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Relationship of Leptin and Adiponectin to Five-year Weight Change in Taiwanese Adolescents

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Background: Leptin is associated with body weight (BW) regulation in adults and adolescents. Decrease in adiponectin in obese adults and adolescents may be associated with the development of obesity and insulin resistance. This study investigated the relationship of plasma leptin and adiponectin levels to changes in BW and body mass index (BMI) over five years among adolescents in Taiwan. **Methods:** This was a prospective study involving school adolescents aged 12 to 15 years. Demographic data, anthropometric variables, and blood specimens were collected from 1500 adolescents at baseline. Body height, weight and body mass index (BMI) were evaluated at baseline, and after five years in 580 adolescents. Plasma leptin and adiponectin levels were measured using radioimmune assay (RIA). **Results:** Baseline serum levels of leptin and adiponectin were higher in girls than in boys. Baseline plasma leptin levels correlated positively, and adiponectin levels negatively with BW and BMI at baseline and after five years. Plasma leptin levels were negatively associated with five-year changes in BW and BMI both in normal-weight boys (β = -0.57, $p < 0.01$, and β = -0.25, $p < 0.001$, respectively) and girls (β = -0.28, $p < 0.001$, and β = -0.11, $p < 0.001$, respectively). The correlation between plasma adiponectin levels and five-year change in BW and BMI in both genders was not statistically significant. **Conclusions:** In Taiwanese adolescents, plasma leptin levels were negatively and significantly associated with the changes in BW and BMI during the five-year follow-up period in both genders, but adiponectin levels were not. Such finding suggests that plasma leptin levels may be a negative marker of body weight gain over time.

Key words: leptin, adiponectin, body weight change, body mass index.

INTRODUCTION

Obesity is a worldwide concern with significant medical, psychological and economic consequences. It is an important public issue in adolescents as well as adults[1,2]. Childhood obesity is epidemic in industrialized countries and associated with chronic disease risk factors such as high blood pressure, hyperlipidemia, or hyperinsulinemia[3]. Overweight adolescents are prone to develop type 2 diabetes or other long-term disorders[4].

Leptin, an adipose tissue-derived product regulated by the obesity (*ob*) gene, is associated with body weight regulation[5] and the occurrence of obesity and related disorders in humans[6]. Leptin levels are strongly and positively correlated with quantity of body fat and body mass index (BMI) in both adults[7] and adolescents[8].

Adiponectin, a novel adipocytokine, is the most abundant adipose-specific protein and is exclusively secreted by adipose tissue[9]. Plasma adiponectin concentrations are decreased in adults[10] or adolescents with obesity[11,12].

Whether blood leptin or adiponectin levels predict weight change in adults and adolescents remains unclear. Hence, we examined whether plasma leptin and adiponectin levels are associated with adiposity of school adolescents, and investigated whether plasma leptin and

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adiponectin levels at baseline can predict change in body weight and BMI over a five-year period of follow-up.

METHODS

Study design and sampling method

The Taipei Children Heart Study was an epidemiological survey conducted in 1995 on cardiovascular disease risk factors among school adolescents in Taipei. Details of sampling methods and results have been described elsewhere[13,14]. Briefly, a cross-sectional survey was conducted to explore a representative distribution of demographic, lifestyle and biochemical characteristics and cardiovascular disease risk factors among junior high school adolescents aged 12 to 15 years. A total of 1500 school adolescents randomly sampled were included in the original survey. In 2000, we followed up these adolescents by phone and questionnaire to determine their changes in body height, body weight and BMI and obtained data from 580 subjects (294 boys and 286 girls). The baseline anthropometric characteristics of response and non-response adolescents were similar.

The Ethical committee of the Scientific Institute approved this study and informed consent was obtained from both parents and adolescents.

Data collection, anthropometric measurements of leptin and adiponectin

All participating adolescents completed a structured questionnaire regarding socio-demographic characteristics, medical history and lifestyle characteristics (including cigarette smoking, alcohol consumption, pubertal development, usual physical activity and dietary intake) at baseline.

