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Plasma leptin concentrations and obesity in relation to insulin resistance syndrome components among school children in Taiwan — The Taipei Children Heart Study

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OBJECTIVE: Leptin, an adipose tissue-derived product of the obesity (*OB*) gene, is an important regulator of energy metabolism and may be associated with the occurrence of insulin resistance and diabetes in humans. The purpose of this study was to evaluate the association of plasma leptin concentration with obesity and the components of insulin resistance syndrome (IRS) among school children in Taiwan.
METHODS: After multistage sampling of 85 junior high schools in Taipei, we randomly selected 1264 children (617 boys and 647 girls) aged 12–16 y. Obesity measurements included body mass index (BMI) and waist-to-hip circumference ratio (WHR). We calculated an IRS summary score for each individual by adding the quartile ranks from the distribution of systolic blood pressure (BP), serum triglyceride (TG), HDL-cholesterol (inverse), and insulin levels.
RESULTS: Boys had a higher BMI and WHR, BP and IRS score and lower leptin, insulin, TG and HDL-C levels than girls. BMI, WHR and plasma leptin levels were significantly associated with the IRS summary score and each of its components in both genders. Children with higher plasma leptin levels ($>$75th percentiles) have significantly higher BP, TG, insulin levels and IRS score than children with low leptin levels. The associations between plasma leptin level and the IRS components and score were still significant after adjusting for BMI in boys, but less so in girls. In both genders, after adjusting for WHR, plasma leptin levels were still significantly associated with the IRS components and summary score ($P<0.001$). The final model that included the standard covariates, BMI and leptin, but not WHR, was the most predictive of the IRS summary score among school children.
CONCLUSIONS: Insulin resistance syndrome in childhood, characterized by high blood pressure, dyslipidemia, and hyperinsulinemia, may be an early marker of cardiovascular risk. From the present BMI and leptin in combination are the most predictive markers of insulin resistance syndrome among school children in Taiwan.
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Introduction

The clustering of obesity, hypertension, hyperinsulinemia, and dyslipidemia has been called insulin resistance syndrome (IRS) or metabolic syndrome X, and is associated with increased risk of non-insulin dependent diabetes mellitus (NIDDM) and cardiovascular disease (CVD).[1–6] Among children and young adults, these markers of IRS track into adulthood and are associated with subsequent risk of NIDDM and CVD.[4,7–11] Typically, screening programs for children only focus on cholesterol levels and family history of cardiovascular disease and do not take into account other factors related to IRS.[12,13]

Leptin, primarily adipose tissue-derived protein product of the obesity (*OB*) gene, originally identified as an important regulator of energy metabolism, is a multifunctional polypeptide which may be associated with the occurrence of insulin resistance and diabetes in humans.[14–17]

Many studies have examined the association between plasma leptin and insulin sensitivity among adults. In general, plasma leptin is independently associated with insulin sensitivity even after adjusting for age, gender, body mass index (BMI), waist-to-hip ratio (WHR) and physical activity.[18–28] This relationship has not been thoroughly examined among children, yet insulin resistance in children may be related to chronic disease later in life.[7,29,30] One complication

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of studying the effects of leptin on insulin is that the relationship between leptin and insulin may be bi-directional and may be modified by extent of obesity and insulin resistance.[31,32] Even if elevated leptin is a consequence rather than a predictor of insulin resistance, it still may be a useful screening tool for children with early metabolic disorders.

The purpose of this study was to evaluate the association between plasma leptin concentrations and markers of the insulin resistance syndrome among school children in Taiwan.

Materials and methods

Study design and sampling method

The Taipei Children Heart Study is an epidemiological survey of cardiovascular disease risk factors among school children in Taipei in 1995. The details of the sampling methods and results are described elsewhere.[33,34] Briefly, we conducted a cross-sectional survey among junior high school students in Taipei to ascertain a representative distribution of demographic, lifestyle and biochemical characteristics and cardiovascular disease risk factors. After multistage sampling of 85 junior high schools in Taipei, we randomly selected 1500 school children for this survey.

Data collection

All participants completed a questionnaire on their disease history and lifestyle characteristics, including cigarette smoking, alcohol consumption, puberty development, usual physical activity and dietary intake.

