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# Elevated total and central adiposity and low physical activity are associated with insulin resistance in children

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**Abstract**

The aim of this study was 2-fold: (1) to examine insulin resistance, blood lipid levels, and inflammatory markers in 9- to 11.5-year-old obese and lean children and (2) to identify factors that influence insulin resistance in this cohort of youths. Body mass index, skinfold thickness, waist circumference, physical activity (4-day triaxial accelerometer), cardiorespiratory fitness (submaximal bicycle ergometer test), and dietary intake (3-day food records) were evaluated in 27 obese and 27 lean boys and girls. Fasting blood samples were analyzed for insulin, glucose, lipids and lipoproteins, C-reactive protein (CRP), interleukin 6, soluble intercellular adhesion molecule, and soluble vascular cell adhesion molecule. Homeostasis model assessment (HOMA) was used to evaluate insulin resistance (HOMA-IR). Obese children presented higher HOMA-IR, CRP, and blood lipid levels (all $P < .01$) compared with lean children. Total body fat and waist circumference were positively associated with fasting insulin ($r \geq 0.51$), HOMA-IR ($r \geq 0.56$), CRP ($r \geq 0.51$), and blood triacylglycerol ($r \geq 0.38$), and were inversely correlated with high-density lipoprotein cholesterol ($r \geq -0.39$; all $P < .01$). Cardiorespiratory fitness was inversely associated with HOMA-IR ($r = -0.24$; $P < .05$), but this association disappeared when adjusted for age, sex, and fat mass. Waist circumference and total daily physical activity explained 49% of the variance in HOMA-IR in these children. In conclusion, these findings suggest that total and central adiposity are positively associated and physical activity is negatively associated with insulin resistance in children. Interventions to improve glucose metabolism in youth should target at reducing total body and abdominal fat and increasing physical activity. The lack of association between inflammatory markers and HOMA-IR suggests that obesity may precede the elevation of these markers in the evolution of insulin resistance in youth.


## 1. Introduction

The prevalence of childhood and adolescent obesity is increasing worldwide [1]. Total and in particular central adiposity are associated with risk factors for cardiovascular disease (CVD), such as hypertriglyceredemia, hypercholesterolemia, insulin resistance, elevated blood pressure, and endothelial dysfunction both in children and adults [2-5]. Among these factors, tissue resistance to insulin action is considered a key factor that might explain the association between obesity and CVD [3].

During the past 10 years, increasing frequency of type 2 diabetes mellitus (non-insulin-dependent diabetes mellitus) and prediabetic stages such as impaired fasting glucose have been reported in children and adolescents [6]. This increase seems to parallel the increase in the prevalence of obesity in this age group. In-depth knowledge of the factors that affect insulin resistance in these age groups will aid in designing more effective programs for the prevention and management of type 2 diabetes mellitus. Current knowledge suggests that insulin resistance is ameliorated after weight loss [4] as well as in the presence of high levels of physical activity and/or cardiorespiratory fitness (CRF) [2,7,8]. Diet composition, in particular, carbohydrate type and amount, and fat intake may also influence insulin resistance [9].

Inflammation, which is present in obesity, may affect insulin action on the target tissues [2]. Elevated C-reactive protein (CRP) and interleukin 6 (IL-6) levels, among others, have been shown to affect certain steps in the

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glucose transport mechanism, thus leading to diminished effect of insulin in glucose disposal by the liver and/or the muscles [10].

A limited number of studies have examined the predictors of insulin resistance in children [11-13]. These studies reported the role of physical activity, aerobic fitness, and body composition on insulin sensitivity. To our knowledge, information on the independent effect and on possible interactions between various factors on insulin resistance in youth is lacking.

The aim of this study was 2-fold: (1) to compare insulin levels, insulin resistance, the lipid-lipoprotein profile, and inflammatory marker concentration in the blood of obese and lean children and (2) to identify predictors of insulin resistance in a group of 9- to 11.5-year-old children. Variables entered in the prediction model included, among others, inflammatory markers that are known to affect insulin resistance.

