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Relation of Leptin to Left Ventricular Hypertrophy (From the Multi-Ethnic Study of Atherosclerosis)

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Abstract

Increasing adiposity increases the risk for left ventricular hypertrophy. Adipokines are hormone-like substances from adipose tissue that influence several metabolic pathways relevant to LV hypertrophy. Data was from participants enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA) who underwent magnetic resonance imaging of the heart and who also had fasting venous blood assayed for 4 distinct adipokines (adiponectin, leptin, tumor necrosis factor – alpha and resistin). 1,464 MESA participants had complete data. The mean age was 61.5 years, the mean body mass index was 27.6 kg/m² and 49% were female. With adjustment for age, sex, race, height and weight, multivariable linear regression modeling revealed that a 1-SD increment in leptin was significantly associated with smaller LV mass (β : -4.66 % predicted, p-value: < 0.01), LV volume (-5.87 % predicted, < 0.01), stroke volume (-3.23 ml, p < 0.01) and cardiac output (-120 mL/min, p = 0.01) as well as a lower odds ratio for the presence of LV hypertrophy (OR: 0.65, p < 0.01), but a higher ejection fraction (0.44%, p = 0.05). Additional adjustment for the traditional cardiovascular disease (CVD) risk factors, insulin resistance, physical activity, education, income, inflammatory biomarkers, other selected adipokines and pericardial fat did not materially change the magnitude or significance of the associations. The associations between the other adipokines and LV structure and function were inconsistent and largely non-significant. In conclusion, the results indicate that higher levels of leptin are associated with more favorable values of several measures of LV structure and function.

Keywords

leptin; left ventricle; hypertrophy; mass

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INTRODUCTION

Increasing adiposity confers an increased risk for left ventricle (LV) hypertrophy.¹ In those who are of normal weight or overweight, this association appears to be independent of the contribution of arterial blood pressure suggesting a non-hemodynamic mechanism of hypertrophy.² In this regard, if the normal regulation of triglycerides is disrupted, they can be deposited in other locations to include the cardiac myocyte³ and, if excessive, may lead to dilated cardiomyopathy.⁴ The metabolism of triglycerides is, at least partially, regulated by cytokines that are secreted from a variety of tissues.⁵ Those that are secreted by adipose tissue are called adipokines and include adiponectin, leptin, tumor necrosis factor – alpha (TNF- α) and resistin. Adiponectin and leptin regulate insulin action and energy metabolism in both adipose and muscle tissues.⁶ As such, these adipokines may influence the accumulation of triglycerides in non-adipose tissue compartments, such as the left ventricle. Given this, we aimed to determine the magnitude and significance of the associations between selected adipokines and different measures of LV structure and function.

METHODS

The MESA is a longitudinal cohort study of multi ethnic groups.⁷ In brief, between July 2000 and August 2002, 6,814 men and women who were 45 to 84 years old and were free of clinically apparent cardiovascular disease (CVD) were recruited from 6 United States communities. Enrolled participants returned for follow-up clinic visits 2, 4 and 6 years after the baseline clinic visit that were labeled as clinic visits 2, 3 and 4. Written informed consent was obtained on IRB approved forms from all participants.

At clinic visits 2 and 3, a random subsample of 1,970 participants enrolled in an ancillary study on body composition and adiposity-associated inflammation. Fasting venous blood was collected on these participants and utilized for measuring different adipokines (see below). These participants are the focus of the current study.

At all clinic visits, standardized questionnaires obtained sociodemographic, ethnicity and health history information. Cigarette smoking was defined as current, former, or never. Height, weight, waist and hip circumferences were measured with participants wearing light clothing and no shoes. Resting blood pressure was measured 3 times in seated participants with a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon). Hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg (measured at the clinic visit) or current use of an antihypertensive medication.

