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Association of Serum Leptin With Future Left Ventricular Structure and Function: The Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

Background/Objectives—Earlier studies differ on whether serum leptin is associated with adverse or beneficial cardiac structure. We determined the association between serum leptin with subsequent cardiac structure and function.

Methods—Multicenter longitudinal study of Black, White, Hispanic and Asian-American men and women. Cardiac MRI (CMR) was completed 6 to 8 years after leptin was measured. Left ventricular (LV) mass and volumes were indexed to body surface area. Multivariable linear regression models were constructed to assess the associations between leptin and risk factor adjusted (age, race, gender, systolic blood pressure, anti-hypertensive usage, LDL, HDL, hyperlipidemia medication usage, diabetes, diabetic medication usage, chronic kidney disease, alcohol and tobacco use, adiponectin and BMI) CMR variables.

Results—Relative to participants in the lowest quintile of leptin concentration, participants in the highest quintile had a lower risk factor adjusted LV mass (-14g), LV mass index (-9g/m^2), LV end diastolic volume index (LVEDVi) (-7 ml/m^2), LV end systolic volume index (LVESVi) (-3 ml/m^2) and stroke volume (-5 ml) (all $p \leq 0.05$). On regression analysis, a doubling of leptin concentration was associated with lower LV mass (-2.5g±0.7g), LV mass index (-1.7±0.3 g/m^2), LVEDVi (-1.5±0.4 ml/m^2), LVESVi (-0.7±0.2 ml/m^2) and stroke volume (-1.0±0.5ml) (all $p \leq 0.05$).

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Conclusions—Higher leptin was associated with more favorable subsequent cardiac structure. Further study is needed to assess the prognostic and therapeutic implications of these observations.

Keywords

Leptin; Adipokine; Cardiac structure; Left ventricular mass

1.1 Introduction

Leptin is a cytokine best known for regulating body weight. Serum leptin levels directly correlate with percent body fat [1]. Animal studies have shown that serum leptin has numerous physiologic effects relevant to the cardiovascular system. For example, leptin protects the heart from lipid deposition, reverses endothelial cell dysfunction, causes coronary artery vasodilation, decreases apoptosis after ischemic injury and aids cardiac tissue in switching from fatty acid to glucose metabolism after ischemic injury, which is a less oxygen-intensive process [2-6]. However, leptin also increases oxidative stress and sympathetic nervous system activation [7-9].

Leptin's role in cardiac remodeling is unclear. Some cross-sectional studies in humans showed that higher leptin was associated with higher left ventricular (LV) mass and wall thickness [10, 11]. In contrast, other cross-sectional studies showed higher leptin was associated with lower LV mass and wall thickness [12, 13]. Two other human studies showed that higher leptin was associated with lower LV mass, wall thickness, volume, stroke volume and cardiac output several years before leptin was measured [14, 15]. Notably, earlier studies have not examined the associations between leptin and future cardiac structure and function. Therefore, we examined the associations between leptin with cardiac structure and function 6 to 8 years later. We also addressed whether body mass index (BMI), gender or race modified these associations.

Methods

2.1 Study Population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a longitudinal study of adult White, Black, Hispanic and Asian-American men and women [16]. MESA recruited 6814 participants (ages 45 to 84 years) without known cardiac disease from July 2000 to August 2002 from six United States communities. Informed consent was obtained from each participant and IRB approval was obtained at each participating institution. In 1960 randomly selected participants, serum leptin was measured at exam 2 or 3, which corresponded to 2 to 4 years after the baseline visit. Cardiac MRI(CMR) was completed at exam 5, ten years after the baseline clinic visit and 6 to 8 years after exams 2 and 3, in 3000 random participants. Leptin and baseline cardiac risk factors along with exam 5 CMR were assessed in 931 participants. These participants comprise the sample for the current study.

