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PRELIMINARY REPORT

Serum Leptin Is Associated With Serum Uric Acid Concentrations in Humans

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This cross-sectional study aimed to evaluate the relationship between leptin and the cluster of abnormalities often referred to as the metabolic syndrome. The serum leptin concentration, body mass index (BMI), percent body fat, total fat mass (FM), waist and hip circumference, waist to hip ratio (WHR), prevalence of hypertension, and triglyceride (TG), lipoprotein, and uric acid concentration were determined in 86 type 2 diabetic (n = 59) and healthy (n = 27) subjects. Multiple regression analyses showed that the estimates of total body obesity (BMI, percent body fat, and total FM), sex, and serum uric acid concentration are independently associated with the serum leptin concentration. The finding of a positive correlation between serum leptin and uric acid levels suggests that leptin could be a pathogenic factor responsible for hyperuricemia in obesity.

LEPTIN, the *ob* gene product, is regarded as an important hormone for energy balance. Predominantly expressed in adipose tissue, it acts as an afferent signal to the brain, informing the hypothalamus about the fat stores. Basal leptin levels are markedly elevated in obese subjects,[1] implying an association between high leptin and the characteristic obesity complications known as the metabolic syndrome.[2] Several studies have focused on the associations between leptin and diabetes, hypertension, dyslipoproteinemia, and regional fat patterns.[3-5] However, to our knowledge, no data exist on the relationship between leptin and uric acid concentrations.

SUBJECTS AND METHODS

Fasting morning serum concentrations of leptin, uric acid, triglycerides (TGs), and lipoproteins and the body mass index (BMI), percent body fat, total fat mass (FM), waist circumference, hip circumference, and waist to hip ratio (WHR) were measured in 86 subjects (male to female ratio, 44/42; ratio of type 2 diabetic to healthy subjects, 59/27). None of the subjects had any endocrine disorder except diabetes. The diagnosis of diabetes was established according to the criteria of the World Health Organization[6] in patients treated by diet alone (nine subjects), or by the prevalence of treatment with hypoglycemic agents (n = one metformin and n = four sulfonylurea) or insulin (n = 45). In subjects with diabetes, the mean duration of diabetes was 14.3 ± 1.2 years and the mean hemoglobin A_{1c} (HbA_{1c}) 7.7% ± 0.2%. Hypertension was prevalent in 54 subjects and was treated by diuretics (n = 23), angiotensin-converting enzyme (ACE) inhibitor (n = 42), and calcium channel antagonists (n = 27). All subjects provided informed consent.

The BMI was estimated by dividing the body weight (in kilograms) by the square of the height (in meters). The percent body fat and total FM were measured by bioelectrical impedance analysis (Body Composition Analyser, Akren-RJL BIA 101/S; Data Input, Frankfurt, Germany). The waist circumference was measured as the narrowest circumference between the lowest costal margin and the iliac crest in the standing position. The hip measurement was the maximum circumference at the level of the trochanter. Leptin serum concentrations were analyzed by a highly sensitive radioimmunoassay (Mediagnost, Tübingen, Germany) with an intraassay and interassay coefficient of variation less than 5.0% and 7.6% and sensitivity less than 0.04 ng/mL. The HbA_{1c} level was measured by high-performance liquid chromatography (normal, <6.8%). Other measurements, ie, lipids and uric acid, were performed by routine clinical methods.

Statistical analysis was performed by SPSS Statistics Program Version 6.0 (SPSS, Chicago, IL). An unpaired Student's *t* test and analysis of covariance (ANCOVA) were used for comparison of variables between subgroups. Partial correlation coefficients were determined and stepwise forward multiple linear regression analysis was performed to detect associations between the serum leptin concentration and the other variables. Leptin levels were logarithmically transformed prior to analysis to achieve a normal distribution. Results are presented as the mean ± SE. A *P* value less than .05 was considered significant.

