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Circulating leptin levels predict the decline in renal function with age in a sample of adult men (The Olivetti Heart Study)

Lanfranco D'Elia[1] · Martina Manfredi[1] · Ludovica Perna[1] · Roberto Iacone[1] · Ornella Russo[1] · Pasquale Strazzullo[1] · Ferruccio Galletti[1]

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Abstract
Leptin (LPT) is associated with a number of cardiovascular risk factors, such as high blood pressure (BP), insulin resistance and excess in body weight. Some studies find an unfavorable cross-sectional association between LPT and renal disease, in particular in patients with already known kidney dysfunction. There are few data on the relationship between LPT and changes in renal function over time in subjects without evidence of kidney dysfunction. Hence, the aim of this study is to estimate the predictive role of LPT on the decline in renal function occurring in an 8-year follow-up observation of a sample of adult apparently healthy men (The Olivetti Heart Study). The study includes 319 untreated normotensive and nondiabetic men without clinical evidence of renal dysfunction (creatinine clearance-CrCl > 60 mL/min/1.73 m^2) at baseline. At baseline, LPT is significantly and positively associated with BMI, abdominal circumference, BP and Homa index, no relationship is found with CrCl. At the end of the 8-year follow-up, a significant association is detected between baseline LPT and changes occurring in BP. Moreover, an inverse correlation with changes in CrCl is found ($r = -0.12$). This unfavorable relationship between baseline LPT and decline in renal function is also confirmed in the multivariate analyses, after adjustment for all potential confounders ($R^2 = 0.42$, $p < 0.01$). The results of this prospective investigation suggest a predictive role of circulating LPT levels on decline in renal function over time, independently of main potential confounders, in normotensive and nondiabetic men with normal renal function at baseline.

Keywords Leptin · Adipocytokines · Adipokines · Renal disease · Kidney damage

Introduction

Chronic kidney disease is a growing public health issue, associated with a high risk of cardiovascular morbidity and mortality [1]. Conversely, a number of traditional risk factors for cardiovascular disease are associated with the development of the kidney disease, such as hypertension and diabetes [2]. However, other factors may be involved in the overall increase of the chronic kidney disease incidence both directly and indirectly. Among these, leptin (LPT) might exert a key role with its pro-atherogenic effects [3]. LPT, mainly produced by adipocytes, is a hormone with *pleiotropic* actions. First of all, LPT is implicated in the regulation of body weight by inducing satiety, inhibiting the feeling of appetite and the desire for food through hypothalamic receptors, and stimulating energy expenditure by a sympathetically mediated rise of thermogenesis in brown adipose tissue. It regulates appetite, food intake and energy expenditure, but it is also involved in the regulation of inflammation and immune response [3]. The majority of obese people have high-circulating LPT levels with LPT resistance; the higher the BMI or the waist circumference, the higher the LPT levels [4]. Our previous studies indicate that circulating LPT levels are able to predict the risk of developing hypertension [5], and metabolic syndrome [6] in a prospective cohort investigation. The association between LPT and blood pressure (BP) or insulin resistance is detected in overweight rather than in normal weight men [7].

In addition, several studies demonstrate a markedly increased increment of LPT in patients with end-stage renal disease. Since LPT is removed from the circulation through

✉ Ferruccio Galletti
galletti@unina.it

[1] Department of Clinical Medicine and Surgery, ESH Excellence Center of Hypertension, "Federico II" University of Naples Medical School, Via S. Pansini, 5, 80131 Naples, Italy

glomerular filtration and degradation in the proximal renal tubule, a major cause of the LPT increment could be the low renal clearance of this protein [8, 9]. Furthermore, it has also been speculated that high LPT may directly contribute to various uremic complications, and might be a supplementary cause of nephron destruction. Indeed, experimental evidence suggests a role in the promotion and progression of endothelial dysfunction and vascular damage, with glomerular endothelial cell proliferation, increased synthesis of collagen and hypertrophy of the mesangium cells [10, 11].