## 2. Methods

### 2.1. Subjects

Participants were recruited from a larger sample of 1000 white Caucasian children [14]. Age- and gender-specific body mass index (BMI) cutoff values [15] were used for the definition of obesity. The cutoff values were 22.77, 23.39, 24.00, 24.57, 25.10, and 25.58 kg/m$^2$ for 9-, 9.5-, 10-, 10.5-, 11-, and 11.5-year-old boys and 22.81, 23.46, 24.11, 24.77, 25.42, and 26.05 kg/m$^2$ for 9-, 9.5-, 10-, 10.5-, 11-, and 11.5-year-old girls. Lean children were identified as those with a BMI less than the 25th percentile according to the National Health and Nutrition Examination Survey III [16]. From the 110 children who were obese and lean, 28 boys and 26 girls (27 obese and 27 lean; age, 9-11.5 years) agreed to participate in the study. All children were healthy as evidenced by their health records and a physical examination made by a pediatrician. The protocol was explained to the parents and the children, and signed informed consent was obtained from one of the parents. The ethical committee of the Harokopio University approved the study design.

### 2.2. Protocol

All measurements were performed from September 2002 to February 2003 and included anthropometric, physical activity, and cardiovascular fitness assessment, dietary analysis, and fasting blood sampling. All physical and physiologic measurements were taken during a period of 15 days or fewer in each child, always during morning school hours. Children were not examined when ill or febrile.

### 2.3. Anthropometry

Height was measured to the nearest 0.5 cm with a standard stadiometer and body weight was recorded to the nearest 0.1 kg, while subjects were dressed in light clothing (Seca scale, Model 770, Hamberg, Germany). Skinfold thickness was determined at 7 sites (triceps, biceps, abdominal, subscapular, suprailium, thigh, and medial calf) according to standard procedures [17]. Each skinfold was measured twice with a Harpenden skinfold caliper (CMS Weighing Equipment, London, UK) on the right side of the body and the average was calculated. If the readings differed by more than 0.2 mm, a third measure was taken and the mean was recorded. Waist (minimal girth of the abdomen) and hip (maximal girth of the buttocks) circumferences were measured to the nearest 0.5 cm with a plastic tape while the subjects were standing erect. Measurements were taken by the same investigator.

Calculated variables included: (1) BMI (= weight [kg]/height$^2$ (m$^2$)], (2) trunk-extremity (TER) skinfold ratio as the sum of central skinfolds (abdominal, subscapular, suprailium) divided by the sum of peripheral skinfolds (biceps, triceps, thigh, calf), (3) percentage of body fat by using the sum of triceps and calf skinfolds [18]. From this value, fat mass and fat free mass were calculated. Visceral adipose tissue (VAT) was estimated by the equation, VAT = −107.39 + 4.159 (SAD) + 108.89 (WHR), where SAD is the sagittal abdominal diameter and WHR is the waist–hip circumference ratio [19].

### 2.4. Physical activity assessment

Physical activity was assessed with a triaxial accelerometer (RT3, Stayhealthy, Moncovia, CA), which was worn for 4 consecutive days. The accelerometer is a small (7.7 × 5.5 × 2.7 cm), lightweight (65.2 g) instrument, which is initialized and downloaded via a computer interface and has no external controls that can be manipulated. The accelerometer was stored in a belt, which the children wore around the waist from the time they got up in the morning until they went to bed at night, except during bathing and showering, for 3 weekdays and 1 weekend day, and it was programmed to record minute-by-minute activity counts. Four days of accelerometry can provide a valid estimation of physical activity as previously shown in children [20]. In addition, children recorded in a diary the time when the monitor was attached and removed each day. The vector magnitude was used to assess activity and inactivity because previous research has shown it to be superior compared to any one vector [21]. Inactivity or sedentary time was defined as fewer than 100 counts per minute [22]. All accelerometers were calibrated with the use of a calibrator provided by the manufacturer.