2.2 Measurements

Standardized questionnaires were used to obtain socio-demographic and health history information including medication usage. All measurements were completed with

participants wearing light clothing and no shoes. At each examination, blood pressure was measured at rest three times in seated participants, and the second and third measurements were averaged and recorded as the blood pressure for the exam. At each clinic visit, fasting morning blood samples were drawn, centrifuged and shipped to the MESA central laboratory. Blood samples were stored at -80°C. Lipid levels, creatinine and adiponectin were measured from these samples. Chronic kidney disease was defined as glomerular filtration rate<60 ml/min. Stored blood samples from exams 2 or 3 were assayed for leptin using Bio-Rad Luminex flow cytometry(Millepore, Maryland) at the MESA central laboratory. The average coefficient of variation for leptin was 1.1% [14].

CMR images were obtained using 1.5T MR scanners (Avanto and Espree, Siemens Medical Systems; Signa LX, GE Healthcare) with a six-channel anterior phased-array torso coil and corresponding posterior coil elements. Cine steady state free precession sequence was used to assess LV mass and volumes. Twelve short axis slices, one 4 chamber view and one 2 chamber view were acquired. LV mass and volumes were measured using commercially available software (CIM v6.2, New Zealand) [17, 18]. CMR variables analyzed were LV mass, LV end diastolic volume (LVEDV), LV end systolic volume (LVESV), Mass/Volume ratio (M/V ratio), stroke volume and LV ejection fraction (LVEF). M/V ratio was defined as LV mass/LVEDV. We also indexed by exam 5 body surface area (BSA) to examine the following variables: LV mass index (LVMi)=LV mass/BSA, LVEDV index (LVEDVi)=LVEDV/BSA and LVESV index (LVESVi)=LVESV/BSA. All three variables were indexed to BSA because indexing to height$^{1.7}$ or height$^{2.7}$ has been validated in echocardiography but not in CMR.

2.3 Statistical Analysis

Covariates adjusted for were age, race, gender, systolic blood pressure, anti-hypertensive use, LDL, HDL, hyperlipidemia medication use, diabetes, diabetic medication use, chronic kidney disease, current alcohol and tobacco use, adiponectin and BMI. CMR variables were adjusted for covariates measured at the time of leptin measurement.

We initially stratified the participants into quintiles based on leptin concentrations. We then compared the mean values for each risk factor adjusted CMR variable for the participants in each quintile.

Separately, leptin concentrations were $\log_2$ transformed to decrease skewness. For each CMR variable, multi-variable adjusted linear regression models were constructed with $\log_2$ leptin as the independent variable. The difference in each CMR variable associated with a doubling of leptin was determined because leptin was initially log transformed by base 2. Also, mean leptin for the highest leptin quintile was 23 times as high as mean leptin for the lowest leptin quintile, so a doubling of leptin concentration was well within the physiologic range, and thus clinically relevant.

Effect modification by BMI was examined by including interaction terms between $\log_2$ leptin and BMI groups (<25, 25-29.9, ≥30). Separately, effect modification by gender and ethnicity was examined by including interaction terms between $\log_2$ leptin with gender and

ethnicity. For models with significant interaction terms, the regression analysis was repeated separately by stratifying by the level of the modifying variable.

3.1 Results

Nine hundred and thirty-one participants were included in this study. Median leptin was 11.9 ng/ml (25^{th} Percentile: 4.9, 75^{th} Percentile: 26.6). Table 1 shows the baseline characteristics of the population studied separated by leptin quintile, while table 2 shows the exam 5 CMR variables for the entire sample. The overall study sample was 51% male, and had a mean age, BMI and LVEF of 63 years, 28 kg/m^2 and 62% respectively. The highest leptin quintile was more likely to be female and Black and less likely to be Asian than the lowest leptin quintile.

