Serum Leptin in Formerly Small-for-Gestational-Age Children During Adolescence: Relationship to Gender, Puberty, Body Composition, Insulin Sensitivity, Creatinine, and Serum Uric Acid

Ferdinand Pulzer, Ute Haase, Matthias Knüpfer, Jürgen Kratzsch, Volker Richter, Fausi Rassoul, Wieland Kiess, and Eberhard Keller

Serum leptin levels reflect body fat mass (FM), and have been described to be related to serum uric acid levels in adult type 2 diabetic and healthy subjects. We therefore aimed to evaluate the interrelationship between leptin and markers of the metabolic syndrome by studying serum leptin concentration, body mass index (BMI), percent body fat (Fat%), total fat mass (FM), sum of skinfolds (SS), triglycerides (TG), total cholesterol (CHOL), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), glucose, insulin, calculated insulin resistance (HOMA), creatinine (CR), and uric acid (UA) concentration in 50 former small-for-gestational-age (SGA) children and 21 infants born adequate for gestational age (AGA) at the time of midpuberty. Our data confirm previous results showing a positive association between leptin and body fatness, and female gender. Twelve children with impaired glucose tolerance (IGT) had higher UA levels than subjects with normal glucose tolerance (NGT) (5.1 ± 1.1 *v* 4.2 ± 1.2 mg/dL, $P < .05$), and showed the strongest relation between serum leptin and UA ($r = .76$, $P < .001$). Multiple regression analyses demonstrated that gender, estimates of total body adiposity (Fat% and SS), birth weight (BW), gestational age (GA), stimulated glucose and insulin, and serum UA are independently associated with serum leptin concentration in former SGA children with dysglycemia ($R^2 = .89$, $P < .001$). A long-term effect of intrauterine growth restriction on body fatness, metabolic syndrome, and serum leptin levels is suggested.

SERUM LEVELS of leptin have been shown to be associated with serum uric acid (UA) levels in humans.[1] The kidney is the major organ for leptin degradation,[2] and clearance of creatinine and UA.[3,4] Fasting leptin levels are elevated in obese subjects,[5] and renal leptin degradation and creatinine clearance are already impaired in type 2 diabetic patients.[3,6] In rodents, intrauterine growth retardation leads to a permanent nephron deficit with impaired renal function.[7] Furthermore, former small-for-gestational-age (SGA) subjects are reported to have a decreased renal function,[8] and are known to have an increased risk of coronary vascular disease (CVD), type 2 diabetes, or impaired glucose tolerance (IGT) in later life.[9] Recent studies demonstrate increased leptin concentrations in infants with former fetal distress,[10,11] and during catch-up growth after intrauterine growth retardation.[12] We therefore aimed to test the relationship of leptin, creatinine (CR), and UA in relation to birth parameters, body composition, metabolic control, blood lipid and lipoprotein parameters in adolescents and young adults with and without former intrauterine growth restriction.

SUBJECTS AND METHODS

In 50 former SGA children (39 with normal glucose tolerance [NGT], 11 with IGT) compared with 21 former adequate-for-gestational-age (AGA) subjects (20 with NGT, 1 with IGT) overnight-fasting serum concentrations of leptin, creatinine (CR), UA, glucose, insulin, calculated insulin resistance (HOMA), triglycerides (TG), total cholesterol (CHOL), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), body mass index (BMI), percent body fat (Fat%), total fat mass (FM), and sum of skinfolds (SS) were measured. To explore potentially important factors for the outcome of SGA infants, these subjects were matched as close as possible for gender, age, birth weight (BW), and birth length to children without intrauterine growth restriction. Thus the control group represents premature AGA children rather than those born at term gestation. Besides the IGT all subjects were healthy without any endocrine disorder as assessed by medical history, routine laboratory tests, and physical examination, at which pubertal development was determined according to the criteria of Tanner.[13] There were 29 subjects in Tanner stage II to IV (pubertal), and 42 in Tanner stage V (young adult). None of the subjects was on any medication known to influence serum UA levels. Every participant underwent an oral glucose tolerance test (OGTT) according to the criteria of the World Health Organization (1.75 g oral glucose per kg body weight; maximum 75 g; DEXTRO O.G-T, Boehringer Mannheim, Germany).[14] Blood samples for the determination of glucose and insulin levels were collected at -30, 0 (fasting state), 30, 60, 90, 120 (stimulated state), and 180 minutes. Insulin resistance was calculated by the HOMA method, using fasting serum glucose and insulin concentrations.[15]

Body weight, height, and waist and hip circumferences were measured in light clothing without shoes, whereas BMI was estimated by dividing the body weight (in kilograms) by the square of the height (in meters). Fat% and total FM were measured by bioelectrical impedance analysis (Body Composition Analyser, Akren-RJL BIA 101/S; Data input, Frankfurt, Germany). Skinfolds were measured using a Holtain-Skinfold-Caliper (Holtain, Crymch Pembs, UK).

