

# Adiponectin and Leptin are Independently Associated with Insulin Sensitivity, but not with Insulin Secretion or Beta-cell Function in Overweight Hispanic Adolescents

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## Key words

- adiponectin
- leptin
- insulin sensitivity
- beta-cell function

## Abstract

The aim of the study was to investigate the independent effects of leptin and adiponectin on insulin sensitivity as well as insulin secretion and beta-cell function in overweight Hispanic adolescents. Despite pubertal changes in hormone secretion, studies investigating the independent effect of both hormones on insulin sensitivity and beta-cell function in adolescents are lacking. In a cross-sectional study, 175 overweight Hispanic adolescent boys (n=101) and girls (n=74) with a family history of diabetes were recruited and insulin sensitivity (SI), acute insulin response to glucose (AIR), disposition index (DI), body composition, total serum adiponectin, and leptin were assessed. Over age, leptin sig-

nificantly increased in girls but not in boys (p for age × gender interaction = 0.005) while adiponectin was similar in boys and girls. Leptin was not correlated to adiponectin. Leptin (partial r = -0.180; p = 0.019) and adiponectin (partial r = 0.230; p = 0.003) predicted SI independent of age, gender, body fat, lean body mass, and Tanner stage but together, they explained 5% of the unique variation in SI (p for R<sup>2</sup>-change < 0.001). Leptin or adiponectin were not related to AIR or DI. With regard to SI, AIR, and DI, no significant gender, age, or Tanner stage interactions were observed suggesting similar effects of adiponectin and leptin among gender, age, and Tanner stages. Leptin and adiponectin were independently associated with SI, but not with insulin secretion or beta-cell function.

## Abbreviations

AIR	acute insulin response
DI	disposition index
FSIVGTT	frequently sampled intravenous glucose tolerance test
SI	insulin sensitivity

## Introduction

As a consequence of the increasing prevalence of obesity among Hispanic children, prediabetes and type 2 diabetes have emerged as significant health issues in this cohort [1]. Hispanic children are more insulin resistant than Caucasian children independent of body fat [2] and experience early deterioration in beta-cell function [3,4]. Several studies have suggested that insulin sensitivity decreases at the onset of puberty [5,6] with a physiological recovery from puberty-related deterioration in insulin resistance after puberty in Caucasians but not in African Americans [7].

However, we have shown in this Hispanic cohort that there is no evidence of transient insulin resistance [8]. The ability to recover from pubertal changes may be a determinant for the future development of type 2 diabetes [9]. However, the factors predicting insulin sensitivity and beta-cell function during puberty are unclear.

Adiponectin and leptin are secreted by adipose tissue and are known to affect both glucose metabolism and insulin sensitivity [10]. Leptin is produced primarily by adipose tissue [11] and acts to reduce food intake and increase energy expenditure by activating specific hypothalamic receptors [12]. However, in human obesity leptin resistance increases with increasing fat mass [11]. Levels of circulating leptin are negatively associated with insulin sensitivity even after adjustment for adiposity [13]. Conversely, adiponectin improves insulin sensitivity by stimulating glucose uptake and fatty acid oxidation in skeletal muscle [14]. Additionally, adiponectin levels are negatively correlated with circulating leptin concentrations [15,16]. In mice, insulin

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resistance can be reversed by the combination of physiological doses of adiponectin and leptin, but only partially by administration of adiponectin or leptin alone [14], suggesting that each may independently affect insulin sensitivity. In nondiabetic adults at risk for type 2 diabetes, low adiponectin levels predict the deterioration of glucose tolerance over time [17].

Less is known about the effect of leptin and adiponectin on insulin secretion and beta-cell function. The effect of leptin is mediated by specific leptin receptors in the hypothalamus. However, leptin receptors are also expressed in the pancreas [18] leading to speculations about potential effects of leptin on insulin secretion. In rats, an increase in plasma leptin acutely inhibited glucose-stimulated insulin secretion [19], but this effect might be limited in human obesity as a consequence of increasing leptin resistance. Adiponectin also has been linked to insulin secretion in some [20] but not in all studies [21]. However, some human studies are limited by experimental approaches and lack of robust measures for insulin secretion [22–25].

In the present study, we have investigated the independent associations of adiponectin and leptin with insulin sensitivity, insulin secretion, and beta-cell function in a cohort of overweight Latino adolescents at risk for diabetes. We hypothesized that both leptin and adiponectin would be predictors of insulin sensitivity after adjustment for body fat mass, but not of insulin secretion or beta-cell function after adjustment for adiposity.

