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Relation of Serum Leptin With Cardiac Mass and Left Atrial Dimension in Individuals >70 Years of Age

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Abstract

Experimental evidence indicates that leptin-deficient animals develop left ventricular (LV) hypertrophy, but data relating circulating leptin levels to cardiac structure and function in individuals older than 70 years are lacking. We related circulating leptin concentrations to echocardiographic measures of cardiac structure and function in 432 participants of the community-based Framingham Heart Study (mean age 75 years, 67% women) who underwent echocardiography at a routine examination (approximately 4 years before leptin concentrations were assayed). In multivariable linear regression, logarithmically-transformed sex-standardized leptin concentrations were related to the following echocardiographic measures: LV mass, left atrial (LA) size, and fractional shortening (primary analysis); LV wall thickness and LV end-diastolic dimensions (the 2 components of LV mass) and the transmitral E/A ratio (secondary analysis). Leptin concentrations were inversely associated with LV mass, LV wall thickness and LA size ($p < 0.04$ for all). The top sex-specific tertile of leptin was associated with an adjusted-LV mass 16 gram lower compared to the lowest tertile ($p = 0.017$ for trend across tertiles). Leptin levels were not associated with LV fractional shortening, the E/A ratio or LV end-diastolic diameter ($p > 0.16$). In conclusion, our cross-sectional observations suggest a cardioprotective influence of leptin on LV remodeling consistent with experimental data, and may provide insight into the potential role of leptin-resistance as a mediator of obesity-associated cardiomyopathy.

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Keywords

leptin; cardiac remodeling; left ventricular mass; left atrial size

Introduction

The adipokine Leptin regulates appetite and food consumption through central nervous system mechanisms¹, but it is increasingly recognized that leptin also exerts a broad range of actions on peripheral organs, including the cardiovascular system. Increasing evidence indicates that leptin influences cardiac remodeling, although it remains unclear whether the net effect is cardioprotective versus adverse. Some studies indicated direct hypertrophic effects of leptin on isolated ventricular rat cardiomyocytes,² whereas other animal models suggest that leptin is essential for maintaining normal cardiac structure.^{3, 4} Clinical studies have reported higher leptin levels in patients with heart failure.⁵ It is, however, unclear whether leptin contributes to the development of heart failure, or if the higher leptin levels are secondary responses to cardiac damage. We tested the hypothesis that leptin is cardioprotective by relating circulating leptin concentrations to echocardiographic measures of cardiac structure and function in an unselected community-based sample (mean age: 75 years, range 68 to 91 years).

Methods

Details about the design and the selection criteria of the Framingham Heart Study have been published elsewhere.⁶ A total of 1407 participants attended their 20th biennial examination cycle. Of these, 686 participants had available echocardiographic information from their 20th biennial examination. Participant without available echocardiographic data were older, heavier, more likely to be men and have diabetes mellitus, and more prevalent cardiovascular disease (CVD) as compared to those in whom echocardiograms could be obtained. No differences were observed between the two groups with respect to systolic and diastolic blood pressure, smoking, total/high-density lipoprotein cholesterol ratio and leptin levels. The worse cardiovascular risk profile in individuals with missing echocardiographic data is well known in epidemiological studies.^{7, 8} Serum leptin concentrations were assayed in attendees at their 22nd biennial examination, approximately 4 years later. We excluded an additional 254 participants because of non-available leptin levels. Participants with missing leptin levels were older, had a higher prevalence of CVD (including heart failure) and atrial fibrillation but did not differ with respect to traditional cardiovascular risk factors (except age) from participants with available leptin levels. After exclusions, 432 participants (mean age 75 years, 67% women) remained eligible for the present analyses. All participants provided written informed consent and the study was performed in accordance with the Helsinki Declaration of 1975 (as revised in 1983) and the study protocol was approved by the Institutional Review Board at the Boston University Medical Center.

Serum leptin concentrations were assayed at the examination cycle 22 with a commercially available radioimmunoassay (Linco Research, Inc., St. Louis, MO).⁹ The inter-assay coefficients of variation ranged from 3.0–6.2%. The lower sensitivity limit was 0.5 ng/ml.

