Associations of adiponectin and leptin with brain natriuretic peptide in African Americans: the Jackson Heart Study

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Background Brain natriuretic peptide (BNP) is elevated in decompensated systolic and diastolic heart failure. The plasma levels of adipokines, such as adiponectin and leptin, may provide evidence for mechanistic differences in BNP concentrations. African-American-specific associations are limited in the literature. The objective of this study was to evaluate the associations of adiponectin and leptin with BNP among African Americans.

Methods Linear and logistic regressions were used to test the associations between adiponectin, leptin, and plasma BNP in 3738 participants of the Jackson Heart Study (JHS), a single-site prospective cohort study of African Americans in Jackson, Mississippi.

Results A direct relationship of adiponectin was observed in multiple multivariate-adjusted linear models: in men ($\beta=0.41-0.47$), and in women ($\beta=0.32-0.38$). Those in the highest quartile of adiponectin expression were twice as likely to have elevated BNP levels after adjustment [odds ratio 2.66 (95% confidence interval, 1.66–4.34)]. An inverse relationship of leptin with BNP was

observed ($\beta=-0.15$) but attenuated after adjustment for aldosterone, renin, and adiponectin.

Conclusions Different linear associations of adiponectin and leptin with BNP were observed. Odds of elevated adiponectin were observed with elevated BNP in multivariate-adjusted models. This paradoxical relationship of adiponectin and plasma BNP is possibly explained through adiponectin resistance. *Cardiovasc Endocrinol Metab* 9: 49–55 Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Adiponectin and leptin are hormones that modulate different obesity-related processes. Adiponectin is a 30-kDa peptide hormone secreted by adipose tissue that mediates insulin sensitivity in peripheral tissues and has protective effects against atherosclerosis [1,2]. Leptin is also secreted by adipose tissue and works via the central nervous system to mediate energy balance regulation, reduce appetite and stimulate metabolic processes [3,4].

Heart failure is a multifactorial condition that results in excessive volume overload, increased sympathetic activity, circulation redistribution and result in changes to myocardial integrity and possible cardiac dysfunction [5]. Brain natriuretic peptide (BNP) is excreted in response to volume expansion and pressure overload, and is a useful biomarker of left ventricular diastolic and systolic dysfunction [6]. Allison *et al.* demonstrated higher levels of adiponectin, but not leptin, were significantly associated with higher levels of N-Terminus (NT)-proBNP (the active fraction of BNP) in a multiethnic cohort, and gender stratified analyses showed higher associations in men [7]. Elevated levels of leptin have been observed in patients with dilated cardiomyopathy,

inferring leptin to be a putative biomarker for disease progression [8,9]. Leptin's actions on blood pressure and heart rate are apparent, and leptin has beneficial actions on cardiac metabolism and lipid accumulation [9].

Multiple studies have demonstrated racial/ethnic differences regarding BNP distributions and stress the importance of racial/ethnic-specific thresholds [10,11]. African-American men and women have been shown to have ~2–3 times higher prevalence of left ventricular hypertrophy (LVH) than whites and will subsequently have a much larger proportional influence of heart failure-related risk factors [12].

Quantifying associations of adiponectin and leptin with BNP may provide a mechanism for the relationship between obesity and heart failure. We hypothesize a reciprocal relationship of adiponectin and leptin with BNP. Specifically, an inverse association between adiponectin and BNP, while a direct association with leptin and BNP. Identification of the magnitude of African-American-specific associations with adipokines and BNP may provide evidence for magnitudes of racial/ethnic burden. Identification of specific associations of adipokines and

BNP should provide information on racial/ethnic mechanistic differences, and possible diagnostic tools.

Methods

The Jackson Heart Study (JHS) is a single-site, prospective cohort study devoted to the study of African-American-specific risk factors, as well as etiology of heart disease. An overview of the study, design and data collection, and recruitment are published elsewhere [13–15]. Annual follow-up and cohort surveillance are ongoing. Documented consent was obtained from each participant at the inception of the study, and the study was approved by the participating JHS institutions: Jackson State University, Tougaloo College, and The University of Mississippi Medical Center.

Our sample included 3738 of the 5306 eligible participants, participants with measured biomarkers levels. Exclusion was performed for missing data of cardiovascular variables, prevalent cardiovascular disease (CVD), as well as prevalent coronary heart disease.