Leptin serum concentrations were analyzed by a highly sensitive in-house radioimmunoassay (RIA) for leptin with a sensitivity of less than 0.02 ng/mL. The intra-assay and interassay coefficient of variation was less than 12.5% in the range between 1 and 8 ng/mL. Leptin levels of our in-house RIA are comparable with data of a commercially available leptin RIA (Mediagnost, Tuebingen, Germany) in sera of normal weight and adipose subjects: $y = -0.13 + 0.96x$ ($n = 92$; $r = .94$, $P < .0001$).

Serum insulin was determined by an enzymeimmunoassay (Enzymun, Boehringer, Mannheim, Germany). Other measurements, such

From the Department of Pediatrics, and the Department of Clinical Chemistry and Pathological Biochemistry, University of Leipzig, Leipzig, Germany.

Submitted May 22, 2000; accepted April 16, 2001.

Supported by a grant from the Deutsche Forschungsgemeinschaft (Ke 578/1-1), Bonn, Germany.

Address reprint requests to Ferdinand Pulzer, Department of Pediatrics, University of Leipzig, D-04317 Leipzig, Germany.

0026-0495/01/5010-0018$35.00/0

doi:10.1053/meta.2001.26746

Table 1. Clinical and Metabolic Characteristics of the Study Population

Variable	SGA (n = 50)	AGA (n = 21)	NGT (n = 59)	IGT (n = 12)
Sex ratio (male/female)	17/33	9/12	22/37	4/8
PS (Tanner II–IV/Tanner V)	19/31	10/11	24/35	5/7
Age (yr)	15.2 ± 2.9	14.3 ± 3.4	14.8 ± 2.9	15.7 ± 3.0
BW (kg)	2.3 ± 0.3	2.2 ± 0.2	2.2 ± 0.2	2.2 ± 0.4
BW (SDS)	−2,57 ± 0.60	−1,23 ± 0.74‡	−1,84 ± 0.87	−2,79 ± 1.02‡
GA (wk)	38.8 ± 1.4	35.8 ± 2.4*	37.8 ± 2.2	38.7 ± 2.3
BMI (kg/m^2)	19.8 ± 3.6	18.0 ± 3.3*	18.9 ± 2.8	21.0 ± 4.7*
Fat%	22.9 ± 4.9	18.9 ± 5.1*	21.4 ± 5.8	23.4 ± 8.2*
FM (kg)	12.1 ± 5.5	9.1 ± 3.5*	10.8 ± 4.7	13.5 ± 6.9*
SS (cm)	4.43 ± 1.80	3.56 ± 1.30*	3.95 ± 1.58	4.74 ± 2.14*
TG (mmol/L)	0.81 ± 0.51	0.77 ± 0.30	0.76 ± 0.45	0.86 ± 0.49
Total CHOL (mmol/L)	4.1 ± 0.66	4.0 ± 0.80	4.07 ± 0.70	4.16 ± 0.71
LDL-C (mmol/L)	2.27 ± 0.66	2.32 ± 0.72	2.27 ± 0.62	2.43 ± 0.73
HDL-C (mmol/L)	1.22 ± 0.33	1.19 ± 0.26	1.25 ± 0.30	1.04 ± 0.33*
FG (mmol/L)	4.55 ± 0.34	4.45 ± 0.30	4.49 ± 0.30	4.78 ± 0.37†
2-h glucose (mmol/L)	5.94 ± 1.40	5.74 ± 0.52	5.36 ± 0.76	7.98 ± 1.27‡
FI (pmol/L)	92.7 ± 36.4	93.4 ± 27.4	89.4 ± 28.9	111.7 ± 49.3*
2-h insulin (pmol/L)	439.4 ± 294.2	449.8 ± 244.9	354.1 ± 187.2	766.8 ± 350.6‡
HOMA	2.3 ± 1.4	2.1 ± 0.9	2.0 ± 1.0	3.4 ± 1.8‡
CR (μmol/L)	44.4 ± 11.7	44.6 ± 11.9	43.2 ± 11.5	46.7 ± 11.0
UA (mg/dL)	5.2 ± 1.4	4.0 ± 0.7*	4.2 ± 1.2	5.1 ± 1.1*
Leptin (ng/mL)	8.36 ± 7.47	4.20 ± 3.42*	6.26 ± 5.73	11.50 ± 9.34*

NOTE. Results are the mean ± SD.