Table 3 shows the risk factor adjusted mean values for each CMR variable stratified by leptin quintile. Other than M/V ratio and LVEF, there were significant differences for all the CMR variables. Relative to participants in the lowest quintile of leptin concentration, participants in the highest quintile had a lower risk factor adjusted LV mass (-14g), LVMi (-9g/m^2), LVEDVi (-7 ml/m^2), LVESVi (-3 ml/m^2) and stroke volume (-5 ml) (all $p \leq 0.05$).

Table 4 shows the regression coefficients for the CMR variables. Higher leptin was associated with lower LV mass, volumes and stroke volume (all $p \leq 0.05$), but not with LVEF or M/V ratio. These associations became more significant after indexing LV mass and volumes for BSA (all $p \leq 0.005$).

The interaction terms between BMI and leptin were significant for the LV mass and M/V ratio models ($p < 0.05$). When stratified by BMI (<25, 25-29.9 and ≥30), regression coefficients±SEM of leptin for LV mass were respectively -1.2±0.9g (p=0.20), -2.6±0.9g (p=0.01) and -1.5±1.3g (p=0.24). For M/V ratio, regression coefficients±SEM were respectively 0.004±0.009 g/ml (p=0.59), -0.005±0.009 g/ml (p=0.55) and -0.04±0.01g/ml (p=0.002).

There were also significant interactions between leptin and gender for LV volumes and M/V ratio (all $p \leq 0.01$) (Table 5). In men, higher leptin was associated with smaller LV volumes, but there was no significant association among women; these differences persisted even after indexing for BSA. Conversely, in women, higher leptin was associated with lower M/V ratio, but there was no significant association in men.

Significant interactions between leptin and race were found for LV mass, LVESV, LVESVi and LVEF (all $p \leq 0.05$) (Table 6). All the regression coefficients that were significant in the overall study cohort were significant among White participants, while there were no associations between leptin and any of the CMR variables among Asian participants. Among Black and Hispanic participants, the associations between leptin and LVEDV were insignificant before indexing for BSA, but became significant after indexing for BSA. Moreover, in Hispanic participants, higher leptin was associated with higher LVEF, which differed from the other ethnic groups. There were significant inverse associations between leptin and LVMi and LVEDVi among all racial groups other than Asian participants (all $p < 0.05$).

4.1 Discussion

The principal finding of this study was that among the overall study cohort, higher leptin was associated with lower future LV mass, volumes and stroke volume, but not LVEF or M/V ratio. This study differed methodologically from earlier human studies because earlier studies examined the associations between leptin and cardiac structure measured either cross-sectionally or prior to leptin measurement. No large scale human studies have assessed the association between leptin and future cardiac structure. Also, an earlier study showed BMI and ethnicity did not modify the association between leptin and LV structure, whereas our study showed that BMI and ethnicity did modify this association; furthermore, earlier studies have not assessed if gender modified this association [14].

The results from the current study resemble data from some earlier studies that showed higher leptin was associated with lower LV mass and volumes [13-15]. However, our results differ from those of an earlier cross-sectional study in a bariatric surgery population which showed higher leptin was associated with higher LV mass [11]. This difference may result from the earlier study using ECG, while the current study used CMR. Earlier studies showed that ECG is a much less sensitive measure of left ventricular hypertrophy relative to CMR [11, 19].

Studies in animal models showed that leptin has a variety of protective effects on the heart. Leptin decreases lipid deposition in the myocardium, which may lead to lower LV mass[4]. Similarly, leptin causes coronary artery vasodilation and reverses endothelial cell dysfunction, both of which promote blood flow to the myocardium. These mechanisms may prevent ischemic dilation of the heart and infarct induced fibrosis [2, 5]. Following a myocardial infarct, leptin decreases apoptosis and aids cardiac tissue in switching from fatty acid to glucose metabolism, which is a less oxygen intensive process [3, 6]. The associated decrease in myocardial necrosis decreases left ventricular hypertrophy and dilation [20]. A similar mechanism at a smaller level in response to ischemia may affect the population we studied even in the absence of clinically evident myocardial infarct. As a result, these protective effects may explain the association we demonstrated between higher leptin and less adverse cardiac structure.