Covariates

Initial physical examination, anthropometric variables, medical history, and medication use were ascertained at JHS Exam I (2000–2004). Biological specimens were collected in the majority of participants. BMI was calculated by dividing body weight in kilograms by height in meters squared. Blood pressure measurement was based on the average of two 1-min blood pressure measurements, separated by a 1-min rest. Smoking status was self-reported in the baseline assessment. Insulin resistance was calculated using the homeostasis model assessment for insulin resistance [16]. Standard laboratory techniques were used to describe lipid variables, fasting plasma glucose, and creatinine. Pharmacological treatment was ascertained at the baseline examination.

Venous blood samples were drawn at baseline from patients that had fasted for at least 8 hours. Serum was stored at -80°C in the JHS central repository in Minneapolis, MN, USA. The inter-assay coefficient of variation was 8.8% and no biological degradation was apparent [17]. Detailed adiponectin and leptin methodologies were described elsewhere [15,17–19].

Cardiovascular risk factor-related measurements were ascertained during JHS exam 1 through standard procedures and questionnaires. Four experienced sonographers performed echocardiograms, while reading was performed by an experienced cardiologist with level III training in echocardiography [20]. Left ventricular mass (LVM) was calculated using the American Society of Echocardiography corrected formula by Devereux and is described elsewhere [20,21].

Missing data reduced the sample sizes for respective echocardiographic measurements. Further reductions

to various measurements occurred due to agreement between the presence of adiponectin, leptin, and echocardiographic measurements. All sample sizes are noted in their respective tables due to variations in available data.

Plasma BNP measurement is described elsewhere [22]. Briefly, the JHS sample used a chemiluminescent immunoassay. The coefficient of variation was measured at three concentrations: level 1 (CV=4.2%), level 2 (CV=3.1%), level 3 (3.4%) and the minimal detectable concentration of BNP in the assay was 2.0 pg/mL.

The study protocol for the ascertainment of the adiponectin sampling was approved by the Morehouse School of Medicine Institutional Review Board. Venous blood measurements of adiponectin and leptin were described elsewhere [17].

Statistical analysis

For each demographic characteristic, echocardiographic measure and biomarker, Student's *t*-test was performed on continuous variables and chi-square tests were performed on categorical variables comparing measurements among men and women.

Multiple linear regression was used to test the associations between BNP and adiponectin or leptin, controlling for pertinent confounders through calculations of β -coefficients, *P*-values and their respective 95% confidence intervals (CIs). Model 1 included standard cardiovascular risk factors including age, gender, BMI, eGFR, diabetes, and hypertension. Model 2 included all covariates in model 1 as well as the echocardiographic measures of LVM and ejection fraction. Model 3 included those in model 1 plus relevant cardiovascular biomarkers, including aldosterone, renin, and the addition of adiponectin or leptin. Effect modification was assessed through the addition of an interaction term to the linear model between gender and adiponectin or leptin.

Multiple adjusted logistic regression was used to report the odds ratios (OR) reflecting the association of adiponectin or leptin with BNP. The covariates adjusted for were identical to those implemented in the multiple linear regression models. Adiponectin, leptin, and BNP were discretized for logistic analysis. Adiponectin and leptin were both divided into quartiles, the cut-point was decided *a priori* to be 75%. The upper 25% was compared to the lower 75%. BNP was discretized based on the clinical cut-point of 100 pg/mL.

Analyses were performed using R version 3.5.3 [23]. Figure 1 was generated with the 'ggplot2' package [24].

Results

Descriptive statistics

Table 1 reports the descriptive statistics of this JHS sample, including demographic, clinical, biomarker, and

Fig. 1

Multivariate adjusted associations of adipokines with brain natriuretic peptide in men and women.

echocardiographic measures. Among the 3738 individuals in our sample, 1362 (36%) were men, and 2376 (64%) were women. Men and women had statistically significant different means among most variables in this study. The mean (SD) age of men was 53 (13) and the mean age of women was 54 (13) ($P < 0.01$). Mean (SD) BMI was 30 (6) in men and 33 (8) in women ($P < 0.01$). Mean (SD) BNP in men 14 (34) pg/mL and 16 (28) in women and were not statistically different ($P = 0.15$).