Research technicians recorded body weight to the nearest 0.1 kg using a standard beam balance scale with subjects barefoot and wearing light indoor clothing. Body height was recorded to the nearest 0.5 cm using a ruler attached to the scale. We calculated BMI as the ratio of body weight to body height squared expressed as kg/m^2. Waist circumference was measured at the distal third of the line from the xyphoid process to the umbilicus. Hip circumference was measured 4 cm below the anterior superior process of the iliac spine. We calculated WHR as the ratio of waist circumference divided by the hip circumference.

After 10 min rest, we measured blood pressure (BP) on the right arm in a sitting position, using an appropriate cuff size; the first and fifth Korotkoff sounds were recorded as systolic and diastolic BP. We measured blood pressure again after a 5 min rest and the average was used in the analysis. Heart rate was measured for 1 min during the first and second blood pressure measurement.

To reduce extraneous between-person variation, we collected a 12 h fasting blood sample only from students who had consumed their usual dietary pattern during the previous 3 days. Children who had recently attended a holiday or family celebration were recontacted several weeks later. Except leptin levels, the biochemical assays were performed within 2 weeks on blood samples stored at $-4°C$. Plasma was stored at $-70°C$ for 2 y before leptin was assayed.

We measured serum total cholesterol using an esterase oxidase method,[35] triglycerides (TG) using an enzymatic procedure,[36] and high density lipoprotein-cholesterol (HDL-C) by an enzymatic method with magnesium precipitation[37] using the Synchron CX5 analyzer (Beckman Instrument, Palo Alto, CA). We measured plasma insulin concentrations by radioimmunoassay (RIA) using a commercial kit (Linco Research Inc. St Charles, MO, USA) which allows accurate assessment with little or no proinsulin or c-peptide cross-reactivity. Plasma leptin concentrations were measured by RIA (Linco Research Inc. St Charles, MO, USA) with the antibody raised to highly purified recombinant human leptin.[38] The inter- and intra-assay coefficients of variation (CVs) for leptin were 8.3 and 3.4%, respectively. Each commercial assay was calibrated with standards from the manufacturer. Because no triglyceride concentration exceeded 400 mg/dl and all samples were collected after a 12 h fast, we used Friedewald's formula[39] to calculate low density lipoprotein-cholesterol (LDL-C): LDL-C (total cholesterol−HDL-C)−(triglyceride/5).

Statistical analysis

To reduce differences due to maturation, gender-specific distributions of anthropometric and biological measures are directly standardized to the age distribution (based on ≤ 12,13 and ≥ 14 y, three categories) of the whole population. Subjects were classified as having a high leptin concentration if their plasma leptin value was greater than the 75th percentile according to age- and gender-specific strata. We calculated a gender-specific insulin resistance syndrome (IRS) summary score by adding the quartile ranks from the distribution of systolic BP, TG, HDL-C and insulin levels of each subject. A higher summary score corresponds to higher levels of BP, TG and fasting insulin and lower levels of HDL-C.

We calculated gender-specific Spearman correlation coefficients between BMI, WHR, BP, lipoproteins, insulin levels, IRS score and plasma leptin concentrations to insure validity of inference without assumptions of normality. We tested for differences in anthropometric and biological measures between children with high plasma leptin and normal leptin levels by analysis of variance (ANOVA) after adjusting for age.

In separate multivariate linear regression models we regressed the IRS score and its components onto plasma leptin level, BMI or WHR. All regression analyses were adjusted for age, cigarette smoking, alcohol drinking, heart rate and puberty development. We used the robust variance by PROC MIXED in

SAS to insure validity of inference without the need to involve normal distribution assumptions. A two-tailed *P*-value less than 0.05 was considered statistically significant. All statistical analyses were conducted using the statistical package SAS (SAS Institute Inc., Cary, NC).