A recent study on a general sample of older subjects reports an inverse association between changes in LPT and glomerular filtration rate after 6 years of follow-up, only in women [12]. Since there are few available data on this relationship in the general population, the aim of the present study is to investigate the predictive role of LPT on changes in renal function during an 8-year follow-up period in a middle-aged population without hypertension or diabetes, and with no evidence of renal dysfunction at baseline.

Materials and methods

Study population

The Olivetti Heart Study (OHS) was an occupational investigation of the male workforce of the Olivetti factories in Southern Italy (Pozzuoli-Naples and Marcianise-Caserta), as previously described [5]. The local Ethics Committee (The Ethics al Committee-Federico II University of Naples) approved the Olivetti study protocol, and the participants provided their informed written consent to participate.

A total of 1085 individuals (95% of the total male workforce) aged 25–75 years (49.8 ± 6.7 years) were examined in 1994–95. For the purposes of the present analysis, we excluded participants with clinical evidence of renal dysfunction (creatinine clearance < 60 mL/min/1.73 m^2) ($n = 268$). We also excluded participants who were diagnosed as hypertensive at baseline (BP ≥ 140/90 mmHg or on current antihypertensive therapy prescribed by the participant's personal physician) ($n = 338$), or diabetic at baseline (fasting blood glucose level ≥ 126 mg/dL or current anti-diabetic therapy) ($n = 24$), and participants whose demographic and anthropometric characteristics or cardio-metabolic risk factors were not available at baseline ($n = 62$). Finally, 393 clinically healthy and initially normotensive, nondiabetic and with no renal dysfunction individuals were included. Of these participants, 319 (81%) were seen again in 2002–04 and were considered eligible for the present analysis.

Examination procedures

The OHS study procedures have been described previously [5]. Physical examinations were performed between 08:00 and 11:00 h, in a quiet and comfortable room, with the participants having fasted for at least 13 h, at baseline and follow-up visit. The baseline visit included a physical examination and anthropometric measurements, a blood test, a fasting timed urine collection and the administration of a questionnaire.

Systolic and diastolic BP (phase V) were measured 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. The diagnosis of incident hypertension during the 8-year follow-up period was defined as systolic BP ≥ 140 or diastolic BP ≥ 90 mmHg or current antihypertensive drug treatment [2].

Body weight, height and abdominal circumference (AC) were measured as previously described [13].

Biochemical measurements

At baseline, a fasting venous blood sample was taken in the seated position between 8:00 AM and 10:00 AM, after the BP measurements. The blood specimens were immediately centrifuged and stored at − 70 °C until analyzed. Serum LPT was measured by an enzyme-linked immunosorbent assay (R&D System GmbH, Wiesbaden-Nordenstadt, Germany). Intra- and inter-assay coefficient of variation were 3.0 and 5.4%, respectively [14]. 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. Time and volume of urinary collections were recorded, and a specimen was used for the analysis. Creatinine in serum was measured by the picric acid colorimetric method, and in urine samples by atomic absorption spectrophotometry, and was used to estimate the renal clearance (CrCl), expressed as: mL/min/1.73 m^2 [13, 15]. High-sensitivity C-reactive protein (CRP) was assessed by an immunoturbidimetric method (Roche Diagnostics, Milan, Italy, automated analyzer). White blood cell count (WBC) was measured by an automated blood cell counter.

At the 8-year follow-up visit, a 24-hour urine collection was obtained, in addition to the physical examination and subjected to the same procedures used at baseline.

Statistical analysis

All statistical analyses were performed using the SPSS software, version 20 (SPSS inc, Chicago,Ill). Because the distribution of LPT, HOMA index, CRP and WBC were skewed, the log-transformed values were used in the analyses. Moreover, the participants were also stratified according to the median of plasma LPT distribution of the whole OHS population [2.97 ng/mL] into subjects with low (LPT[−]) and subjects with high LPT (LPT[+]) levels. Changes (Δ) in the participants' main characteristics were calculated as final minus basal measurements. The Δ in CrCl over the time was calculated as the difference between calculated at the final rank value and baseline rank value. Bivariate relationships between the variables under investigation were evaluated by Pearson's correlation analysis, while Chi-squared test was used to evaluate differences between categorical variables. Paired *t* tests were used to assess differences between baseline and follow-up visit in any of the variables under investigation. Analysis of variance (ANOVA) was used to assess differences in baseline main characteristics and its Δ between group below and above the median of LPT values. The multivariable linear regression analysis was used to determine the independent effect of LPT on ΔCrCl, adjusting for the main potential confounders. A post hoc evaluation detected a power of 80% (alpha error: 5%) for this study.