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Table 1. Clinical and Metabolic Characteristics of the Study Population

Variable	Men (n = 44)	Women (n = 42)	Controls (n = 27)	Diabetic Patients (n = 59)
Sex ratio (male/female)	—	—	17/10	27/32
Diabetes (present/absent)	27/17	32/10	—	—
Age (yr)	57.3 ± 1.7	64.3 ± 2.1*	59.1 ± 3.0	61.5 ± 1.5
BMI (kg/m²)	28.5 ± 0.7	28.7 ± 1.0	27.8 ± 0.9	29.0 ± 0.8
Fat %	28.1 ± 1.1	35.1 ± 0.9‡	30.4 ± 1.5	32.0 ± 1.0
FM (kg)	25.2 ± 1.5	27.5 ± 1.5	25.5 ± 1.8	26.7 ± 1.3
Waist circumference (cm)	103.7 ± 2.1	98.7 ± 2.4	96.7 ± 2.9	103 ± 1.9
Hip circumference (cm)	101.4 ± 1.0	103.8 ± 1.7	101.8 ± 1.3	102.8 ± 1.3
WHR	1.02 ± 0.02	0.95 ± 0.02†	0.95 ± 0.02	1.01 ± 0.02*
TG (mg/dL)	79.2 ± 11.2	229.7 ± 34.0	155.6 ± 15.4	227.1 ± 24.6
Total cholesterol (mg/dL)	218.9 ± 6.4	243.9 ± 11.0	225.0 ± 3.5	233.9 ± 8.4
LDL cholesterol (mg/dL)	144.7 ± 2.7	158.5 ± 10.0	150.6 ± 4.9	152.1 ± 60.1
HDL cholesterol (mg/dL)	44.2 ± 2.9	44.1 ± 2.1	44.0 ± 1.6	44.2 ± 2.4
Uric acid (mg/dL)	6.2 ± 0.3	5.9 ± 0.4	6.1 ± 0.2	6.0 ± 0.3
Leptin (ng/mL)	6.46 ± 0.75	23.90 ± 2.8‡	10.8 ± 1.3	16.7 ± 2.4
Log-leptin	1.54 ± 0.13	2.80 ± 0.14‡	1.84 ± 0.15	2.30 ± 0.14

NOTE. Results are the mean ± SE.

*$P < .05$, †$P < .01$, ‡$P < .001$: men *v* women and diabetic *v* control.

RESULTS

Table 1 shows a comparison of all variables between men and women and between diabetic and healthy subjects in the study population. Women had a significantly higher percent body fat ($P < .001$), lower WHR ($P < .01$), and higher log-transformed leptin ($P < .001$). The difference in leptin levels between men and women remained significant after adjusting for percent body fat (ANCOVA, $P < .001$). Leptin levels and the estimates of total body obesity (BMI, percent body fat, and total FM) did not differ between diabetic and healthy subjects (Table 1). Log-transformed leptin levels also did not differ between diabetics who received insulin therapy, diabetics treated with oral agents or diet alone, and healthy subjects (2.30 ± 1.61 *v* 2.29 ± 0.29 *v* 1.84 ± 0.22, respectively, all $P > .05$). Correlations between all variables are listed in Table 2 for subjects with diabetes and in Table 3 for healthy subjects. In both diabetic and healthy subjects, log-transformed leptin levels were significantly correlated with the BMI, percent body fat, total FM, waist circumference, hip circumference, WHR, and serum uric acid (all $P < .05$). In stepwise multiple linear regression analysis, female gender, increased total body obesity (BMI, percent body fat, and total FM), and the uric acid concentration were independently associated with increased serum leptin (Table 4). In contrast, the diabetes or hypertension prevalence, HbA_{1c}, TG, cholesterol fractions, waist or hip circumference, WHR, and intake of different antihypertensive agents were not independently related to the serum leptin level.

To determine the effects of hypertension or antihypertensive therapy on uric acid and leptin levels, we subdivided the study population according to the prevalence of hypertension and antihypertensive medication (Table 5). Subjects receiving diuretics had higher uric acid levels than the other subjects ($P < .001$),

Table 2. Correlations Between All Variables in 59 Subjects With Type 2 Diabetes

Variable	Age	Diabetes Duration	BMI	Fat %	FM	WC	HC	WHR	TG	CHOL	LDL	HDL	HbA_{1c}	Uric Acid
Diabetes duration	.48‡													
BMI	−.23*	−.25*												
Fat %	−.19	−.25*	.72‡											
FM	−.28*	−.32†	.87‡	.92‡										
WC	−.03	−.18	.87‡	.68‡	.83‡									
HC	−.05	−.25*	.75‡	.59‡	.71‡	.67‡								
WHR	−.01	−.02	.48‡	.36†	.45‡	.73‡	−.02							
TG	.07	−.02	−.11	−.15	−.09	−.03	−.15	.10						
CHOL	.11	.04	−.25*	−.36†	−.31*	−.23	−.12	−.21	.25*					
LDL	.07	.02	−.21	−.35†	−.29*	−.24	−.09	−.26*	.17	.98‡				
HDL	.15	.19	−.15	−.16	−.21	−.13	−.01	−.16	−.29*	.25*	.21			
HbA_{1c}	.19	.19	−.03	−.22	−.13	−.10	−.13	−.01	.08	.16	.11	−.06		
Uric acid	.27*	.25*	−.02	.02	.02	.05	.10	−.03	.36†	.01	−.02	−.39†	.10	
Log-leptin	−.02	−.07	.62‡	.52‡	.57‡	.60‡	.55‡	.31*	.10	−.15	−.17	−.22	.07	.30*

NOTE. Correlation coefficients are adjusted for sex.