### 2.5. CRF assessment

Cardiorespiratory fitness was assessed with the physical work capacity at 170 beats per minute test ($PWC_{170}$) performed on a Monark cycle ergometer (Ergo Medic 839E, Vasberg, Sweden) [23]. The protocol consisted of 9-minute cycling at 60 revolutions per minute with increasing resistance every 3 minutes. Heart rate was monitored during the test with a Polar Accurex Plus (Polar Electro,

Kempele, Finland) and the last-minute value of each stage was recorded. $PWC_{170}$ was calculated as:

$$PWC_{170} = \frac{(W_3 - W_2)}{(HR_3 - HR_2)}(170 - HR_3) + W_3$$

where $W_3$ and $W_2$ are the power output (in watts per kilogram body weight) during the third and the second stage, respectively, and $HR_3$ and $HR_2$ the heart rate during the third and the second stage, respectively. The validity of $PWC_{170}$ in assessing maximal oxygen uptake in children is high ($r$ = 0.56-0.90 between $PWC_{170}$ and directly assessed maximum oxygen consumption [$\dot{V}O_2$max]) [24]. The repeatability was also high ($r$ = 0.94) in a subgroup (n= 7) of children in the present study. CRF was also evaluated with the predicted $\dot{V}O_2$max according to the following equations [25]:

$$Y = 10.6 + 14.7(X) \text{ for girls}$$

$$Y = 40.0 + 4.8(X) \text{ for boys}$$

where $X$ is $PWC_{170}$ per kilogram body mass and $Y$ is $\dot{V}O_2$max (mL · $kg^{-1}$ · $min^{-1}$).

The average error between the actual and the predicted values from $PWC_{170}$ $\dot{V}O_2$max has been reported to be 3.4 mL · $kg^{-1}$ · $min^{-1}$ in girls and 2.8 mL · $kg^{-1}$ · $min^{-1}$ in boys [25].

### 2.6. Dietary assessment

Dietary intake was assessed with 3-day food records. All subjects were provided with a dated diary and were instructed by a nutritionist on how to keep a record of the amount and type of food consumed on 3 consecutive days, either from Thursday to Saturday or from Sunday to Tuesday. To give an estimation of portion size, youths were provided by sets of photographs. The children completed these records with their parents' assistance. When necessary, the nutritionist checked and completed the records in a personal interview with each subject or parent. From these food records, total energy intake, amount of carbohydrates, fats, and proteins were calculated by using the Nutritionist V program (Version 1.0, First DataBank, San Bruno, CA) adapted for Greek foods.

### 2.7. Blood sample collection and analysis

After a 10- to 12-hour overnight fast, venous blood samples were collected after 10 to 15 minutes of rest. Four milliliters of the sample was immediately transferred to nonadditive tubes for serum and allowed to clot at room temperature for 30 minutes. The rest (6 mL) of the sample was immediately distributed into EDTA-treated tubes for plasma analysis. Samples were centrifuged at 4°C; plasma and serum containing tubes were stored at −70°C until analysis. Serum insulin was determined by radioimmunoassay (DiaSorin, Saluggia, Italy). The assay sensitivity is less than 4 $\mu$U/mL, whereas the within-assay and between-assay coefficients of variation are 6.6%, 10.6%, and 5.5% and 6.2%, 10.8%, and 9.7%, respectively, for insulin concentrations of 24.1, 73.6 and 130.8 $\mu$U/mL, respectively. Plasma glucose, serum total cholesterol (TC), triacylglycerol (TG), and high-density lipoprotein cholesterol (HDL-C) analyses were performed with the Bayer ADVIA 1650 Clinical Chemistry System (Bayer Corp, Tarrytown, NY). CRP, apolipoproteins apo A-1 and apo B concentrations were determined by particle-enhanced immunonephelometry using the Dade-Behring BN Prospec nephelometer (Dade-Behring, Marburg, Germany). Low-density lipoprotein cholesterol (LDL-C) values were calculated with the Friedewald formula. IL-6, soluble intercellular adhesion molecule (sICAM) and soluble vascular cell adhesion molecule (sVCAM) levels were assayed by a validated commercial enzyme-linked immunosorbent assay (ELISA, Quantikine, R&D Systems, Minneapolis, MN). All analyses were performed in duplicate.

