 331), the association was a statistically significant direct association that persisted after adjustment for age, sex, BMI, HDL-cholesterol, triglycerides and alcohol drinking; β = 1.55, p = 0.04 (Table 3). The equivalent raw values of the log-transformed beta coefficients (obtained by exponentiation of the initial values) are in the order of 5 to 13, thus of a very large magnitude. The Table 1 of the online supplemental material presents the beta coefficients for LVMI across adiponectin quartiles using raw values of adiponectin levels in order to assure an easier interpretation of the regression models results. This table confirms a non-linear complex trend in the association between adiponectin and LVMI.

Using spline regression with multivariable adjustment, a significant curvilinear bidirectional relationship was observed between adiponectin and LVMI among normotensive participants (p = 0.001, N = 1,206; Figure 1). The spline regression analysis among hypertensives with insulin resistance exhibited the same curvilinear adiponectin – LVMI relationship (p = 0.04, N = 331; Figure 2). Among participants with hypertension a direct relationship between adiponectin and LVMI emerged although not statistically significant (Figure 1 of the online supplemental material). Curvilinear bidirectional adiponectin – LVMI relationships also emerged among those without hypertension and without insulin resistance (N = 998), among those without hypertension and with insulin resistance (N = 208), as well as among those

with hypertension and without insulin resistance (N = 1,087), relationships that reached statistical significance in the second mentioned group (Figures 2, 3 and 4 of the online supplemental material).

Similar results were obtained among participants without medication for hypertension (N = 1,531). Specifically, the beta coefficients changed their sign from $\beta = -0.78$ ($p = 0.02$) among participants without hypertension and without insulin resistance (age- and sex-adjusted model) to $\beta = 3.32$ ($p = 0.008$) among those with both hypertension and insulin resistance (fully-adjusted model). Moreover, in the assessment of the potential confounding effects of the use of medication that inhibits the renin-angiotensin-aldosterone system and of statins we did not find among hypertensives any statistical significant effect on the adiponectin – LVMI relationship (the online data supplement). Similarly, we did not observe significant differences in the mean level of adiponectin among hypertensives compared with normotensives either with or without insulin resistance (data not shown).

The association between adiponectin and LVMI according to hypertension, diabetes and abdominal obesity stratified by age (an effect modifier when dichotomized using the median age of 50 years as the cutpoint) and sex is presented in the Table 2 of the online supplemental material and in the Table 3 of the online supplemental material. Among participants without hypertension, the inverse association became non-significant after adjustment for age, BMI or insulin resistance in both men and women, but was maintained among younger participants.

Discussion

Principal findings

In accordance with previous studies, we observed a modest negative correlation between adiponectin and left ventricular mass index in the overall JHS community-based sample of African Americans. Hypertension and insulin resistance emerged as the major effect modifiers of the adiponectin – LVMI relationship. A statistically significant inverse association was evident among normotensives in the crude model, but this association was attenuated in multivariate models by the effects of adiposity and insulin resistance. Intriguing is the observation of a statistically significant direct association between adiponectin and LVMI among those with both hypertension and insulin resistance that was not hypothesized *a priori*.

In the context of previous studies

The prevalence of cardiovascular disease and diabetes is greater in African Americans (AA) than in whites.[25] Several studies such as CARDIA[26, 27], HyperGen[28] and Dallas Heart Study[29] have shown that AA have an increased left ventricular mass and an increased prevalence of concentric left ventricular hypertrophy (LVH) in comparison with whites. In epidemiological investigations, cardiovascular risk factors such as diabetes, hypertension, smoking and obesity have been shown to be associated with increased LVMI. [30–32]