Results

General characteristics of study children

We excluded 236 subjects who refused the survey protocol or had missing or incomplete data. The final sample for analysis included 1264 children (617 boys and 647 girls) with the mean age of 13.3 y (range 12–16 y). The percentiles (25th, median and 75th percentile), distributions and age-adjusted mean values of anthropometric variables, blood pressure, lipids, lipoproteins, insulin, leptin levels and the IRS summary score are shown in Table 1. In general, boys were taller, heavier and had a larger BMI and WHR than girls. Boys also had a higher systolic BP and lower cholesterol, TG, HDL-C, LDL-C, insulin and leptin levels than girls.

The Spearman correlation coefficients between BMI, WHR, BP, lipoproteins, insulin, IRS score and plasma leptin level are shown in Table 2. BMI, WHR and plasma leptin level are significantly positively correlated with IRS score and its components (ie BP, TG and insulin levels) and negatively correlated with HDL-C in both genders.

Because there is no clear definition of high plasma leptin level in children, in this study we defined children with high plasma leptin if their value was greater than the 75th percentile for their age- and gender-specific strata. The differences in BP, lipoproteins, insulin levels and IRS score between children with high and normal leptin level are presented in Table 3. For both genders, children with high plasma leptin had higher age-adjusted blood pressure, triglyceride, insulin levels and IRS score and lower HDL-C levels than those with normal leptin in both genders.

Regression models of BMI and plasma leptin on insulin resistance syndrome

Table 4 shows the multivariate regression models of plasma leptin concentrations and insulin resistance

Table 1 Baseline characteristics of 1264 study children

	Total (n = 1264)				Boys (n = 617)				Girls (n = 647)			
	Mean (s.d.)[a]	Percentile			Mean (s.d.)	Percentile			Mean (s.d.)	Percentile		
		25	50	75		25	50	75		25	50	75
Age (y)	13.3 (0.9)	13	13	14	13.3 (0.9)	13	13	14	13.3 (0.9)	13	13	14
Body height (cm)	158.9 (7.5)	154	158.5	164	161.8 (8.2)	156.5	162	168	156.2 (5.5)	152.5	156	160
Body weight (kg)	53.0 (11.4)	45	51	58.5	55.4 (12.6)	45.5	53.5	63.0	50.7 (9.5)	45.0	49.5	54.5
BMI (kg/m^2)[b]	20.9 (3.7)	18.4	20.1	22.5	21.1 (3.9)	18.2	20.1	23.1	20.7 (3.4)	18.6	20.2	22.1
Waist (cm)	65.6 (8.5)	60	63.6	69	68.2 (9.1)	61.8	66.1	72.8	63.1 (7.1)	58.6	61.9	65.7
Hip (cm)	88.5 (7.5)	83.4	87.9	92.7	87.9 (8.2)	82.3	87.2	92.9	89.1 (6.9)	85.0	88.7	92.5
Waist-to-hip Ratio	0.74 (0.06)	0.70	0.73	0.77	0.77 (0.05)	0.74	0.77	0.80	0.71 (0.04)	0.68	0.70	0.73
Systolic BP (mmHg)	109.1 (13.5)	100	110	118	114.0 (12.9)	105	114	123	104.4 (12.3)	97	104	112
Cholesterol (mmol/L)[c]	4.10 (0.77)	3.61	4.03	4.52	3.96 (0.70)	3.48	3.90	4.39	4.23 (0.81)	3.72	4.13	4.68
Triglyceride (mmol/L)	0.84 (0.39)	0.58	0.75	0.99	0.80 (0.39)	0.55	0.71	0.92	0.88 (0.38)	0.62	0.80	1.04
HDL-C (mmol/L)	1.40 (0.33)	1.17	1.38	1.61	1.38 (0.35)	1.14	1.38	1.59	1.42 (0.31)	1.20	1.40	1.61
LDL-C (mmol/L)	2.31 (0.70)	1.86	2.24	2.68	2.21 (0.64)	1.78	2.14	2.57	2.40 (0.75)	1.94	2.32	2.77
Insulin (nmol/L)	109.5 (60.9)	76.9	95.7	123.3	106.6 (64.5)	72.5	91.4	119.6	111.7 (57.3)	81.9	100.8	125.4
IRS Score[d]	10.4 (2.6)	8	10	12	10.8 (2.5)	9	11	13	10.0 (2.60)	8	10	12
Leptin (ng/ml)	7.2 (6.3)	2.4	5.8	9.9	4.1 (4.4)	1.5	2.4	4.8	10.1 (6.4)	6.0	8.8	12.4

