RAPID COMMUNICATION

# Leptin-to-adiponectin ratio as independent predictor of insulin sensitivity during growth in overweight Hispanic youth

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**ABSTRACT. Because leptin and adiponectin are counter-regulated *in vivo* and exert opposing effects on glucose metabolism, fat oxidation and insulin sensitivity, the ratio of leptin-to-adiponectin has been investigated as a potential atherogenic index, suggesting that the index is a better biomarker for atherosclerotic risk in obese Type 2 diabetic patients than either leptin or adiponectin alone. However, no information is available regarding the leptin-to-adiponectin ratio during adolescence in Hispanic adolescents. Therefore, the present study was designed to investigate the leptin-to-adiponectin ratio during growth and to establish whether the leptin-to-adiponectin ratio is a better predictor for insulin sensitivity compared to leptin and adiponectin alone in a regression model. From the age of 8 to 14, the leptin-to-adiponectin ratio increased from 2.0±0.8 to 5.8±2.2 in girls, with no significant change noted in boys (gender x age interaction *p*=0.007). In a multiple regression analysis, including both adiponectin and leptin as independent variables, leptin and adiponectin explained 5% of the variation in insulin sensitivity independent of gender, age, Tanner stage, total fat mass and lean body mass (*p* for $R^2$-change <0.001). The leptin-to-adiponectin ratio also explained 5% of the variation in insulin sensitivity, after controlling for the same covariates (*p* for $R^2$-change <0.001). These data indicate that the leptin-to-adiponectin ratio is not a better predictor of insulin sensitivity during growth than the additive effects of leptin and adiponectin levels.**
(J. Endocrinol. Invest. 30: RC13-RC16, 2007)
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## INTRODUCTION

Leptin and adiponectin are hormones secreted by the adipose tissue, which exert important effects on the regulation of glucose uptake and insulin sensitivity. In humans, circulating adiponectin is positively and leptin negatively associated with insulin sensitivity independent of adiposity (1, 2).

During childhood and puberty, leptin levels increase dramatically with a more pronounced increase in girls compared to boys (3). Results of a longitudinal study suggest that high fasting serum leptin is a risk factor for greater growth in weight and body fat during childhood independent of adiposity (4). During puberty, adiponectin has been shown to decline in boys but not in girls (5).

Because leptin and adiponectin are counter-regulated *in vivo* and exert opposing effects on glucose metabolism, fat oxidation, and insulin sensitivity, the ratio of leptin-to-adiponectin has been investigated as a potential atherogenic index, suggesting that the index is a better biomarker for atherosclerotic risk in obese Type 2 diabetic patients than either leptin or adiponectin alone (6, 7). No information is available about different ethnic groups such as Hispanic populations, who have a higher risk for Type 2 diabetes. In children, leptin-to-adiponectin has been suggested as marker for metabolic disorders (8). However, no information is available about the leptin-to-adiponectin ratio at different ages and its relation to insulin sensitivity.

Therefore, the present study was designed to (a) investigate the leptin-to-adiponectin ratio during growth and (b) determine whether the leptin-to-adiponectin ratio is a better predictor for insulin sensitivity than either leptin or adiponectin alone in a regression model.

## SUBJECTS AND METHODS

### Study design and subjects

The SOLAR (Study of Latino Adolescents at Risk) Diabetes Project is an ongoing longitudinal study investigating potential risk factors for the development of Type 2 diabetes in Latino adolescents with a family history of diabetes. Detailed study descriptions have been published previously (9, 10). For the present study, the baseline data for 175 overweight Latino adolescents with complete leptin and adiponectin data was analyzed. 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 yr; 2) BMI ≥85th percentile for age and sex according to the Centers for Disease Control and Prevention (11); 3) Latino ancestry (all 4 grandparents Latino by self report); 4) family history of Type 2 diabetes in at least one parent, sibling, or grandparent; 5) absence of Type 1 or Type 2 diabetes using the guidelines of the American Diabetes Association (12). Children were excluded if they had any major illness, including Type 1 or Type 2 diabetes, or if they 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 was obtained from both parents and written informed assent was obtained from all children.