The role of adiponectin in relation to cardiac mass and function has attracted some recent attention. Studies performed in small study samples have reported inverse association between adiponectin and LVM, but the study participants for these investigations were mainly from hospital-based or convenience samples or involved patients with preexisting disease, such as type 2 diabetes, hypertension or obesity.[6–12] Only three large, community-based studies with adequate adjustment for potential confounders are available. [13–15] A significant inverse association between adiponectin and ECG-measured LVH in apparently healthy individuals with normal and high blood pressure was observed in 2,839

Japanese male workers who were not taking medications for hypertension.[13] In two community-based samples of Swedish elderly, adiponectin concentrations were inversely associated with ejection fraction in men but not with LVMI after adjustment for potential confounders.[14] In 2,615 participants from the Framingham Offspring Study, adiponectin concentrations were inversely related to LVM but not to cardiac structure and function markers in linear regression models that adjusted for clinical correlates.[15] To our knowledge, the current study is among the first to examine the adiponectin – LVM relationship in AA, a population group at high-risk for left ventricular hypertrophy.

Potential mechanisms

A growing body of evidence suggests that a decrease in adiponectin plasma levels plays an important part in the pathogenesis of many comorbid conditions such as insulin resistance, diabetes and atherosclerosis.[3, 33, 34] Experimental studies have demonstrated that decreased plasma adiponectin levels can predispose to left ventricular hypertrophy. Similarly, increased adiponectin expression can attenuate LVH induced by pathological stimuli.[5] Adiponectin may directly inhibit hypertrophic signaling in the myocardium by activating adenosine monophosphate-activated kinase (AMPK), which activates eukaryotic elongation factor-2 kinase and the inhibitor of cardiac myocyte protein synthesis.[35] Adiponectin protects the ischemic heart from injury through the activation of independent pathways involving both AMPK-mediated anti-apoptotic actions and COX-2-mediated anti-inflammatory actions.[22] These mechanistic studies of the anti-hypertrophic properties of adiponectin are consistent with the finding of an inverse association between adiponectin and LVMI.

Although we observed an inverse adiponectin – LVMI relationship among normotensive African-Americans, we are intrigued by the ‘paradoxical’ observation of a direct adiponectin – LVMI relationship among hypertensives with insulin resistance. The mechanistic basis of this finding remains to be further defined. Although the primary determinants of adiponectin levels are related to adipose tissue, it is important to note that adiponectin is also expressed in both cardiac and skeletal muscle under certain circumstances. Increased levels of adiponectin have been described in patients with both systolic and diastolic forms of heart failure.[36, 37] Moreover, increased adiponectin expression has been noted in the context of a high salt diet and increased activation of the renin-angiotensin-aldosterone system.[38–42] We speculate that the positive adiponectin – LVM relationship reflects a common set of determinants – high salt diet, activation of the renin-angiotensin-aldosterone system and hypertension. These findings suggest that the prognostic value of adiponectin levels may be contextual and depend on factors involved in blood pressure regulation in addition to metabolic factors such as adiposity.

In addition, recent studies have documented that adiponectin exerts an anti-apoptotic effect that is mediated by elevated sphingosine-1-phosphate levels.[43] These findings suggest that adiponectin could contribute to the expansion of the total number of cells in the heart and increase LVM in the cardiotoxic context of hypertension and insulin resistance. Similarly, there is evidence that certain anti-hypertrophic pathways induced by adiponectin can become down-regulated in certain contexts characterized by a state of ‘adiponectin resistance’.[44, 45] Taken together, these studies are consistent with the possibility that the nature of the adiponectin – LVM relationship may be context-specific. Future studies are needed to define the implications of both direct and inverse associations between adiponectin and LVM.