At the baseline clinic visit, MRI exams of the heart were performed using scanners with 1.5-T magnets to determine specific measures of cardiac structure and function.⁸ Imaging consisted of fast gradient echo cine LV images using a phased-array surface coil with time resolution of <50 milliseconds and the following scan protocol: 6 mm slice thickness, 400 mm FOV, 256×128 matrix, 20° flip angle, TE = 3 – 5 msec and TR = 8 – 10 msec. Imaging data were read using MASS software at a single reading center by readers trained in the MESA protocol and without knowledge of risk factor information.⁹ Reliability (by intraclass correlations) was 0.97 for LV mass, 0.98 for end-diastolic volume and 0.95 for end-systolic volume.¹⁰

At the baseline clinic visit, all subjects underwent ultrafast computed tomography of the thorax to ascertain the presence and extent of coronary artery calcium. The images from these scans were analyzed for the extent of adipose tissue in the pericardium (pericardial fat). The method for this procedure has been described.¹¹

At all clinic visits, fasting morning blood samples were collected, centrifuged and shipped overnight to the MESA central laboratory, stored at -80°C and subsequently assayed for total and high-density lipoprotein cholesterol, triglycerides, and glucose levels, as well as markers C-reactive protein, fibrinogen, interleukin-6 and insulin concentration. Dyslipidemia was defined as a total-cholesterol/HDL-cholesterol ratio > 5.0 or if the participant used medication to reduce cholesterol. Diabetes was defined as fasting glucose ≥ 126 mg/dL or use of hypoglycemic medication.

Stored fasting blood samples from visits 2 and 3 were analyzed to provide levels of adiponectin, leptin, TNF – α and resistin. These adipokines were measured using Bio-Rad Lumines flow cytometry at the MESA central laboratory. Average analytical coefficients of variation across control samples for these analytes ranged from 6.0–13.0%.

LV hypertrophy was defined as having an indexed LV mass $>$ the 95th percentile, relative to body size and gender. Since body size is strongly related to leptin and both LV mass and volume, and to account for the potential confounding by body size, we constructed outcome variables for LV mass and volume that were indexed and resulted in the predicted % of LV mass and volume based on height, weight and gender.¹² The results using these indices were similar to analyses using unindexed variables and that were adjusted for height and weight. Therefore, we utilized *non-indexed* values for LV mass and volume and adjusted for height and weight in the models.

The adipokines were skewed and therefore log transformed. To provide comparability across the different adipokines, we utilized 1-SD increments in these variables. Potential confounding was assessed by sequential linear regression modeling: Model 1 adjusted for the adipokine, age, gender, race/ethnicity, height, weight and the waist to hip ratio; Model 2 additionally controlled for hypertension, dyslipidemia, smoking, diabetes mellitus, family history of coronary heart disease, education, income, physical activity and insulin resistance (by HOMA); Model 3 added C-reactive protein, interleukin-6, fibrinogen and the other adipokines; and Model 4 further added pericardial fat. Of note, when height and weight was replaced with body mass index, the results were not different. Therefore, and since height and weight explained a higher proportion of the variance than body mass index (R^2 : 0.54 vs. 0.49, respectively), we elected to use height and weight in the multivariable models.

Generalized additive models were then used to test for non-linearity in the relationships between each adipokine and each endpoint. Significant non-linearity was detected in the models for leptin and both LV mass and LV volume and further quantified by utilizing quartiles of leptin.

RESULTS

Of the 1,970 participants that were included in the ancillary study on abdominal body composition, 1,464 had baseline MRI scans of the heart and complete biomarker data for the adipokines. The characteristics of this study cohort are provided in Table 1.

With adjustment for age, sex, race, height and weight, multivariable linear regression modeling revealed that a 1-SD increment in leptin was significantly associated with smaller LV mass, volume and stroke volume, as well as and cardiac output and a lower odds ratio for the presence of LV hypertrophy, but a higher ejection fraction (Table 2). After the same adjustment, higher adiponectin was associated with larger LV volume, LV stroke volume and cardiac output, but a lower LV ejection fraction. Adiponectin was not significantly associated with LV mass or the odds for LV hypertrophy. When the other adipokines were assessed, the only significant associations were between resistin and both LV ejection fraction and LV hypertrophy.