### Detailed methods and blood analysis

The methods of the study have been previously reported in detail elsewhere (9). Briefly, total body fat was assessed by a whole body scan using dual energy x-ray absorptiometry (Hologic 45 QDR 4500W, Hologic, Bedford, MA). A frequently sampled iv glucose tolerance test was performed after an overnight fast to determine insulin dynamics (9). At time zero, glucose (25% dextrose; 0.3 g/kg of body weight) was administered iv. Blood samples were then collected at 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, and 180 min. Insulin (0.02 U/kg of body weight; Humulin R - regular insulin for human subjects; Eli Lilly and Company, Indianapolis, IN) was injected iv at 20 min. Plasma was analyzed for glucose and insulin and values were entered into the Minmod Millennium 2003 computer program (version 5.16, Richard N. Bergman, Los Angeles, CA) for determination of insulin sensitivity. Fasting plasma adiponectin and leptin was measured using radioimmunoassay kits (Linco Research, St. Charles, MO).

### Statistical analysis

All data are reported as mean and SE. Baseline characteristics of boys and girls were compared using Student's t-test or Chi-square test where appropriate. Insulin sensitivity, total fat mass and lean body mass were log transformed to normalize distribution before performing statistical analyses. To investigate the relation between leptin, adiponectin, its ratio and age, analysis of variance (ANOVA) models were performed including gender, age, Tanner stage, total fat mass, and lean body mass and a gender x age interaction term. If the interaction term was not significant, it was not included in the final model (for adiponectin). Significance of the gender x age interaction term is provided. To investigate the relation between insulin sensitivity as the dependent variable and leptin, adiponectin, and their ratio as the independent variables, multiple regression analyses were performed. Gender, age, Tanner stage, total fat mass and lean body mass were included as covariates. Partial Pearson coefficients of variation are given as well as $R^2$ change and significance of $R^2$ change. Possible gender interactions were tested by gender stratification but no such interactions were present. All analyses were performed using Statistical Package for the Social Sciences (SPSS) 11 (SPSS Inc., Chicago, IL).

## RESULTS

The mean age of the cohort was 11.1±1.7 yr, mean body mass index (BMI) was 28.4±5.3 kg/m², and mean BMI percentile was 97.2±3.0. Boys and girls were similar in age, BMI, and BMI percentile. Insulin sensitivity, acute insulin response and disposition index have been published elsewhere (9, 13). The mean insulin sensitivity was 2.0±1.4 x10$^{-4}$ min$^{-1}$/(μU/ml), the acute insulin response 1753±1191 (μIU/ml), and the disposition index 2608±1146 (x10$^{-4}$ min$^{-1}$).

Adiponectin levels were higher at age 8 yr compared to 14 yr (10.5±2.6 mg/l *vs* 7.9±3.4 mg/l; *p*=0.03) and were similar in boys and girls. Plasma leptin levels increased sharply from 22.6±8.7 to 40.7±12.7 μg/l in girls but remained constant in boys (19.5±5.7 to 19.4±9.7 μg/l; gender x age interaction *p*=0.005). Consequently, leptin-to-adiponectin ratio increased from 2.0±0.8 in girls age 8 yr to 5.8±2.2 in girls age 14, with no significant change in boys (gender x age interaction *p*=0.007) (Fig. 1). In a multiple regression analysis, the potential confounder gender, age, Tanner stage, total fat mass, and lean body mass explained 48% of the variance of insulin sensitivity (*p* for $R^2$-change <0.001). Including both adiponectin and leptin as independent variables, leptin (partial r=−0.180, *p*=0.019) and adiponectin (partial r=−0.230, *p*=0.003) explained together 5% of insulin sensitivity variation after adjusting for gender, age, Tanner stage, total fat mass and lean body mass (*p* for $R^2$-change <0.001). The leptin-to-adiponectin ratio (partial r=−0.297, *p*<0.001) (Fig. 2) also explained 5% of the variation of insulin sensitivity after adjusting for gender, age, Tanner stage, total fat mass, and lean body mass (*p* for $R^2$-change <0.001) indicating that the ratio is not a stronger index for insulin sensitivity during puberty in the study population than the combination of both, leptin and adiponectin.
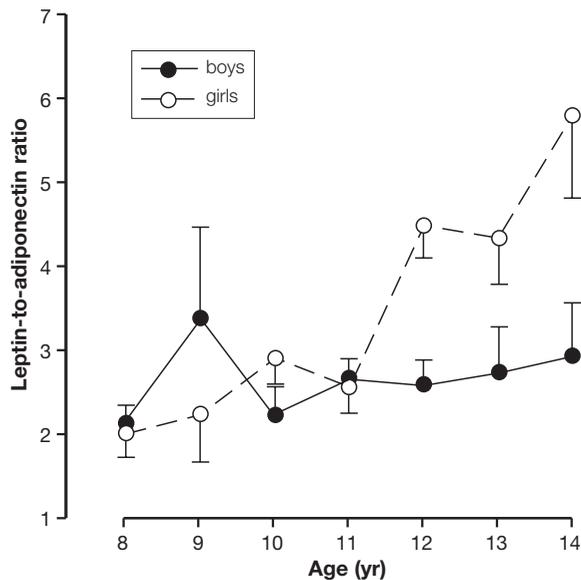
Fig. 1 - *Serum leptin, adiponectin, and leptin-to-adiponectin ratio over age in overweight Hispanic boys (no.=101) and girls (no.=74). A significant age x gender interaction was observed for leptin and leptin-to-adiponectin ratio with a sharp increase over age in girls, but not in boys (p=0.007).*