The homeostasis model assessment (HOMA) estimate of insulin resistance (HOMA-IR) was calculated from fasting

Table 1
Body composition for the children participating in the present study

| | Obese | | Lean | |
|---|---|---|---|---|
| | Boys (n = 16) | Girls (n = 11) | Boys (n = 12) | Girls (n = 15) |
| Age (y) | 9.8 ± 0.7 | 10.0 ± 0.6 | 10.3 ± 0.8 | 10.9 ± 0.8 |
| Weight (kg)* | 56.9 ± 7.0 | 55.4 ± 10.2 | 29.7 ± 3.2 | 29.5 ± 3.7 |
| Height (cm)* | 147.5 ± 7.4 | 143.1 ± 6.4 | 139.5 ± 5.8 | 139.1 ± 7.1 |
| BMI ($kg/m^2$)[a],* | 26.0 ± 1.2 | 26.5 ± 2.9 | 15.2 ± 0.7 | 15.2 ± 0.6 |
| Estimated BF (%)[a],* | 41.7 ± 6.0 | 41.7 ± 7.3 | 14.2 ± 2.1 | 18.1 ± 2.8 |
| Estimated FM (kg)[a],* | 23.9 ± 5.2 | 23.7 ± 8.4 | 4.6 ± 1.0 | 5.3 ± 1.1 |
| Estimated FFM (kg)*,**,**** | 33.0 ± 4.0 | 31.7 ± 3.2 | 25.0 ± 2.6 | 24.1 ± 3.0 |
| Estimated VAT ($cm^2$)[a],*,*** | 74.2 ± 8.8 | 64.5 ± 15.3 | 34.1 ± 7.9 | 29.7 ± 5.7 |
| Waist circumference (cm)[a],*,** | 80.5 ± 5.7 | 77.1 ± 5.2 | 56.5 ± 2.3 | 55.7 ± 1.5 |
| Sum of 7 skinfolds (mm)[a],*,*** | 221.1 ± 37.8 | 235.3 ± 48.5 | 57.8 ± 13.9 | 68.2 ± 11.5 |
| TER ratio (units)* | 0.9 ± 0.1 | 0.9 ± 0.1 | 0.5 ± 0.1 | 0.5 ± 0.1 |

Values are presented as mean ± SD. BF indicates body fat; FM, fat mass; FFM, fat-free mass.

[a] Values were log transformed.

* $P < .01$, group effect.

** $P < .01$, sex effect.

*** $P < .05$, sex effect.

**** $P < .01$, sex and group interaction.

Table 2
Physical activity and CRF for the obese and lean children

| | Obese | | Lean | |
|---|---|---|---|---|
| | Boys (n = 16) | Girls (n = 10) | Boys (n = 12) | Girls (n = 15) |
| Recorded time (min · $d^{-1}$) | 831.9 ± 42.1 | 783.5 ± 86.2 | 827.2 ± 56.6 | 821.6 ± 56.0 |
| VM (counts $min^{-1}$ · $d^{-1}$)*** | 621.3 ± 103.5 | 504.9 ± 71.7 | 632.5 ± 126.5 | 518.0 ± 104.0 |
| Sedentary time (min · $d^{-1}$) | 196.6 ± 60.7 | 222.1 ± 97.7 | 200.9 ± 47.1 | 201.1 ± 62.5 |
| Physical activity (min · $d^{-1}$) | 620.7 ± 63.9 | 572.1 ± 94.7 | 622.1 ± 68.4 | 615.1 ± 102.5 |
| $PWC_{170}$ (W · $kg^{-1}$)*·** | 1.3 ± 0.3 | 0.9 ± 0.2 | 1.8 ± 0.6 | 1.4 ± 0.3 |
| $\dot{V}O_2max_{pred}$ (mL · $kg^{-1}$ · $min^{-1}$)*·** | 46.2 ± 1.6 | 24.0 ± 4.2 | 48.8 ± 2.2 | 30.6 ± 4.9 |
| $\dot{V}O_2max_{pred}$ (mL [kg] · FFM)$^{-1}$ · $min^{-1}$)*·** | 79.7 ± 10.1 | 41.9 ± 8.1 | 58.0 ± 3.6 | 37.5 ± 3.0 |