Research technicians recorded body weight to the nearest 0.1 kg using a standard beam balance scale with adolescents barefoot and wearing light indoor clothing. Body height was measured with a wall-mounted stadiometer to the nearest 0.5 cm. In 2000, we re-contacted these adolescents by telephone for response the same questionnaire. We asked and recorded the most recent body height and body weight status among these adolescents. We calculated BMI as the ratio of body weight to body height squared expressed as kg/m^2.

In 1995, a 10-ml blood specimen was collected and stored at -80^{o}C from each participant. Plasma leptin levels were measured twice using a commercial radioimmunoassay (RIA) kit (Linco Research St. Charles, MO, USA.). Plasma leptin remained stable after being stored at -80^{o}C for five years and the inter- and intra-assay coefficients of variation were 8.3% and 3.4%, respectively. Serum adiponectin was assayed by a commercial RIA kit (Linco Research St. Charles, MO, USA). This assay had a sensitivity of 1 ng/mL and intra- and inter-assay coefficients of variation being less than 8%.

Definitions of overweight

We considered adolescents to be overweight if their BMI was greater than or equal to the eighty-fifth percentile of age- and gender-specific strata[15]. For boys, the cutoff points designating overweight were 25.0 kg/m^2, 24.6 kg/m^2 and 25.5 kg/m^2 for 12, 13, and 14 years old or above, respectively. For girls, the cutoff points designating overweight were 22.4 kg/m^2, 23.3 kg/m^2, and 24.8 kg/m^2, respectively. We conducted subanalyses using different body weight categories (normal and overweight) to evaluate more detailed relationships between these variables.

Statistical analyses

We used mean and standard deviation (SD) to describe the distributions of age; baseline and five-year body weight, height, and BMI; and changes in these anthropometric measures after five years with gender specification. Analysis of variance (ANOVA) test was employed to evaluate the difference between genders. We calculated the Spearman correlation coefficient between plasma leptin and adiponectin levels on baseline and five-year anthropometric measurements and changes in these measurements with gender specification. We performed multiple regression analysis of leptin and adiponectin on changes in weight among baseline normal-weight or overweight subgroups with gender specification. In the final models, we used multivariate linear regression analyses to evaluate the association of different plasma leptin subgroups on changes in five-year BMI with gender specification after adjusting for potential confounders. All models were adjusted for age, cigarette smoking, alcohol intake, and pubertal development. 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, USA).

RESULTS

In brief, boys were taller, heavier and had higher BMIs and lower plasma leptin and adiponectin levels than did girls at baseline. Changes in body weight and BMI after five years were also greater in boys than in girls. In girls,

Table 1 General characteristic of study adolescents

	Boys (n=294)	Girls(n=286)
Variable	Mean±SD	Mean ± SD
Age# (years)	13.3±0.9	13.3±0.9
BH95 (cm)	161.5±8.6	156.3±5.7***
BW95 (kg)	55.3±13.1	50.4±9.5***
BMI95 (kg/m^2)	21.1±4.1	20.6±3.4
BH00 (cm)	172.4±6.1	160.5±5.4***
BW00 (kg)	64.6±11.3	52.5±8.4***
BMI00 (kg/ m^2)	21.7±3.5	20.4±3.0***
△BH (cm)	10.9±6.8	4.2±2.9***
△BW (kg)	9.3±7.8	2.1±5.7***
△BMI (kg/ m^2)	0.7±2.4	-0.2±2.2***
Leptin (ng/ml)	4.1±4.2	10.0±6.4***
Adiponectin (mg/L)	16.3±9.7	18.3±9.4*

#: age at 1995; BH95, body height at 1995; BW 95, body weight at 1995; BMI95, body mass index at 1995; BH00, body height at 2000; BW 00, body weight at 2000; BMI00, body mass index at 2000; Δ BH, BH00-BH95; Δ BW, BW00-BW95; Δ BMI, BMI00-BMI95.

*p<0.05, **p<0.01, ***p<0.001 using ANOVA test.