## Research Design and Methods

### Study design and subjects

The SOLAR (Study of Latino Adolescents at Risk) Diabetes Project is an ongoing natural history study investigating potential risk factors for the development of type 2 diabetes in Latino adolescents with a family history of type 2 diabetes. Detailed study descriptions have been published previously [3,26]. The total study cohort consisted of 247 overweight Latino children. For the present study, a cross-sectional subgroup of 175 subjects was used based on the availability of leptin and adiponectin data measured at entry into the study. Participants were recruited from the greater Los Angeles County through community health clinics, health fairs, and word of mouth. Inclusion criteria were 1) age 8–13 years; 2) BMI  $\geq 85^{\text{th}}$  percentile for age and sex according to the Centers for Disease Control and Prevention [27]; 3) Latino ancestry (all four grandparents Latino by self report); 4) family history of type 2 diabetes in at least one parent, sibling, or grandparent; and 5) absence of type 1 or type 2 diabetes using the guidelines of the American Diabetes Association [28]. Children were excluded if they had any major illness including type 1 or type 2 diabetes, or took medications or had a condition known to affect body composition, insulin sensitivity, or insulin secretion. The Institutional Review Board of the University of Southern California approved the study protocol. Written informed consent from parents and assent from children were obtained.

### Study protocol

For this study, data were collected over two separate clinical visits in the first annual visit. Children were admitted to the USC General Clinical Research Center at approximately 0800h after an overnight fast. A trained pediatrician conducted a detailed medical history and assessed Tanner staging based on breast stage in girls and pubic hair stage in boys according to the Mar-

shall and Tanner guidelines [29]. Children who met the aforementioned inclusion criteria were asked for further participation in the study and then completed a 2-hour oral glucose tolerance test (OGTT) on the same day. At the second clinical visit, a frequently sampled intravenous glucose tolerance test (FSIVGTT) was conducted and body composition was assessed. The evening before, the children were served dinner and an evening snack, and only water and noncaloric and noncaffeinated beverages were permitted after 2000h.

### Detailed methods and blood analysis

The methods of the study have been previously reported in detail [3]. Briefly, total body fat was assessed by a whole body scan using dual energy X-ray absorptiometry (Hologic QDR 4500W, Hologic, Bedford, MA). After an overnight fast, the FSIVGTT was performed to determine insulin dynamics. A topical anesthetic (EMLA cream; Aztrozeneca, Wilmington, DE) was applied to the antecubital area of both arms and an hour later a flexible intravenous catheter was inserted into both of the arms. Two fasting blood samples, at  $-15$  and  $-5$  minutes, were obtained for determination of basal glucose and insulin values. At time zero, glucose (25% dextrose; 0.3 g/kg of body weight) was administered intravenously. Blood samples were then collected at the following time points: 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, and 180 minutes. Insulin (0.02 units/kg of body weight; Humulin R - regular insulin for human subjects; Eli Lilly and Company, Indianapolis, IN) was injected intravenously at 20 minutes. Plasma was analyzed for glucose and insulin, and values were entered into the Minmod Millennium 2003 computer program (version 5.16, Richard N. Bergman, University of Southern California, Los Angeles, CA) for determination of insulin sensitivity (SI), the acute insulin response (AIR=insulin area under the curve above basal for the first 10 minutes of the FSIVGTT, a measure of acute insulin secretion), and the disposition index (DI=product of AIR and SI as a measure of pancreatic  $\beta$ -cell function). Blood samples from the FSIVGTT were centrifuged immediately for 10 minutes at 2500 RPM and  $8-10^{\circ}\text{C}$  to obtain plasma, and aliquots were frozen at  $-70^{\circ}\text{C}$  until assayed. Glucose was assayed in duplicate on a Yellow Springs Instrument 2700 Analyzer (Yellow Springs Instrument, Yellow Springs, OH) using the glucose oxidase method. Insulin was assayed in duplicate using a specific human insulin ELISA kit (Linco Research, St. Charles, MO). Fasting total serum adiponectin was measured using radioimmunoassay kits (Linco Research, St. Charles, MO) with an intra-assay coefficient of variation (CV) of 3.9% and an inter-assay CV of 8.5%. For fasting serum leptin, radioimmunoassay kits were used (Linco Research, St. Charles, MO) with an intra-assay CV of 3.9% and an inter-assay CV of 8.5%.