Values are presented as mean ± SD. VM indicates vector magnitude; $\dot{V}O_2max_{pred}$, predicted $\dot{V}O_2max$; FFM, fat-free mass.
* $P < .01$, group effect.
** $P < .01$, sex effect.
*** $P < .05$, sex effect.

insulin ($I_F$) and fasting glucose ($G_F$) as follows: HOMA-IR = [$I_F$ ($\mu$U/mL) × $G_F$ (mmol/L)]/22.5 [26]. HOMA-IR has been previously validated against the euglycemic clamp in 8- to 19-year-old females ($r^2$ = 0.82) [27]. $\beta$-Cell function was estimated with the same model as follows: $\beta$-cell function (%) = 20 × $I_F$/($G_F$ · 3.5). Atherogenic index (AI) was calculated as: AI = [(TC − HDL-C) × (apo B)]/(apo A × HDL-C) [28].

### 2.8. Statistical analysis

Statistical analysis was carried out with the SPSS software (Version 10.0, SPSS, Chicago, IL). Normality of distribution was checked for all variables with the Kolmogorov-Smirnov test. When all subjects were considered as a group, BMI, waist circumference, fat mass, sum of skinfolds, estimated VAT, HOMA-IR and fasting insulin were nonnormally distributed and were log transformed. For obese children, $\dot{V}O_2max$ was the only nonnormally distributed variable and was therefore log transformed. A 2-way analysis of variance was used to examine the differences between obese and lean children as well as between boys and girls. Analysis of covariance (ANCOVA) was also used to control for the effect of age, fat mass (kilograms), waist circumference, and $\dot{V}O_2max$ (milliliters per kilogram per minute) on blood parameters. Pearson correlation coefficient was used to examine the relationships among variables. Relationships among CRF, physical activity, and blood parameters were adjusted for age, sex, and fat mass. Multiple regression with forward elimination was used to identify the factors that affect insulin resistance. Statistical significance was set at $P$ less than .05.

## 3. Results

Waist circumference and estimated VAT were higher ($P < .01$) in the obese than the lean youths (Table 1). In

Table 3
Insulin resistance, inflammatory marker concentration, and lipid-lipoprotein profile characteristics for the obese and lean children

| | Obese | | Lean | |
|---|---|---|---|---|
| | Boys (n = 15) | Girls (n = 10) | Boys (n = 11) | Girls (n = 14) |
| Fasting insulin ($\mu$U/mL)*·*** | 21.0 ± 8.6 | 28.6 ± 9.5 | 12.1 ± 1.7 | 14.2 ± 3.7 |
| Fasting glucose (mg/dL)*** | 94.4 ± 7.0 | 89.0 ± 4.2 | 92.6 ± 6.0 | 87.3 ± 5.9 |
| HOMA-IR (units)* | 4.9 ± 2.1 | 6.2 ± 0.3 | 2.7 ± 2.6 | 3.1 ± 1.1 |
| Estimated $\beta$-cell function (%)*·*** | 242.0 ± 79.5 | 414.3 ± 191.3 | 150.9 ± 25.0[c] | 217.9 ± 53.5 |
| IL-6 (pg/mL)**** | 1.21 ± 0.50 | 1.12 ± 0.45[d] | 1.86 ± 1.42 | 0.72 ± 0.70[e] |
| sICAM (ng/mL)** | 303.5 ± 46.8 | 314.6 ± 61.6 | 281.3 ± 30.5 | 260.4 ± 38.3 |
| sVCAM (ng/mL) | 307.4 ± 65.3 | 307 ± 67.6 | 333.5 ± 70.6 | 308.7 ± 10.7 |
| CRP (mg/L)*·# | 2.33 ± 1.72 | 2.73 ± 2.08 | 0.78 ± 0.34[c] | 1.30 ± 1.48 |
| TC (mg/dL) | 188.5 ± 22.0 | 179.4 ± 31.3 | 177.0 ± 26.1 | 177.1 ± 21.1 |
| TG (mg/dL)*·*** | 66.3 ± 31.7 | 94.5 ± 31.0 | 36.8 ± 8.6 | 61.1 ± 17.5 |
| HDL-C (mg/dL)*·**** | 46.1 ± 8.4 | 43.6 ± 9.1 | 56.4 ± 9.2 | 48.2 ± 7.3 |
| LDL-C (mg/dL) | 129.0 ± 20.8 | 116.8 ± 26.6 | 108.7 ± 26.5 | 116.6 ± 18.3 |
| Apo A (mg/dL)** | 117.0 ± 29.4 | 117.6 ± 16.4 | 140.7 ± 15.9 | 123.1 ± 12.3 |
| Apo B (mg/dL) | 80.7 ± 26.5[a] | 75.3 ± 10.4[b] | 71.7 ± 14.2[c] | 72.9 ± 12.2[b] |
| TC/HDL-C* | 4.2 ± 0.9 | 4.1 ± 0.6[d] | 3.1 ± 0.3 | 3.7 ± 0.5 |
| Atherogenic index** | 2.5 ± 1.8[a] | 2.0 ± 0.6[b] | 1.0 ± 0.3[c] | 1.5 ± 0.5[b] |