The results are reported, as appropriate, as mean ± standard deviation (SD) or standard error (SE) or 95% confidence interval (CI), unless otherwise indicated. Two-sided *p* values below 0.05 were considered statistically significant.

Results

The relevant characteristics of the study participants at baseline are reported in Table 1.

The analysis of the comparison between LPT levels and the most relevant characteristics of participants at baseline shows a significant and positive association with BMI ($r = 0.54$, $p < 0.019$, AC ($r = 0.53$, $p < 0.01$), BP (systolic: $r = 0.18$, $p < 0.01$; diastolic: $r = 0.27$, $p < 0.01$), Homa index ($r = 0.21$, $p < 0.01$) and CRP ($r = 0.14$, $p = 0.01$), but not with CrCl ($p = 0.6$) and WBC ($p = 0.8$).

After 8-year follow-up, the overall incidence of hypertension is 49%, and diabetes 7%. Table 2 shows the changes in relevant variables observed during the 8-year follow-up, a significant trend to increased BMI, AC and BP was observed with a concomitant significant decline in renal function. The analysis of the correlation underlines a significant positive association of basal LPT levels with the parameters Δ over the time, but on the contrary it detects an inverse significant trend with Δ in CrCl ($r = -0.12$, $p = 0.03$). The multivariate analysis confirms the predictive role of LPT on CrCl Δ ($p < 0.01$), in addition to the expected significant role of age ($p < 0.01$) and the CrCl at baseline ($p < 0.01$) (R^2 of the model = 42%) (Table 3). Furthermore, in the model including incidence of hypertension and diabetes as covariate, LPT levels remain significantly associated with the decline in renal function ($R^2 = 42\%$, $p < 0.01$) (Table 3). Given the strong relationship between LPT, BMI and AC, other analyses were separately adjusted also for BMI or AC. In both

Table 1 Baseline characteristics of the study participants

	Total	LPT(−)	LPT(+)
No. of participants	319	177	142
Age (years)	49.5 (6.8)	50.0 (6.9)	48.9 (6.8)
BMI (kg/m^2)	26.4 (2.9)	25.3 (2.7)	27.9 (2.5)*
Overweight (%)	56	50	63*
Obesity (%)	12	4	22*
Abdominal circumference (cm)	92.6 (8.1)	89.1 (8.1)	97.0 (6.1)*
Central obesity (%)	12	5	20*
Systolic BP (mmHg)	119.1 (10.2)	117.9 (9.9)	120.6 (10.5)*
Diastolic BP (mmHg)	78.4 (6.4)	76.8 (6.4)	80.3 (6.0)*
Creatinine clearance (mL/min/1.73 m^2)	91.8 (18.4)	91.4 (19.1)	92.3 (17.5)
HOMA index (U)	2.0 (1.6)	1.8 (1.1)	2.4 (2.1)*,a
C-reactive protein (mg/L)	1.1 (2.6)	1.0 (2.7)	1.2 (2.3)a
White blood cell count (10^3/uL)	7.1 (2.0)	7.0 (2.1)	7.1 (1.9)a
LPT (ng/mL)	3.3 (2.4)	1.6 (0.7)	5.3 (2.3)*,a

Data are expressed as means (SD), or as percentages

LPT(−) leptin levels below the median, *LPT*(+) leptin levels above the median, *BP* blood pressure

*$p < 0.05$ LPT(−) vs LPT(+)

[a]Analysis performed on log-transformed variable

Table 2 8-year changes in the participants' main characteristics and their correlation with baseline Leptin levels

