

High-Circulating Leptin Levels Are Associated with Greater Risk of Hypertension in Men Independently of Body Mass and Insulin Resistance: Results of an Eight-Year Follow-Up Study

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Background: We previously reported a significant association between plasma leptin (LPT) concentration and blood pressure (BP), which was partly independent of serum insulin levels and insulin resistance. The aims of this study were to detect whether serum LPT levels predict the development of hypertension (HPT) in the 8-yr follow-up investigation of a sample of an adult male population (the Olivetti Heart Study), and to evaluate the role of body mass index (BMI) and insulin resistance in this putative association.

Patients and Methods: The study population was made up of 489 untreated normotensive subjects examined in 1994–1995 (age: 50.1 ± 6.7 yr; BMI: 26.3 ± 2.8 kg/m²; BP: $120 \pm 10/78 \pm 6$ mm Hg; and homeostatic model assessment index: 2.1 ± 1.6).

Results: The HPT incidence over 8 yr was 35%. The participants with incident HPT had similar age but higher BMI ($P < 0.001$), serum LPT ($P < 0.001$), and BP ($P < 0.01$) at baseline. One sd positive difference in baseline serum LPT log was associated at univariate analysis with a 49% higher rate of HPT [95% confidence interval (CI) 22–83; $P < 0.001$]. In three different models of multivariable logistical regression analysis, LPT was respectively associated with a 41% greater risk to develop HPT (95% CI 15–74; $P < 0.001$) upon adjustment for age and baseline BP, with a 48% (95% CI 20–81) greater risk when adding the homeostatic assessment model index to the model, and with 33% greater risk (95% CI 6–67; $P < 0.02$) upon adjustment for BMI.

Conclusions: In this sample of originally normotensive men, circulating LPT level was a significant predictor of the risk to develop HPT over 8 yr, independently of BMI and insulin resistance. (*J Clin Endocrinol Metab* 93: 3922–3926, 2008)

Although the association between overweight and high blood pressure (BP) has been known for a long time (1, 2), its pathophysiological bases are not fully clarified. Recently, a role for leptin (LPT) has been suggested (3). LPT is produced by differentiated adipocytes in white adipose tissue, but also in other organs such as the hypothalamus (4). By acting on specific structures in this region of the brain, it suppresses the desire for

food and increases energy expenditure by a sympathetically mediated stimulation of thermogenesis in brown adipose tissue (5). In addition, it may increase the skeletal mass sensitivity to insulin (6). Obesity is characterized by elevated plasma LPT levels, the higher the body mass index (BMI) or the waist circumference, a measure of abdominal adiposity, the higher the serum LPT level. Moreover, a statistically sig-

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Abbreviations: BMI, Body mass index; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; HOMA, homeostatic model assessment; HPT, hypertension; LPT, leptin; NT, normotensive; SBP, systolic blood pressure.

nificant direct association has been described between plasma LPT and insulin concentrations.

It has been reported that central sympathetic activation by adipose tissue-derived and also by locally produced LPT (7) is translated into increased sympathetic discharge not only to brown adipose tissue but also to other organs and, in particular, to the kidney (8), with possible effects on BP control. Several animal studies are in favor of an effect of LPT on BP. In ob/ob obese mice, in which serum LPT levels are not detectable, BP is normal (7), whereas transgenic skinny mice and obese mice, both of which are hyperleptinemic, are more prone to develop hypertension (HPT) compared with control animals (7, 9).

In a previous cross-sectional investigation of a sample of an untreated adult male population, we reported a graded positive relationship between serum LPT levels and BP. That association was independent of age, body mass, abdominal adiposity, fasting serum insulin, and creatinine levels (10). To evaluate whether the increase in plasma LPT precedes the increase in BP and whether hyperleptinemia involves a greater risk of HPT, we used the database of the Olivetti Heart Study, an epidemiological investigation of the metabolic, nutritional, and genetic precursors of cardiovascular diseases in an occupational-based sample of an adult male population in Southern Italy.