Values are presented as mean ± SD. [a]n = 12; [b]n = 8; [c]n = 10; [d]n = 9; [e]n = 13.
* $P < .01$, group effect.
** $P < .05$, group effect.
*** $P < .01$, sex effect.
**** $P < .05$, sex effect.
# Values were log transformed.

Table 4
Correlation coefficients, adjusted for age, among BMI, fat mass, abdominal obesity, and CVD risk factors in 9- to 11.5-year-old boys and girls (n = 50 unless otherwise indicated)

| | BMI (kg/m$^2$)[a] | Fat mass (kg)[a] | Waist circumference (cm)[a] | Estimated VAT (cm$^2$)[a] | TER (units) |
|---|---|---|---|---|---|
| Fasting insulin ($\mu$U/mL) | 0.62** | 0.60** | 0.64** | 0.51** | 0.68** |
| HOMA-IR[a] | 0.66** | 0.64** | 0.69** | 0.56** | 0.73** |
| CRP (mg/L),[a] n = 48 | 0.58** | 0.59** | 0.57** | 0.51** | 0.53** |
| IL-6 (pg/mL), n = 48 | −0.02 | 0.08 | −0.09 | −0.11 | −0.03 |
| TG (mg/dL) | 0.48** | 0.42** | 0.45** | 0.38** | 0.45** |
| LDL-C (mg/dL) | 0.16 | 0.13 | 0.19 | 0.14 | 0.08 |
| HDL-C (mg/dL) | −0.39** | −0.39** | −0.43** | −0.41** | −0.40** |
| TC (mg/dL) | 0.11 | 0.05 | 0.11 | 0.08 | 0.01 |
| Atherogenic index, n = 48 | 0.41* | 0.36* | 0.44* | 0.38* | 0.47** |

[a] Values were log transformed.
* $P < .05$.
** $P < .01$.

