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Gender differences exist in the association of leptin and adiponectin levels with insulin resistance parameters in prepubertal Arab children

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Abstract

Aim: Differences in correlations between leptin, adiponectin and insulin resistance in children exist in different ethnic populations. No such information is available in Arab children. This study aims to fill this gap.
Methods: Three hundred and twenty-five prepubertal children were recruited in this cross-sectional study. Body mass index (BMI), waist and hip circumferences and fasting glucose were measured by standard procedures. Serum insulin, leptin and adiponectin were assayed by ELISA.
Results: Leptin and adiponectin levels were significantly correlated with anthropometric parameters, HOMA-IR and insulin in all subjects and with fasting glucose in girls only. Correlations of adiponectin with HOMA-IR and insulin in boys and of leptin with insulin in girls were independent of BMI, waist and hip circumferences.
Conclusion: Gender differences exist in the distribution of adipocytokines in prepubertal children. The associations of adipocytokines with obesity biomarkers in prepubertal children suggest a causal link between childhood obesity and the risk of an early diabetes onset.

Keywords: adiponectin; childhood obesity; insulin resistance; leptin.

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Introduction

Childhood obesity is a major public health problem owing to its association with multiple clinical complications, widespread prevalence and increasing incidence in developed and developing nations (1, 2). Obesity, in adults, is a well-known risk factor for insulin resistance, which in turn can contribute to the development of type 2 diabetes mellitus (T2DM). Likewise, there is an increased incidence of T2DM in children and adolescents, attributed mainly to the obesity induced insulin resistance (3, 4). In obesity, increased adipose tissue infiltration of proinflammatory cytokines and the altered production of adipocytokines interfere with insulin signaling and contribute to obesity induced impairment of insulin sensitivity (5). Consistently, studies have described the correlation of inflammatory components, and adipocytokines with insulin resistance in children and adolescents, establishing a causal relationship between obesity and insulin resistance (6–8).

Leptin and adiponectin are the major adipose tissue derived protein hormones and play crucial roles in insulin sensitivity, fatty acid oxidation and energy homeostasis (9, 10). Leptin levels are directly related to degree of obesity as an increase in fat mass is associated with an increase of leptin, which makes leptin an indicator of total body fat content (11). Adiponectin levels on the other hand are negatively correlated with adiposity (12). A number of studies have reported a positive correlation of leptin and a negative correlation of adiponectin levels with anthropometric and insulin resistance parameters in children and adolescents in different ethnic populations, albeit with considerable variations (7, 13–20). Additionally, the association of leptin and adiponectin levels with the components of insulin resistance is reported to be independent of potential confounding factors, underscoring the usefulness of these adipokines in predicting the insulin resistance status in children (16–18, 21). There is a significant increase in the incidence of childhood obesity in Saudi Arabia, attributed mainly to a sedentary life style (22). However, to the best of our knowledge, no information is available with regard to the relationships between obesity, adipokines and insulin sensitivity or the usefulness of these associations in predicting the insulin resistance status in Saudi children. Thus, here we examined the association of leptin and adiponectin with anthropometric and insulin resistance parameters and their predictive value of the insulin resistance status in a cohort of Saudi child population.

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Materials and methods

Subjects

A total of 325 normal healthy prepubertal Saudi Arabian children consisting of 159 boys with a mean age of 8.8 years and 166 girls with a mean age of 9.3 years were randomly recruited from primary health care centers in Riyadh, Saudi Arabia. Subjects with any medical complication or those having parental history of diabetes were excluded from the study. Demographic, health and dietary information of children as well as parents was collected through generalized questionnaire. Informed consents were obtained from the parents before enrolling the children for the study. Study was conducted in accordance with the guidelines set by Ethics Committee of the Research Center, College of Science, King Saud University, Riyadh.