	Δ	LPT(−)	LPT(+)
Δ BMI (kg/m^2)	0.5 (1.0)*	0.4 (0.1)	0.5 (0.2)
Δ Abdominal circumference (cm)	3.8 (0.3)*	4.0 (0.5)	3.5 (0.4)
Δ SBP (mm Hg)	13.9 (0.8)*	12.2 (1.0)	16.0 (1.3)**
Δ DBP (mm Hg)	8.7 (0.5)*	8.7 (0.7)	8.8 (0.8)
Δ Creatinine clearance (mL/min/1.73 m^2)	−2.6 (1.4)*	−0.1 (1.9)	−5.8 (1.9)**,a

Data are expressed as means (SE); Δ: changes after 8 years were calculated as final minus basal measurements

LPT(−) leptin levels below the median, *LPT*(+) leptin levels above the median, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

*$p<0.05$ final vs baseline; **$p<0.05$ LPT[−] vs LPT[+]

[a]Analysis performed on rank-transformed variables

Table 3 Change in creatinine clearance (CrCl) over time for variation in leptin values (LPT) at baseline

	CrCl change[a] for ↑ in LPT[b] β (95% CI)	*p* value
Multivariate model[c]	−53.9 (−85.1 to −22.7)	<0.01
Multivariate model[d]	−51.1 (−82.4 to −19.8)	<0.01
Multivariate model[e]	−64.7 (−100.5 to −29.0)	<0.01
Multivariate model[f]	−54.2 (−89.7 to −18.6)	<0.01

[a]CrCl changes are expressed as rank values

[b]LPT values are expressed as log

[c]Model adjusted for age, creatinine clearance, systolic blood pressure, Homa index (log), C-reactive protein (log), and white blood cell count (log) at baseline

[d]Model adjusted for the same covariates of Model[c] plus incidence of hypertension and diabetes at follow-up

[e]Model adjusted for the same covariates of Model[d] plus BMI

[f]Model adjusted for the same covariates of Model[d] plus abdominal circumference

models, the inverse trend between LPT levels and CrCl Δ is confirmed ($R^2=42\%$, $p<0.01$) (Table 3).

We also stratified the group as a whole for baseline LPT median: LPT(+) group had significantly higher LPT, BMI, AC, BP and Homa index than LPT(−) although the two groups do not differ in age, CrCl, CRP and WBC (Table 1). Next, when the changes over time were also stratified for the LPT median, Δ in CrCl and systolic BP are significantly higher in LPT(+) compared to LPT(−) group (Table 2). The linear regression analyses of the Δ observed in CrCl confirms the significant negative association between LPT and decline of renal function over time [Δ CrCl: LPT(−) group = −0.1 mL/min/1.73 m^2, CI: −3.6 to 3.5 vs LPT(+) = −5.8 mL/min/1.73 m^2, −9.8 to −1.8; $p=0.01$] (Fig. 1). This association remains statistically significant in multivariate analysis, accounting for potential confounders including age, CrCl, systolic BP and Homa index at baseline ($R^2=41\%$; $p<0.01$) (Table 4). The unfavorable relationship between LPT and CrCl is confirmed, also accounting for the incidence of hypertension and diabetes at follow-up ($R^2=42\%$; $p<0.01$) (Table 4). Likewise, similar significant association is detected when the models are also separately adjusted for BMI ($R^2=0.42$; $p<0.01$) or AC ($R^2=0.42$; $p=0.01$) (Table 4).

Discussion

The main results of our study show that high LPT values are associated with greater decline in renal function in 8 years. The association remains statistically significant upon accounting for a number of measured potential confounders, including age, renal function, insulin sensitivity, blood pressure, adiposity indices and inflammatory markers at baseline, and incidence of hypertension and diabetes. The present report is the first one directly relating to baseline LPT levels to the decline in renal function over the time, in a relatively large middle-aged sample of individuals who were normotensive, nondiabetic, and without clinical evidence of renal dysfunction at baseline, observed for a long period of time.