## DISCUSSION

Adiponectin and leptin exert opposite effects on insulin sensitivity. Insulin resistance has been shown to be reversible by co-administration of physiological doses of adiponectin and leptin, but only partially by adiponectin or leptin alone (14), leading to the assumption that an index of leptin corrected by adiponectin levels might be an accurate predictor of insulin resistance. However, the present study suggests
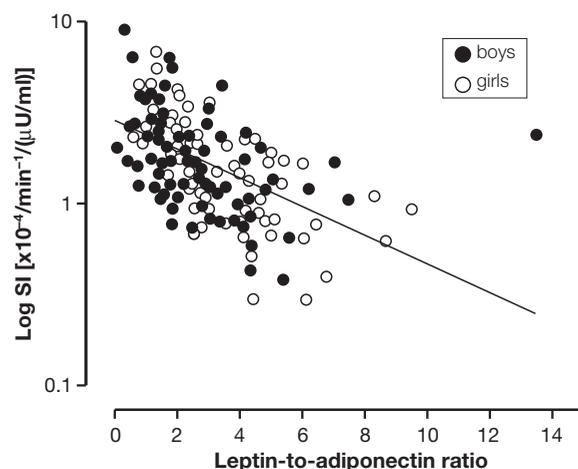
that the leptin-to-adiponectin ratio is not a better predictor of insulin sensitivity than leptin and adiponectin combined in the same regression model. The variance explained by the leptin-to-adiponectin ratio is the same as for both hormones combined. Furthermore, the main determinant of the leptin-to-adiponectin ratio during adolescence and the apparent gender difference in the slope of the ratio over age are plasma leptin levels and their puberty-related changes. Scarce information is available about the leptin-to-adiponectin ratio during growth. Only one study has focused on the leptin-to-adiponectin ratio in obese *vs* non-obese children (8). The leptin-to-adiponectin ratio was 8-fold higher in obese compared to non-obese children and strongly correlated with other metabolic markers such as BMI, HDL cholesterol, and skinfold thickness. These results suggested that the leptin-to-adiponectin ratio might be a promising marker for morbidities associated with childhood obesity. Additionally, the leptin-to-adiponectin ratio was correlated with pulse wave velocity – an index of aortic stiffness – in Type 2 diabetics in adults, whereas leptin or adiponectin alone did not show any significant correlation (7), suggesting that the leptin-to-adiponectin ratio may serve as a potential atherogenic index. However, in both studies no measures of insulin sensitivity were provided.

In conclusion, the leptin-to-adiponectin ratio increased with age in girls but not in boys similar to leptin levels. The leptin-to-adiponectin ratio as an index reflecting increased leptin corrected for by reduced adiponectin is not a stronger predictor of insulin sensitivity than leptin and adiponectin levels themselves in overweight Latino youth.

Fig. 2 - *Linear regression between insulin sensitivity (SI) as dependent and leptin-to-adiponectin ratio in overweight Hispanic boys (no.=101) and girls (no.=74).*

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