CIRCULATING LEPTIN IS ASSOCIATED WITH SERUM URIC ACID LEVEL AND ITS TUBULAR REABSORPTION IN A SAMPLE OF ADULT MIDDLE-AGED MEN

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ABSTRACT

Purpose. Leptin is associated with cardiovascular risk factors (e.g. hypertension, insulin resistance, kidney disease and excess body weight). Experimental studies showed that leptin might affect serum uric acid, by modulation of the uric acid excretion. However, there are few observational data on the relationship between leptin and uric acid in general population. Therefore, the aim of the present study was to evaluate the relationship between leptin and uric acid and its excretion in a large middle-aged male general population.

Methods. A sample of 930 adult male individuals (mean age: 52 years) without therapy for high uric acid was included in the analysis (the Olivetti Heart Study).

Results. Uric acid was significantly and positively associated with blood pressure, BMI, waist circumference, insulin resistance, C-reactive protein and leptin ($p<0.01$), while inversely with renal function ($p=0.01$). The multivariate analysis confirmed the association between leptin and uric acid after adjustment for potential confounders ($p<0.01$). After division for adiposity, this trend was confirmed separately for normal weight and excess body weight participants. Moreover, leptin was inversely associated with excretion of uric acid ($p<0.01$), also in multivariate analysis ($p=0.03$).

Conclusion. The results of this study indicate a positive association between circulating leptin levels and uric acid, independently of potential confounders, both in normal and excess body weight men. Furthermore, an inverse association between leptin and uric acid excretion was detected.

Key words: Cardiovascular risk; Uric Acid; Uric acid excretion; Adipocytokines; Adipokines; Leptin.

INTRODUCTION

Leptin (LPT) is a protein hormone mainly produced by adipose tissue [1]. LPT exerts different effects, in particular it is implicated in the regulation of body weight modulating appetite, energy expenditure and satiety, but it is also involved in the regulation of inflammation [1,2]. High circulating LPT levels are common in excess body weight individuals, the higher the BMI or the waist circumference (WC), the higher the LPT level [1,3], suggesting a LPT resistance.

However, our previous data suggested that LPT was positively associated with increased cardiovascular risk independently of body weight, increasing the development of hypertension [4], metabolic syndrome [5], insulin resistance [6] and declining renal function [7].

Serum uric acid (SUA), major product of the purine metabolism, is catabolized by xanthine oxidase and predominantly eliminated by the kidney. Although some studies indicated contrasting data on SUA oxidant effects [8,9], clinical studies suggested a positive and strong association between SUA and cardio-metabolic risk factors (e.g. obesity, insulin resistance, hypertension and metabolic syndrome [8,10,11,12], or early and overt cardiovascular organ damage [8]. In addition, genetic studies detected variants in SUA reabsorption and excretion transporters that are involved in this regulation [13] both in general population [14] and in patients at high cardiovascular risk [15]. In this context, the balance between overproduction and excretion of SUA may play a key role in determining SUA plasma levels [13]. The role of LPT on SUA is supported by experimental data that pointed out the effect on modulation of SUA excretion. High LPT stimulates the sympathetic nervous system (SNS) independently of body weight, and this increased sympathetic activity mainly at kidney level may led to stimulate renin release and to increase proximal sodium reabsorption [16], that in turn is positively associated with reabsorption of SUA [17]. The effect of LPT could be also mediated by the strong positive relationship with insulin levels and insulin resistance [3,6], that are positively associated with SUA [18]. Indeed, also insulin may increase proximal sodium reabsorption though an activation of sodium-hydrogen exchange in proximal renal tubular cells, that in turn promotes a parallel increase in urate reabsorption [17]. As expected, this increased activity is also associated with insulin resistance [19]. On the other hand, since more than 90% of filtered urate is reabsorbed by the kidney, renal damage could affect this complex process, and in this context LPT may play a crucial role. Indeed, LPT may unfavourably contribute to the decline in renal function [7] both by a direct effect of nephron disruption and by an indirect effect though an inflammation status and a higher insulin resistance [20,21]. High LPT is involved in the promotion and progression of endothelial dysfunction and vascular damage, in particular it exerts the effects through glomerular endothelial cell proliferation, increased synthesis of collagen and hypertrophy of the mesangium cells [20,21], increased serum levels of adhesion molecules [20] and contributing to vascular remodelling [22]. However, so far there are few observational studies aimed to evaluate the

