Original Article

Leptin levels predict the development of left ventricular hypertrophy in a sample of adult men: the Olivetti Heart Study

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Objective: A higher leptin (LPT) is associated with a greater cardiometabolic risk. Some studies also showed a positive association between LPT and cardiovascular organ damage but no consistent data are available about a predictive role of LPT on cardiac remodelling. Hence, the aim of this study was to evaluate the potential role of LPT on the incidence of left ventricular hypertrophy (LVH) in a sample of adult men.

Methods: The study population was made up of 439 individuals (age: 51 years) without LVH at baseline, participating in The Olivetti Heart Study. The ECG criteria were adopted to exclude LVH at baseline and echocardiogram criteria for diagnosis of LVH at follow-up were considered.

Results: At baseline, LPT was significantly and positively correlated with BMI, waist circumference, ECG indices, SBP and DBP but not with age and renal function. At the end of the 8-year follow-up period, there was an incidence of 23% in LVH by echocardiography. Individuals who developed LVH had higher baseline age, LPT, BMI, waist circumference, blood pressure and ECG indices ($P < 0.05$). Furthermore, those that had LPT above the median had greater risk to develop LVH (odds ratio: 1.7; $P < 0.05$). This association was also confirmed after adjustment for main confounders, among which changes in blood pressure and anthropometric indices.

Conclusion: The results of this study suggest a predictive role of circulating LPT levels on cardiac remodelling expressed by echocardiographic LVH, independently of body weight and blood pressure changes over the years.

Keywords: adipocytokines, adipokines, hypertension, left ventricular hypertrophy, left ventricular mass, leptin

Abbreviations: BP, blood pressure; HOMA, homeostasis model assessment; LPT, leptin; LVH, left ventricular hypertrophy; OHS, the Olivetti Heart Study; OR, odds ratio; RAAS, renin–angiotensin–aldosterone system; SD, standard deviation; WC, waist circumference

INTRODUCTION

Leptin (LPT) is a hormone mainly produced by differentiated adipocytes in white adipose tissue [1]. It plays a key role in the regulation of body weight by suppression of the desire for food and the increment of energy expenditure by rise of thermogenesis in brown adipose tissue [2,3].

However, excess body weight condition is associated with high LPT levels [1,4], suggesting that, in the presence of hyperleptinemia, the main metabolic actions of LPT are largely ineffective, namely LPT resistance [5,6]. On the other hand, our previous analyses detected that LPT levels was positively associated with cardiovascular and metabolic risk, also independently of body weight [7–12].

Given this unfavourable association, a number of studies in different settings were performed to assess the relationship between LPT and cardiac remodelling that is associated with increase cardiovascular risk [13].

Experimental studies showed an unfavourable effect of LPT on cardiovascular system in particular by reduction in nitric oxide bioavailability [14], modulation of myocardial endothelin-1 expression [15], increase in sympathetic nerve activity [16,17] and in reactive oxygen species formation [18], and stimulation of renin–angiotensin–aldosterone system (RAAS) [19]. Nevertheless, epidemiological investigations were not univocal and in the majority of the cases reported cross-sectional observations [20–24].

Given these premises and in particular that no prospective data were available on the predictive role of LPT on cardiac remodelling, the aim of our study was to prospectively analyse baseline LPT levels in relation to the development of left ventricular hypertrophy (LVH), in a sample of men participating in the Olivetti Heart Study (OHS).

METHODS

Study population

The OHS was an occupational investigation of the male workforce of the Olivetti factories in Southern Italy

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(Pozzuoli-Naples and Marcianise-Caserta), as previously described [25,26]. A total of 1085 individuals (95% of the total male workforce) aged 25–75 years was examined in 1994–1995 and 84% were seen again in 2002–2004. For the purposes of the present analysis, we sequentially excluded: participants whose demographic and anthropometric characteristics and cardiometabolic risk factors were not available at baseline and at follow-up ($n = 321$); participants with antihypertensive therapy at baseline ($n = 105$); participants with LVH at baseline ($n = 46$). Finally, the evaluation of LVH risk was performed on 439 participants. The Ethics Committee of 'Federico II' University in Naples approved the Olivetti study protocol and the participants provided their informed written consent to participate.