Because the associations appeared to be the most robust and consistent for leptin, we constructed general additive model (GAM) plots to determine if these associations were non-linear (Figure 1). After adjustment, there were significant *non-linear* associations with LV mass and LV volume ($p < 0.01$ for both) but not for ejection fraction, stroke volume or cardiac output ($p = 0.25, 0.37, 0.23$, respectively). For both LV mass and volume, the inflection points were between leptin values of 20 and 40 pg/ml.

Based on these findings, we categorized leptin into quartiles and conducted multivariable linear regression analyses (Table 3). With adjustment for age, gender, ethnicity, height and weight, and compared to quartile 1, quartiles 2 – 4 were significantly associated with progressively smaller LV mass, LV volume and LV stroke volume, as well as significantly lower odds for the presence of LV hypertrophy. Additional adjustment for the traditional CVD risk factors, education, income, physical activity and insulin resistance (model #2), inflammatory biomarkers including the other adipokines (model #3) and the extent of pericardial fat (model #4), did not materially change the magnitude or significance of the associations. Higher levels of leptin were not significantly associated with LV ejection fraction or cardiac output.

There were no significant interactions between leptin and body mass index, ethnicity and blood pressure medication use (separately) for LV mass and volume.

DISCUSSION

In this cross-sectional study of a multi-ethnic population, we found significant inverse associations between leptin and LV mass, volume and stroke volume, as well as a significantly reduced odds for the presence of LV hypertrophy. These associations were independent of age, gender, ethnicity, the traditional CVD risk factors, insulin resistance, physical activity, inflammatory biomarkers (including other adipokines) and the extent of pericardial fat. Moreover, the associations with mass and volume were non-linear and demonstrated threshold effects. Conversely, there were very few significant associations between adiponectin, resistin and TNF – α and the different measures of LV structure and function.

Leptin is produced by adipose tissue and, besides regulating insulin sensitivity⁶ and appetite¹³, regulates plasma free fatty acid clearance by stimulating their uptake and/or oxidation in liver and muscle.¹⁴ More specifically and in normal situations, deposition of triglycerides in non-adipocyte tissues is tightly regulated [by leptin] such that *none* are deposited in these locations and intracellular fatty acids are maintained at normal physiologic levels in non-adipose tissues by oxidation and limitation of *de novo* synthesis. When this regulation is disrupted, triglycerides may accumulate in ectopic locations, such as the myocardium, and result in non-ischemic dilated cardiomyopathy.³

Given this, one potential mechanism by which higher leptin levels could result in smaller left ventricular mass is by inhibiting the deposition of triglycerides in the myocardium in normal weight, overweight and early obese individuals. This hypothesis is supported by studies of animals demonstrating the development of LV hypertrophy (due to myocyte hypertrophy) among those that were either lacking leptin or its receptor. Notably, the LV hypertrophy regressed significantly only among those mice that later received leptin infusions and not those who lost weight due to caloric restriction.¹⁵ In other studies, administration of adenoviral leptin ameliorated the presence of myocardial steatosis and prevented the progression to dilated cardiomyopathy¹⁶, while leptin repletion in deficient mice has been shown to result in a reduction in the extent of LV hypertrophy.¹⁷

Why, then, have higher leptin levels been previously associated with unfavorable levels of LV structure in some previous studies?¹⁸ One potential explanation is leptin resistance.¹⁹ That is, as *obesity* increases, the likelihood of desensitization of the leptin receptor increases.²⁰ If this is the case, the levels of leptin will increase as the level of adiposity does the same, but the ability of leptin to minimize deposition of triglycerides in ectopic locations will be eliminated. In this regard, prior studies have demonstrated a reduction in the metabolic effects of leptin at higher levels of obesity.²¹ Moreover, leptin has been associated with higher myocardial wall thickness among those who are insulin resistant²², and individuals with insulin resistance have many of the same characteristics as those who appear to be leptin resistant (e.g. metabolic syndrome).²³