association between LPT and SUA. In particular, LPT was positively associated with SUA in a large sample of Japanese women [23], as well as in a small sample of diabetic [24] or obese men [25] or middle-aged adult men [26], while in healthy [27] or non-obese male subjects [25] there was not relationship. These conflicting results may be due to the heterogeneity in size and features of the samples and to the covariates included in the multivariate models.

In consideration of this premise, the primary aim of the present study was to evaluate the relationship between LPT and SUA in a large middle-aged male general population participating in the Olivetti Heart Study (OHS). Moreover, the study also aimed to assess the association between LPT plasma levels and excretion of SUA.

MATERIALS AND METHODS

Study Population

The OHS was an occupational investigation of the male workforce of the Olivetti factories in Southern Italy, as previously described [28,29]. From a total of 1085 individuals aged 25–75 years examined in 1994-95, 930 participants without therapy for high SUA and with variables available for this study were included in the present analysis. 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 previously described [28,29]. Briefly, the participants were allowed to pursue their normal activities, but they were discouraged from engaging in vigorous exercise. They were asked to abstain from smoking and drinking alcohol, coffee, tea and other beverages containing caffeine starting on the night before the visit. The visit included a physical examination and anthropometric measurements, a blood test, a fasting timed urine collection and the administration of a detailed questionnaire on demographic and medical information. Body weight, height, WC and systolic/diastolic blood pressure (BP) were measured as previously described [28,29]. The diagnosis of hypertension was defined as systolic BP $\geq$ 140 and/or diastolic BP $\geq$90 mmHg or current antihypertensive drug treatment [30]. Body mass index (BMI) was measured according to the formula weight [kg]/height^2. Excess body weight was defined as a BMI $\geq$ 25 kg/m^2. Central obesity was given by a WC value $\geq$ 102 cm. A fasting venous blood sample was taken in the seated position to obtain the determination of metabolic parameters. Blood specimens were immediately centrifuged and stored at -70 °C until analysis (Cobas-Mira; Roche, Milan, Italy). Serum LPT was measured by an enzyme-linked immunosorbent assay (R&D System GmbH, Wiesbaden-Nordenstadt, Germany) [31].

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 creatinine clearance (CrCl), expressed as: mL/min/1.73 m^2. Serum insulin concentration was measured by radioimmunoassay (Insulina Lisophase; Technogenetics, Milan, Italy). Insulin sensitivity was estimated by the homeostasis model assessment (Homa) using the formula: fasting plasma insulin (μU/mL) x fasting plasma glucose (mmol/L)/22.5. High-Sensitivity C-Reactive Protein (CRP) was assessed by an immunoturbidimetric method (Roche Diagnostics, Milan, Italy, automated analyser).

The protocol for the assessment of the timed urine collection was previously reported [32]. Volume and length of urinary collections were recorded and specimens were examined for electrolytes, creatinine, SUA and lithium determinations. Standard formulas were used to calculate the clearances of creatinine, sodium, lithium, and SUA. Data were then expressed as fractional excretion (FE) by dividing the respective clearance by the CrCl and were expressed as percentages (%).

Statistical analysis

All statistical analyses were performed using the SPSS software, version 23 (SPSS inc, Chicago,Ill). Because the distribution of LPT, SUA, CRP and Homa were skewed, the log-transformed values were used in the analyses. Bivariate relationships between the variables under investigation were evaluated by Pearson correlation analysis. Moreover, the participants were also stratified according to the tertiles of the sample LPT distribution and by body weight. The analysis of variance (ANOVA) was used to assess differences in main features among LPT tertiles and unpaired t-test to assess differences between normal weight and excess body weight participants. The multivariate linear regression analysis was used to determine the relationship between continuous variables, adjusting for the main potential confounders. Given the strong relationship between BMI and WC ($r=0.81$, $p<0.001$) in this sample, multivariate analyses were separately adjusted for BMI or WC. The results are reported as mean or geometric mean (with standard deviation – SD) or percentages, unless otherwise indicated. A post-hoc evaluation detected a power of 90% (alpha error: 5%) to detect in this sample a true difference of 0.64 mg/dl (SD= 1.2) in SUA between the highest and the lowest tertile of LPT. Two-sided P values below 0.05 were considered statistically significant.