Subjects and Methods

Population

The Olivetti Heart Study population is given by the male workforce of the Olivetti factories of Pozzuoli (Naples) and Marcianise (Caserta). The methodology of the study has been previously described (11). The local Ethics Committee approved the study protocol, and participants gave their informed consent to participate. A total of 1085 individuals in the age range of 25–74 yr (51.5 ± 7.2) was examined in 1994–1995; 907 of them (83.6%) were seen again at the 8-yr follow-up visit in 2002–2004 and were considered for the present analysis. The relevant characteristics of the subjects lost to follow-up were not significantly different compared with the rest of the population.

To evaluate the predictive role of LPT and related variables with respect to the subsequent development of arterial HPT, we identified the study participants who were normotensive (NT) at baseline ($n = 489$). These individuals were the object of our prospective evaluation.

Examination procedures

Body weight and height were measured on a standard beam balance scale with an attached ruler. Body weight was measured to the nearest 0.1

kg, and body height was measured to the nearest 1.0 cm, with subjects wearing light indoor clothing without shoes. BMI was calculated according to the standard formula. Overweight was defined as a BMI of 25 or more and obesity as a BMI of 30 or more. The waist circumference, taken as an index of abdominal adiposity, was measured at the umbilicus level with the subject standing erect with abdomen relaxed, arms at the sides, and feet together; measurements were performed at the nearest 0.1 cm with a flexible inextensible plastic tape.

Smoking habits, alcohol consumption, and degree of habitual physical activity were investigated by a standardized questionnaire.

Systolic BP (SBP) and diastolic BP (DBP) (phase V) were taken three times 2 min apart with a random zero sphygmomanometer (Gelman Hawksley Ltd., Sussex, UK) after the subject had been sitting for at least 10 min. The average of the second and third reading was recorded. For the purpose of our analyses, HPT was based on two different criteria: 1) BP 140 or more and/or 90 mm Hg, or current antihypertensive drug treatment according to current European Society of Hypertension/International Society of Hypertension guidelines for HPT; or 2) BP 160 or more and/or 95 mm Hg, or current antihypertensive drug treatment. Resting, supine heart rate was measured. A fasting venous blood sample was taken in the seated position between 0800 and 1000 h, after the BP measurements, for determination of serum LPT and serum insulin, lipids, and glucose.

The blood specimens were immediately centrifuged and stored at -70 C until analyzed. Serum LPT was measured by an ELISA (R&D System GmbH, Wiesbaden-Nordenstadt, Germany). Intraassay and interassay coefficients of variation were less than 3 and 5.4%, respectively (12).

Serum cholesterol, triglyceride, and glucose levels were measured with automated methods (Cobas-Mira, Roche, Italy). Serum insulin was determined by RIA (Insulin Lisophase; Technogenetics, Milan, Italy). The homeostatic model assessment (HOMA) index was used to estimate insulin resistance, and calculated as fasting serum insulin ($\mu\text{U/ml}$) \times fasting serum glucose (mmol)/22.5 (13).

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS-PC, version 15; SPSS, Inc., Chicago, IL). Because the distributions of LPT, glucose, triglyceride, and HOMA index deviated significantly from normal, they were normalized by log transformation, and log-transformed values were used in the analysis. Binary logistical regression was used to estimate the predictive role of selected variables with respect to the incidence HPT. In all logistical regression analyses, the independent variables included in the equation were expressed as their respective z scores to normalize for SD. Results were expressed as mean \pm SD or 95% confidence interval (CI), unless otherwise indicated. Two-sided P values less than 0.05 were considered statistically significant.