Adiponectin

Table 2 reports the main effects of the associations of adiponectin and leptin with BNP, as gender significantly modified the relation between adiponectin and BNP at $\alpha = 0.10$ ($\beta = 0.11$, $P = 0.06$) the analysis was stratified by gender. In men (Table 3), a direct relation with adiponectin and BNP was observed in all three models: model 1 [$\beta = 0.47$ (95% CI, 0.38–0.55)], model 2 [$\beta = 0.45$ (95% CI,

0.34–0.55)], and model 3 ($\beta = 0.41$ (95% CI, 0.26–0.57)]. Among women (Table 4), a direct relation with adiponectin and BNP was observed in all three models, model 1 [$\beta = 0.38$ (95% CI, 0.31–0.46)], model 2 [$\beta = 0.38$ (95% CI, 0.38–0.47)], and model 3 [$\beta = 0.32$ (95% CI, 0.18–0.44)]. Figure 1 depicts the beta coefficients and CIs for the associations of adiponectin and BNP in all three models.

Table 5 reports the odds ratios of BNP levels being higher than 100 pg/mL among participants in the highest quartile compared to the lower three quartiles. In the parsimonious model, participants in the highest quartile were 1.70 times more likely to have an elevated BNP compared to participants in the lower three quartiles (95% CI, 1.07–2.72). After the model was adjusted for left ventricular mass and ejection fraction, the relative odds of elevated BNP increased to 2.08 (95% CI, 1.01–4.32). The association was attenuated after adjustment for common cardiovascular-related biomarkers.

Table 1 Descriptive statistics for Jackson Heart Study sample

	Men (n=1362)	Women (n=2376)	P value
Demographic characteristics			
Age, years	53.03 (13.20)	54.22 (12.77)	<0.01
BMI (kg/m ²)	29.97 (6.34)	32.92 (7.71)	<0.01
Clinical characteristics			
Smoking (%)			
Never n=2565	790 (58.39%)	1775 (75.15%)	<0.01
Previous n=663	315 (23.28%)	348 (14.73%)	
Current n=487	248 (18.33%)	239 (10.12%)	
eGFR by MDRD	88.69 (16.77)	86.12 (18.69)	<0.01
Fasting plasma glucose (mg/dL)	99.49 (30.40)	99.85 (33.70)	0.75
LDL/HDL ratio	2.98 (1.24)	2.44 (0.99)	<0.01
Triglycerides (mg/dL)	116.30 (96.88)	100.7 (68.84)	<0.01
Diastolic blood pressure (mmHg)	81.45 (10.56)	77.52 (10.10)	<0.01
Systolic blood pressure (mmHg)	127.60 (17.56)	125.70 (17.56)	<0.01
Waist circumference, cm	101.2 (15.47)	100.40 (16.88)	0.13
Biomarker			
BNP (pg/mL)	14.19 (33.73)	15.76 (27.97)	0.15
Adiponectin (µg/mL)	4.00 (3.12)	5.95 (3.12)	<0.01
Leptin (ng/mL)	11.32 (10.45)	37.85 (24.74)	<0.01
Aldosterone (ng/mL)	5.80 (4.34)	5.85 (6.54)	0.75
Renin (ng/mL)	1.31 (3.80)	1.79 (6.99)	0.06
Echocardiographic measures			
M-mode left ventricular mass in grams n=2696	168.50 (49.50)	139.50 (36.84)	<0.01
Left ventricular ejection fraction % (SD) n=3999	60.63 (7.22)	62.89 (6.94)	<0.01

Results reported as mean (SD) unless otherwise noted.

BNP, brain natriuretic peptide; MDRD, Modification of Diet in Renal Disease (Study).

Table 2 Associations of adipokines with brain natriuretic peptide in men and women

	Associations with brain natriuretic peptide			
	Adiponectin		Leptin	
	β	P value	β	P value
Model 1: biomarker + age + sex + BMI + smoking + eGFR + DM + HTN	0.42	<0.001	-0.14	<0.001
Model 2: model 1 + left ventricular mass + ejection fraction	0.40	<0.001	-0.15	<0.001
Model 3: model 1 + aldosterone + renin + adiponectin OR leptin	0.34	<0.001	-0.16	0.01

To satisfy the assumption of normality, all biomarkers were transformed by natural logarithms. DM, diabetes mellitus; HTN, hypertension.