Concomitantly, there are several studies reporting an inverse association between leptin and LV mass among those with a body mass index in the *non-obese* (< 30) range. For example, among adult men and women with an average body mass index of approximately 26, leptin was inversely associated with LV mass.²⁴ Similarly, studies of postmenopausal women with an average body mass index of 27, as well as men and women with a body mass index of 26 and over the age of 70 years, reported significant *inverse* associations between leptin and LV mass.^{25,26}

Strengths of this study include a relatively large, well-characterized, multi-ethnic cohort from across the United States, valid and reproducible measures of four different adipokines and a novel method for measurements of LV structure and function by magnetic resonance imaging. Limitations include few subjects at the highest levels of obesity and a cross-sectional study design. Also, the MRI scanning protocol used for this study results in more artifact and signal to noise issues than current protocols, which may influence assessment of diastolic function and potentially measurement of LV volume (but not LV mass). These limitations are largely overcome by employing a larger sample size.

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FIGURE 1.
 GENERALIZED ADDITIVE MODEL (GAM) PLOT FOR LEPTIN AND DIFFERENT
 MEASURES OF LEFT VENTRICULAR STRUCTURE
 Adjusted for age, gender, ethnicity, height and weight LV Mass in grams, LV Volume in ml,
 Leptin in ng/ml

TABLE 1

COHORT CHARACTERISTICS

Characteristic	Value
Age (years) [†]	61.5 (9.6)/61.0
Female [‡]	720 (49%)
Caucasian [‡]	590 (40%)
Chinese American [‡]	214 (15%)
African American [‡]	278 (19%)
Hispanic American [‡]	382 (26%)
High School Graduate or Higher [‡]	1207 (82%)
Income > \$49,000 [‡]	578 (39%)
Body Mass Index (kg/m ²) [†]	27.6 (4.7)/27.0
Fasting Glucose (mg/dL)	97.8 (27.3)/91.0
Urine Creatinine (mg/dL)	118.9 (67.7)/111.9
Systolic Blood Pressure (mmHg)	123 (20.5)/120
Diastolic Blood Pressure (mmHg)	70 (10.0)/70
Current Smoker [‡]	184 (13%)
Former Smoker [‡]	519 (35%)
Impaired Fasting Glucose [‡]	175 (12%)
Untreated Diabetes [‡]	42 (3%)
Treated Diabetes [‡]	116 (8%)
Hypertension Medication Use [‡]	500 (34%)
Total Cholesterol (mg/dL)	189 (35)
LDL Cholesterol (mg/dL)	112 (31)
Triglycerides (mg/dL)	134 (95)
Lipid Lowering Medication Use [‡]	235 (16%)
Family History of Cardiovascular Disease [‡]	191 (13%)
C-reactive protein (mg/L) [†]	3.3 (4.8)/1.7
Interleukin - 6 (pg/mL) [†]	2.3 (1.7)/1.8
Fibrinogen (mg/dL) [†]	431 (84.0)/424
Adiponectin (ng/ml) [†]	20.9 (13.3)/17.6
Leptin (pg/ml) [†]	19.4 (21.6)/12.1
Tumor Necrosis Factor- α (pg/ml) [†]	5.8 (10.7)/4.6
Resistin (pg/ml) [†]	16.0 (6.7)/14.8
Left Ventricular Mass (grams)	146.8 (38.6)/141.0
Left Ventricular Volume (mL)	127.9 (30.5)/124.1

Characteristic	Value
Left Ventricular Ejection Fraction (%)	69.2 (7.3)/69.8
Cardiac Output (L/min)	5.8 (1.4)/5.6
Left Ventricular Mass/Volume Ratio (g/mL)	1.2 (0.2)/1.1