[a]Age-adjusted mean values.
[b]BMI, body mass index; waist, waist circumference; hip, hip circumference; BP, blood pressure; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TCHR, total cholesterol-to-HDL ratio; IRS, insulin resistance syndrome.
[c]To convert conventional unit, multiply by 38.7 for cholesterol, HDL-C and LDL-C, multiply by 87.5 for triglyceride and multiply by 0.138 for insulin (μU/ml).
[d]IRS score is defined as the sum of the quartile ranks form the distribution of systolic BP, TG, HDL-C and insulin levels of each subject. A higher summary score corresponds to higher levels of BP, TG and fasting insulin and lower levels of HDL-C.

Table 2 Spearman correlation coefficients of plasma leptin and IRS[a] components among boys and girls

	Leptin	*BMI*	*WHR*	*SBP*	*CHOL*	*TG*	*HDL-C*	*LDL-C*	*Insulin*	*IRS score*[a]
					Boys[b]					
Leptin	**1.00**	0.64***	0.52***	0.12**	0.10*	0.24***	−0.17***	0.13**	0.54***	0.40***
BMI[c]	0.66***	**1.00**	0.53***	0.37***	0.003	0.19***	−0.28***	0.09*	0.42***	0.39***
WHR	0.21***	0.34***	**1.00**	0.10*	0.06	0.19***	−0.16***	0.09*	0.30***	0.29***
SBP	0.26**	0.43***	0.14***	**1.00**	0.001	0.10*	−0.15***	0.07	0.12**	0.20***
CHOL	0.04	−0.01	0.01	0.04	**1.00**	0.20***	0.34***	0.84***	−0.002	−0.06
TG	0.11**	0.04	0.08*	0.05	0.24***	**1.00**	−0.22***	0.10*	0.29***	0.67***
HDL-C	−0.11**	−0.18***	−0.17***	−0.13**	0.30***	−0.22***	**1.00**	−0.09*	−0.19***	−0.62***
LDL-C	0.08*	0.08	0.08*	0.09*	0.88***	0.15***	−0.08*	**1.00**	0.04	0.10*
Insulin	0.29***	0.21***	0.12**	0.09*	0.07	0.16***	−0.06	0.04	**1.00**	0.64***
IRS Score[a]	0.31***	0.34***	0.18***	0.53***	0.02	0.60***	−0.57***	0.15***	0.53***	**1.00**
					Girls					

[a]IRS score is defined as the sum of the quartile ranks from the distribution of systolic BP, TG, HDL-C and insulin levels of each subject. A higher summary score corresponds to higher levels of BP, TG and fasting insulin and lower levels of HDL-C.
[b]Boys are in right upper triangle and girls are in left lower triangle.
[c]BMI, body mass index; waist, waist circumference; hip, hip circumference; WHR, waist-to-hip ratio; BP, blood pressure; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TCHR, total cholesterol-to-HDL ratio; IRS, insulin resistance syndrome.
$^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$.

Table 3 Comparison of IRS[a] components among normal and high plasma leptin subjects in boys and girls

	Boys (n = 617)				*Girls (n = 647)*			
	High[b] *(n = 149)*		*Normal (n = 468)*		*High (n = 157)*		*Normal (n = 490)*	
	Mean	*s.d.*	*Mean*	*s.d.*	*Mean*	*s.d.*	*Mean*	*s.d.*
SBP (mmHg)[c]	117.3*	13.3	113.0	12.6	109.5*	11.1	102.8	12.2
CHOL (mmol/L)[d]	4.09*	0.70	3.92	0.70	4.30	0.78	4.21	0.82
TG (mmol/L)[e]	1.00*	0.49	0.74	0.33	0.94*	0.45	0.87	0.36
HDL-C (mmol/L)	1.29*	0.37	1.41	0.33	1.37*	0.26	1.44	0.33
LDL-C (mmol/L)	2.34*	0.63	2.17	0.64	2.50*	0.69	2.37	0.67
Insulin (nmol/L)[e]	147.9*	81.2	93.5	52.2	129.1*	68.2	105.9	52.2
IRS score[a]	12.5*	2.2	10.2	2.2	11.2*	2.5	9.6	2.5