Anthropometric parameters

Anthropometric measurements were obtained by trained personnel of health care centers. Height and body weight were measured without shoes and the study subjects wearing light clothes. Height was measured to the nearest 0.5 cm and weight to the nearest 0.1 kg. Waist circumference was measured to the nearest 0.5 cm at the levels between the midpoint of the lowest rib and iliac crest parallel to the floor in a standing position, while the hip circumference was measured to the nearest 0.5 cm at maximum extension of the buttocks. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$.

Analytical methods

Blood samples were collected after overnight fasting. Plasma glucose levels were measured by routine laboratory procedure. Insulin was assayed by a solid phase enzyme amplified sensitivity immunoassay (Medgenix INS-ELISA, Biosource, Belgium). Plasma leptin and adiponectin levels were measured by radioimmunoassay following the manufacturer's instructions (Linco Research, Inc, St Charles, MO, USA). Insulin resistance was assessed by homeostasis model assessment (HOMA-IR) calculated using the formula; insulin (μU/mL)×glucose (mmol/L)/22.5.

Statistical analysis

All statistical analyses were done using SPSS (Statistical Package for Social Sciences version 11.5). Data were presented as mean±standard deviation. Skewed variables (Insulin, HOMA-IR, leptin and adiponectin) were logarithmically transformed prior to comparisons. Independent t-test was done for comparisons between boys and girls. Spearman analysis was applied to establish correlation among adipocytokines, anthropometric and insulin resistance parameters. Multiple linear regression analyses were carried out to determine associations between leptin and adiponectin (dependent variables) and the insulin resistance components, adjusting for age, BMI and waist circumference. Significance was set at $p<0.05$.

Table 1 Anthropometric, biochemical and insulin resistance parameters of studied children.

Parameters	Boys	Girls	p-Value
n	159	166	
Age, years	8.8±1.9	9.3±2.0	0.23
BMI, kg/m^2	19.4±4.7	18.8±5.2	0.12
Waist circumference, cm	58.6±13.4	58.2±13.9	0.15
Hip circumference, cm	69.6±13.6	74.7±15.9	0.08
Glucose, mmol/L	4.9±1.3	5.9±3.2	0.02
Insulin, IU/mL[a]	5.6±4.0	7.9±5.1	0.01
HOMA-IR[a]	1.2±1.0	2.2±2.6	0.01
Leptin, ng/mL[a]	7.2±11.3	11.9±12.2	0.03
Adiponectin, μg/mL[a]	21.5±9.9	22.5±11.8	0.61

Data presented as mean±SD. [a]Indicates logarithmically transformed variables; independent t-test was applied for comparisons between the groups; BMI, body mass index.

Results

Gender differences exist in insulin resistance parameters in children

Anthropometric parameters including BMI, waist and hip circumferences were found to be similar in age matched girls and boys (Table 1). On the other hand, in girls as compared to boys fasting glucose (5.9±3.2 mmol/L vs. 4.9±1.3 mmol/L, $p<0.02$), insulin (7.9±5.1 mmol/L vs. 5.6±4.0 mmol/L, $p<0.01$) and HOMA-IR (2.2±2.6 mmol/L vs. 1.2±1.0 mmol/L, $p<0.01$) were significantly elevated (Table 1). Among the adipocytokines, girls had significantly elevated leptin levels than boys (11.9±12.2 ng/mL vs. 7.2±11.3 ng/mL, $p<0.03$), while the adiponectin levels were comparable between the sexes (22.5±11.8 ng/mL vs. 21.5±9.9 ng/mL, $p<0.61$) (Table 1).