The finding that higher leptin was associated with lower M/V ratio among obese participants is interesting because obesity is associated with concentric remodeling, and therefore worse cardiovascular outcomes [21, 22]. Because obesity is also associated with higher leptin, leptin may be a compensatory mechanism to limit concentric remodeling in obesity

Our results differ from the one earlier study assessing the interaction between ethnicity and leptin, which showed no interaction when assessing LV mass and volumes [14]. Indexing for BSA made the association between leptin and LVEDV significant in Blacks and Hispanics. As a result, differences in body size likely contributed to the lack of significance of the unindexed volumes in these groups. Because the leptin regression coefficients for the LVMi model were similar for Blacks and Whites, racial differences in the association between leptin and LV mass are unlikely to explain why Blacks have a higher risk factor-adjusted LV mass than Whites [23].

One of the more significant findings from this ethnic stratification was that among Hispanics, doubling leptin was associated with a 0.8% higher LVEF. Because mean leptin in the highest leptin quintile was 23 times as high as mean leptin in the lowest quintile, the difference in LVEF is larger than 0.8% within the physiologic range of leptin. Left ventricular hypertrophy is a compensatory mechanism to maintain LVEF in response to cardiac injury, and an earlier analysis showed that Hispanics were at higher risk of left ventricular hypertrophy than non-Hispanic Whites [24]. However, we showed that even in Hispanics, higher leptin was associated with lower LVMi. As a result, an underlying increase in LV mass to maintain LVEF does not appear to explain the association between higher leptin and higher LVEF.

Another significant finding from this ethnic stratification was that there was no association between leptin and cardiac structure or function among Asians, which differed from other races. In contrast, an earlier study from MESA showed that the association of traditional cardiac risk factors with CMR parameters did not differ between Asians and other races [25]. Because of these discrepancies, ethnic differences in the associations between leptin with cardiac structure and function require further study.

One of the strengths of this study was that CMR was used to assess LV mass and volumes rather than echocardiography. Another strength of this study was the sample size of this study was much larger than most earlier studies examining the relationship between leptin and cardiac structure. One limitation of this study was that this was an observational study. Another limitation was that MESA participants were initially recruited only if they were free of cardiovascular disease and results may differ in individuals with existing cardiovascular disease. Also, another limitation was that CMR variables were measured at only one time point. As a result, we were only able to show leptin was associated with less adverse cardiac structure 6-8 years later.

5.1 Conclusions

Higher leptin was associated with lower future LV mass and end diastolic volume, which are associated with lower risk of all-cause mortality, myocardial infarction and stroke [22, 26, 27]. Even physiologic range differences in leptin were associated with large risk factor adjusted differences in structure because participants in the highest quintile of leptin had a 13% lower LVMi and 11% lower LVEDVi relative to the participants in the lowest quintile of leptin. As a result, we were able to present the novel finding of an association between serum leptin and less adverse cardiac structure 6-8 years later; earlier studies were mainly cross-sectional. Further study is required to assess if leptin has prognostic significance as a predictor of clinical cardiovascular status in addition to cardiac structure several years later. Also, further study, likely in animals, is required to assess if leptin receptor agonists have potential clinical benefits for cardiac remodeling.

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Abbreviations

LV	Left ventricular
BMI	Body mass index
MESA	Multi-Ethnic Study of Atherosclerosis
CMR	Cardiac MRI
LVEDV	Left ventricular end diastolic volume
LVESV	Left ventricular end systolic volume
M/V Ratio	Mass/Volume ratio
LVEF	Left ventricular ejection fraction
LVMi	Left ventricular mass index
LVEDVi	Left ventricular end diastolic volume index

LVESVi	Left ventricular end systolic volume index

Highlights

- We assessed the association between leptin and cardiac structure and function.
- Higher leptin was associated with less adverse future cardiac structure.
- Among men, higher leptin was associated with smaller left ventricular volumes.
- Among Hispanics, higher leptin was associated with higher LVEF.
- Among Asians, there were no significant associations.