### Statistical analysis

All data are reported as mean and SE. General characteristics of boys and girls were compared using Student's *t*-test or Chi-squared test where appropriate. Variables not normally distributed (adiponectin, leptin, insulin sensitivity, disposition index, acute insulin response, total fat mass, and lean body mass) were log transformed before performing statistical analyses.

Zero-order correlations and multiple regression analyses were performed to investigate the relation between dependent variables (insulin sensitivity, acute insulin response, and disposition index) and independent variables (serum leptin and adiponectin). In multiple regression analyses, gender, age, Tanner stage, total fat mass, and lean body mass were included as potential

confounding variables. For acute insulin response, we additionally adjusted for insulin sensitivity. Zero-order and partial Pearson coefficients of variation were reported as well as R<sup>2</sup> change and significance of R<sup>2</sup> change. Significance level was set at  $\alpha=0.05$ . Analyses were performed using SPSS 11 (SPSS Inc., Chicago, IL).

## Results

### General characteristics

Overweight Latino boys and girls were similar in age, BMI, and BMI percentile ( $p>0.400$ ) but girls had a higher total body fat ( $p=0.002$ ) and a higher Tanner stage than boys ( $p=0.001$ ; **Table 1**). There were no significant gender differences in insulin sensitivity and serum adiponectin ( $p>0.200$ ), but boys had higher acute insulin response and disposition index than girls ( $p<0.001$ ; **Table 2**). Adiponectin was inversely related to age in boys and girls ( $r=-0.231$ ,  $p=0.002$ ) while serum leptin was positively correlated with age in girls ( $r=0.445$ ,  $p<0.001$ ) but not in boys (age  $\times$  gender interaction  $p=0.005$ ). Serum leptin was not correlated to serum adiponectin ( $r=0.088$ ;  $p=0.245$ ). Leptin was highly correlated with total fat mass ( $r=0.767$ ,  $p<0.001$ ), while adiponectin showed a weak but inversely correlation with total fat mass ( $r=-0.207$ ,  $p=0.006$ ). Insulin sensitivity was also inversely correlated with total fat mass ( $r=-0.627$ ,  $p=0.001$ ). Zero-order correlation analysis showed that serum adiponectin ( $r=0.340$ ,  $p<0.001$ ) and leptin ( $r=-0.492$ ,  $p<0.001$ ) were each significantly correlated with insulin sensitivity (● **Fig. 1**). In a multiple regression analyses, including both adiponectin and leptin as independent variables, adiponectin (partial  $r=0.230$ ,  $p=0.003$ ) and leptin (partial  $r=-0.180$ ,  $p=0.019$ ) were both independent predictors of insulin sensitivity and together explained an additional 5% of its variation beyond the variation

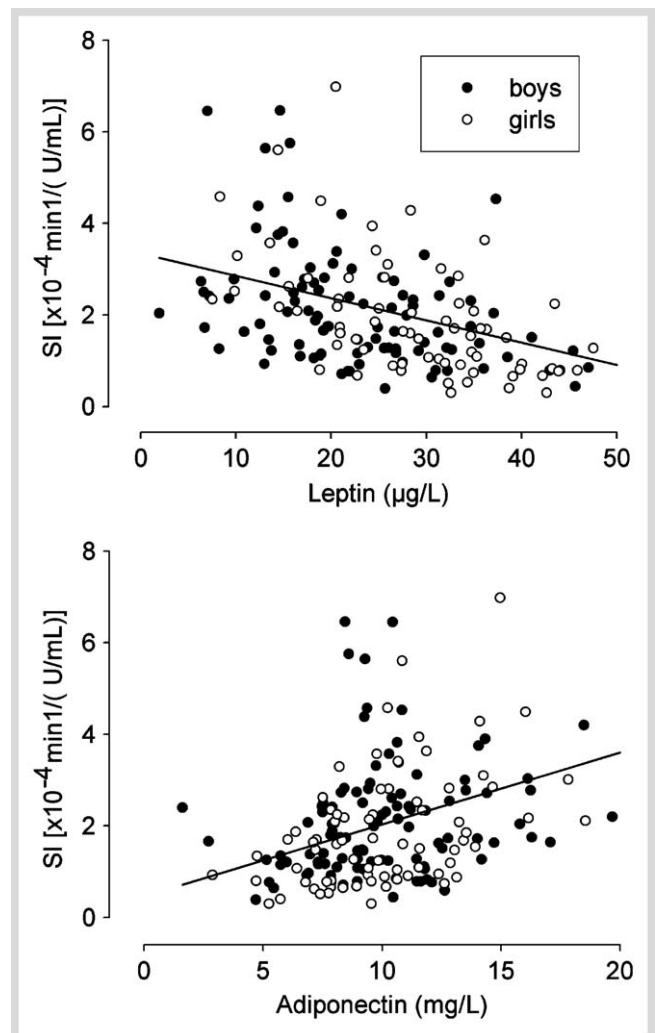
explained by gender, age, Tanner stage, total fat mass, and lean body mass ( $p$  for R<sup>2</sup>-change  $<0.001$ ). In zero-order correlation analyses, serum adiponectin and leptin were also significantly correlated to acute insulin response ( $r=0.363$  and  $r=-0.292$ ,  $p<0.001$ ), but not after adjusting for insulin sensitivity as well as gender, age, Tanner stage, total fat mass, and lean body mass. Serum adiponectin and leptin did not correlate with disposition index in zero-order correlation or after adjustment in multiple regression analysis. The relation between serum adiponectin and leptin and insulin sensitivity, acute insulin response, and disposition index markers