Examination procedures

The OHS study procedures have been described previously [25,26]. Briefly, physical examinations for both baseline and follow-up visit were performed with the participants having fasted for at least 13 h. Baseline and 8-year follow-up visits included the administration of a questionnaire, a physical examination, anthropometric measurements and a blood test.

The questionnaire classified the participants into current smokers, never smokers and ex-smokers. Participants were also classified according to their alcohol intake into two groups: at least one glass of wine (or an equivalent amount of other alcoholic beverages per day) (yes) or no alcohol consumption (no).

A fasting venous blood sample was taken in the seated position. Blood specimens were immediately centrifuged and stored at −70 °C until analysis. Serum LPT was measured by an enzyme-linked immunosorbent assay (R&D System GmbH, Wiesbaden-Nordenstadt, Germany) [27]. Serum glucose levels were measured with automated methods (Cobas-Mira, Roche, Italy). Serum insulin was determined by radioimmunoassay (Insulin Lisophase; Technogenetics, Milan, Italy). Insulin sensitivity was estimated by the homeostasis model assessment (HOMA index) using the formula: fasting plasma insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5. A HOMA index greater than 2.77 UI was considered as a cut-off value for insulin resistance [28].

Serum creatinine was measured by the picric acid colorimetric method. Estimated glomerular filtration rate (eGFR) was estimated by standard formula [29].

Body weight and height were measured on a standard beam balance scale with an attached ruler. BMI was measured according to the formula weight (kg)/height^2 (m). Excess body weight was defined as a BMI at least 25 kg/m^2. Waist circumference, expression of abdominal adiposity, was measured at the level of the umbilicus with the individual standing erect with a flexible inextensible plastic tape. Abdominal obesity was defined as a waist circumference greater than 102 cm.

SBP and DBP (phase V) were measured three times at 2 min intervals, with a random zero sphygmomanometer (Gelman Hawksley Ltd., Sussex, UK) after the individual had been sitting for at least 10 min. The average of the second and third reading was recorded.

Each individuals underwent a 12-lead surface ECG, in the supine position. The ECG was measured at a paper speed of 25 mm/s, at a gain of 10 mm/mV, using a standard ECG device. Analyses of ECG parameters were performed off-line by two independent observers after conversion in digital format. Moreover, at follow-up examination, a transthoracic echocardiogram was also performed according to the recommendations of the American Society of Echocardiography [30], using commercially available machines (SIM7000/Challenge or AU3; ESAOTE) equipped with 2.5–3.5 MHz annular-array transducers, connected to S-VHS tape recorders. Examinations were subsequently converted in a digital format and evaluated off-line by expert sonographers. The ECG criteria (i.e. Cornell voltage duration product greater than 2440 mm ms or Cornell voltage >28 mm or Sokolow–Lyon index >35 mm or and R wave in aVL >11 mm) at baseline and echocardiographic criteria (left ventricular mass >50 g/m$^{2.7}$) at follow-up were considered for diagnosis of LVH [13].

Statistical analysis

All statistical analyses were performed using the SPSS software, version 23 (SPSS Inc, Chicago, Illinois, USA).

The participants were stratified into individuals that developed LVH (LVH[+]) and did not develop LVH (LVH[−]). As LPT distribution was skewed, the participants were also stratified according to the median of plasma LPT distribution of whole OHS population (2.97 ng/ml) into individuals with low (LPT [−]) and individuals with high LPT (LPT[+]) levels, and in addition also in tertiles of LPT [median, first tertile (I-T): 1.30 ng/ml, second tertile (II-T): 2.98 ng/ml, third tertile (III-T): 5.99 ng/ml]. Changes in the participants' main characteristics were calculated as final minus basal measurements. Bivariate relationships between the variables under investigation were evaluated by Spearman's correlation analysis. A multivariable linear regression analysis was carried out to determine the independent effect of baseline LPT on left ventricular mass at follow-up, adjusting for the main potential confounders, after log-transformation of LPT and left ventricular mass values.

To evaluate statistical differences between groups (LVH[+] versus LVH[−]) was used in the analysis of variance (ANOVA) when the variables were normally distributed, whereas the Mann–Whitney *U*-test when the variables were skewed. The chi-squared test was used to evaluate differences between categorical variables. The binary logistic regression analysis was used to estimate the role of LPT (LPT[+] versus LPT[−], or across tertiles of LPT) on the development of LVH, adjusting for the main potential confounders. Given the strong relationship between BMI and waist circumference and its changes over the years ($r = 0.80$, $P < 0.01$), multivariate analyses were separately adjusted for BMI or waist circumference. In addition, baseline ECG indices were transformed into rank to include them individually as covariate in the multivariate analysis of the LVH risk.