At the 20th examination cycle, participants underwent routine transthoracic echocardiography with Doppler color flow imaging using a Sonos 1000 Hewlett-Packard machine. M-Mode measurements of the left ventricular (LV) septal and posterior wall thickness (both measured at end-diastole), left atrial (LA) size (end-systole) and LV internal dimensions at end-diastole and at end-systole were obtained using a leading edge technique as recommended by the American Society of Echocardiography.¹⁰ LV fractional shortening was defined as (LV end-diastolic diameter – LV end-systolic diameter)/LV end-diastolic diameter and served as a

measure of LV systolic function. The ratio of the early/late (E/A) transmitral diastolic filling velocities was also measured at the index examination, as described previously.¹¹ LV mass was calculated using the formula: $LV\ mass = 0.8\{1.04[(LV\ end-diastolic\ diameter + LV\ posterior\ wall\ thickness + LV\ septal\ wall\ thickness)^3 - (LV\ end-diastolic\ diameter)^3]\} + 0.6$.¹²

Leptin levels were natural logarithmically-transformed, and standardized within each sex (to a mean of 0 and a standard deviation [SD] of 1), given the known sex-related differences in the distribution of leptin levels.¹³ Echocardiographic traits were likewise standardized within each sex (mean=0, SD=1), except for the E/A ratio. All analyses were for pooled sexes, given the lack of a statistically significant interaction of leptin with sex for any of the echocardiographic traits (*p* exceeded 0.20 for all traits).

In primary analyses, we related log-leptin (independent variable) to 3 echocardiographic traits (dependent variables), i.e., LV mass, LA size, and fractional shortening). Multivariable linear regression models adjusted for the following correlates of echocardiographic measurements: age, sex, height, and weight (model 1); age, sex, height, weight, systolic blood pressure, antihypertensive treatment, diabetes, current smoking (smoking within the year prior to the examination), and the ratio of total to high-density lipoprotein cholesterol (multivariable-adjusted model 2). We reran the analyses with LV mass and LA size indexed to body surface area as outcome variables, omitting height and weight from the multivariable-adjusted model.

We performed secondary analyses to evaluate if the association of LV mass with leptin was mediated by a relation to LV wall thickness versus LV end-diastolic dimensions, the 2 components used to calculate LV mass and we also related leptin to the E/A ratio. The multivariable model for the E/A ratio was additionally adjusted for heart rate.¹¹ Since the primary analyses used log-transformed leptin levels and sex-standardized echocardiographic measures, we performed additional analyses to simplify the interpretation of changes in echocardiographic measurements in original units in relation to increments of leptin in original units. Therefore, we estimated least squares adjusted-means for LV mass (and its 2 components, LV wall thickness and LV end-diastolic dimensions) across sex-specific leptin tertiles using analyses of covariance adjusting for covariates in model 2. Furthermore, we repeated our analyses after excluding participants with prevalent myocardial infarction (*n*=29) or heart failure (*n*=12) at examination cycle 20.

Results

The clinical, biochemical and echocardiographic features of the study sample are shown in Table 1. The sample was predominantly female (67%) and characterized by a high prevalence of diabetes and cardiovascular disease. As previously reported in the literature,¹³ leptin levels were significantly higher in women. Mean age was 75 years (range 68 to 91 years).

We observed a statistically significant inverse association of leptin levels with LV mass, LV wall thickness and LA size (Table 2). Consistent with these observations, LV mass decreased by 16 gm and LV wall thickness was about 1 mm lower in the top sex-specific leptin tertile compared to the lowest tertile (Figure 1, Panels A and B). Leptin levels were not associated with fractional shortening, the E/A ratio or with LV end-diastolic dimensions (Table 2 and Figure 1, Panel C). Indexing LV mass and LA size to body surface area (and omitting height and weight from the multivariable model) yielded comparable results (LV mass, β (SE): -0.110 (0.048) per 1-SD increment in sex-standardized log-leptin, *p*=0.02; LA size, β (SE): -240 (0.048) per 1-SD increment in sex-standardized log-leptin, *p*<0.0001). In secondary analyses after the exclusion of participants with prevalent myocardial infarction or heart failure, the association of leptin with LV mass and LA size remained robust, whereas the association with

LV wall thickness was attenuated (Online Supplementary Table). Additional adjustment for weight change from exam 20 to 22 revealed similar results (data not shown).

Discussion

We observed a significant inverse association of circulating leptin concentrations with LV mass, LV wall thickness and with LA size in our community-based sample of individuals older than 68 years. In contrast, we did not observe any association of leptin with fractional shortening, the E/A ratio or LV end-diastolic diameter. These findings, although cross-sectional, are consistent with the notion that leptin favorably influences cardiac structure. This concept is in agreement with published epidemiological and experimental data. In the community, obesity (which is characterized by leptin resistance¹⁴) is associated with larger LA size¹⁵, higher LV mass¹⁶ and wall thickness¹⁶, diastolic dysfunction¹⁷, and confers an increased risk of heart failure.¹⁸

As noted above, recent experimental data also support a cardioprotective effect of leptin.^{3, 4} Other investigators also have reported worse cardiac function and prognosis after experimentally-induced myocardial infarction in leptin-deficient mice,⁴ consistent with this notion. However, the experimental and clinical data on leptin effects on the heart are not entirely consistent. A few experimental studies have reported adverse cardiac effects of leptin on isolated cardiomyocytes.^{2, 19} Thus, leptin inhibited contractility¹⁹ and promoted hypertrophy of rat ventricular myocytes in some² but not in other reports.²⁰ Likewise, some previous clinical studies found positive associations between leptin levels and LV mass, geometry and cardiac function in selected patient groups.^{21–23}