Table 3 Multiple regression analyses of plasma leptin and adiponectin on body weight change among adolescents

	Boys (n=294)		Girls(n=286)	
	Normal (248)	Overweight (46)	Normal (233)	Overweight (43)
Variable	β (se β)	β (se β)	β (se β)	β (se β)
Leptin				
△BH (cm)	-0.05(0.13)	0.297(0.15)	-0.06(0.03)	0.01(0.02)
△BW (kg)	-0.57(0.18)**	-0.56(0.29)	-0.28(0.07)***	-0.22(0.12)
△BMI(kg/m^2)	-0.25(0.05)***	-0.31(0.09)**	-0.11(0.03)***	-0.09(0.05)
Adiponectin				
△BH (cm)	- 0.01(0.03)	0.01(0.12)	0.03(0.02)	0.03(0.02)
△BW (kg)	0.01(0.04)	0.12(0.23)	0.04(0.03)	-0.14(0.17)
△BMI (kg/m^2)	0.01(0.01)	0.06(0.08)	0.01(0.01)	-0.06(0.07)

Δ BH, BH00-BH95; Δ BW, BW00-BW95; Δ BMI, BMI00-BMI95; β, regression coefficient. Adolescents to be overweight if their BMI was greater than or equal the 85th percentile of age- and gender-specific strata. For boys, the cut point for overweight was 25.0 kg/m^2, 24.6 kg/m^2 and 25.5 kg/m^2 for 12, 13, and 14 or greater years old; for girls, the cut point for overweight was 22.4 kg/m^2, 23.3 kg/m^2 , and 24.8kg/m^2 respectively.

*p<0.05, **p<0.01, ***p<0.001 after adjustment for age, smoking, drinking and Tanner's stage.

Table 2 Spearman correlation of plasma leptin and adiponectin on anthropometric measures among adolescents

	Boys (n=294)		Girls(n=286)	
Variable	Leptin	Adiponectin	Leptin	Adiponectin
BH95 (cm)	-0.11	-0.03	0.20**	0.04
BW95 (kg)	0.45***	-0.19**	0.65***	-0.22**
BMI95 (kg/m^2)	0.63***	-0.23***	0.65***	-0.28***
BH00 (cm)	0.02	0.05	0.07	0.09
BW00 (kg)	0.44***	-0.17**	0.42**	-0.15*
BMI00 (kg/ m^2)	0.48***	-0.20**	0.42***	-0.24***
△BH (cm)	0.13*	0.05	-0.28***	0.09
△BW (kg)	-0.12*	0.08	-0.43***	0.16***
△BMI (kg/ m^2)	-0.36***	0.10	-0.42***	0.16**

BH95, body height at 1995; BW 95, body weight at 1995; BMI95, body mass index at 1995; BH00, body height at 2000; BW 00, body weight at 2000; BMI00, body mass index at 2000; Δ BH, BH00-BH95; Δ BW, BW00-BW95; Δ BMI, BMI00-BMI95.

*p<0.05, **p<0.01, ***p<0.001

mean BMI actually decreased at five-year follow-up (Table 1).

Table 2 shows the Spearman correlation coefficients of plasma leptin and adiponectin levels at baseline and at five-year follow-up, and changes in these anthropometric measurements among adolescents. Plasma leptin levels were positively and adiponectin negatively correlated with baseline and five-year follow-up body weight and BMI in both genders. Plasma leptin levels were negatively correlated with five-year changes in body weight and BMI in both genders. However, plasma adiponectin levels were positively correlated with changes in five-year body weight and BMI in girls only.

When subjects were divided into baseline normal-weight or overweight subgroups, the relationship of plasma leptin levels to change in five-year BMI persisted in boys, but only in normal-weight girls. The relationship of plasma adiponectin to change in weight or BMI was attenuated and became insignificant after adjusting for confounding factors (Table 3).