Abbreviations: WC, waist circumference; HC, hip circumference; CHOL, cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol.

*$P < .05$.

†$P < .01$.

‡$P < .001$.

Table 3. Correlation Between All Variables in 27 Control Subjects

Variable	Age	BMI	Fat %	FM	WC	HC	WHR	TG	CHOL	LDL	HDL	Uric Acid
BMI	−.03											
Fat %	−.11	.80‡										
FM	−.27	.90‡	.92‡									
WC	.28	.81‡	.36*	.58†								
HC	.02	.75‡	.34*	.63‡	.77†							
WHR	.37*	.70‡	.29	.43*	.49†	.52†						
TG	−.03	.50†	.46*	.49†	.45*	.28	.45*					
CHOL	.03	.53†	.34	.42*	.57†	.60†	.49†	.23				
LDL	.01	.49†	.30	.38*	.54†	.57†	.46*	.07	.96‡			
HDL	.00	.14	.15	.11	.02	.09	.03	−.21	.57†	.46*		
Uric acid	.24	.21	.38*	.23	−.03	−.08	−.01	.29	−.12	−.11	.33	
Log-leptin	.03	.69‡	.56†	.61‡	.52†	.58†	.40*	.22	.25	.22	.16	.39*

NOTE. Correlation coefficients are adjusted for sex.

Abbreviations: WC, waist circumference; HC, hip circumference; CHOL, cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol.

*$P < .05$.

†$P < .01$.

‡$P < .001$.

but leptin levels did not differ between these two subgroups ($P = .925$). To exclude the potentially confounding influence of diuretics, which are known to increase serum uric acid levels, on the association found between serum uric acid and leptin, we analyzed the data after excluding subjects who were receiving diuretics. Multiple regression analysis in the remaining subjects showed essentially the same result as the analysis in the whole study population. Again, leptin levels were independently associated with sex, total body obesity, and serum uric acid (Table 6).

DISCUSSION

The present data show a strong positive association between serum leptin and uric acid in humans. Since we analyzed a large number of variables, it is unlikely that the observed association is based on confounding factors. Importantly, the association between leptin and uric acid remained significant after excluding from the analyses subjects who received diuretics, because these agents are known to increase the serum uric acid concentration.

Table 4. Multiple Linear Regression Models With Log-Leptin (ng/mL) as the Dependent Variable

Model	Variable	β	SE (β)	*P*
1	BMI	0.087	0.012	<.001
	Sex	1.277	0.141	<.001
	Uric acid	0.119	0.033	<.001
2	% Body fat	0.065	0.012	<.001
	Sex	0.859	0.174	<.001
	Uric acid	0.106	0.036	.004
3	FM	0.038	0.007	<.001
	Sex	1.004	0.164	<.001
	Uric acid	0.105	0.036	.005

NOTE. BMI, percent body fat, or total FM were subsequently included in the models as estimates of total body obesity (N = 86, β = regression coefficient, $R^2 = .66$, .59, and .59 in model 1, 2, and 3, respectively). The prevalence of diabetes and hypertension, waist and hip circumference, WHR, HbA_{1c}, TG, lipoproteins, and use of diuretics, ACE inhibitors, and calcium channel antagonists did not reach significance in stepwise forward multiple regression analysis.

The serum leptin level was correlated with the serum uric acid level in both diabetic and healthy subjects, indicating that the association between these two metabolic parameters is independent of diabetic status. The prevalence of diabetes did not affect serum leptin and uric acid, as indicated by the comparison of these variables between diabetic and healthy subjects (Table 1). Moreover, none of the anthropometric and metabolic parameters, measured in the present study explained the association between serum leptin and uric acid. However, since insulin levels were not measured in the present study, we cannot exclude a covariance between insulinemia and the uric acid concentrations. A major feature of obesity and type 2 diabetes is hyperinsulinemia and the associated insulin-resistant state. Insulin is thought to be a major regulator of leptin expression in humans.[7-9] Thus, it is still possible that insulinemia contributed to the association found between uric acid and leptin. Although a possible contribution of insulin cannot be directly excluded, the present data provide evidence for an independent association between serum leptin and uric acid levels.