Leptin

Gender did not significantly modify the relation between leptin and BNP. Table 2 includes the main effects of leptin with BNP; an inverse relation of leptin to BNP was observed in model 1 and model 2: model 1 [$\beta = -0.14$ (95% CI, -0.24 to -0.03)], [$\beta = -0.17$ (95% CI, -0.30 to -0.04)]. Adjustment of aldosterone and renin attenuated the magnitude and significance of the association: Model 3 [$\beta = -0.16$ (95% CI, -0.33 to 0.01)]. The coefficients for the effect of leptin on BNP did not differ across gender and are reported in Tables 3 and 4. Figure 1 depicts the beta coefficients and CIs for the associations of Leptin and BNP in all three multivariate-adjusted models.

Table 5 reports the odds ratios of upper quartile to lower three quartiles of leptin; no association was found to be statistically significant.

Discussion

In this cross-sectional analysis, differential associations of leptin and adiponectin on BNP were observed among participants of the JHS. Adiponectin was directly associated with BNP while leptin was inversely associated

with BNP. The associations were found to be statistically significant after adjusting for standard demographic and echocardiographic variables. The relationship with leptin and BNP was attenuated after the addition of the renin-angiotensin-aldosterone system (RAAS)-related variables aldosterone and renin.

Our finding of the differential association of adiponectin and leptin with BNP is contrary to our initial hypothesis. *In vivo*, adiponectin and leptin are consistently reported to be inversely correlated and a differential association of adiponectin and leptin has been observed with increasing obesity [25]. Adiponectin is relatively abundant in healthy individuals and reduced in obese participants, and insulin-resistant hypertensive subjects [26,27].

The direct association of adiponectin and BNP has been consistently reported in observational studies [28,29]. Cross-sectional analyses have reported positive correlations of adiponectin and BNP in noncachectic patients with systolic heart failure [30]. Increased levels of adiponectin were associated with elevated BNP levels and LVH in hemodialysis patients with type 2 diabetes

Table 3 Associations of adipokines with brain natriuretic peptide in men

	Associations of adiponectin with BNP			
	Men		Women	
	β	95% CI	β	95% CI
Model 1: biomarker + age + BMI+ smoking + eGFR + DM + HTN	0.47	(0.38, 0.55)	0.38	(0.31, 0.46)
Model 2: model 1 + left ventricular mass + ejection fraction	0.45	(0.34, 0.55)	0.38	(0.38, 0.47)
Model 3: model 1 + aldosterone + renin + adiponectin OR leptin	0.41	(0.26, 0.57)	0.32	(0.18, 0.44)]

To satisfy the assumption of normality, all biomarkers were transformed by natural logarithms. BNP, brain natriuretic peptide; DM, diabetes mellitus; HTN, hypertension.

Table 4 Associations of adipokines with brain natriuretic peptide in women

	Associations with brain natriuretic peptide			
	Adiponectin		Leptin	
	β	<i>P</i> value	<i>B</i>	<i>P</i> value
Model 1: biomarker + age + BMI+ eGFR + DM + smoking + HTN	0.38	<0.001	−0.17	0.01
Model 2: model 1 + left ventricular mass + ejection fraction	0.38	<0.001	−0.17	0.04
Model 3: model 1 + aldosterone + renin + adiponectin OR leptin	0.32	<0.001	−0.17	0.07

To satisfy the assumption of normality, all biomarkers were transformed by natural logarithms. DM, diabetes mellitus; HTN, hypertension.

Table 5 Odds ratios of adipokines with brain natriuretic peptide

	Associations with brain natriuretic peptide	
	Adiponectin	Leptin
	OR (95% CI)	OR (95% CI)
Model 1: biomarker + age + sex + BMI+ eGFR + diabetes + HTN	2.68 (1.66–4.31)	0.97 (0.65–1.44)
Model 2: model 1 + left ventricular mass + ejection fraction	4.01 (1.85–8.68)	1.47 (0.75–2.89)
Model 3: model 1 + aldosterone + renin + adiponectin OR leptin	4.39 (1.37–14.10)	1.13 (0.40–3.26)

Brain natriuretic peptide was dichotomized by clinical cut point of 100 pg/mL, adipokine was dichotomized by 75th percentile.

mellitus [31]. A prospective cohort of 5574 men and women without heart failure at baseline also found a direct association between plasma adiponectin and NT-proBNP [32]. The current literature suggests a compensatory mechanism between adiponectin, BNP, and congestive heart failure attributed to pathophysiological stress. Release of BNP in response to ventricular dysfunction promotes the expression of adiponectin for its protective effects. Adiponectin signaling dysregulation, that is, ‘adiponectin resistance’, may also lead to sustained-elevated levels of adiponectin [17].