We further divided these adolescents into four subgroups according to their baseline plasma leptin levels (≦1.5; 1.5-2.45; 2.45-4.8; and ≧4.8 ng/ml in boys and ≦6.2; 6.2-8.95; 8.95-12.3; and ≧12.3 ng/ml in girls). Baseline and five-year follow-up anthropometric measurements and their changes among different plasma leptin subgroups are presented in Table 4. Generally, adolescents with the highest plasma leptin were heavier and had greater BMIs at baseline and at five-year follow up when compared with the adolescents with relatively normal leptin level. Adolescents with higher plasma leptin levels showed lesser change in body weight and BMI. However, boys with the highest leptin levels had smaller

Table 4 Anthropometric measures among different leptin subgroup (quartiles) children with gender specification

	Boys (n=294)				Girls(n=286)			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Leptin (ng/ml)	<1.5	1.5-2.45	2.45-4.8	>4.8	<6.2	6.2-8.95	8.95-12.3	>12.3
BH95 (cm)	161.9±0.9	160.4±0.8	161.5±0.8	162.4±0.8	155.2±0.7	156.0±0.6	157.2±0.6	156.8±0.6[b]
BW95(kg)	47.6±1.2	49.1±1.0	56.3±1.1	67.8±1.1[ab]	44.7±0.9	48.1±0.9	51.3±0.9	57.5±0.9[ab]
BMI95 (kg/m^2)	18.1±0.4	19.0±0.3	21.4±0.3	25.6±0.3[ab]	18.4±0.3	19.8±0.3	20.7±0.3	23.3±0.3[ab]
BH00(cm)	173.2±0.8	171.9±0.7	171.6±0.7	173.2±0.7	160.0±0.7	160.1±0.6	161.0±0.7	160.9±0.7
BW00(kg)	58.7±1.2	59.8±1.0	65.4±1.1	74.2±1.1[ab]	49.2±1.0	51.2±0.9	52.4±0.9	57.0±0.9[ab]
BMI00 (kg/m^2)	19.6±0.4	20.2±0.3	22.2±0.3	24.7±0.3[ab]	19.2±0.3	20.0±0.3	20.2±0.3	22.0±0.3[ab]
△BH (cm)	11.2±0.6	11.5±0.5	10.0±0.6	10.8±0.6	4.8±0.3	4.2±0.3	3.7±0.3	4.1±0.3[ab]
△BW (kg)	11.1±0.9	10.7±0.8	9.1±0.8	6.4±0.8[ab]	4.6±0.6	3.1±0.6	1.1±0.6	-0.5±0.6[ab]
△BMI (kg/m^2)	1.5±0.3	1.3±0.2	0.8±0.3	-0.9±0.3[ab]	0.8±0.2	0.2±0.2	-0.6±0.2	-1.3±0.2[ab]

BH95, body height at 1995; BW 95, body weight at 1995; BMI95, body mass index at 1995; BH00, body height at 2000; BW 00, body weight at 2000; BMI00, body mass index at 2000; Δ BH, BH00-BH95; Δ BW, BW00-BW95; Δ BMI, BMI00-BMI95.

[a] $p < 0.001$ when Q4 subgroup compared with Q1 after adjustment for age, smoking, drinking and Tanner's stage.

[b] $p < 0.001$ for trend. The Q1 to Q4 of leptin levels were based on their baseline plasma leptin levels by quartile in both gender.

five-year weight gain than boys with normal plasma leptin level, though the difference was not significant (6.4 ±0.8 kg *vs.* 11.1±0.9 kg). Boys with the highest leptin levels had a significant decline in BMI over five years when compared with boys with normal leptin level (-0.9 ±0.3 *vs.* 1.5±0.3, $p < 0.001$). Girls with the highest plasma leptin levels had even lower five-year weight and BMI gain than girls with relatively normal leptin level (-0.5±0.6 *vs.* 4.6±0.6, and -1.3±0.2 *vs.* 0.8±0.2 respectively, $p < 0.001$).

