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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: MESA is a 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 (−14 g), LV mass index (−9 g/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 (−2.5 g ± 0.7 g), 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 ± 0.5 ml) (all $p \leq 0.05$).

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.

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 that 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.

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.

☆ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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2. 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 having a 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.

2.4. Results

Nine hundred and thirty-one participants were included in this study. Median leptin was 11.9 ng/ml (25th percentile: 4.9, 75th 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 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.