The results are reported as mean with standard deviation (SD) as percentages or as odds ratio (OR) and 95% confidence interval (95% CI), unless otherwise indicated. Two-sided P values below 0.05 were considered statistically significant.

TABLE 1. Baseline characteristics of the total study participants, and stratified by development of left ventricular hypertrophy at follow-up

	Total	[LVH−]	[LVH+]
Number of participants	439	339	100
Age (years)	50.9 (7.4)	50.2 (7.4)	53.5 (6.7)*
BMI (kg/m^2)	26.6 (2.9)	26.2 (2.8)	27.9 (2.9)*
Waist circumference (cm)	93.7 (8.3)	93.0 (7.8)	96.3 (9.6)*
SBP (mmHg)	125.6 (15.1)	124.8 (14.6)	128.4 (16.3)*
DBP (mmHg)	81.8 (8.9)	81.5 (8.7)	83.2 (9.7)*
eGFR (ml/min per 1.73 m^2)[b]	97.7 (1.2)	97.7 (1.2)	97.7 (1.2)[a]
HOMA index (unit)[b,c]	1.9 (1.7)	1.8 (1.7)	2.0 (1.7)[a]
LPT (ng/ml)[b]	2.6 (2.2)	2.4 (2.2)	3.0 (2.4)*,[a]
ECG indices			
CP (mm ms)[b]	1096 (1.6)	1047 (1.6)	1259 (1.4)*,[a]
CV (mm)[b]	11.2 (1.5)	10.7 (1.6)	12.9 (1.3)*,[a]
SL (mm)[b]	19.9 (1.3)	19.8 (1.3)	20.4 (1.3)[a]
RaVL (mm)[b]	4.0 (1.8)	3.8 (1.8)	4.7 (1.7)*,[a]

Data are expressed as means (SD) or as percentages. BP, blood pressure; CP, Cornell voltage duration product; CV, Cornell voltage; eGFR, estimated glomerular filtration rate; HOMA, homeostatic model assessment; LPT, leptin; LVH, left ventricular hypertrophy at follow-up; RaVL, R wave in aVL; SL, Sokolow–Lyon index.
[a]Analysis performed by the Mann–Whitney *U* test.
[b]Data expressed as geometric mean.
[c]$n = 413$
*$P < 0.05$ (LVH [+] versus LVH [−]).

RESULTS

The baseline characteristics of the whole sample were reported in Table 1. The mean age was 51 years, with 71% in excess body weight, 15% with abdominal obesity, and 20% with insulin resistance. In addition, smokers were 46% and alcohol drinkers 82%.

The analysis of the correlation between LPT levels and the most relevant characteristics of participants at baseline showed a significant and positive association with BMI ($r = 0.55$, $P < 0.01$), waist circumference ($r = 0.57$, $P < 0.01$), BP (SBP: $r = 0.19$, $P < 0.01$; DBP: $r = 0.24$, $P < 0.01$), HOMA index ($r = 0.26$, $P < 0.01$), but not with age, renal function and ECG indices ($P > 0.05$).

After 8 years of follow-up, an overall incidence of echocardiographic LVH of 23% was detected. The differences in baseline characteristics between LVH[+] and LVH[−] participants were reported in Table 1. The LVH[+]] group had higher age, BMI, WC, BP, Cornell voltage duration product, Cornell voltage and R wave in aVL than the LVH[−] group (Table 1). Although, no difference was found in renal function, insulin sensitivity, cigarette smoking and alcohol consumption. LPT was significantly greater in LVH[+] than LVH[−] participants (Fig. 1) and was significantly correlated with left ventricular mass at follow-up ($r = 0.20$, $P < 0.01$). The correlation between baseline LPT and left ventricular mass was also confirmed in the linear regression analysis adjusted for baseline age, ECG indices, BP, renal function, smoke, alcohol consumption, insulin resistance, antidiabetic and hypolipidemic therapy [beta: 0.06; 95% confidence interval (CI) 0.03–0.09, $P < 0.001$].