[†]Mean (SD)/Median;

[‡]N(%)

TABLE 2

ASSOCIATIONS BETWEEN ADIPOKINES AND DIFFERENT MEASURES OF LEFT VENTRICULAR STRUCTURE AND FUNCTION*

Mass		Volume		Ejection Fraction		Stroke Volume		Cardiac Output		Hypertrophy		
Panel 1 – Adipokines Modeled Separately												
Adipokine	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI	OR	95% CI
Leptin	-4.66	-6.3, -3.0 [†]	-5.87	-7.4, -4.4 [†]	0.44	0.0, 0.9 [†]	-3.23	-4.3, -2.2 [†]	-0.12	-0.2, 0.0 [†]	0.65	0.5, 0.9 [†]
Adiponectin	0.83	-1.8, 3.4	4.07	1.7, 6.4 [†]	-0.68	-1.4, 0.0 [†]	1.77	0.1, 3.4 [†]	0.16	0.0, 0.3 [†]	0.82	-0.5, 1.3
Resistin	1.63	-1.8, 5.0	-0.01	-3.1, 3.1	-0.95	-1.8, -0.1 [†]	-1.33	-3.5, 0.8	-0.05	-0.2, 0.1	2.24	1.2, 4.1 [†]
TNF-alpha	1.65	-0.8, 4.1	-0.80	-3.0, 1.4	-0.54	-1.2, 0.1	-1.24	-2.8, 0.3	-0.03	-0.2, 0.1	1.06	-0.7, 1.6
Panel 2 – Adipokines Modeled Together												
Adipokine	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI	OR	95% CI
Leptin	-4.86	-6.6, -3.1 [†]	-5.38	-6.8, -3.8 [†]	0.41	-0.1, 0.9	-2.92	-4.0, -1.8 [†]	-0.10	-0.2, 0.0 [†]	0.60	0.5, 0.8 [†]
Adiponectin	-0.18	-2.8, 2.5	2.76	0.4, 5.1 [†]	-0.47	-1.2, 0.2	1.25	-0.4, 2.9	0.15	0.0, 0.3 [†]	0.69	-0.4, 1.1
Resistin	1.77	-1.7, 5.2	-0.10	-3.2, 3.0	-0.63	-1.5, 0.3	-0.87	-3.1, 1.3	-0.04	-0.2, 0.1	2.64	1.4, 2.5 [†]
TNF-alpha	2.23	-0.3, 4.8	0.14	-2.1, 2.4	-0.50	-1.2, 0.2	-0.55	2.2, 1.1	-0.00	-0.1, 0.1	1.06	-0.7, 1.7

Per 1-SD increment of each ln leptin

[†] p < 0.05, β = parameter estimate, OR = odds ratio, CI = confidence interval

Units (β): LV Mass in grams, LV Volume in ml, LV Ejection Fraction in %, Stroke Volume in ml, Cardiac Output in ml/min