Table 1

Baseline characteristics of the cohort studied

Clinical Characteristic	Quintile				
	I	II	III	IV	V
Age	61±9	63±9	62±9	63±9	63±9
White	44%	51%	48%	36%	39%
Black	9%	13%	18%	21%	30%
Hispanic	22%	22%	24%	32%	24%
Asian	25%	15%	11%	11%	6%
Male	87%	72%	55%	32%	10%
BMI(kg/m^2)	24±3	26±3	27±4	29±4	32±5
Systolic blood pressure(mm Hg)	117±18	120±19	121±20	123±20	126±22
Anti-Hypertensive Use	24%	32%	41%	44%	52%
Diabetes	12%	8%	11%	15%	14%
LDL(mg/dl)	110±29	113±29	110±30	116±34	113±34
HDL(mg/dl)	51±16	51±17	52±16	51±16	53±14
Current Smoker	15%	13%	13%	5%	9%
Current Alcohol Use	63%	58%	60%	48%	39%
Adiponectin (ug/mL)	20±14	20±13	19±11	21±14	19±10
Leptin (ng/mL)	2.3±1.0	6.3±1.4	12.2±2.3	22.8±4.3	51.9±27.1
Leptin Measured at Exam 3	67%	61%	66%	63%	67%

Values are stratified by leptin quintile and noted as mean±SD or percent of total.

Table 2

Exam 5 CMR Variables

CMR Variable	Value
LV Mass(g)	124±33
LV Mass Index(g/m^2)	67±13
LV End Diastolic Volume(ml)	118±30
LV End Diastolic Volume Index(ml/m^2)	64±13
LV End Systolic Volume(ml)	46±17
LV End Systolic Volume Index(ml/m^2)	25±8
Mass/Volume Ratio(g/ml)	1.07±0.23
LV Stroke Volume(ml)	73±18
LV Ejection Fraction(%)	62±7

Values are noted as mean±SD

Table 3

Risk Factor Adjusted CMR Variables by Leptin Quintile

CMR Variable	Leptin Quintile				
	I	II	III	IV	V
LV Mass(g)	131±2	126±2‡	122±2*	124±2‡	117±2*
LV Mass Index(g/m^2)	71±1	68±1†	65±1*	66±1*	62±1*
LV End Diastolic Volume(ml)	126±2	120±2‡	113±2*	118±2‡	115±2‡
LV End Diastolic Volume Index(ml/m^2)	69±1	65±1‡	61±1*	63±1†	62±1†
LV End Systolic Volume(ml)	49±1	46±1‡	42±1*	46±1	44±1‡
LV End Systolic Volume Index(ml/m^2)	27±1	25±1‡	23±1*	25±1‡	24±1‡
Mass/Volume Ratio(g/ml)	1.07±0.02	1.07±0.02	1.10±0.02	1.07±0.02	1.03±0.02
LV Stroke Volume(ml)	76±1	74±1	71±1†	71±1‡	71±2‡
LV Ejection Fraction(%)	61±1	62±1	63±1‡	61±1	62±1

CMR variables are noted as mean±SEM. Comparisons are made to quintile I:

*p≤0.0005,

†p≤0.005,

‡p≤0.05.

Adjusted for age, race, gender, systolic blood pressure, anti-hypertensive usage, LDL, HDL, hyperlipidemia medication usage, diabetes, diabetic medication usage, chronic kidney disease, current alcohol and tobacco use, adiponectin and BMI.