The percentage of participants who developed LVH was greater in the LPT[+] group in comparison with LPT[−] (27 versus 18%, $P = 0.02$). This trend was confirmed by logistic regression analysis, LPT[+] was associated with higher risk to develop LVH over time [odds ratio (OR): 1.67; 95% CI 1.06–2.62] (Table 2). The association remained statistically significant also accounting for baseline age, ECG indices, BP, renal function, smoke, alcohol consumption, insulin resistance, antidiabetic and hypolipidemic therapy (Table 2). The results were confirmed also including changes in body weight or waist circumference over the years as covariates (changes in BMI, OR: 1.67, 95% CI: 1.03–2.73;

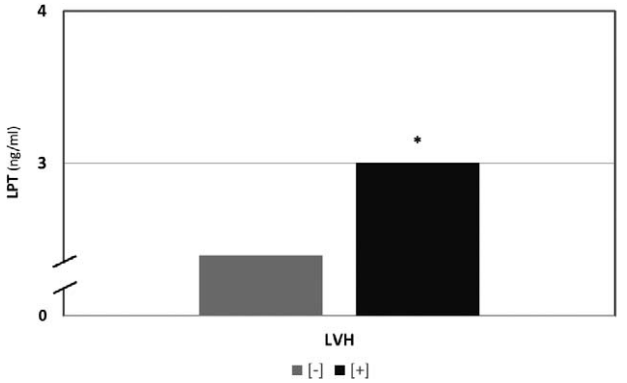

FIGURE 1 Baseline leptin levels and development of left ventricular hypertrophy. LVH[−]: not left ventricular hypertrophy, LVH[+]: left ventricular hypertrophy. LPT data expressed as geometric mean. *$P < 0.01$. LTP, leptin.

TABLE 2. Eight-year risk of left ventricular hypertrophy incidence for increase in leptin

	Risk of LVH OR (95% CI)	*P* value
LPT[+][a]		
Unadjusted	1.67 (1.06–2.62)	0.027
Multivariable model[b]	1.70 (1.05–2.77)	0.032
Multivariable model[c]	1.74 (1.06–2.87)	0.029
Multivariable model[d]	1.67 (1.03–2.73)	0.040
Multivariable model[e]	1.71 (1.03–2.82)	0.037

LVH, left ventricular hypertrophy; OR, odds ratio.
[a]LPT[+]: leptin greater than 2.97 ng/ml.
[b]Adjusted for baseline age, Cornell voltage duration product (rank), SBP, renal function (log-transformed eGFR), smoke, alcohol consumption, hypolipidemic and antidiabetic therapy.
[c]Adjusted for model a with Insulin resistance ($n = 413$).
[d]Adjusted for model a with body weight changes over time.
[e]Adjusted for model a with Insulin resistance and body weight changes over time ($n = 413$).

changes in waist circumference, OR 1.94, 95% CI 1.17–3.23). Similar results were found also adjusting the models for antihypertensive therapy at follow-up and for changes in BP over time ($P < 0.05$), as well as after adjustment for prevalence of hypertension at follow-up (63%), insulin resistance at follow-up, and hypolipidemic and antidiabetic treatment at follow-up (OR 1.76, 95% CI 1.04–2.99).

Finally, we also carried out separate analyses after stratification by tertiles of LPT. At the end of follow-up, the percentage of participants that developed LVH linearly increased across LPT tertiles (I-T: 19%, II-T: 20%, III-T: 31%, $P = 0.02$). The logistic regression analysis confirmed the positive-predictive role of LPT, also in this occasion (P for trend $= 0.01$). On the other hand, the comparison among tertiles showed a significant increased risk only in III-T in respect to I-T (OR 2.00, 95% CI 1.15–3.46, $P = 0.01$). This association remained statistically significant also in the multivariate models (OR 1.93, 95% CI 1.03–3.63, $P = 0.04$).

DISCUSSION

The results of our study indicate that LPT levels are predictive of echocardiographic LVH development and greater left ventricular mass, also after accounting for potential confounders, such as age, insulin sensitivity, anthropometric measures and BP levels and its changes over time. To our knowledge, this is the first study directly relating baseline LPT levels to risk of cardiac remodelling over time, in a relatively large middle-aged sample selected from a general population, observed for a reasonably long period. The results of this article are in line with our previous studies on the relationship between LPT and cardiovascular and metabolic risk both at baseline and at follow-up [7–12].