Leptin and adiponectin levels are significantly correlated with anthropometric and insulin resistance parameters in children

Spearman correlation analysis revealed that leptin levels were significantly and positively correlated with BMI, waist and hip circumferences in both boys ($r=0.69$, $p<0.01$; $r=0.67$, $p<0.01$ and $r=0.71$, $p<0.01$, respectively) and girls ($r=0.72$, $p<0.01$; $r=0.66$, $p<0.01$; $r=0.64$, $p<0.01$, respectively) (Table 2). Contrarily, adiponectin levels were negatively correlated with BMI, waist and hip circumferences in boys ($r=-0.49$, $p<0.01$; $r=-0.47$, $p<0.01$, $r=-0.44$, $p<0.01$, respectively) as well as in girls ($r=-0.29$, $p<0.05$; $r=-0.39$, $p<0.05$; $r=-0.31$, $p<0.01$, respectively) (Table 2). Leptin levels in boys were in linear correlation with fasting insulin ($r=0.53$, $p<0.01$) and HOMA-IR ($r=0.48$, $p<0.01$) but

Table 2 Spearman correlation coefficients between anthropometric and insulin resistance parameters in boys and girls.

	BMI	Waist	Hips	FG	FI	HOMA-IR
Boys						
Leptin	0.69[a]	0.67[a]	0.71[a]	–0.11	0.53[a]	0.48[a]
Adiponectin	–0.49[a]	–0.47[a]	–0.44[a]	–0.12	–0.56[a]	–0.53[a]
Girls						
Leptin	0.72[a]	0.66[a]	0.64[a]	0.14[a]	0.67[a]	0.48[a]
Adiponectin	–0.29[b]	–0.39[b]	–0.31[a]	–0.16[a]	–0.24[b]	–0.39[a]

[a]$p<0.01$, [b]$p<0.05$. BMI, body mass index; FG, fasting glucose; FI, fasting insulin; HOMA-IR, homeostasis model assessment-insulin resistance.

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not with fasting glucose, whereas in girls they were positively correlated with fasting insulin (r =0.67, p<0.01), fasting glucose (r=0.14, p<0.01) and HOMA-IR (r=0.48, p<0.01) (Table 2). In contrast, adiponectin levels were negatively correlated with fasting insulin (r=–0.56, p<0.01) and HOMA-IR (r=–0.53, p<0.01) but not with fasting glucose in boys and with fasting glucose (r=–0.16, p<0.01), fasting insulin (r=–0.24, p<0.05) and HOMA-IR (r=–0.39, p<0.01) in girls (Table 2).

Leptin and adiponectin levels are independently correlated with insulin resistance markers

Multiple linear regression analysis revealed that leptin levels in boys were not significantly correlated with HOMA-IR, fasting insulin and glucose levels after adjusting for age, BMI and adiponectin (Table 3). On the other hand leptin levels in girls remained significantly correlated with fasting insulin [β (SE)=0.27 (0.11), p=0.02] but not with fasting glucose and HOMA-IR after adjusting for age, adiponectin and BMI (Table 3). After adjusting for age, BMI and leptin, adiponectin levels were negatively correlated with HOMA-IR [β (SE)=–0.033 (0.012), p=0.04] and fasting insulin [β (SE)=–0.122 (0.06), p=0.039] in boys but not in girls (Table 3). Adiponectin levels were not correlated with fasting glucose in both boys and girls (Table 3). Additionally, leptin and adiponectin significantly predicted 22% of the variance in HOMA-IR (R^2=0.22, p=0.017) and 31% variance in serum insulin levels (R^2=0.31, p=0.001) among boys, and 33% of the variance in serum insulin levels (R^2=0.33, p=0.0005) among girls, independent of age and BMI (Table 3).

Waist circumference provides an indirect measure of fat centralization and has been shown to be a better predictor of abdominal fat and associated with insulin resistance in children (23, 24). Therefore, we studied the association of leptin and adiponectin with HOMA-IR, fasting insulin and glucose levels after adjusting for age, waist and hip circumferences. Multiple linear regression analysis revealed that adiponectin levels remained significantly and negatively correlated with HOMA-IR (β±SE=–0.039±0.015, p<0.015) and fasting insulin (β±SE=–0.135±0.058, p<0.023) levels but not with fasting glucose levels in boys and correlated with none of the insulin resistance markers in girls after adjusting for age, leptin, hip and waist circumferences (Table 4). On the other hand leptin was not correlated with HOMA-IR, fasting insulin and glucose levels in boys, while correlated only with fasting insulin [β±(SE)=0.224 (0.063), p<0.001] in girls after adjusting for age, adiponectin, waist and hip circumferences (Table 4). Thus, these data are consistent with the associations found after the adjustment for BMI (Table 3).