Table 4

Regression models for CMR variables

CMR Variables	Regression Coefficients
LV Mass(g)	**-2.5±0.7***
LV Mass Index(g/m^2)	**-1.7±0.3***
LV End Diastolic Volume(ml)	**-2.2±0.8**‡
LV End Diastolic Volume Index(ml/m^2)	**-1.5±0.4***
LV End Systolic Volume(ml)	**-1.2±0.5**‡
LV End Systolic Volume Index(ml/m^2)	**-0.7±0.2**†
Mass/Volume Ratio(g/ml)	0.004±0.006
LV Stroke Volume(ml)	**-1.0±0.5**‡
LV Ejection Fraction(%)	0.2±0.2

Noted as B±SEM. P values:

* p≤0.0005,

† p≤0.005,

‡ p≤0.05.

A 1 unit increase in log2 leptin represents a doubling of the leptin level. Adjusted for age, race, gender, systolic blood pressure, anti-hypertensive usage, LDL, HDL, hyperlipidemia medication usage, diabetes, diabetic medication usage, chronic kidney disease, current alcohol and tobacco use, adiponectin and BMI.

Table 5
Regression models for CMR variables stratified by gender

CMR Variable	Interaction Term P Value	Men	Women
LV End Diastolic Volume(ml)	0.01	**-3.3±0.9***	-0.1±1.2
LV End Diastolic Volume Index(ml/m^2)	0.002	**-2.1±0.4***	-0.1±0.6
LV End Systolic Volume(ml)	0.01	**-1.9±0.5***	0.2±0.7
LV End Systolic Volume Index(ml/m^2)	0.0004	**-1.2±0.3***	0.2±0.4
Mass/Volume Ratio(g/ml)	0.001	0.01±0.01	**-0.03±0.01‡**

Only CMR variables with significant interaction terms between leptin and gender are included. Noted as B±SEM. P values:

* p≤0.0005,

† p≤0.005,

‡ p≤0.05.

A 1 unit increase in log2 leptin represents a doubling of the leptin level. Adjusted for age, race, systolic blood pressure, anti-hypertensive usage, LDL, HDL, hyperlipidemia medication usage, diabetes, diabetic medication usage, chronic kidney disease, current alcohol and tobacco use, adiponectin and BMI.

Table 6

Regression models for CMR variables stratified by race

CMR Variable	Interaction Term p value	White N=404	Black N=170	Hispanic N=229	Asian N=128
LV Mass(g)	0.04	**-4±1***	**-3±1**‡	**-2±1**‡	-0.04±1.3
LV Mass Index(g/m^2)	0.27	**-2.2±0.4***	**-1.8±0.6**†	**-1.5±0.5**†	-0.9±0.6
LV End Diastolic Volume(ml)	0.21	**-3±1**†	-2±1	-2±1	-0.06±1.5
LV End Diastolic Volume Index(ml/m^2)	0.62	**-1.8±0.5***	**-1.3±0.7**‡	**-1.5±0.6**‡	-0.8±0.7
LV End Systolic Volume(ml)	0.02	**-2±1**†	-0.4±0.8	**-2±1**†	1±1
LV End Systolic Volume Index(ml/m^2)	0.05	**-0.9±0.3**†	-0.4±0.4	**-1.2±0.3**†	0.04±0.4
Mass/Volume Ratio(g/ml)	0.99	-0.004±0.009	0.001±0.01	-0.005±0.01	-0.002±0.01
Stroke Volume(ml)	0.30	**-2±1**‡	-2±1	-0.2±0.7	-0.8±0.9
LV Ejection Fraction(%)	0.03	0.2±0.3	-0.2±0.4	**0.8±0.3**‡	-0.4±0.4

Noted as B±SEM. P values:

*p≤0.0005,

†p≤0.005,

‡p≤0.05.

A 1 unit increase in $\log_2$ leptin represents a doubling of the leptin level. Adjusted for age, gender, systolic blood pressure, anti-hypertensive usage, LDL, HDL, hyperlipidemia medication usage, diabetes, diabetic medication usage, chronic kidney disease, current alcohol and tobacco use, adiponectin and BMI.