Strengths and limitations

Strengths of the present study include the largest community-based cohort of exclusively African Americans with a wide range of biological, behavioral and demographic attributes with strict quality control methods. Some limitations should be acknowledged. As this is a cross-sectional study, causality cannot be elucidated nor can it be determined if LVM is related to the longitudinal tracking of adiponectin concentrations. Second, measures of different multimeric forms of serum adiponectin were not available for the present study. This could be of importance, since some studies suggest a difference in biological activity between different isoforms of adiponectin with regard to metabolic abnormalities[46] and ventricular mass.[10]

Conclusion

The major finding of the present study was an inverse relationship between serum adiponectin and LVMI in normotensive and non-insulin resistant participants. This association became non-significant after multivariable adjustment that included obesity measures. On the contrary, serum adiponectin was directly associated with LVMI in participants with hypertension and insulin resistance. This suggests that plasma adiponectin levels may have different prognostic value related to LVM depending on the metabolic context and the underlying risk factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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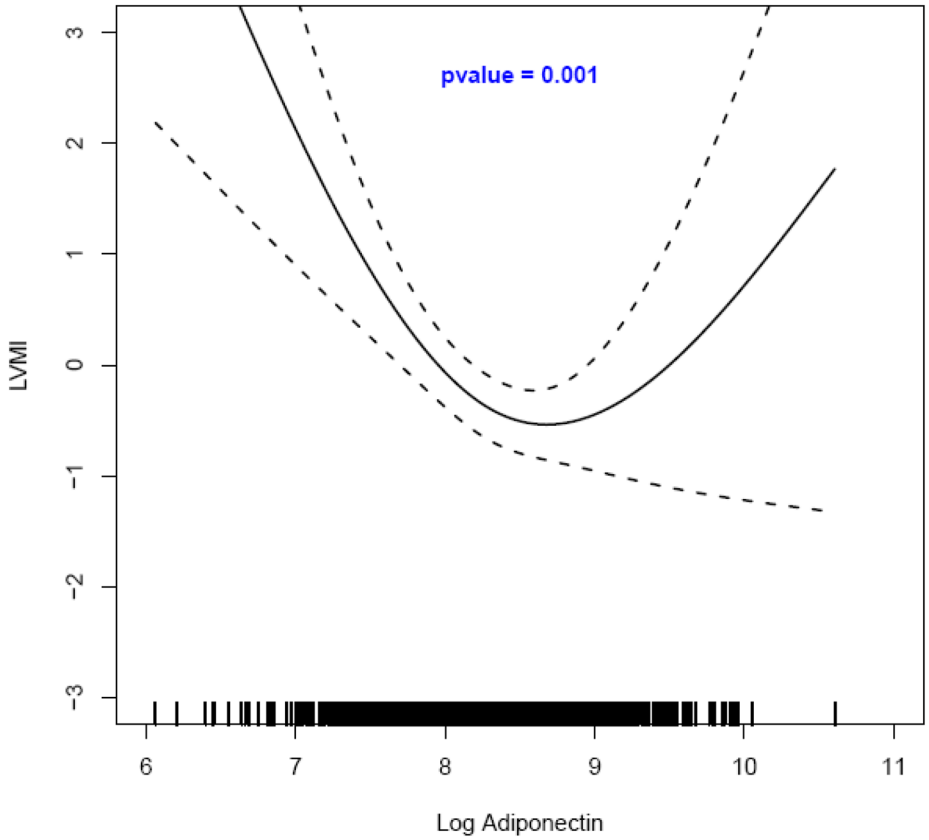

Figure 1. The relationship between adiponectin* and left ventricular mass index† by spline regression modeling‡ among participants without hypertension (N = 1,206)

*Adiponectin was log-transformed from units expressed as μg/mL (in order to have logarithmic values above the unit);

†Multivariable-adjusted values (residuals) of left ventricular mass index (LVMI);

‡ Adjustment was performed for age, sex, BMI, alcohol drinking, HDL-cholesterol, triglycerides and HOMA-IR (log-transformed).