Incremental increase of LPT in patients with end-stage of renal disease has been reported in several studies. These investigations suggest that since LPT is removed from the circulation through glomerular filtration and degradation in the proximal renal tubule, in end-stage of renal disease, the high-LPT levels might be determined by a low clearance of this substance [8, 9, 16]. To support these potential mechanisms, it was reported that circulating LPT levels "normalized" after renal transplantation [17]. On the contrary, it has also been suggested that these high LPT levels, in turn, could contribute to a faster decline in renal clearance probably both by a direct effect of nephron disruption, and by an indirect effect though an inflammation status and a higher insulin resistance. Some experimental evidence indicates a key role of LPT in the promotion and progression of endothelial

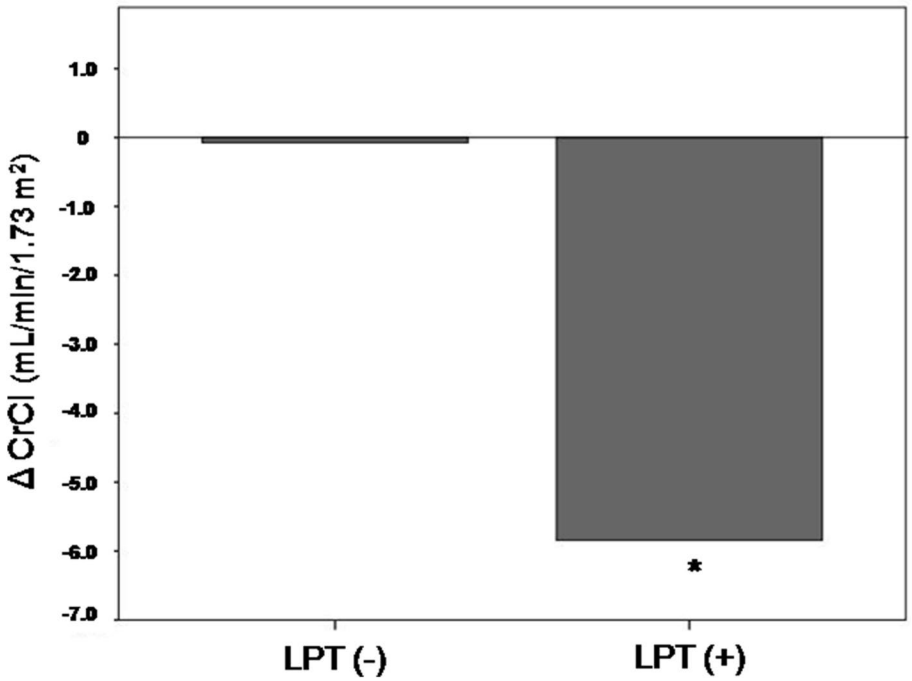

Fig. 1 Changes in creatinine clearance (ΔCrCl) stratified for median of baseline leptin (LPT) levels. *LPT*(−) low leptin, *LPT*(+) high leptin. Model unadjusted (*$p = 0.01$ for rank values)

Table 4 Comparison between baseline leptin levels above [LPT(+)] and below [LPT(−)] the median in changes over time in creatinine clearance (CrCl)

	CrCl changes[a] for comparison LPT(+) vs LPT(−) β (95% CI)	*p* values
Multivariate model[b]	−33.9 (−55.8 to −12.0)	<0.01
Multivariate model[c]	−32.0 (−54.1 to −9.9)	<0.01
Multivariate model[d]	−35.8 (−59.5 to −12.1)	<0.01
Multivariate model[e]	−31.9 (−56.2 to −7.6)	0.01

[a]CrCl changes are expressed as rank values

[b]Model adjusted for age, creatinine clearance, systolic blood pressure, Homa index (log), C-reactive protein (log), and white blood cell count (log) at baseline

[c]Model adjusted for the same covariates of Model[b] plus incidence of hypertension and diabetes at follow-up