RESULTS

The relevant characteristics of the study participants are reported in Table 1. The mean age was 52.0 (7.5) years, with 74% having excess body weight, 18% central obesity, 42% hypertension, 7% diabetes, and 15% high SUA (more than 7.0 mg/dl). The analysis of the comparison between SUA levels and the most relevant characteristics of the participants showed a significant and positive association with LPT ($r=0.19$, $p<0.001$), BP (systolic: $r=0.14$, $p<0.001$; diastolic:

r=0.19, p<0.001), BMI (r=0.26, p<0.001), WC (r=0.24, p<0.001), Homa (r=0.12, p<0.001) and CRP (r=0.14, p<0.001), inversely with CrCl (r=-0.09, p=0.01), while no association was found with age (p=0.5). The multivariate analysis confirmed the association between LPT and SUA, after accounting for age, BP, therapy, CrCl, Homa and CRP (Table 2). Separate analyses adjusted also for BMI or WC found a significant trend between LPT and SUA (p<0.05) (Table 2). Likewise, also after exclusion of participants with high SUA, LPT was significantly associated with SUA (for 1-SD increase in log-LPT, β= 0.10, 0.03 to 0.18, p<0.01). In addition, the relationship between LPT and SUA was explored in normal and excess body weight participants, separately. The individuals with excess body weight had higher WC, BP, BP, CRP, Homa, SUA and LPT than normal weight participants (p<0.01) (Table 3). Also after this stratification, a significant and positive association between LPT and SUA was detected in both normal and excess body weight participants (for 1-SD increase in log-LPT (2.4 ng/mL): normal weight, β= 0.18, 0.03 to 0.33, p=0.02; excess body weight, β= 0.10, 0.02 to 0.18, p=0.01). Finally, the analysis on urinary excretions showed that FE of uric acid was inversely associated with LPT (r= -0.11, p=0.001), in addition to the expected association with SUA (r= -0.46, p<0.001). The association between LPT and FE of uric acid was confirmed after adjusting for age, BMI and therapy (for 1-SD increase in log-LPT: β= -0.29, -0.57 to -0.02, p=0.03).

We also stratified the group as a whole by tertiles of LPT: highest tertile of LPT had significantly higher SUA and age, and as expected greater BP, BMI, WC, Homa and CRP than lower tertiles (Figure 1 and Table 4). Conversely, the groups did not differ for CrCl (Table 3). The multivariate analysis confirmed the significant positive association between LPT tertiles and SUA also accounting for potential confounders such as age, BP, BMI (or WC), CrCl, Homa, CRP and therapy (p for trend=0.01). Moreover, FE of uric acid decreased through LPT tertiles form the lowest to the highest (p<0.01) (Figure 1).

DISCUSSION

Our results are in line with our previous studies indicating a strong relationship between LPT, BP, anthropometric indices, insulin sensitivity and PCR [3-7]. In addition to our knowledge, this is the first study, in a relatively large general adult population of men without treatment for high SUA, indicating that LPT levels are associated positively with SUA and inversely with FE of uric acid, after accounting for potential confounders, such as age, BP, insulin sensitivity, renal function, inflammation marker, therapy and anthropometric measures. In addition, this relationship was confirmed in participants with “normal” SUA and detected in both normal and excess body weight participants, separately.