Results

Table 1 reports the most relevant baseline features of the originally NT individuals included in the present analysis. Over-

TABLE 1. Prevalence of specified metabolic abnormalities in the study population ($n = 489$)

Baseline characteristics	Mean \pm SD	Baseline features	Prevalence (%)
Age (yr)	50.1 ± 6.7	None	0
SBP (mm Hg)	120 ± 10.1	None	0
DBP (mm Hg)	78.7 ± 6.5	None	0
BMI (kg/m^2)	26.4 ± 2.8	Overweight ($25 < \text{BMI} < 30 \text{ kg/m}^2$), Obesity ($\text{BMI} > 30 \text{ kg/m}^2$)	58, 11
Abdominal Circ (cm)	92.8 ± 8.0	Abdominal obesity (abdominal Circ > 102 cm)	8.5
Glucose (mg/dl)	98.6 ± 18.5	Diabetes (glu ≥ 126 mg/dl or Tx)	5
Triglycerides (mg/dl)	152.7 ± 98.4	Hypertriglyceridemia (tg ≥ 150 mg/dl)	38
Total cholesterol (mg/dl)	222.3 ± 42.8	Hypercholesterolemia (Chol ≥ 200 mg/dl)	66
HOMA index (U)	2.11 ± 1.6	Insulin resistance (HOMA ≥ 2.77) ^a	17

Chol, Cholesterol; Circ, circumference; glu, glucose; tg, triglyceride; Tx, treatment.

^a According to HOMA distribution in nonobese male subjects with no metabolic disorders (43).

TABLE 2. Baseline (1994–1995) characteristics of the 2002–2004 NT and HPT groups

Variables	NT (n = 318)	HPT (n = 171)
Age (yr)	49.7 ± 7.2	50.7 ± 5.7
BMI (kg/m ²)	26.0 ± 2.7	27.1 ± 2.8 ^a
Abdominal Circ (cm)	92.1 ± 6.0	93.6 ± 7.6 ^a
SBP (mm Hg)	118.2 ± 10.2	123.3 ± 9.1 ^a
DBP (mm Hg)	77.9 ± 6.6	80.2 ± 5.9 ^a
Triglycerides (mg/dl)	146.5 ± 85.9	164.2 ± 117.6
HOMA index (unit)	2.0 ± 1.6	2.2 ± 1.5
Glucose (mg/dl)	96.9 ± 15.0	101.7 ± 23.4 ^a
Insulin (μU/ml)	8.5 ± 6.7	8.8 ± 5.3
LPT (ng/ml)	3.3 ± 2.3	4.3 ± 3.0 ^a

Circ, Circumference.

^a *P* < 0.01.

weight and obesity affected 70% of the participants, altogether. At the end of the 8-yr follow-up period, 264 new cases of HPT were detected using the European Society of Hypertension/European Society of Cardiology 2007 criteria (SBP ≥140 and/or DBP ≥90 mm Hg, or antihypertensive therapy). At univariate analysis, a positive difference in log-transformed serum LPT of 1 SD was associated with a 39% higher rate of HPT (95% CI 16–67; *P* < 0.001). Given the overestimation of HPT deriving from the measurement of BP on a single occasion, in further analyses, however, we adopted a harder criteria for the diagnosis of HPT, *i.e.* SBP 160 or more and/or DBP more than or equal to 95 mm Hg, or current antihypertensive treatment, which led to the identification of two groups of persistent NT (n = 318) and newly hypertensive (HPT, n = 171) subjects, corresponding to an incidence of HPT of 35% in 8 yr. These two groups were used in the following analyses.

Table 2 shows that the NT and HPT groups were significantly different at baseline with respect to serum LPT levels, but also to BMI, abdominal circumference, SBP, DBP, and plasma glucose levels. BMI and plasma LPT concentration were positively and significantly associated in all populations (n = 489; *r* = 0.482; *P* < 0.001).