Abbreviations: PS, pubertal stage; BW, birth weight; SDS, standard deviation score; GA, gestational age; BMI, body mass index; Fat%, percent body fat; FM, fat mass; SS, sum of skinfolds; TG, triglycerides; CHOL, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FG, fasting glucose; 2h glucose, stimulated glucose; FI, fasting insulin; 2h insulin, stimulated insulin; HOMA, calculated insulin resistance; CR, creatinine; UA, uric acid.

*$P < .05$, †$P < .01$, ‡$P < .001$: SGA *v* AGA, and NGT *v* IGT.

as glucose, lipids, lipoproteins, CR, and UA, were performed by routine clinical methods.

The study protocol was approved by the local ethics committee. Informed consent was obtained from the parents of each participant in the study.

Statistical analysis was carried out using the program Statistica (Statsoft, Tulsa, OK). An unpaired Student's *t* rest and analysis of covariance (ANCOVA) were used for comparison of variables between subgroups. Leptin levels were logarithmically transformed prior to analysis to achieve a normal distribution. Pearson's and partial correlation coefficients and stepwise forward multiple linear regression analysis were used to detect associations between serum leptin and the other variables. Results are presented as the mean ± SD. Statistical significance is implied by *P* less than .05.

RESULTS

Leptin, Gender, and Pubertal Development

Table 1 compares all variables between SGA and AGA children, and subjects with NGT or IGT. After log-transformation leptin levels did not differ between SGA and AGA children (1.60 ± 1.11 *v* 1.32 ± 0.98, $P > .05$). Forty-five girls had significantly higher estimates of total body adiposity (BMI [$P < .001$], Fat% [$P < .001$], FM [$P < .01$], SS [$P < .01$]) than 26 boys. Log-leptin concentrations were higher in females than in males (1.74 ± 1.20 *v* 0.58 ± 0.98 ng/mL, $P < .001$). The mean pubertal stage was IV in both groups. In 29 pubertal children (mean age, 12.2 ± 1.9 years; mean pubertal stage, III) compared with 42 young adults (mean age, 16.8 ± 2.0 years; all pubertal stage V) leptin levels differed significantly (6.26 ± 5.72 *v* 11.50 ± 9.33 ng/mL, $P < .05$). After adjusting for gender, pubertal stage, and SS, these differences remained significant only in former SGA children (4.81 ± 3.69 *v* 10.32 ± 8.25 ng/mL, $P < .05$) compared to AGA children (3.64 ± 1.91 *v* 7.01 ± 6.80 ng/mL, $P > .1$; ANCOVA, $P < .05$).

Controlling for gender, log-leptin was predicted differently in pubertal children and young adults of the whole group (SS [$R^2 = .62$], BMI [$R^2 = .44$], FM [$R^2 = .36$], and Fat% [$R^2 = .33$] *v* SS [$R^2 = .67$], BMI [$R^2 = .62$], FM [$R^2 = .61$], and Fat% [$R^2 = .57$], respectively; all $P < .001$). When combining the data of all subjects, and adjusting for gender, SS ($R^2 = .66$) was the strongest predictor of log-leptin among the estimates of total body adiposity, prior to BMI ($R^2 = .57$; all $P < .001$). Since BMI does not provide a sensitive measure of adiposity during adolescence, SS was used to account for body composition when necessary.[16]

Leptin, Glucose Tolerance, and Calculated Insulin Sensitivity

Eleven SGA children and 1 child of the AGA group ($P < .05$) had IGT as defined by World Health Organization criteria.[14] Children with IGT (12/59), as demonstrated in Table 1, had significantly higher estimates of total body adiposity (BMI, Fat%, FM, and SS) in addition to elevated fasting and stimulated glucose levels, fasting and stimulated insulin concentrations, calculated insulin resistance, UA, and serum leptin levels. All of these differences, except stimulated glucose, and insulin levels remained significant after adjusting for gender, and SS (ANCOVA, $P < .05$).