Previous epidemiological studies indicated that high SUA level is a risk factor for cardiovascular disease [11,33,34] and it is strongly and positively associated with high BP, obesity, insulin resistance and metabolic syndrome [8,34,35,36]. High levels of SUA could be determined by dysregulation and imbalance between overproduction and renal excretion. In addition, also genetics may be involved in this regulation, probably by genetic polymorphisms of GLUT9 urate transporter gene that was associated with SUA and urinary urate excretion in our general population [14] and with cardiovascular risk factors in patients at high risk [15].

At our knowledge few observational data were available on the association between LPT and SUA: in a large sample of Japanese women, LPT was independently associated with SUA after adjusting for main confounders [23]. Although in agreement with our results, these findings cannot be compared with ours because of the well-known differences in LPT and SUA levels between men and women. The significant association between LPT and SUA was also found in a small sample of obese diabetic and non-diabetic male and female participants [24]. However, this association was not accounted for any expression of insulin sensitivity. A similar limitation may be pointed out for an analysis including a small sample of healthy middle-aged adults, in which LPT was positively associated with SUA only in men [26]. Another positive correlation between LPT and SUA was also found in a sample of 200 men, but it was significant only in overweight and obese participants, after adjusting for potential confounders [25]. Conversely, in a small sample of healthy men there was no association between LPT levels and SUA [27]. These conflicting results in male populations may be due to the small sample size and to the heterogeneity of the participants' characteristics.

As a matter of a fact, experimental data suggest that LPT may play a role on the regulation of the SUA excretion [37] by modulation of renal sodium handling, by activation of SNS [16,17] and alteration of insulin sensitivity [3,6,17,18,19,38], and on the other hand by damage at glomerular site [20]. Of note, in our sample LPT levels were positively associated with proximal fractional sodium reabsorption (data not show) (independent predictor of hypertension in the same population [39]), and that in turn was also inversely associated with FE of uric acid (data not show). This finding is supported by the detection of an inverse relationship between SUA excretion and lithium excretion (data not show), as well as found in previous study [40].

Several studies found a direct relationship between LPT, inflammation and SUA [41,42,43,44].. Our data confirmed the positive association between LPT and CRP, as well as reported in previous analysis [7]. However, the role of LPT on SUA did not change after inclusion of this covariate in the analysis.

Some classes of drugs may affect both LPT and SUA levels. LPT is reduced by the administration of antidiabetic therapy [45,46,47,48,49] or statins [50]. While, SUA may be affected by antihypertensive drugs [51]. Anyhow, in consideration of this evidence the models were adjusted for these covariates, hence the results were independent by drugs use.

In previous epidemiological studies, LPT was higher than in our sample [24,25,27], while SUA was greater in obese diabetic and non-diabetic participants [24], similar in a small general population sample [25], while lower in healthy subjects [27]. This difference may be due to the large homogeneous unselected sample included in our analysis in respect to the selected and small samples of other studies. Important of note is that although LPT resistance is essentially present in obese or overweight individuals, our results show that LPT is associated with SUA in normal weight subjects; in addition, SUA increased towards to higher tertiles of LPT.

In the absence of a threshold for the LPT resistance, the results substantially confirm the threshold detected in our previous study [6] suggesting that for a 2.4 ng/mL LPT increase there was a significant change in SUA levels, independently of body weight.

The strengths of our study are: the relatively large general population of men, the careful standardization of data collection, the comprehensive covariates included in the models (i.e. age, BP, antihypertensive-hypolipidemic-antidiabetic therapy, BMI, WC, Homa, CRP and CrCl), and the large availability of urinary determinations.

Nevertheless, the study has some limitations: the first one is the cross-sectional design. However, this limitation is overcome by evaluation of potential mechanisms involved. The second potential limitation is the participation of only adult white men, which makes our results only generalizable to male Caucasian people. Third, the circulating leptin-receptor and the serum LPT interacting proteins were not evaluated.

CONCLUSIONS

The present analysis of a non-selected sample of adult male population drawn from the Olivetti Heart Study database, indicated that LPT levels are positively associated with SUA, independently of the main potential confounders, in particular body weight, BP, insulin sensitivity, therapy, inflammation and renal function. In addition, this relationship is supported by the independent association between LPT and FE of uric acid, in turn supported by its interaction with proximal fractional sodium reabsorption. The results of this investigation are in line with our previous studies on the relationship between LPT and cardio-metabolic and cardiovascular risk. Hence, different strategies to reduce LPT levels are beneficial to decrease SUA and cardiovascular risk.