The present data also confirm the results of previous studies showing a strong positive correlation between the leptin level and estimates of obesity, higher leptin in women versus men, and similar leptin levels in subjects with type 2 diabetes compared with healthy subjects.[3-5] The latter finding seems surprising, since insulin is thought to be a potent stimulator of leptin secretion[7-9] and patients with type 2 diabetes are frequently found to be hyperinsulinemic. However, recent research provides strong evidence that insulin-stimulated glucose uptake rather than insulin per se regulates leptin secretion.[10-12] Insulin resistance is a common feature of type 2 diabetes, resulting in a reduced effectiveness of insulin to stimulate glucose uptake. Therefore, the insulin resistance in type 2 diabetic subjects may explain why hyperinsulinemia in such individuals does not result in higher leptin levels as compared with healthy subjects. Since insulin levels were not measured here, the present data

Table 5. Log-Leptin and Serum Uric Acid Concentrations in the Study Population Divided According to the Prevalence of Hypertension and Use of Antihypertensive Agents

	Hypertension		Diuretics		ACE Inhibitors		Ca Channel Antagonists	
Variable	Yes	No	Yes	No	Yes	No	Yes	No
BMI (kg/m^2)	29.6 ± 0.8	26.9 ± 0.9*	27.7 ± 1.1	29.0 ± 0.8	30.0 ± 1.0	27.2 ± 0.7*	28.5 ± 0.8	28.5 ± 0.8
Uric acid (mg/dL)	6.4 ± 0.3	5.2 ± 0.3*	8.2 ± 0.5	5.2 ± 0.2‡	6.6 ± 0.3	5.4 ± 0.3†	6.1 ± 0.3	6.0 ± 0.3
Log-leptin	2.42 ± 0.13	1.70 ± 0.21	2.22 ± 0.21	2.20 ± 0.14	2.52 ± 0.15	1.81 ± 0.17*	2.13 ± 0.16	2.2 ± 0.17

NOTE. Comparisons of uric acid and log-leptin between subgroups are adjusted for sex and BMI.
*$P < .05$.
†$P < .01$.
‡$P < .001$.

Table 6. Multiple Linear Regression Models With Serum Log-Leptin (ng/mL) as the Dependent Variable in Subjects Not Receiving Diuretics

Model	Variable	β	SE (β)	*P*
1	BMI	0.072	0.015	<.001
	Sex	1.391	0.185	<.001
	Uric acid	0.196	0.068	.006
2	% Body fat	0.057	0.015	<.001
	Sex	1.087	0.222	<.001
	Uric acid	0.209	0.071	.005
3	FM	0.038	0.009	<.001
	Sex	1.369	0.188	<.001
	Uric acid	0.201	0.069	.005

NOTE. BMI, percent body fat, or total FM were subsequently included in the models as estimates of total body obesity (n = 63, β = regression coefficient, R^2 = .65, .62, and .64 in model 1, 2, and 3, respectively. The prevalence of diabetes and hypertension, waist and hip circumference, WHR, HbA_{1c}, TG, lipoproteins, and use of ACE inhibitors and calcium channel antagonists did not reach significance in stepwise forward multiple regression analysis.

cannot directly prove this hypothesis. However, the present finding that insulin therapy, which commonly causes hyperinsulinemia, is not associated with higher leptin as compared with the level in subjects without insulin therapy may provide support for this view.

Two possible mechanisms may explain the observed association between leptin and uric acid. First, leptin may modulate the uric acid concentration. Hyperuricemia in obese people is mainly attributed to impaired renal clearance of uric acid rather than overproduction.[13,14] Leptin influences renal function, ie, human leptin has diuretic/natriuretic activity in the rat.[15] Therefore, we speculate that leptin may directly impair uric acid excretion in the kidney. Previous observations that low caloric intake and weight reduction result in both a rapid decrease of serum leptin[1,16] and a rapid increase of uric acid excretion[13] may provide further support for this possible mechanism. Second, uric acid may also modulate leptin levels, eg, by increasing leptin gene expression or decreasing leptin clearance. In conclusion, the present study suggests that leptin could be the missing link between obesity and hyperuricemia.

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