[a]IRS score is defined as the sum of the quartile ranks from the distribution of systolic BP, TG, HDL-C and insulin levels of each subject. A higher summary score corresponds to higher levels of BP, TG and fasting insulin and lower levels of HDL-C.
[b]High leptin is defined as plasma leptin level greater than the 75th percentile in each gender.
[c]SBP, systolic blood pressure; CHOL, cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; IRS, insulin resistance syndrome.
[d]To convert conventional unit, multiply by 38.7 for cholesterol, HDL-C and LDL-C, multiply by 87.5 for triglyceride and multiply by 0.138 for insulin (μU/ml).
[e]Tested using the log-transformed values.
$^{*}P<0.05$ when compared with the same gender group with high and normal leptin group using ANOVA after adjusting for age.

syndrome components. To determine if leptin was a useful marker of IRS independent of anthropometric measures, we fitted multivariate regression models of the IRS score (and its components) with and without controlling for BMI and WHR to assess the change in the association with leptin. Because the coefficients for leptin were not substantially changed after including WHR in most models (data not shown), we excluded WHR from further analyses. In general for both genders, before controlling for BMI, leptin was strongly associated with BP, TG, HDL-C and IRS score. The associations between leptin and SBP, DBP and HDL-C were almost completely eliminated after controlling for BMI. However, the coefficients for leptin in models predicting cholesterol, TG, LDL-C and insulin were only modestly attenuated, if at all, after controlling BMI. For the overall IRS score in boys and girls, adding BMI to the model did somewhat attenuate the association for leptin, but the coefficients remained significant.

Discussion

In this cross-sectional study of 1264 school-aged children, we found that obesity and leptin were independently associated with the insulin resistance syndrome. Although no clinical cut-off point has been established for leptin and CVD risk among children, our data suggest that children in the top 25% of the leptin distribution have a more adverse cardiovascular profile. Furthermore, leptin may be a useful independent marker of insulin resistance syndrome among school-aged children.

Table 4 Multivariate regression coefficients for plasma leptin before and after controlling for body mass index in different models predicting insulin resistance syndrome components

	Boys (n = 617)				Girls (n = 647)			
	Leptin[a]		Leptin (controlling for BMI)[b]		Leptin[a]		Leptin (controlling for BMI)[b]	
Dependent Variables	β^c (s.e.β)	*P*	β^c (s.e.β)	*P*	β^c (s.e.β)	*P*	β^c (s.e.β)	*P*
SBP[d] (mmHg)	0.544 (0.102)	< 0.001	−0.480 (0.133)	< 0.001	0.440 (0.070)	< 0.001	−0.088 (0.077)	0.256
CHOL (mmol/L)[e]	0.014 (0.006)	0.027	0.026 (0.010)	0.010	0.010 (0.005)	0.033	0.015 (0.006)	0.013
TG (mmol/L)	0.029 (0.005)	< 0.001	0.024 (0.008)	0.002	0.006 (0.002)	0.010	0.003 (0.003)	0.292
HDL-C (mmol/L)	−0.017 (0.001)	< 0.001	−0.0004 (0.005)	0.929	−0.005 (0.002)	0.023	0.003 (0.002)	0.255
LDL-C (mmol/L)	0.018 (0.006)	0.002	0.015 (0.009)	0.094	0.012 (0.005)	0.013	0.011 (0.006)	0.077
Insulin (nmol/L)	6.37 (0.73)	< 0.001	4.59 (0.87)	< 0.001	2.47 (0.40)	< 0.001	1.61 (0.41)	< 0.001
IRS Score[f]	0.240 (0.022)	< 0.001	0.125 (0.030)	< 0.001	0.124 (0.017)	< 0.001	0.039 (0.019)	0.045