**Table 1** Characteristics of the study cohort

Characteristics <sup>1</sup>	Boys (n = 101)	Girls (n = 74)	p-value <sup>2</sup>
age (years)	11.2 ± 0.2	11.1 ± 0.2	0.704
BMI (kg/m <sup>2</sup> )	28.2 ± 0.5	28.7 ± 0.6	0.435
BMI percentile	97.1 ± 0.3	97.4 ± 0.3	0.449
total body fat (%)	37.6 ± 0.7	40.6 ± 0.6	0.002
Tanner stage (n and %)			<0.001
1	53 (53)	17 (23)	
2	34 (34)	19 (26)	
3	5 (5)	8 (11)	
4	5 (5)	20 (27)	
5	4 (4)	10 (14)	

<sup>1</sup>Data are means ± SE, n (%)

<sup>2</sup>Students t-tests and Chi-squared test used to compare differences between males and females



**Fig. 1** Linear regression between insulin sensitivity (SI) as dependent and serum adiponectin and leptin as independent variables in overweight Hispanic boys (n = 101) and girls (n = 74).

**Table 2** Leptin, adiponectin, markers of glucose handling and lipid metabolism in overweight male and female Hispanic adolescents

Characteristics <sup>1</sup>	Boys (n = 101)	Girls (n = 74)	p-value <sup>2</sup>	
			gender	gender $\times$ age
SI ( $\times 10^{-4} \text{ min}^{-1} / (\mu\text{U/ml})$ )	2.17 ± 0.14	1.88 ± 0.15	0.104	0.626
AIR ( $\mu\text{U/ml}$ )	1806 ± 124	1681 ± 129	<0.001	0.419
DI ( $\times 10^{-4} \text{ min}^{-1}$ )	2873 ± 118	2246 ± 116	<0.001	0.389
serum leptin ( $\mu\text{g/l}$ )	23.2 ± 1.1	31.1 ± 1.5	0.533	0.005
serum adiponectin (mg/l)	10.2 ± 0.3	10.0 ± 0.4	0.220	0.338

<sup>1</sup>Data are means ± SE, n (%)

<sup>2</sup>Gender differences adjusted for age, Tanner stage, body fat mass, lean body mass (and for AIR additionally for SI)

were similar in boys and girls. Despite a significantly different slope in leptin over age between boys and girls, no gender difference in the independent effect of serum leptin on insulin sensitivity, acute insulin response and disposition index was observed. No significant interactions of leptin and adiponectin with age or Tanner stage were observed indicating that the effects of leptin and adiponectin were consistent over age and Tanner stage.

## Discussion

The present study demonstrates that leptin and adiponectin are significant and independent predictors of insulin sensitivity, but not of insulin secretion or beta-cell function in overweight Hispanic youth. Even though both leptin and adiponectin were related to insulin sensitivity, they only explained 5% of the variation over and above that explained by gender, age, Tanner stage, total fat mass, and lean body mass.