Table 2. Correlations Between All Variables in 12 Subjects With IGT

Variable	Age	PS	BW	BW SDS	GA	BMI	Fat %	FM	SS	TG	CHOL	LDL-C	HDL-C	FG	2-h Glucose	FI	2-h Insulin	HOMA	CR	UA
PS	.80‡																			
BW	−.15	−.08																		
BW SDS	−.29	−.03	.42																	
GA	−.22	−.06	.24	−.40																
BMI	.56	.69*	−.75†	−.60*	−.16															
Fat %	.49	.42	−.55	−.68*	.16	.83‡														
FM	.52	.65*	−.71†	−.62*	−.10	.97‡	.89‡													
SS	.52	.59*	−.72†	−.59*	−.12	.66*	.61*	.59*												
TG	−.07	−.21	−.28	−.23	−.01	.32	.12	.26	.62*											
CHOL	.07	−.02	−.29	−.43	.41	.19	.24	.12	.39	.13										
LDL-C	.04	.03	.02	−.58*	.16	.20	.31	.20	.26	.14	.80†									
HDL-C	−.43	−.10	.63*	.19	.44	−.56	−.31	−.59*	−.30	−.15	.25	−.31								
FG	.45	.04	−.57*	−.50	−.10	.34	.22	.24	.58*	.10	.35	.51	−.26							
2-h glucose	.26	.00	−.05	−.20	.16	−.18	−.49	.21	.17	.08	.22	.26	−.32	.30						
FI	.02	−.10	−.41	−.59*	.10	.45	.71†	.59*	.46	.18	.09	.29	−.45	.58*	.27					
2-h insulin	−.06	.15	−.30	−.18	−.36	.39	.58*	.53	.18	.07	.39	−.13	−.35	.11	.45	.72†				
HOMA	.30	−.03	−.65*	−.79†	−.03	.61*	.72†	.69*	.63*	−.09	.11	.24	−.49	.62*	.50	.88‡	.46			
CR	.78†	.70	−.40	−.17	−.11	.41	−.09	.28	.29	.27	.21	.30	−.31	.56	.53	.34	.40	.11		
UA	.15	.30	−.68*	−.20	−.67*	.57*	.31	.45	.67*	.40	−.01	.19	−.42	.33	.41	.12	.27	.30	.40	
Log-leptin	.14	.37	−.73*	−.59*	−.68*	.79†	.73†	.86‡	.87‡	.29	−.27	.06	−.46	.32	.42	.52	.54	.61*	.36	.76†

NOTE. Correlation coefficients are adjusted for sex.
*$P < .05$, †$P < .01$, ‡$P < .001$.

In the whole group, sex-adjusted log-leptin concentrations correlated inversely with BW (partial $r = -.30$, $P < .05$), and calculated insulin resistance (partial $r = -.33$, $P < .05$), and positively with fasting glucose levels (partial $r = .29$, $P < .05$), and stimulated glucose and insulin levels (partial $r = .26$, and partial $r = .34$, $P < .05$). Tables 2 and 3 display the correlation results of sex-adjusted log-leptin concentrations for different parameters in subjects with IGT and NGT. Multiple-step forward regression analysis in these children demonstrated that gender (partial $r = .56$, $P < .01$), gestational age (partial $r = -.25$, $P < .05$), BW (partial $r = -.57$, $P < .01$), SS (partial $r = .38$, $P < .01$), Fat% (partial $r = .34$, $P < .05$), stimulated glucose (partial $r = .28$, $P < .05$), stimulated insulin (partial $r = .35$, $P < .05$), and UA (partial $r = .76$, $P < .01$) were independently associated with serum leptin ($R^2 = .89$, $P < .001$).

Leptin, Creatinine, and Uric Acid

Serum leptin concentration correlated with UA in girls ($r = .83$, $P < .05$) and with IGT in boys ($r = .70$, $P = .07$) as shown in Fig 1. After controlling for gender, the strongest correlation between leptin and serum UA concentrations was found in former SGA children with IGT ($r = .76$, $P < .001$), whereas no relation could be observed in former AGA children with NGT ($r = .11$, $P = .66$). Sex-adjusted CR levels tend to correlate positively in former SGA children with IGT ($r = .36$, $P = .17$), and inversely in former AGA children with NGT ($r = -.21$, $P = .39$).