We acknowledge several limitations. The sample size was moderate, which may have limited our statistical power to detect modest associations of leptin with other echocardiographic measurements. Furthermore, the generalizability of our results is limited: our sample included participants 68 to 91 years of age, predominantly white of European ancestry. The echocardiograms were obtained on average four years prior to the examination at which leptin was assayed. We would expect that this time lag between echocardiography and leptin measurements would result in random misclassification and would bias us towards the null hypothesis of no association of leptin with cardiac measurements. Also, the cross-sectional design precludes any causal inference. An investigation of serial leptin and echocardiographic measurements would be needed to more precisely quantify the relationship between leptin levels and echocardiographic traits. BMI does not distinguish between adipose and non-adipose tissue, and is thus a suboptimal measure of body composition. Additionally, no other adipokines or measures of insulin resistance were measured in the original cohort at the index examination; so we are unable to further elucidate the relations of other biomarkers of adipose tissue origin, insulin resistance and cardiac remodeling.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Least squares means of left ventricular (LV) mass (Panel A), wall thickness (Panel B) and LV end-diastolic diameters (LVEDD; Panel C) according to sex-specific tertiles of leptin. All models adjust for age, sex, height, weight, systolic blood pressure, antihypertensive treatment, diabetes, current smoking, and the ratio of total to high-density lipoprotein cholesterol.

Table 1Clinical, biochemical and echocardiographic characteristics of the study sample (n=432).^a

<i>Variable</i>	Women (n=290)	Men (n=142)
Age (years)	74.8±4.5	74.2±4.1
Systolic blood pressure (mm Hg)	145±20	149±22
Diastolic pressure (mm Hg)	75±10	78±11
Body mass index (kg/m ²)	26.0±4.6	27.0±3.8
Antihypertensive treatment	130 (45%)	62 (44%)
Current smoker	29 (10%)	13 (9%)
Diabetes mellitus	67 (23%)	33 (23%)
Prevalent heart failure	6 (2.0%)	6 (4%)
Prevalent cardiovascular disease	52 (18%)	51 (36 %)
Total/high-density lipoprotein cholesterol (mg/dL)	4.4±1.5	5.4±1.6
Leptin (ng/ml)	16.8 (9.9–25.5)	6.5 (4.4–10.3)
Log-leptin	2.8±0.7	1.9±0.7
LV mass (g)	161±36	216±54
LV wall thickness (cm)	1.99±0.24	2.15±0.33
LV end-diastolic diameter (cm)	4.62±0.41	5.18±0.43
Left atrial size (cm)	3.96±0.59	4.33±0.55
LV fractional shortening (%)	38.25	35.09
Mean peak velocity E/A	0.71±0.32	0.73±0.30

LV, left ventricular; E/A, early/late transmitral diastolic filling velocities.

^a Clinical and echocardiographic features were measured at the 20th biennial examination cycle; leptin was assayed at the 22nd examination cycle.

Data are percent for binary traits and mean±SD for continuous traits; except for leptin (median (Q1, Q3)).

Table 2
Association of log-leptin with echocardiographic measures of left ventricular (LV) structure and function in the entire dataset (n=432).

	Model 1		Model 2	
	Beta (SE)	p-value	Beta (SE)	p-value
Primary traits				
LV mass	-0.143 (0.056)	0.01	-0.134 (0.056)	0.02
Left atrial size	-0.115 (0.060)	0.06	-0.131 (0.062)	0.04
Fractional shortening	0.005 (0.061)	0.94	-0.015 (0.062)	0.81
Secondary traits				
LV wall thickness	-0.148 (0.059)	0.01	-0.137 (0.059)	0.02
LV end-diastolic diameter	-0.032 (0.059)	0.59	-0.030 (0.061)	0.62
Mean peak velocity E/A *	-0.034 (0.019)	0.075	-0.028 (0.020)	0.16

SE, standard error; E/A, early/late transmitral diastolic filling velocities.

The regression coefficient indicates the change in the echocardiographic traits (in standardized units) per one-SD increase in log-leptin. Thus, a change in leptin of $e^{SD \log \text{leptin}}$ (which is an increase 2.0-fold in men and women) is associated with a decrement of LV mass of 9.1 gms (4.2%) in men and 6.1 gms (3.8%) in women.

Model 1 adjusted for age, sex, height and weight.

Model 2 adjusted for age, sex, height, weight, systolic blood pressure, antihypertensive treatment, diabetes, current smoking and total/high-density lipoprotein ratio.

* Multivariable model for mean peak velocity E/A was additionally adjusted for heart rate.