Discussion

Altered levels of leptin and adiponectin are associated on one hand with obesity and on the other with insulin resistance, thereby linking the two metabolic complications. Thus, examining the correlations of these adipocytokines with anthropometric and insulin resistance parameters and whether such correlation are independent of potential confounding factors are of significant clinical importance. The primary findings of our study are that; both leptin and adiponectin levels are significantly associated with anthropometric parameters including BMI, waist and hip circumferences and with insulin resistance parameters including HOMA-IR, fasting insulin and glucose in prepubertal Saudi children. Additionally, these associations are independent of age, BMI, waist and hip circumferences. We further found that both leptin and adiponectin levels can significantly predict the insulin resistance status in these children.

In the present study, anthropometric measures including BMI, waist and hip circumferences were identical in age matched boys and girls. Although the lean body mass and fat content concomitantly increase in boys and girls along with pubertal development, the gain of fat mass is relatively high in female sex over male, accounting for higher body weight in boys. However, this mode of weight gain is unlikely to take place in children at prepubertal age and could explain the similarities in anthropometric measurements in boys and girls found in this study. Elevated leptin concentrations measured in girls as opposed to boys, corroborate with similar findings (17, 18, 25). Since leptin levels linearly correlate with body fat in vivo, its elevated levels

Table 3 Multiple regression analysis showing leptin and adiponectin as independent variables and HOMA-IR, insulin and glucose as dependent variables in boys and girls.

	HOMA-IR			Insulin			Fasting glucose		
	β	SE	p-Value	β	SE	p-Value	β	SE	p-Value
Boys									
Leptin	–0.006	0.02	0.81	0.03	0.09	0.74	–0.006	0.033	0.848
Adiponectin	–0.033	0.02	0.04	–0.122	0.06	0.039	–0.035	0.021	0.111
Model R^2	0.22[a]			0.31[b]			0.08		
Girls									
Leptin	0.02	0.068	0.76	0.27	0.11	0.02	–0.121	0.089	0.179
Adiponectin	0.008	0.035	0.83	0.004	0.06	0.94	0.015	0.045	0.737
Model R^2	0.12			0.33[c]			0.01		

Each model was adjusted for age, BMI, [a]p=0.017; [b]p=0.001; [c]p=0.0005.

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Table 4 Multiple regression analysis showing leptin and adiponectin as independent variables and HOMA-IR, insulin and glucose as dependent variables in boys and girls.

	HOMA-IR			Insulin			Fasting glucose		
	β	SE	p-Value	β	SE	p-Value	β	SE	p-Value
Boys									
Leptin	0.005	0.017	0.75	0.057	0.063	0.375	–0.014	0.023	0.553
Adiponectin	–0.039	0.015	0.015	–0.135	0.058	0.023	–0.034	0.021	0.102
Girls									
Leptin	0.056	0.045	0.211	0.224	0.063	0.001	–0.044	0.059	0.458
Adiponectin	–0.007	0.032	0.838	–0.009	0.055	0.878	–0.015	0.042	0.723

Each model was adjusted for age, waist and hip circumferences. p-Value significant at <0.05.