Performing 3 multiple regression analysis models in former SGA children with Fat%, FM, and SS ($R^2 = .64$, .68, and .74, respectively) reveals that only gender and UA were significantly and independently related to serum leptin levels in each model (Table 4). Whereas in former AGA children (model 3, $R^2 = .82$), SS ($\beta = .68$, $P < .001$), gender ($\beta = .27$, $P < .05$), and CR ($\beta = -.31$, $P < .05$) were associated with serum leptin levels, while serum UA together with the birth parameters, TG, cholesterol fractions, prevalence of glucose tolerance, and calculated insulin resistance remained nonsignificant.

For the whole group, stepwise forward multiple regression analysis shows a significant relationship between log-leptin levels and gender ($\beta = .22$, $P < .001$), SS ($\beta = .72$, $P < .001$), UA ($\beta = .23$, $P < .001$), CR ($\beta = -.16$, $P < .05$), BW ($\beta = -.16$, $P < .05$), BW standard deviation score (SDS) ($\beta = -.16$, $P < .05$), and gestational age ($\beta = .17$, $P < .05$), whereas pubertal stage, TGs, total CHOL, HDL-C, LDL-C, basal and stimulated glucose, basal and stimulated insulin, and calculated insulin resistance did not reach significance.

DISCUSSION

This study was undertaken to test the hypothesis whether or not serum leptin levels are associated with serum UA levels in children and young adults. Our data from former SGA and AGA children demonstrate that (1) leptin levels correlate with estimates of total body adiposity; (2) gender differences in leptin persist after puberty independent of adiposity; (3) SS is a better predictor of leptin levels than BMI during puberty; (4) in children with IGT, leptin is correlated with calculated insulin resistance, but not with stimulated insulin independent of adiposity; (5) in former SGA subjects with dysglycemia, BW and gestational age are independent predictors of serum leptin levels; and (6) serum leptin and UA are positively related in children and young adults.

The present cross-sectional results suggest that leptin levels in children most strongly reflect body FM, and are correlated with gender and pubertal development. In this study, SS was the strongest predictor of serum leptin concentration prior to BMI, FM, and Fat% in pubertal children and young adults, thus emphasizing the idea that, in contrast to adult studies, determining the BMI in adolescents does not provide a sensitive and reliable measure of adiposity.[16]

Table 3. Correlations Between All Variables in 59 Subjects With NGT

Variable	Age	PS	BW	BW SDS	GA	BMI	Fat %	FM	SS	TG	CHOL	LDL-C	HDL-C	FG	2-h Glucose	FI	2-h Insulin	HOMA	CR	UA
PS	.84‡																			
BW	.01	.03																		
BW SDS	−.04	.03	.25																	
GA	.05	−.01	.64‡	−.56‡																
BMI	.45‡	.58‡	−.12	−.11	−.00															
Fat %	.22	.16	−.05	.00	.01	.58‡														
FM	.51‡	.56‡	−.00	.03	.00	.84‡	.83‡													
SS	.11	.17	−.24	−.06	−.14	.74‡	.74‡	.71‡												
TG	.03	−.01	−.11	−.01	−.08	−.03	−.06	−.04	.01											
CHOL	.08	−.15	.07	−.02	.13	.01	.12	−.02	−.01	.13										
LDL-C	.01	−.11	.11	−.00	.14	−.00	.01	−.06	−.02	.14	.85‡									
HDL-C	.10	−.06	−.01	−.04	.02	.08	.14	.07	.05	−.23	.39†	−.06								
FG	−.15	−.07	.06	.16	−.05	.13	.12	.17	.25	−.10	−.15	.05	−.26*							
2-h glucose	−.21	−.25	−.15	.21	−.28*	−.02	.20	.05	.10	−.15	−.05	−.14	.18	.21						
FI	−.10	−.06	−.12	.15	−.26*	.12	.08	.03	.29*	.09	−.09	−.06	.02	.24	.22					
2-h insulin	.11	.21	−.25	.16	−.36†	.28*	.26*	.28*	.32*	.14	−.10	−.06	−.07	.29*	.28*	.57‡				
HOMA	−.15	−.08	−.07	.18	−.20	.18	.14	.12	.37†	−.02	−.16	−.02	−.15	.70‡	.27*	.84‡	.56‡			
CR	.62‡	.62‡	−.07	.13	−.17	.35†	.07	.38†	−.04	.01	−.02	−.01	−.04	−.01	−.11	−.12	.20	−.09		
UA	.17	.25	−.13	.05	−.17	.17	−.19	.03	−.06	.02	−.22	−.17	−.05	.08	−.18	−.01	−.00	−.01	.41†	
Log-leptin	.10	.16	−.23	−.11	−.13	.58‡	.52‡	.55‡	.72‡	−.02	.09	.07	.13	.27*	.10	.18	.35†	.28*	−.04	.10