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COMPLIANCE WITH ETHICAL STANDARDS

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

Ethical approval. The study protocol was approved by the Ethics Committee of "Federico II" University in Naples.

Informed consent. All participants provided their informed written consent to participate.

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Legend to Figure

Figure 1. Serum uric acid (SUA) and fractional excretion (FE) of uric acid stratified by tertiles of leptin (LPT). The analysis of variance (ANOVA) was used to assess the differences in SUA and its FE among LPT tertiles. Data expressed as mean and standard error. SUA is expressed as geometric mean.

* $p<0.01$.

Table 1. Baseline characteristics of the study participants.

N. of participants	930
Age (yrs)	52.0 (7.5)
BMI (kg/m^2)	26.9 (3.0)
Waist Circumference (cm)	94.7 (8.3)
Systolic BP (mmHg)	130.2 (17.3)
Diastolic BP (mmHg)	84.2 (10.0)
HOMA index (U)‡	2.0 (1.8)
C-Reactive Protein (mg/L)‡	1.2 (2.5)
Uric Acid (mg/dL)‡	5.6 (1.3)
LPT (ng/mL)‡	2.7 (2.4)
Creatinine Clearance (mL/min*1.73 m^2)	84.7 (28.2)
Therapy (%)	
Antihypertensive drugs	17
Hypolipidaemic drugs	13
Antidiabetic drugs	3

Data are expressed as means (SD) or as percentages; BP: Blood Pressure; ‡ Data expressed as geometric mean

Table 2. Association between uric acid and leptin levels by linear regression analysis.

	Increase in UA (1-SD log-UA*) β (95% CI)	P-value
1-SD ↑ in log-Leptin*		
Unadjusted	0.19 (0.13 to 0.26)	<0.001
Multivariable Model [a]	0.14 (0.08 to 0.21)	<0.001
Multivariable Model [b]	0.08 (0.01 to 0.15)	0.038
Multivariable Model [c]	0.08 (0.01 to 0.16)	0.02

UA: uric acid; *1-SD log-Leptin=2.4 ng/mL, 1-SD log-UA= 1.3 mg/dL.

[a] Adjusted for age, creatinine clearance, systolic blood pressure, antihypertensive-hypolipidemic-antidiabetic treatment, Homa, CRP.

[b] Adjusted for Model a plus BMI.

[c] Adjusted for Model a plus waist circumference.

Table 3. Characteristics of the participants stratified by body weight (n=930).

	Normal weight	Excess body weight
N. of participants	242	688
Age (yrs)	52.0 (7.8)	52.0 (7.5)
BMI (kg/m^2)	23.3 (1.4)	28.2 (2.3)*
Waist Circumference (cm)	86.7 (5.8)	97.6 (7.1)*
Systolic BP (mmHg)	126.0 (15.9)	131.7 (17.4)*
Diastolic BP (mmHg)	80.8 (9.2)	85.3 (9.9)*
C-Reactive Protein (mg/L)‡	0.95 (2.75)	1.32 (2.51)†*
HOMA index (U)‡	1.55 (1.66)	2.23 (1.73)†*
Creatinine Clearance (mL/min*1.73 m^2)	82.4 (26.1)	85.6 (28.9)
Uric Acid (mg/dL)‡	5.2 (1.3)	5.7 (1.2) †*
LPT (ng/mL)‡	1.62 (2.29)	3.23 (2.3)†*

Data are expressed as means (SD); BP: Blood Pressure. The unpaired t-test was used to assess differences in main features between normal weight and excess body weight participants. ‡ Data expressed as geometric mean; † analysis performed on log-transformed variable; * $p<0.01$.