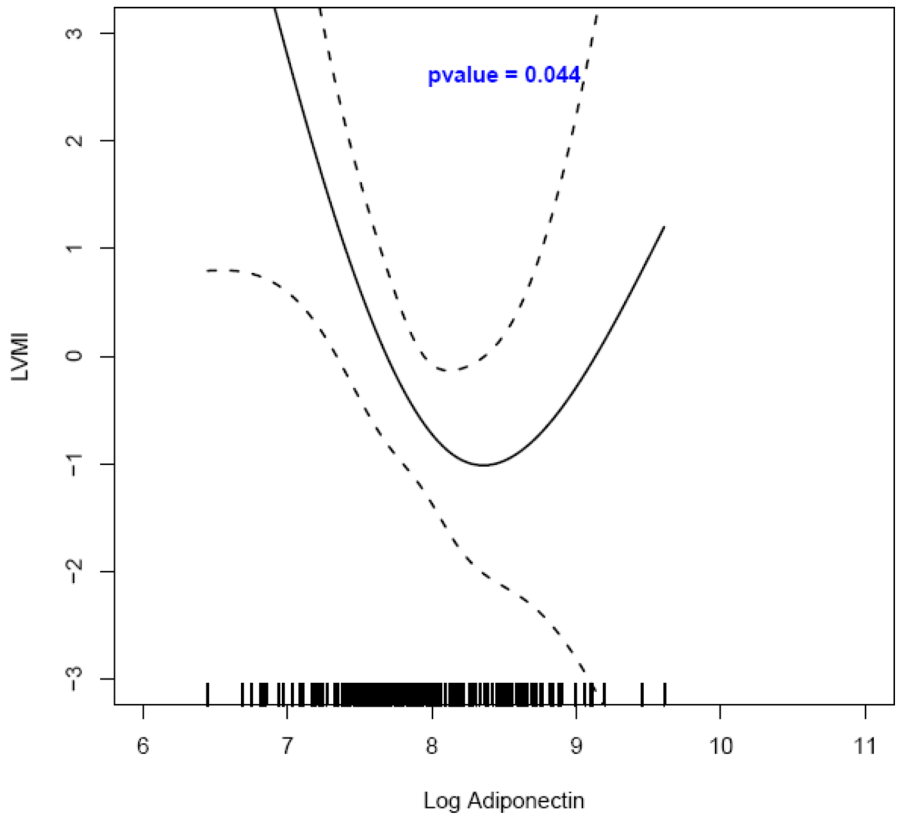

Figure 2. The relationship between adiponectin* and left ventricular mass index† by spline regression modeling‡ among participants with hypertension and insulin resistance (N = 331)

*Adiponectin was log-transformed from units expressed as μg/mL (in order to have logarithmic values above the unit);

†Multivariable-adjusted values (residuals) of left ventricular mass index (LVMI);

‡ Adjustment was performed for age, sex, BMI, alcohol drinking, HDL-cholesterol and triglycerides.

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Table 1

Baseline characteristics (mean ± SD or percentage) of the participants across adiponectin quartiles (N = 2,649)