addition, boys presented higher values than girls. Both sedentary time and physical activity did not differ between groups and sex, whereas CRF was higher in the lean children (Table 2). Dietary analysis did not differ between groups and genders (energy intake, 8478.3 ± 1243.5 kJ/d vs 8331.7 ± 1297.9 kJ/d for the obese and lean, respectively; carbohydrates, 221 ± 47 vs 227 ± 38 g/d; fat, 94 ± 16 vs 88 ± 19 g/d; protein, 79 ± 16 vs 75 ± 17 g/d). Fasting insulin and HOMA-IR levels were higher in the obese group ($P < .01$; Table 3). TG concentration was higher ($P < .01$), whereas apo A and HDL-C levels were lower ($P < .05$) in the obese compared with the lean children (Table 3). IL-6 did not differ between groups but CRP was higher in the obese children ($P < .01$). Gender differences were also presented in some variables (Table 3). By using ANCOVA, group differences were found only in fasting insulin ($P < .05$), $\beta$-cell function ($P < .01$), and HDL-C ($P < .05$). In addition, sex difference was presented for estimated $\beta$-cell function ($P < .01$). $PWC_{170}$ was inversely associated with insulin resistance ($r = -0.24$; $P < .05$) and positively related to HDL ($r = 0.30$; $P < .05$), but these associations disappeared after adjusting for age, sex, and fat mass. $\dot{V}O_2$max was also related to TG concentration ($r = -0.36$; $P = .01$), but not after accounting for the effects of age, sex, and fat mass ($r = 0.10$; $P > .05$). Total and central adiposity were positively related to HOMA-IR (Table 4) whereas physical activity presented a strong tendency for correlation ($r = -0.22$; $P = .07$). In the prediction model, waist circumference was positively associated and physical activity was negatively associated with insulin resistance ($R^2 = 0.49$; $P < .01$), and these variables explained 49% of the variance in HOMA-IR (Table 5).

## 4. Discussion

The main finding of this study was that fasting insulin and insulin resistance were associated with elevated total body fat and central adiposity and low levels of physical activity in this group of 9- to 11.5-year-old children. Comparison between the 2 groups (obese and lean) revealed that pediatric obesity was associated with dyslipidemia, impaired glucose metabolism, and chronic inflammation. These data suggest that interventions to improve hyperinsulinemia and to manage insulin resistance in childhood should aim at reducing both total and central fatness and increasing physical activity.

The relationship between physical activity and insulin resistance has been examined in a number of studies in adults [7,29]. Less information is available, however, on this issue in children and adolescents [11-13]. From these correlation studies, it appears that physical activity is associated with improved insulin resistance. Data from intervention studies show that elevated physical activity may improve insulin resistance in youth [8,30]. Recently, we reported that aerobic exercise training performed 3 times a week for 12 weeks resulted in lower insulin response during a 2-hour oral glucose tolerance test in overweight and obese 9- to 14-year-old girls [8]. A previous study from our laboratory has also shown that overweight and obese youth with high CRF have lower waist circumference compared with youth with low CRF [31]. Our findings agree with data by others [32,33] and support the hypothesis that elevated physical activity and high CRF may protect from obesity-related morbidity and mortality.

Table 5
Multiple regression model with HOMA-IR (log transformed) as the dependent variable (n = 38)

| Independent variable | Coefficient ± SE | $P$ |
|---|---|---|
| Sex | 0.09 | .57 |
| Age (y) | −0.13 | .33 |
| Fat mass (kg)[a] | −0.11 | .80 |
| Waist circumference (cm)[a] | 0.62 ± 0.13 | <.001 |
| Total physical activity (min/d) | −0.30 ± 0.14 | .044 |
| Sedentary time (min/d) | −0.21 ± 0.15 | .17 |
| $\dot{V}O_2$max (mL · kg$^{-1}$ · min$^{-1}$) | −0.04 | .78 |
| CRP (mg/L)[a] | 0.06 | .72 |
| IL-6 (pg/mL) | −0.16 | .22 |
| Energy intake (kJ/d) | 0.02 | .89 |
| Carbohydrate intake (g/d) | 0.01 | .94 |
| Intercept | −1.16 ± 0.42 | <.001 |

$R^2 = 0.49$; F = 7.779; standard error of estimate = 0.093; $P < .01$.
[a] Values were log transformed.

The mechanisms by which physical activity may improve insulin sensitivity and thereby glucose homeostasis are currently under intensive investigation. Exercise may reduce fasting insulin and improve insulin sensitivity through structural and biochemical changes in skeletal muscles [29]. Briefly, aerobic exercise may increase glucose transporter-4 concentration in skeletal muscle, increase the number of highly oxidative and insulin-sensitive type I fibers, and augment muscle capillarization [29,34]. Exercise may also improve muscle glycogen synthase activity, decrease the amount of muscle lipid content, and enhance fat oxidation [35]. Finally, regular aerobic exercise may induce changes in insulin signaling within the working skeletal muscle [29].