NOTE. Correlation coefficients are adjusted for sex.
*$P < .05$, †$P < .01$, ‡$P < .001$.

In several studies intrauterine growth retardation has been linked to a higher risk of developing complications of the metabolic syndrome like diabetes mellitus, microvascular and macrovascular disease,[9,17] and hypercholesterolemia, especially in children with reduced postnatal growth.[18] The present data cannot directly prove this hypothesis. However, the finding that BW SDS is inversely related to serum leptin in our subjects with IGT might strengthen this premise. Accumulating evidence suggests that diabetes-associated macrovascular disease already develops when glucose tolerance is impaired.[17] Thus, in the light of the elevated rate of IGT found among former SGA subjects, these children have a higher risk of developing complications of the syndrome X in later life. Our study in healthy former SGA and AGA children demonstrates that fasting insulin is not related to leptin levels in subjects with IGT. This is in agreement with other studies.[19] Additionally, we found that in the majority of children with IGT, particularly in the obese, insulin responses during OGTTs are higher than in the mean for age-adjusted but not weight-adjusted controls; these individuals have some resistance to the effects of insulin rather than a total inability to secrete it. In vitro studies have shown that insulin stimulates leptin production of human adipocytes,[20] and that leptin increases during insulin treatment in patients with type 1 diabetes.[21] Recent studies show that insulin-stimulated glucose uptake rather than insulin per se regulates leptin secretion.[22]

Investigations in obese people showed that hyperuricemia is

Table 4. Multiple Linear Regression Models With Log-Leptin (ng/mL) as the Dependent Variable for the Former SGA Children (n = 50)

Model	Variable	β	SE (β)	P	R^2
1	Fat %	0.59	0.11	<.001	
	Sex	0.40	0.10	<.01	0.64
	UA	0.31	0.09	<.01	
2	FM	0.56	0.10	<.001	
	Sex	0.51	0.12	<.001	0.68
	CR	−0.23	0.09	<.05	
	UA	0.27	0.10	<.01	
3	SS	0.61	0.09	<.001	
	Sex	0.42	0.09	<.001	0.74
	CR	−0.26	0.08	<.05	
	UA	0.33	0.09	<.01	

NOTE. Fat %, FM, and SS were subsequently included in the models as estimates of total body adiposity (β = regression coefficient, R^2 = .64, .68, and .74 in models 1 to 3, respectively). In stepwise forward multiple regression analysis, the prevalence of BW, BW SDS, GA, PS, TG, total CHOL, HDL-C, LDL-C, basal and stimulated glucose, basal and stimulated insulin, and calculated insulin resistance did not reach significance.

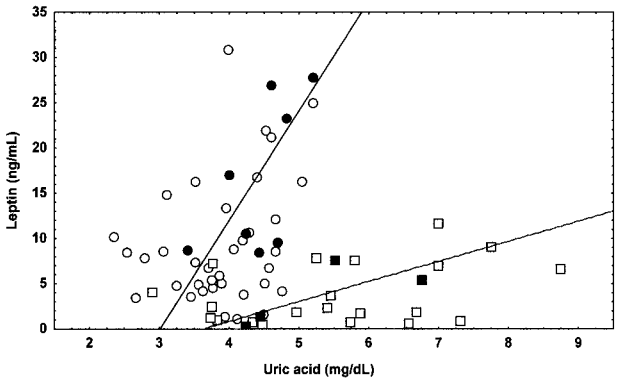

Fig 1. Correlation between serum leptin and UA concentration in 50 former SGA children and 21 controls (AGA): 38 girls (○), and 21 boys (□) with NGT (regression lines not shown), and in 8 girls (●)(λ, — , y = 3.55x + 0.07, r = .83, P < .05), and 4 boys (■)(λ, ····· , y = 10.41x - 30.77, r = .70, P = .07) with IGT.