	Quartile 1 (N = 663)	Quartile 2 (N = 662)	Quartile 3 (N = 662)	Quartile 4 (N = 662)	P-Value[§]
Age, years	48.7±11.7	50.7±12.0	51.9±12.4	53.9±12.9	< 0.001
Women, %	43.4	59.2	69.6	81.4	< 0.001
BMI, kg/m2	32.1±6.4	31.9±6.7	31.3 (6.9)	29.9±7.2	< 0.001
Waist circumference, cm	102.9±14.5	100.9±14.5	98.8±16.0	93.7±15.5	< 0.001
Obesity[*], %	58.1	56.0	49.6	42.8	< 0.001
Abdominal obesity[†], %	62.6	63.9	61.8	53.6	0.001
Systolic blood pressure, mm Hg	123.2±15.5	123.4±17.0	124.1±17.5	124.8±17.7	0.29
Diastolic blood pressure, mm Hg	79.9±9.9	78.6±10.3	78.3±10.1	77.5±10.6	< 0.001
Hypertension, %	53.4	53.9	53.9	55.0	0.56
Total cholesterol, mg/dL	197.2±39.0	197.2±41.6	197.4±37.8	199.3±40.6	0.74
Triglycerides, mg/dL	126.2±83.8	103.6±81.0	100.3±99.9	85.6±66.9	< 0.001
HDL-cholesterol, mg/dL	44.6±11.1	49.1±11.2	53.2±12.8	60.4±15.6	< 0.001
Fasting plasma glucose, mg/dL	104.8±36.2	98.0±26.6	96.3±27.8	94.3±27.7	< 0.001
HOMA-IR	4.6±2.6	3.7±2.0	3.4±1.9	2.6±1.4	< 0.001
Type II Diabetes, %	19.0	16.2	13.7	15.1	< 0.001
Current Smokers, %	14.3	12.6	12.0	11.6	0.13
Alcohol drinking[‡], % yes	53.4	50.5	49.9	47.0	0.02
Physical activity score	8.9±2.5	8.8±2.5	8.7±2.5	8.6±2.6	0.06
Adiponectin, μg/mL	1.8 (0.5)	3.3 (0.4)	5.2 (0.7)	10.2 (4.4)	< 0.001
Left ventricular mass, g	152.0±40.4	145.2±36.2	142.9±41.7	138.1±39.6	< 0.001
LVMI, $g/m^{2.7}$	35.1±8.1	34.8±8.0	34.6±9.2	34.8±9.6	0.82

[*] Body Mass Index equal or above 30 kg/m2;

[†] Defined as waist circumference equal or above 88 cm in women and 102 cm in men;

[‡] Alcohol drinking in the past 12 months (yes vs. no);

[§] Differences in mean values were tested by 1-way ANOVA. Difference in the proportions was tested by t-test.

Table 2

The relationship of left ventricular mass index with adiponectin* according to hypertension status

	Without Hypertension N = 1,206		With Hypertension N = 1,418	
	β	P-value	β	P-value
Crude (unadjusted)	−0.92‖	0.001	0.47	0.17
Age-adjusted	−2.08	0.07	−0.94	0.59
Sex-adjusted	−1.08	0.0004	−0.002	0.99
BMI-adjusted	−0.29	0.28	0.73	0.02
HOMA-IR-adjusted†	−0.50	0.11	0.98	0.02
Fully-adjusted‡	−0.69	0.04	0.43	0.36

*Per 1 standard deviation increment in the log values;

†Adjusted for HOMA-IR;

‡Adjusted for age, sex, BMI, alcohol drinking in the past 12 months (yes vs. no), HDL-cholesterol, triglycerides and HOMA-IR (log-transformed).

Table 3

The relationship of left ventricular mass index with adiponectin* according to hypertension and insulin resistance (IR) status

	Without Hypertension				With Hypertension			
	Without IR N = 998		With IR N = 208		Without IR N = 1,087		With IR N = 331	
	β	P-value	β	P-value	β	P-value	β	P-value
Crude (unadjusted)	−0.54	0.08	−0.24	0.78	0.17	0.67	2.61	0.0008
Age-adjusted	−0.66	0.03	−0.51	0.56	−0.08	0.84	2.40	0.003
Sex-adjusted	−0.62	0.06	−0.50	0.58	−0.31	0.47	2.12	0.01
BMI-adjusted	−0.17	0.56	−0.49	0.54	0.32	0.40	1.97	0.004
Cholesterol-adjusted†	−0.41	0.25	−1.01	0.29	0.18	0.69	2.59	0.002
Fully-adjusted‡	−0.20	0.56	−1.57	0.08	−0.22	0.63	1.55	0.04

*Per 1 standard deviation increment in the log values;

†Adjusted for HDL-cholesterol and triglycerides;

‡Adjusted for age, sex, BMI, alcohol drinking in the last 12 months (yes vs. no), HDL-cholesterol and triglycerides.