Currently, the effects of adiponectin and leptin on insulin sensitivity, insulin secretion and beta-cell function during puberty independent of adiposity are unclear. Few studies in adolescents have simultaneously investigated both adiponectin and leptin especially in humans [30], while in others robust measures of insulin sensitivity and/or beta-cell function were lacking [31–34]. Our results show the potential roles of adiponectin and leptin as modulators of insulin action in adolescents independent of pubertal stage or age. Adiponectin increases insulin sensitivity by 1) enhancing tissue fat oxidation resulting in reduced circulating fatty acids and triglycerides in liver and muscle [14], and 2) increasing the skeletal muscle insulin receptor tyrosine kinase activity [35]. In the present study, adiponectin was a significant positive predictor of insulin sensitivity even after adjustment for potential confounding factors including circulating leptin, which has been suggested to counterregulate adiponectin [15]. However, circulating leptin and adiponectin were not correlated in Latino adolescents, which might be explained, in part, by changes in these hormones during puberty.

In contrast to adiponectin, leptin improves not only skeletal muscle glucose uptake by AMP-kinase dependent pathways [36], but also reduces at elevated levels the binding of insulin to its receptor and impairs insulin signaling in adipose tissue by decreasing mitogen-activated protein kinase, insulin receptor tyrosine phosphorylation, and increasing suppressor of cytokine signaling-3 protein [37]. In obesity, increase in fat mass is associated with hyperleptinemia and increasing leptin resistance [11] explaining the negative correlation between leptin and insulin sensitivity. In the present study, leptin was an independent negative predictor of insulin sensitivity.

The effect of leptin and adiponectin on insulin secretion is less clear. In the present study, leptin and adiponectin were not related neither to acute insulin response to glucose as a marker of insulin secretion nor to disposition index as a marker of beta-cell function. The presence of the leptin receptor in pancreatic cells [38] suggests that leptin might be an adipose tissue signal to alter insulin secretion in states of increased fat depots and decreased insulin sensitivity. Plasma leptin acutely inhibits glucose-stimulated insulin secretion in rats [19] and in isolated rodent and human pancreatic cells [39]. Chronic leptin exposure in high concentrations did not exert pronounced effects [22]. In human obesity, high leptin levels are associated with leptin resistance [36] and, therefore, leptin resistance might also exist

in pancreatic islet cells leading to a loss of the repressive control of insulin secretion by leptin [40].

The effects of adiponectin on beta-cell function are speculative. A significant relationship between adiponectin and proinsulin-to-insulin ratio has been reported in one study, whereby the proinsulin-to-insulin ratio was used as a marker for beta-cell function [20]. However, this is not confirmed by other studies *in vitro* and *in vivo* [21]. The present study does not support the hypothesis that adiponectin has direct effects on insulin secretion via beta-cell stimulation.

During childhood and puberty, leptin levels increase dramatically with a more pronounced increase in girls compared to boys [41]. Circulating concentrations of leptin normalized to body fat mass are 2–3-fold higher in adult females than in males [42], but not in childhood [43]. Several studies indicate that this sexual dimorphism is due to a suppression of leptin secretion by androgens in males and to an estrogen-mediated augmentation of leptin secretion in females. However, despite different slope in leptin over age in boys and girls, the present study does not suggest any sexual dimorphism with respect to the effect of leptin on insulin action and insulin sensitivity, neither early nor late during puberty. This is not consistent with the study of Kennedy et al. [42] who demonstrated a relation between insulin sensitivity and leptin was only visible in males but not in females. However, this study was in lean and overweight adults. On the other hand, circulating adiponectin decreased similarly in girls and boys over age with similar effects of adiponectin on insulin sensitivity over age and between genders, suggesting a lack of sexual dimorphism for adiponectin secretion and action. This is in contrast to other studies showing an decline in adiponectin in lean boys and not in girls during puberty [30].

The present study has limitations to be acknowledged. The cross-sectional in design does not allow addressing changes that may occur longitudinally. Future analyses of adiponectin and leptin of these participants' subsequent visits may be used to address this issue. Moreover, the study cohort consists only of overweight Latino adolescents and we have no data from a normal weight control group, which limits the variance in our outcome measures. However, this homogeneous sample allows us the unique opportunity to investigate the role of adiponectin and leptin on insulin sensitivity and beta-cell function in a high-risk insulin resistant population independent of adiposity.

In conclusion, leptin and adiponectin independently affect insulin sensitivity, but have no apparent effects on insulin secretion and beta-cell function in Hispanic adolescents. This might be indicative of pancreatic leptin resistance as a potential factor in the pathogenesis of type 2 diabetes and the metabolic syndrome.

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