[d]Model adjusted for the same covariates of Model[c] plus BMI

[e]Model adjusted for the same covariates of Model[c] plus abdominal circumference

dysfunction and vascular damage, with glomerular endothelial cell proliferation, increased synthesis of collagen and hypertrophy of the mesangium cells [10, 11]. In vitro experiment on human umbilical vein endothelial cells shows that after exposure to a high concentration of LPT there is a development of endothelial dysfunction, through changes of the cytoskeleton observed at the cell periphery. Likewise, vinculin, a necessary protein for cross-linking of actin filaments, is also highly expressed after LPT treatment [11]. High circulating LPT levels are also significantly associated with increased serum levels of ICAM-1 (soluble intercellular adhesion molecule-1) and VCAM-1 (soluble vascular cell adhesion molecule-1), adhesion molecules markers of endothelial disorder, and reduced arterial compliance in patients with CKD [11]. In addition, in hypertensive rats, LPT may induce vasoconstriction, by increasing intracellular calcium, and contribute to vascular remodeling [18].

In consideration that adipocytes are a common source for LPT and inflammatory cytokines [19], several studies suggest a direct relationship between LPT and inflammation. In particular, LPT induces CRP expression (indicator of cardiovascular risk [20, 21]) in vitro in human hepatocytes [22] and in human coronary artery endothelial cells [23]. This relationship is supported by the evidence that LPT induces the production of IL-6 [24], that in turn regulates the hepatic synthesis of CRP [25]. In addition, the LPT receptor has signaling capabilities of IL-6–type cytokine receptors [26].

Some investigations report an association between LPT and WBC [27, 28], a traditional marker of chronic low-grade inflammation [29]. Indeed, LPT stimulates the proliferation of the white blood cell system [30]. Moreover, LPT also promotes intimal monocyte recruitment [31], and elicits macrophage foam cell formation [32].

Our data confirm the positive association between LPT and CRP [33], along with what we report in our previous paper (7), while, CRP is not associated with CrCl and its changes over the time (data not show). On the other hand, WBC is not associated with LPT nor with renal function (data not show). However, the predictive role of LPT does not change after inclusion of these covariates in the analyses.

Since only baseline CRP and WBC were available for the analyses, we cannot exclude the potential effect of other inflammatory markers in the relationship between LPT and renal function.

Recently, a study on a general sample of older subjects finds that changes of LPT during 6 years are inversely associated with changes in glomerular filtration rate, but only in women [12]. Our findings are in agreement with the inverse relationship between LPT levels and decline in renal function, but we underline the predictive role of LPT on decline in renal function in a different sample for age and without strong risk factors of decline in renal function at baseline.

These results are in line with our previous studies on the relationship between LPT and cardio-metabolic risk [5–7], in particular in this analysis there is also a strong relationship between LPT and both BP and insulin sensitivity. It is worth noting that the multivariate analyses include a number of covariates that may affect the relationship. Indeed, in addition to age and values of CrCl at baseline, we considered the development of hypertension and diabetes and eventual treatment at follow-up, insulin sensitivity, and the expression of excess in body weight such as BMI or AC.

The strengths of our study are its prospective design, the relatively long follow-up observation period, the inclusion of subjects only with normal renal function, untreated non-diabetic and normotensive participants at baseline, the carefully standardized direct measurement of CrCl and related variables at both baseline and follow-up, and, in general, the careful standardization of data collection. However, we also acknowledge a few limitations. The first one is the participation of only adult white male individuals, which makes our results only generalizable to people of male gender and of Caucasian ethnicity. Another weakness is the lack of intermediate parameter measurements during the 8-year follow-up observation period with the consequent inability to perform a time-to-event analysis relative to the rate of decline in renal function. Finally, we do not have measurements of the serum LPT-interacting proteins and of the circulating leptin-receptor, all factors able to bind circulating LPT and to alter the active free LPT concentration in the blood.

Following the results of previous studies by our and by other research groups, the present analysis of a selected sample of adult male population drawn from the Olivetti Heart Study database tests the hypothesis that high LPT levels predict a greater risk of decline in renal function. The results of our study add to the evidence accumulated through previous studies in favor of a causal role of LPT on metabolic-cardio-renal risk over time.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Statements on human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The local Ethics Committee (The Ethics Committee-Federico II University of Naples) approved the Olivetti study protocol.

Informed consent Written informed consent was obtained from all individual participants included in the study.

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