mainly attributed to impaired renal clearance,[4] and an animal model revealed a diuretic/natriuretic effect of leptin.[23] A recent study demonstrated the association between serum leptin and UA levels in an older, mostly obese, population independent of the status of carbohydrate metabolism.[6] Together with the previous finding that energy restriction results in both a rapid decrease of serum leptin[24] and an increase of UA excretion,[25] a direct modulation of renal UA excretion by leptin was postulated.[1] Furthermore, elevated CR and leptin levels have been described in patients with end-stage renal disease[26] and in type 2 diabetic patients with macroalbuminuria and microalbuminuria.[6,27] In our study, the highest UA levels were found in former SGA children with IGT, whereas serum CR levels in these subjects only tended to be higher. Several investigators demonstrated an impaired renal function with regard to glomerular as well as tubular function,[28] and a markedly reduced renal function within the first years of life in very low-birthweight infants.[29] Our finding that serum leptin shows a strong positive correlation with serum UA, and an inverse relation to BW, especially in subjects with dysglycemia, may provide further support for the hypothesis that former SGA children with IGT show several abnormalities often referred to the metabolic syndrome already in the second decade of life.

Recent studies have reported lower leptin levels as a marker of reduced adipose tissue stores in former SGA children, especially in those who did not show catch-up growth in early life.[30-32] However, interestingly, higher leptin levels are found in former intrauterine growth-restricted children with catch-up growth, and are proposed to be an adaptive process beneficial for their development and/or an indicator of a defect in adipose tissue function.[12] This is in line with our findings in former intrauterine growth-restricted children since they have higher serum leptin concentrations during puberty, which remain elevated thereafter independent of gender and subcutaneous FM. By describing increased fetal leptin in the presence of hypoxia, lactacidemia, and maternal pre-eclampsia as signs of fetal distress, other investigators give leptin a putative role as a possible regulator of fetal development.[10,11] Although the underlying mechanisms linking restricted fetal growth with cardiovascular disease have not yet been recognized, the present data add to the notion that the endocrine axes are presumed to be programmed during critical phases of fetal development.

In summary, the present cross-sectional study in healthy, former SGA and AGA children with or without IGT demonstrates that leptin levels most strongly reflect FM, prior to gender- or puberty-related differences. Leptin concentrations are higher in subjects with IGT and do correlate positively with serum UA levels, and inversely with BW SDS, suggesting that renal leptin degradation and UA excretion might be impaired already in formerly intrauterine growth-restricted subjects with hyperinsulinemia and dysglycemia at younger age.