in girls could be attributed to possibly higher percentage of body fat and lower lean mass than boys. Nonetheless, other factors including ethnicity, gender based differences in leptin synthesis, clearance rates, bioactivity, and/or leptin transport or the factors other than those related to pubertal development could contribute to sexual dimorphism in leptin levels (26). Contrary to leptin concentrations, adiponectin levels in the present study are identical in both boys and girls. These observations are in contrast to earlier studies (25, 27, 28), which have reported an elevated adiponectin levels in girls than boys. It has been shown that adiponectin levels decline with age, in association with changes in sex hormones and growth factors and this relationship appears to be more pronounced in boys than girls (20, 28, 29), implying that leptin levels are identical in both boys and girls at prepubertal or very young age, even before the sex hormones could exert any effect. Consistently, studies have found comparable adiponectin levels in prepubertal children irrespective of gender (20, 30–32). These findings support our observations of matching adiponectin levels in both sexes, considering the prepubertal status of the studied children. Nevertheless, girls even at prepubertal age have shown to have higher adiponectin levels than age matched boys based on a large cohort study (28). Insulin resistance components including HOMA-IR, fasting insulin and glucose values were all significantly higher in girls in comparison to boys, suggesting that girls at prepubertal age can be intrinsically more insulin resistant than boys (32, 33).

In the present study, we found that leptin levels were positively correlated and adiponectin levels were negatively correlated with both anthropometric and insulin resistance markers (HOMA-IR and fasting insulin) in both boys and girls, linking obesity and insulin resistance. Compared to adiponectin, leptin levels were more strongly correlated with anthropometric measures in both sexes, agreeing with the linear correlation of leptin with BMI and other obesity markers in vivo. Interestingly, however, leptin and adiponectin levels were positively and negatively correlated with fasting glucose levels only in girls but not in boys, indicating that insulin sensitivity in girls might be more prone to the effect of adiponectin, at least at prepubertal age. Studies representing different ethnic populations have found significant associations between leptin, adiponectin and insulin resistance, albeit with a considerable variation (4, 13, 17–19, 21, 34, 35). These differences could stem from the several possible determinants including ethnicity, race, pubertal status, genetic predisposition, body composition and sample size as well as exclusion and inclusion criteria of the subjects. In this study we found that adiponectin in boys but not in girls remained significantly correlated with HOMA-IR and fasting insulin after adjusting for age, BMI and leptin. On the other hand, leptin sustained its associated with fasting insulin levels only in girls but not in boys even after adjusting for age, BMI and adiponectin. These data suggest that adiponectin levels in boys and leptin levels in girls strongly influenced the insulin sensitivity compared to BMI. Similar associations were found in boys and girls after adjusting for waist and hip circumference, suggesting that leptin and adiponectin are associated with the markers of insulin resistance independent of abdominal fat, though measured indirectly by waist circumference. These associations among preadolescents greatly affect BMI, and are significantly influenced by their parent's metabolic profile (36). Additionally, leptin and adiponectin significantly predicted 22% of the variance in HOMA-IR and 31% variance in serum insulin levels among boys, and 33% of the variance in serum insulin levels among girls (p=0.0005) independent of BMI underscoring the usefulness of leptin and adiponectin as independent predictors of insulin resistance status. Correlation of leptin and adiponectin levels on one hand with anthropometric parameters and on the other hand with insulin resistance parameters underscores the contribution of childhood obesity to the risk of developing insulin resistance and thus emphasizes the need of healthy lifestyle to avoid the obesity and associated morbidities.

In summary, we showed that leptin levels are positively and adiponectin levels were negatively associated with BMI and waist circumference, fasting insulin, HOMA-IR, and fasting glucose. Correlations between leptin, adiponectin and the insulin resistance components were different in boys and girls and were independent of age, BMI, waist and hip circumference. Additionally, we found that both leptin and adiponectin were useful independent predictors of insulin

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resistance status. The associations of adipocytokines on one hand with anthropometric parameters and on the other hand with insulin resistance parameters in both the sexes suggest a causal link between the childhood obesity and the risk of developing diabetes at an early age. Due to cross-sectional nature of this study and a modest sample size, the observations need to be followed up and in a prospective setup to make a causal inference.

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