Logistical regression analysis was then used to estimate the relationship between baseline serum LPT and the risk of developing HPT accounting for potential confounders. Due to the high collinearity of the variables associated with the development of arterial HPT, four different logistical regression models were used, all including baseline serum LPT as an independent variable, age as covariate, and HPT as a dependent variable. In the basic model, a positive difference in baseline serum log-LPT of 1 SD was associated with a 52% greater risk of developing HPT (*P* < 0.001). In a second model, which included baseline SBP as a covariate in addition to serum LPT and age, the same difference in baseline serum log-LPT was independently associated with a 41% greater risk of developing HPT (*P* = 0.001) (Fig. 1). SBP was also a highly significant predictor of incident HPT. Similar results were obtained upon substitution of DBP in place of SBP (data not shown). By the third model, which included BMI in addition to serum LPT and age, 1 SD higher log-LPT concentration and 1 SD higher BMI were both independently associated with a, respectively, 33% (*P* = 0.016) and 37% (*P* = 0.006)

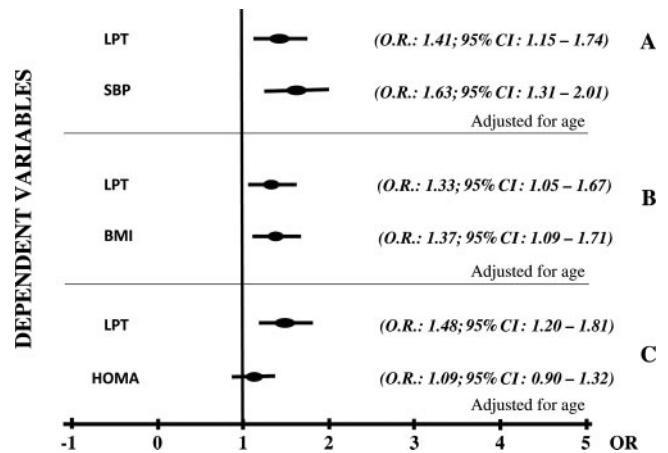


FIG. 1. Multivariate logistical regression analysis showing the relative risk of developing arterial HPT over 8 yr according to 1 SD increase in baseline serum LPT concentration. A–C, Three different models of logistical regression analysis with the incidence of HPT as a dependent variable. O.R., Odds ratio.

greater risk of developing HPT. Finally, in the last model, including again serum LPT and, in addition, age and HOMA index as covariates, 1 SD higher log-LPT level predicted a 48% higher incidence of HPT (*P* = 0.0001), whereas no significant relationship was detected for the HOMA index (Fig. 1).

Discussion

This study provided the first demonstration that higher plasma LPT levels in NT adult male individuals are associated with an increased risk of developing HPT independently of several potential confounders. Our work confirmed the well-known statistical association between BMI and plasma LPT concentration; nevertheless, a major finding of the study was that LPT remained a strong predictor of incident HPT also after adjustment for BMI and for the HOMA index. Thus, although epidemiological associations do not allow to establish cause-effect relationships, these results raise the possibility to speculate that LPT exerts a pro-hypertensive effect *per se*, independently of the degree of adiposity. This notwithstanding, because elevated plasma LPT levels occur much more commonly in obese individuals, this unfavorable effect is by no means relevant to the obese condition. The results of the present study are in line with those of previous reports of cross-sectional association between plasma LPT and BP both in animal models of HPT and in human HPT. Indeed, several animal studies indicated that LPT might play an important role in modulating BP levels through its vascular, renal, and sympathetic effects (14). Transgenic mice with LPT overexpression had higher BP as compared with control animals (9, 15, 16). In the same model, HPT was reversed by α -adrenergic or sympathetic ganglionic blockade (16). Acute systemic LPT administration in rats increases sympathetic nerve discharge to brown adipose tissue, kidneys, adrenal glands, and hind limbs (18, 19), whereas chronic LPT administration was reported to shift the pressure-natriuresis curve to the right, presumably by increasing renal sympathetic nerve activity and then tubular sodium reabsorption (17). In addition, chronic intracarotid and intracere-

broventricular administration of LPT also seems to affect the sympathetic tone and to produce an increment in BP in rats (20, 21). Several pieces of evidence from animal studies also elucidate the possible role of hyperleptinemia in the development of HPT. Thus, despite severe obesity, LPT-deficient ob/ob mice have lower BP than lean controls (7), and LPT administration to these mice increases their BP up to the level observed in lean controls, despite lower food intake and decrease of body weight (16).