Apart from physical activity, insulin resistance and fasting insulin were associated with total and central adiposity in the present study. It is of note that all 3 indices of body fat distribution (waist circumference, TER ratio, and estimated VAT) presented a moderate to high correlation with fasting insulin and insulin resistance (Table 4). These findings are in agreement with data from the Bogalusa Heart Study showing a relationship among waist circumference, skinfold thickness, and fasting insulin [36]. In other studies that used direct methods for the assessment of abdominal obesity, such as magnetic resonance imaging [37] and computed tomography [38,39], visceral fat was associated with elevated fasting insulin but not insulin resistance. The failure to detect a significant effect of visceral fat on insulin resistance in these studies is in accordance with the hypothesis that visceral fat is relatively lower in children and adolescents compared with adults [40]. This could explain the absence of a significant effect of IL-6 on insulin resistance in the present as well as in previous studies [8]. IL-6, an adipose tissue–derived cytokine, is secreted at a higher rate from visceral than subcutaneous fat [41]. One potential mechanism explaining the link between high visceral fat and elevated fasting insulin is through its effect on hepatic insulin extraction. It is suggested that exposure of the liver to free fatty acids from visceral fat may decrease hepatic insulin clearance and this might result in elevated fasting insulin [42].

CRP, adjusted for age, sex, and fat mass, was not related to either fasting insulin or insulin resistance in the present study and this is in agreement with recent data on 10- to 16-year-old children [43]. In that study [43], CRP was related to fasting insulin, but this association was not significant after adjustment for BMI. These findings are consistent with the hypothesis that obesity may precede the elevation of CRP in the evolution of insulin resistance in youth [43,44].

Obese children were more insulin resistant and presented a poorer lipid-lipoprotein profile and elevated CRP levels than lean counterparts in the present study and this is in agreement with the literature [4,45-49]. These findings suggest that pediatric obesity is associated with dyslipidemia, impaired glucose metabolism, and chronic inflammation. It is of interest, though, that some of these differences disappeared when adjusting for potential confounders, such as age, fat mass, waist circumference, and maximal oxygen uptake. Our results also revealed sex differences in blood lipids, fasting glucose and insulin, estimated $\beta$-cell function, and IL-6, and this is in accordance with the literature [38,50]. These differences could be partially attributed to many potential confounding factors such as maturity, total body fat, body fat distribution, and aerobic fitness. Indeed, when we performed the ANCOVA, almost all sex differences, except for the estimated $\beta$-cell function, disappeared.

Although there is information in the literature on the effect of body fat, age, and sex on insulin sensitivity, limited information exists regarding insulin secretion in children [51]. In the present study, group and sex differences in estimated $\beta$-cell function were found. Sex differences could be due to differences in the maturity level because previous data show that $\beta$-cell function may decrease with increasing Tanner stage [51].

Insulin resistance and $\beta$-cell function were indirectly estimated in the present study and this should be kept in mind when interpreting the data. The youth's maturity level was not evaluated and this might have affected our conclusions. Furthermore, total body fat and body fat distribution were indirectly assessed and this is also a limitation. Future studies should include a larger number of subjects and adopt more sophisticated methods for the assessment of insulin resistance and body composition. Sex differences on the determinants of insulin resistance should also be explored.

In conclusion, the results of the present study suggest that elevated central adiposity and low levels of daily physical activity were the main predictors of insulin resistance in these 9- to 11.5-year-old children. The novelty of this study is that these associations persisted even when including inflammatory markers, which are considered to affect insulin resistance, in the regression model. Programs aiming at improving pediatric obesity complications, such as hyperinsulinemia, should target both at reducing total body and central adiposity as well as at enhancing physical activity. The lack of association between inflammatory markers and HOMA-IR suggests that obesity may precede the elevation of these markers in the evolution of insulin resistance in youth.

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