Several experimental data support this relationship. LPT may exert effects on cardiac remodelling and geometry increasing sympathetic nerve activity [16,17], binding to specific receptors in the central nervous system and in the kidney [31,32]. LPT may regulate myocardial endothelin-1 expression [15,33], leading to cardiac hypertrophy without cellular hyperplasia in rats [34]. The LPT effect may be also mediated by stimulation of the RAAS [19], increase in the reactive oxygen species formation [18], reduction in nitric oxide bioavailability [14], promotion of endothelial cell growth [35], and induction of cardiovascular smooth muscle cell proliferation [36]. In addition, the positive relationship of LPT with insulin resistance [10], uric acid levels [12] and arterial stiffening [37], and inverse with renal function [11] could contribute to this cardiovascular damage [38].

Although there is this large bulk of experimental evidence in support of the association between LPT and LVH, the results of epidemiological studies showed not univocal results.

Some epidemiological studies found a positive association between LPT and echocardiographic parameters of ventricular remodelling [20,21,39]. Two cross-sectional studies detected this association, one in a small hypertensive sample [20] and other one in a small sample of participants with coronary heart disease [21]. In addition, one intervention study detected that the reduction in left ventricular mass was associated with LPT reduction in obese patients after 1 year from bariatric surgery [39]. By contrast, other cross-sectional studies found an inverse relationship between LPT and left ventricular mass. Two of them detected the inverse relationship in cohorts including male and female participants [22,23]. However, both studies performed the parameters' determinations not at the same time, and one of them included a sample of older participants [23]. Another cross-sectional study including only black participants found an inverse association between LPT and left ventricular mass only in obese women [24]; whilst, no significant association was detected in men.

Although there is not a threshold for the LPT, in line with our previous studies, these results suggest that LPT values more than 2.9 ng/ml (median) are associated with a two-fold increased risk to develop LVH, independently of body weight, BP and insulin resistance.

Study strengths and limitations

The strengths of our study are: the prospective design; the careful standardization of data collection at baseline and follow-up examination; the large number of included participants from a general population, without LVH at baseline; the large availability of echocardiographic and ECG measurements and LPT; no bias by any pharmacological treatment; the association between LPT and organ damage was independent of body weight, as the echocardiographic left ventricular mass values were adjusted for height$^{2.7}$ [13] and the models were adjusted both for changes in BMI or waist circumference.

Nevertheless, the study has some limitations. The first one is the nature of epidemiological investigation, and although we account for many covariates, there is still a possibility of residual confounding. Another limitation is that our results are generalizable only with a comparable white adult male population. Indeed, there is difference between LPT levels between male and female participants [40], likewise also a sex or race difference on the influence of LPT on cardiovascular organ damage cannot be ruled out [41,42].

The utilization of the ECG criteria at baseline could be a limitation as these criteria have poor sensitivity. However, to overcome this drawback, we considered more than one criteria to exclude participants with potential LVH. In addition, the average of the indices was very low in respect to the cut-off.

Also, some classes of drugs may affect the role of LPT both modulating LPT levels and interacting with BP-linked organ damage [43–46]. However, LPT levels and its association with risk of LVH in our sample were not affected by therapy. Indeed, patients with antihypertensive therapy at baseline were excluded, and a multivariate model included antihypertensive therapy at follow-up as covariate. Moreover, the logistic model adjusted for antidiabetic and hypolipidemic therapy at baseline and at follow-up, confirmed the association between LPT and LVH.

Finally, the lack of intermediate parameters measured during the follow-up period, leads to the consequent inability to perform a time-to-event analysis relative to development of cardiovascular damage.

In conclusion, the results of this analysis indicate that higher LPT levels predict the development of echocardiographic LVH and a greater left ventricular mass independently of the main potential confounders, in a selected sample of adult male population. This association consistent with the previous knowledge concerning this topic supports a direct role of LPT on cardiovascular risk, and in addition, it suggests a role of early marker to predict cardiovascular disease.

In consideration of the crucial role of LVH on cardiovascular risk, further investigations are needed to confirm these conclusions and to better elucidate the mechanisms involved.

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Conflicts of interest

There are no conflicts of interest.

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