* Adipokine adjusted for age, sex, ethnicity, height and weight

TABLE 3

ASSOCIATIONS BETWEEN QUANTILES OF LEPTIN AND DIFFERENT MEASURES OF LEFT VENTRICULAR STRUCTURE AND FUNCTION

	Mass	Volume	Ejection Fraction	Stroke Volume	Cardiac Output	Hypertrophy
Leptin Quartile	β ; 95% CI	β ; 95% CI	β ; 95% CI	β ; 95% CI	β ; 95% CI	OR; 95% CI
<i>Model 1</i>						
Q2	-6.5; -10.3, -2.7 [†]	-9.4; -12.8, -6.1 [†]	0.50; -0.5, 1.5	-5.9; -8.3, -3.6 [†]	-0.25; -0.4, -0.1 [†]	0.45; 0.2, 0.9 [†]
Q3	-10.2; -14.5, -5.9 [†]	-11.0; -14.8, -7.1 [†]	0.83; -0.3, 2.0	-6.3; -9.0, -3.6 [†]	-0.12; -0.3, 0.1	0.40; 0.2, 0.9 [†]
Q4	-13.9; -19.3, -8.6 [†]	-12.9; -17.6, -8.2 [†]	0.62; -0.8, 2.00	-7.7; -11.1, -4.4 [†]	-0.23; -0.5, 0.1	0.31; 0.1, 0.8 [†]
<i>Model 2</i>						
Q2	-6.5; -10.2, -2.9 [†]	-8.9; -12.3, -5.5 [†]	0.23; -0.8, 1.2	-6.0; -8.4, -3.7 [†]	-0.23; -0.4, 0.0 [†]	0.35; 0.2, 0.8 [†]
Q3	-10.1; -14.4, -5.9 [†]	-10.2; -14.1, -6.2 [†]	0.69; -0.5, 1.9	-6.0; -8.8, -3.3 [†]	-0.11; -0.3, 0.1	0.31; 0.1, 0.7 [†]
Q4	-15.5; -20.7, -10.2 [†]	-12.1; -16.9, -7.2 [†]	0.50; -0.9, 1.9	-7.5; -10.9, -4.0 [†]	-0.22; -0.5, 0.1	0.17; 0.1, 0.5 [†]
<i>Model 3</i>						
Q2	-6.5; -10.3, -2.8 [†]	-8.9; -12.3, -5.5 [†]	0.17; -0.8, 1.2	-6.1; -8.6, -3.7 [†]	-0.24; -0.4, 0.0 [†]	0.37; 0.2, 0.8 [†]
Q3	-10.8; -15.1, -6.4 [†]	-10.4; -14.4, -6.4 [†]	0.81; -0.4, 2.0	-6.0; -8.8, -3.2 [†]	-0.12; -0.4, 0.1	0.28; 0.1, 0.7 [†]
Q4	-16.0; -21.5, -10.6 [†]	-12.1; -17.1, -7.0 [†]	0.63; -0.8, 2.1	-7.3; -10.8, -3.7 [†]	-0.21; -0.5, 0.1	0.14; 0.1, 0.4 [†]
<i>Model 4</i>						
Q2	-6.1; -9.8, -2.4 [†]	-8.4; -11.9, -5.0 [†]	0.24; -0.8, 1.3	-5.8; -8.2, -3.3 [†]	-0.25; -0.5, -0.1	0.39; 0.2, 0.9 [†]
Q3	-10.3; -14.7, -6.0 [†]	-9.9; -13.9, -5.9 [†]	0.89; -0.3, 2.1	-5.6; -8.4, -2.8 [†]	-0.13; -0.4, 0.1	0.29; 0.1, 0.7 [†]
Q4	-15.5; -21.3, -10.4 [†]	-11.8; -16.9, -6.8 [†]	0.66; -0.8, 2.1	-7.10; -10.6, -3.6 [†]	-0.22; -0.5, 0.1	0.13; 0.1, 0.4 [†]

[†] p < 0.05; β = parameter estimate from linear regression, OR = Odds Ratio, CI = Confidence Interval

Q1: 0 – 5.6 (Referent Quartile), Q2: 5.6 – 13.5, Q3: 13.5 – 28.3, Q4: > 28.13 pg/ml.

Model 1: Leptin adjusted for age, gender, ethnicity, height and weight, waist/hip ratio.

Model 2: Leptin adjusted for model 1 + systolic BP, hypertensive meds, dyslipidemia, smoking, diabetes, family history of CHD, education, income, moderate/vigorous physical activity, insulin resistance (HOMA).

Model 3: Leptin adjusted for model 2 + C-reactive protein, interleukin-6, fibrinogen, resistin, TNF- α and adiponectin.

Model 4: Leptin adjusted for model 3 + pericardial fat