Several clinical studies in man led to the hypothesis that hyperleptinemia and selective LPT resistance may contribute to HPT and cardiovascular disease (22–27). Whereas Mackintosh and Hirsch (28) reported that LPT administration to lean individuals for 6 d did not alter 24 h urinary norepinephrine, dopamine, and epinephrine excretion, Eikelis *et al.* (29) demonstrated that in men with different body size, serum LPT concentration correlated with the degree of adiposity and with renal sympathetic nerve activity determined by renal noradrenaline spillover. Moreover, α 1-receptor blockade affected by bunazosin hydrochloride was shown to improve insulin resistance and to decrease serum LPT levels in hypertensive patients with hyperleptinemia. Altogether, these data indicate that excess LPT causes sympathetic activation in human obesity (30). In particular, renal sympathetic stimulation, mediated by LPT (8) and possibly by other mechanisms, is followed by increased sodium and water retention, and by stimulation of renin secretion, which are plausible contributors to the obesity associated increase in BP.

In epidemiological studies in humans, discordant results have been obtained with regard to the relationship between serum LPT levels and BP. Takizawa *et al.* (31) detected a significant association between serum LPT levels and BP only in men, whereas Suter *et al.* (32) reported a positive relationship in women. Masuo *et al.* (33) detected a direct relationship in a sample of Japanese men, and Lindgärde *et al.* (34) reported the occurrence of high LPT levels in Swedish overweight women with high BP. A BMI-dependent relationship between LPT and BP was also observed in a rural Chinese population sample (35). Several authors found higher serum LPT concentrations as part of a cluster of cardiovascular risk factors, including BP (36–38). Finally, few studies in hypertensive patients reported the finding of high plasma LPT levels, although the confounding influence of overweight could not be excluded (39, 40). According to Uçkaya *et al.* (41), plasma LPT was higher in hypertensive patients, but a continuous relationship between LPT and BP was not detected. In our previous cross-sectional examination of the Olivetti Heart Study population, we detected a statistically significant association between serum LPT concentration and BP; we also showed that this association was at least partly independent of serum insulin levels and insulin resistance estimated by the HOMA index (9). More recently, we reported from an 8-yr prospective evaluation that circulating serum LPT was a significant predictor of the risk to develop metabolic syndrome, mainly due to increases in BP and fasting blood glucose (42).

Study limitations

In epidemiological studies both the prevalence and incidence of HPT may be overestimated because the diagnosis is based on a single examination. To try and overcome this limitation, we

adopted a more severe cutoff for the diagnosis of HPT. Nevertheless, some overestimation of the incidence of HPT could be still present. A second limitation of the present work is that the Olivetti Study cohort was made of white male participants only. Thus, its results may be generalized only to a comparable white male population. Finally, because intermediate BP measurements during the 8-yr follow-up period were not available, time-to-event analyses with respect to the development of HPT as a function of baseline serum LPT levels and related variables, were not feasible.

Conclusion and perspectives

In summary, our study provided the first demonstration of the ability of serum LPT concentration to predict the risk of developing arterial HPT in a sample of an adult male population, independently of baseline BP, which was the first determinant of subsequent BP levels, and BMI, which nevertheless remained an independent predictor of HPT with a power similar to that of plasma LPT. These results support the hypothesis raised by the results of previous studies in animal models, and in man of a pathogenic role of hyperleptinemia and LPT resistance in the development of HPT. As a consequence, they also strengthen the potential benefits deriving from correction of overweight and obesity in the prevention of HPT and cardiovascular disease.

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