REFERENCES

1. Fruehwald-Schultes B, Peters A, Kern W, et al: Serum leptin is associated with serum uric acid concentrations in humans. Metabolism 48:677-680, 1999
2. Esler M, Vaz M, Collier G, et al: Leptin in human plasma is derived in part from the brain, and cleared by the kidneys. Lancet 351:879, 1998
3. Shoji T, Nishizawa Y, Morii H, et al: Renal function and insulin resistance as determinants of plasma leptin levels in patients with NIDDM. Diabetologia 40:676-679, 1997
4. Takahashi S, Yamamoto T, Tsutsumi Z, et al: Close correlation between visceral fat accumulation and uric acid metabolism in healthy men. Metabolism 46:1162-1165, 1997
5. Considine RV, Sinha MK, Heiman ML, et al: Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 334:292-295, 1996
6. Fruehwald-Schultes B, Kern W, Beyer J, et al: Elevated serum leptin concentrations in type 2 diabetic patients with microalbuminuria and macroalbuminuria. Metabolism 48:1290-1293, 1999
7. Merlet-Benichou C, Gilbert T, Muffat-Joly M, et al: Intrauterine growth retardation leads to a permanent nephron deficit in the rat. Pediatr Nephrol 8:175-180, 1994
8. Rossing P, Tarnow L, Nielsen FS, et al: Short stature and diabetic nephropathy. BMJ 310:296-297, 1995
9. Barker DJ, Martyn CN, Osmond C, et al: Abnormal liver growth in utero and death from coronary heart diseases. BMJ 310:703-704, 1995
10. Hytinantti T, Koistinen HA, Andersson S, et al: Increased leptin concentration in preterm infants of pre-eclamptic mothers. Arch Dis Child Fetal Neonatal Ed 83:F13-F16, 2000
11. Cetin I, Morpurgo PS, Beck-Peccoz P, et al: Fetal plasma leptin concentrations: Relationship with different intrauterine growth patterns from 19 week to term. Pediatr Res 48:646-651, 2000
12. Jaquet D, Leger J, Levy-Marchal C, et al: High serum leptin concentrations during catch-up growth of children born with intrauterine growth retardation. J Clin Endocrinol Metab 84:1949-1953, 1999
13. Tanner JM: Growth and maturation during adolescence. Nutr Rev 39:43-55, 1981
14. Diabetes mellitus. Report of a WHO Study Group. World Health Organ Tech Rep Ser 727:1-113, 1985
15. Matthews DR, Hosker JP, Rudenski AS, et al: Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28:412-419, 1985
16. Arslanian S, Suprasongsin C, Kalhan SC, et al: Plasma leptin in children: Relationship to puberty, gender, body composition, insulin sensitivity, and energy expenditure. Metabolism 47:309-312, 1998
17. Schmidt MI, Watson RL, Duncan BB, et al: Clustering of dyslipidemia, hyperuricemia, diabetes, and hypertension and its association with fasting insulin and central overall obesity in a general population. Atherosclerosis Risk in Communities Study Investigators. Metabolism 45:699-706, 1996
18. Tenhola S, Martikainen A, Voutilainen R, et al: Serum Lipid concentrations and growth characteristics in 12-year-old children born small for gestational age. Pediatr Res 48:623-628, 2000
19. Haffner SM: The importance of hyperglycemia in the nonfasting state to the development of cardiovascular disease. Endocr Rev 19:583-592, 1998
20. Wabitsch M, Jensen PB, Blum WF, et al: Insulin and cortisol promote leptin production in cultured human fat cells. Diabetes 45: 1435-1438, 1996
21. Kiess W, Anil M, Blum WF: Serum leptin levels in children and adolescents with insulin-dependent diabetes mellitus in relation to metabolic control and body mass index. Eur J Endocrinol 138:501-509, 1998
22. Mueller WM, Gregoire FM, Stanhope KL, et al: Evidence that glucose metabolism regulates leptin secretion from cultured rat adipocytes. Endocrinology 139:551-558, 1998

23. Jackson EK, Li P: Human leptin has natriuretic activity in the rat. Am J Physiol 272:F333-F338, 1997

24. Dubuc GR, Phinney SD, Stern JS, et al: Changes of serum leptin and endocrine and metabolic parameters after 7 days of energy restriction in men and women. Metabolism 47:429-434, 1998

25. Yamashita S, Matsuzawa Y, Tokunaga K, et al: Studies of the impaired metabolism of uric acid in obese subjects: Marked reduction of renal urate excretion and its improvement by a low-calorie diet. Int J Obes Relat Metab Disord 10:255-264, 1986

26. Merabet E, Dagogo-Jack S, Coyne DW, et al: Increased plasma leptin concentration in end-stage renal disease. J Clin Endocrinol Metab 82:847-850, 1997

27. Shoji T, Nishizawa Y, Morii H, et al: Renal function and insulin resistance as determinants of plasma leptin levels in patients with NIDDM. Diabetologia 40:676-679, 1997

28. Vanpee M, Ergander U, Herin P, et al: Renal function in sick, very low-birth-weight infants. Acta Paediatr 82:714-718, 1993

29. Vanpee M, Blennow M, Linne T, et al: Renal function in very low birth weight infants: Normal maturity reached during early childhood. J Pediatr 121:784-788, 1992

30. Bjarnason R, Boguszewski M, Carlsson LMS, et al: Leptin levels are strongly correlated with those of GH-binding protein in prepubertal children. Eur J Endocrinol 137:68-73, 1997

31. Boguszewski M, Dahlgren J, Albertsson-Wikland K, et al: Serum leptin in short children born small for gestational age: Relationship with the growth response to growth hormone treatment. Eur J Endocrinol 137:387-395, 1997

32. Albertsson-Wikland K, Boguszewski M, Karlberg J, et al: Children born-small-for-gestational age: Postnatal growth and hormonal status. Horm Res 49:7-13, 1998 (suppl 2)