[a]All models adjusted for age, cigarette smoking, alcohol drinking, heart rate and puberty development.
[b]Further adjusted for body mass index.
[c]Regression coefficient from multivariate regression models. Interpreted as the predicted change in dependent variables for a unit change in leptin level (ng/ml).
[d]SBP, systolic blood pressure; CHOL, cholesterol; TG, triglyceride; HDL-C, high density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; IRS, insulin resistance syndrome.
[e]To convert conventional unit, multiply by 38.7 for cholesterol, HDL-C and LDL-C, multiply by 87.5 for triglyceride and multiply by 0.138 for insulin (μU/ml).
[f]IRS score is defined as the sum of the quartile ranks from the distribution of systolic BP, TG, HDL-C and insulin levels of each subject. A higher summary score corresponds to higher levels of BP, TG and fasting insulin and lower levels of HDL-C.

The cross-sectional survey design limits our ability to evaluate the causal relationships between leptin and insulin resistance. In an adult population, a similar cross-sectional study of obesity and insulin resistance syndrome may yield biased or confounded results if subjects are on a special diet or on treatment for hypertension, hyperlipidemia, diabetes or obesity, factors which may or may not also alter leptin levels. However, children of this age group are rarely on special diets, exercise or treatment regimens for obesity or insulin resistance syndrome. Measurement errors in assessing obesity or the biological markers of IRS are likely to be minimal. Any error would likely to be random and only attenuate our results.

Many studies have highlighted the association between insulin concentration and various metabolic and cardiovascular disorders including obesity, dyslipidemia, glucose intolerance, insulin resistance, hypertension and ischemic heart disease. The clustering of several of these factors is associated with increased risk for the development of NIDDM and CVD.[1–6,40,41] Recent evidence suggests that the components of IRS track from childhood to adulthood.[7–11] Therefore, the early detection of IRS may be important for identifying children or adolescents at highest risk of adult-onset NIDDM and CVD. With the exception of obesity, no other single marker has been used to predict insulin resistance among children.[11,42]

We found that girls had higher plasma leptin levels than boys, even after controlling for BMI, which may suggest that there are gender differences in leptin synthesis, transport or clearance rates.[43–45] The difference in genders may be explained by later puberty development among boys, since leptin levels increase during children and decline later. These adolescent changes suggest that human puberty and gonad hormone metabolism regulate leptin levels.[43–47] Increased leptin synthesis or relative leptin resistance in children could be important for growth and development.[43] Leptin concentration is significantly higher in obese children than non-obese, which suggests that resistance to the effects of leptin may start in early childhood.[43,47]

The relationship between plasma leptin and insulin levels is complicated and may be bi-directional. Although plasma leptin concentrations are highly correlated with BMI, insulin levels and insulin sensitivity in humans,[14,15,22–28,38,48,49] it is not yet known whether leptin has a direct effect on insulin sensitivity or if it is only a marker of obesity and related disorders.[18] This relationship has become increasingly difficulty to study among adults because some evidence suggests that the level of glucose intolerance may modify the association.[31,32] In general, leptin may increase the activity of insulin receptor substrate-1 (IRS-1) associated phosphatidylinositol 3-kinase which may regulate insulin activity in obese individuals.[21] The development of hyperleptinemia is associated with the development of obesity and subsequent metabolic abnormalities such as hyperinsulinemia and insulin resistance.[26,50,51]

Others also have found that insulin resistance is associated with elevated plasma leptin levels independent of body fat mass,[19,23,28,52] but these studies have been limited to adult populations. In a population of 87 lean men, Haffner *et al* showed plasma leptin levels were correlated with insulin levels and insulin sensitivity even after controlling for BMI.[23] We extend these results to children and further show that a single assessment of leptin is a better predictor of insulin resistance syndrome than WHR.

In summary, we found that, among school-aged children in Taiwan, plasma leptin levels are associated with fasting insulin levels, the IRS summary score and its components, even adjusting for BMI. Our results suggest that BMI and plasma leptin levels, in combination, are a significant predictive marker of the insulin resistance syndrome among school children. Since the insulin resistance syndrome may be a precursor to NIDDM and cardiovascular disease, the assessment of leptin in childhood may lead to earlier detection and a better opportunity for prevention of chronic disease in later life.

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