We observed an inverse association of leptin and BNP levels in men and women. This relationship was present after adjustment for measures of left ventricular geometry and function (left ventricular mass and ejection fraction) but attenuated after the addition of RAAS hormones (aldosterone and renin). Thus, RAAS-related hormones explain similar variance to leptin and BNP and may confound the association of leptin and BNP. Natriuretic peptides have been identified as vasodilators and suppression of RAAS, and increase renal blood flow [33]. Leptin has been associated with higher blood pressure levels, the

prevalence of hypertension, as well as activation of RAAS [33,34]. While similar results in the literature are sparse, a study of adiponectin and leptin as prognostic indicators of pulmonary arterial hypertension found leptin to be associated with lower NT-proBNP [35]. The sympathetic nervous system and the RAAS have independent mechanism for progression of ventricular remodeling and different etiological pathways [36]. The three traditional criteria for confounding, the exposure relating to outcome, the confounder being a risk factor for the outcome and the absence of the confounder on the causal pathway are thereby met, providing for the confounding of RAAS on the leptin-BNP pathway.

We hypothesized consistent results to those of Allison *et al.* [7], who utilized data from the Multi-Ethnic Study of Atherosclerosis (MESA). Both studies report effect modification of adiponectin and BNP levels by gender. We observed consistently stronger associations of adiponectin concentration with BNP levels in men. Unlike the analysis performed by Allison *et al.*, leptin was found to be significant prior to the adjustment for related hormones.

Average measurements of leptin remained consistent among NT-proBNP defined quartiles of MESA participants (19.5–20.8 ng/mL) while this JHS sample had more variability [Leptin in men 11.32 (SD 1.45), women 37.85 (SD 24.74)]. It is possible that differences among adiponectin, leptin, and BNP between the two cohorts could be explained by cohort makeup or selection biases. The most apparent difference between the two studies may rely on the cohort makeup. JHS is a community sample of African-American participants in Jackson, Mississippi, while MESA is multiethnic (28% White, 22% African-American, 22% Hispanic, and 12% Chinese) from six regions around the USA (North Carolina, New York, Maryland, Minnesota, Illinois, and California). Obesity and blood pressure values are higher in the base JHS cohort. These imbalances may explain some of the differences between leptin and BNP levels across both cohorts. Additionally, JHS measured BNP, while MESA measured NT-proBNP. While there may not be complete harmonization among the measurement, the two peptides have comparable diagnostic performance [37].

Strengths and limitations

Our study was conducted with participants from the JHS, the largest community-based sample of African Americans, which implements high-quality data collection techniques. To limit bias, we excluded participants with prevalent CVD or missing echocardiographic measurements, which may limit the generalizability of the study. Our study is cross-sectional, and thus we cannot characterize further this complex interrelationship of adiponectin, leptin, and BNP with renin–angiotensin–aldosterone system. Measurements of biomarkers were limited to one time-point. It is also worth noting that this population has a high frequency of participants using antihypertensive medication, which may be suppressing BNP levels and attenuating the sample level associations. Finally, researchers have suggested that the different oligomers of adiponectin (low, medium, and high molecular weight) may exert distinct actions on specific target tissues. The ability to stratify or control for these differential effects is currently limited due to a lack of JHS measurements as well as current sample size restrictions. Such analyses should be considered in the future.

In conclusion, we consistently observed different linear relationships of adiponectin and leptin with BNP, and adiponectin was linearly associated with BNP. Odds of elevated BNP in participants with elevated adiponectin levels were observed in multivariate-adjusted models. These relationships were maintained after the addition of left ventricular geometry and function, but confounded by the addition of RAAS-related hormones, renin, and aldosterone. These findings provide evidence towards the paradoxical relationship between adiponectin and plasma BNP, possibly through adiponectin resistance.

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Conflicts of interest

There are no conflicts of interest.

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