DISCUSSION

The etiology of obesity in humans is complex and multifactorial. Factors such as dietary composition, physical activity and genetics play an important role in the development of obesity. However, positive energy balance over time is believed to be its primary cause[16,17]. Several variables may predict obesity, such as low basal metabolic rate[17]; parents who are overweight[18]; insulin secretion[19]; and insulin sensitivity[20]. Adipocytes and their products have recently been found to have a significant role in energy and body weight regulation. Adipocytokines such as leptin and adiponectin may also influence the sequence of weight change.

In an animal experimental model, leptin was found to reduce food intake, increase energy expenditure, and cause loss of body weight[21]. However, there are limited data in adolescents concerning whether baseline serum leptin levels predicts future weight gain. We found that lower baseline serum leptin levels predict changes in body weight and BMI among boys, but only among normal-weight girls. Similar results were reported in another study but only in non-obese, pre-pubertal girls, and not in boys[22]. In a one-year study, a cohort of pre-pubertal, normal-weight adolescents also yielded similar results[23]. It seems likely that lower baseline plasma leptin levels predict further changes in weight or adiposity among adolescents. However, Savoye et al. showed that high basal leptin levels were positively associated with much greater BMI gain in girls than in boys[24]. Subjects in that study were younger, had higher baseline weight, and higher baseline plasma leptin levels than ours.

Adiponectin is believed to decrease body weight via central effects on energy homeostasis[25]. Data regarding plasma adiponectin levels after weight reduction are conflicting. Plasma adiponectin levels have been found to increase after medically[26] or surgically[27] induced weight loss. However, in some studies, serum adiponectin levels did not change after weight reduction[28,29]. The discrepancy may be due to the degree of weight loss. Baseline serum adiponectin levels may also be predictive of the extent of weight loss[27]. However, few studies address whether baseline serum adiponectin levels predict weight change. In a study of Pima adults without diabetes, Vizarova et al. observed that baseline adiponectin levels did not predict weight gain[30]. Similar results were seen in another study in adolescents[12]. This finding is consistent

with our study, which found that baseline plasma adiponectin level was not associated with changes in weight and BMI over time, after adjusting for potential confounders.

It is interesting that we found that plasma leptin level had a stronger association with changes in weight than did adiponectin in adolescents. Leptin levels are higher in obese subjects than in non-obese subjects and the association has been found to be independent of measures of insulin sensitivity[31]. However, the negative correlation between adiponectin and BMI has been found to be attenuated after adjusting for insulin sensitivity in some studies, suggesting that obesity per se may not influence the level of plasma adiponectin[32]. This suggests that low serum adiponectin levels are most likely a consequence rather than a cause of obesity.

However, there are some potential bias and limitations in our study. First, plasma leptin and adiponectin levels were measured only once at baseline, which may be influenced by fasting status, timing of sample, and stress at time of sampling. Moreover, it has been shown that leptin production is influenced by some factors, such as nutritional state, puberty stage and diurnal rhythm of secretion. These also remind us to interpret our results with caution. However, the leptin levels were compared after adjustment of age, smoking, and Tanner's stage; and the samples were drawn universally in the morning after fasting, which may ameliorate the bias of the analysis. Second, the follow-up rate was relatively low in our study. However, the baseline anthropometric characteristics were similar between response and non-response adolescents (table not shown). No or minimal selection bias was considered in the condition. Third, underreporting of BW among overweight and obese adolescents should be considered in such recall measurement, especially in girls. Girls at this age paid more attention to their body weight, which may be associated with decrease in BMI over the five-year follow-up period. However, the degree of changes in BW/or BMI between normal- or overweight adolescents were similar. Therefore, this limitation was minimized. Finally, lifestyle factors, such as energy intake and physical activity, and parent's factors (education level and body weight) were not evaluated accurately in our study, and they may play a central role on the development of obesity.

In conclusion, we have demonstrated that baseline plasma leptin, but not adiponectin, levels were associated with changes in five-year body weight and BMI among Taiwanese adolescents. Plasma leptin levels appeared to be a negative marker of body weight gain over time. It is possible that interventions to prevent obesity in individuals could be initiated according to this observation, but further studies are needed to clarify our observation.

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