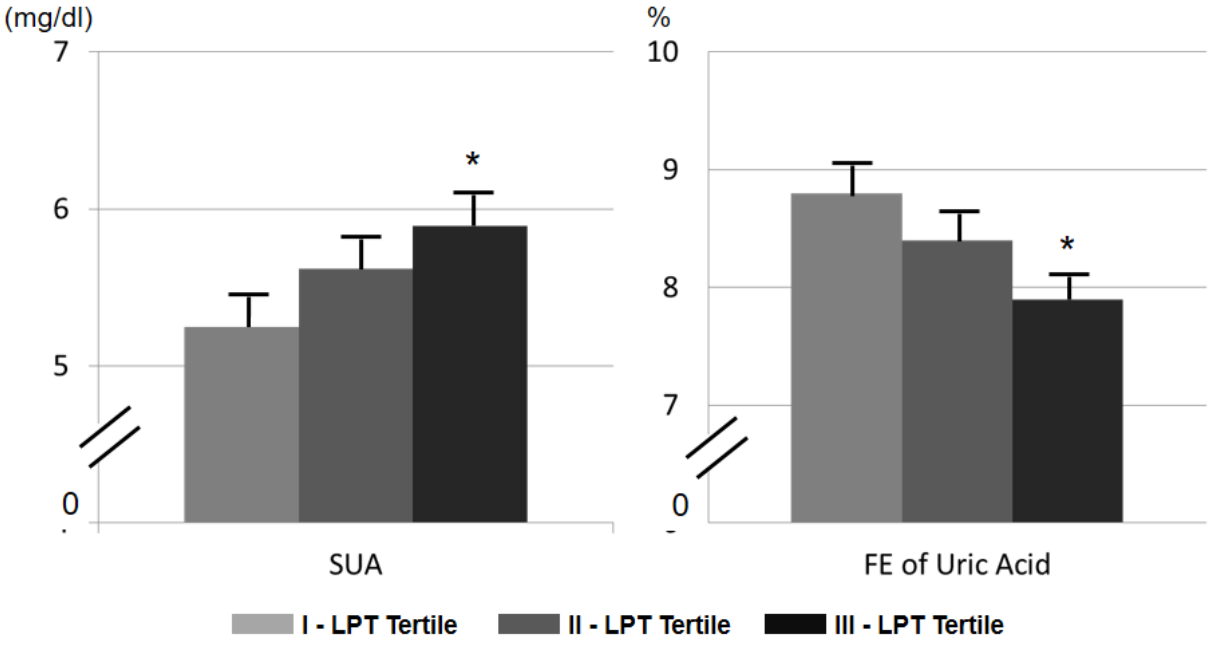
Table 4. Characteristics of the participants stratified by tertiles of leptin (n=930).

	I tertile	II tertile	III tertile
N. of participants	307	310	313
Age (yrs)	51.9 (7.5)	51.2 (7.1)	53.0 (7.8)*
BMI (kg/m^2)	25.2 (2.8)	26.7 (2.3)	28.8 (2.9)*
Waist Circumference (cm)	90.0 (7.6)	94.0 (6.7)	100.0 (7.4)*
Systolic BP (mmHg)	128.0 (18.0)	128.0 (16.4)	134.7 (16.7)*
Diastolic BP (mmHg)	81.9 (10.4)	83.7 (9.2)	87.9 (9.6)*
C-Reactive Protein (mg/L)‡	1.07 (2.75)	1.10 (2.63)	1.55 (2.34)†*
HOMA index (U)‡	1.70 (1.74)	2.04 (1.70)	2.45 (1.74)†*
Creatinine Clearance (mL/min*1.73 m^2)	84.1 (26.9)	85.6 (29.6)	84.5 (28.2)
LPT (ng/mL)‡	0.98 (2.04)	5.49 (1.20)	6.46 (1.48)†*

Data are expressed as means (SD); BP: Blood Pressure. The analysis of variance (ANOVA) was used to assess differences in main features among LPT tertiles. ‡ Data expressed as geometric mean; † analysis performed on log-transformed variable; * $p<0.01$.

1

Figure 1


(mg/dl)
7
6
5
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*
SUA
%
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9
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FE of Uric Acid
I - LPT Tertile
II - LPT Tertile
III - LPT Tertile

2