Interleukin-6 in Obese Children and Adolescents With and Without Glucose Intolerance

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In recent years, the increased prevalence of obesity in industrialized countries has been accompanied by a parallel rise in the incidence of type 2 diabetes, both in adults and children (1–3). Obese children and adults, after a period of time with obesity (4), may develop type 2 diabetes. Glucose intolerance, an intermediate stage in the progression toward type 2 diabetes, may become apparent in obesity (5,6). Insulin resistance in obese children frequently precedes the development of type 2 diabetes, metabolic syndrome, or both (7,8), and type 2 prediabetes has been reported in obese adolescents (9,10). The mechanisms implicated in insulin resistance in obese subjects remain to be fully established. Adipose tissue is the source of a wide variety of molecules involved in the regulation of energy output and carbohydrate metabolism. Among these, proinflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6, in particular, appear to play a role in modulating insulin sensitivity in peripheral tissues and have been associated with the development of insulin resistance in adults (11). Furthermore, glucose induces oxidative stress and increased nuclear factor-κB binding, and it also increases the transcription of nuclear factor-κB–dependent proinflammatory genes (TNF-α and IL-6) (12,13).

Early detection of subjects with obesity-associated metabolic disorders, especially those at risk for glucose intolerance, is considered to be a priority in the public health system, given the significant medical and social repercussions of type 2 diabetes (14). To date, no sensitive accessible parameter has been defined that permits adequate identification of patients with glucose intolerance, although the oral glucose tolerance test (OGTT) is currently used for this purpose (15).

The aims of this work were to ascertain the relationship among the degree of adiposity, circulating fasting insulin levels, and insulin-sensitive indexes with plasma IL-6 in an obese child and adolescent population and to compare cytokine concentrations among obese children and adolescents with or without glucose intolerance to determine whether these parameters could reliably identify obese children with glucose intolerance.

RESEARCH DESIGN AND METHODS

— A total of 105 obese children and adolescents (48 male subjects) aged 8–16 years (12.6 ± 2.0) with BMI >2 SDs were included. All were Caucasian, did not belong to ethnic minority groups, had no chronic diseases, and were not taking long-term medication. BMI values were compared with those of an age- and sex-matched reference population (16). The control population comprised 27 subjects (10 boys) of a similar mean age (12.1 ± 2.1 years). Waist and hip circumferences, blood pressure, plasma levels of IL-6, and lipid fractions (total cholesterol, LDL cholesterol, HDL cholesterol, VLDL cholesterol, lipoprotein A, and apolipoprotein B) were measured, and patients underwent an OGTT (Table 1).

Plasma levels of IL-6

Levels of plasma IL-6 were measured by the highly sensitive quantitative sandwich enzyme immunoassay technique with the Human IL-6 Quantikine HS ELISA kit (R&D Systems) (17). The mean of the minimum detectable concentration was 0.039 pg/ml. Intra- and interassay coefficients of variation were <9.8 and <11.2%, respectively.

Statistical analysis

The Kruskal-Wallis test for independent samples was used to study the differences in medians of the different studied variables among the obese population with a normal response to the OGTT and glucose intolerance. Correlations between two quantitative variables were evaluated by Spearman's correlation analysis. A P value <0.05 was considered statistically significant.

RESULTS

— A total of 91 obese children and adolescents (47 girls and 44 boys) had a normal response to the OGTT, and 14 (4 girls and 10 boys) had a response consistent with glucose intolerance. None had type 2 diabetes criteria. The frequency of glucose intolerance in this cohort of obese children and adolescents was 13.3%.

Circulating plasma levels of IL-6 (in picograms per milliliter) in glucose-intolerant obese patients were statistically and significantly higher (2.7 ± 1.1) compared with normotolerant obese patients (1.9 ± 0.9) and control subjects (1.4 ± 0.6; $P = 0.004$). IL-6 was positively correlated with BMI ($r = 0.33$; $P < 0.001$), waist and hip circumferences ($r = 0.33$ and 0.32, respectively; $P < 0.001$), insulin levels ($r = 0.27$; $P < 0.001$), homeostasis model assessment indexes ($r =$

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Received for publication 10 November 2006 and accepted in revised form 22 March 2007.

Published ahead of print at http://care.diabetesjournals.org on 6 April 2007. DOI: 10.2337/dc06-2289.

Abbreviations: IL, interleukin; OGTT, oral glucose tolerance test; TNF, tumor necrosis factor.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Values for sex, age, pubertal status, BMI, blood pressure, waist and hip circumference, glucose, insulin, insulin resistance indexes, and lipid fractions according to OGTT results*

	Control subjects	Obese subjects with a normal OTGG	Obese subjects with glucose intolerance	*P*
n	27	91	15	
Sex (male/female)	10/17	44/47	4/10	NS
Age (years)	12.6 ± 2.0	12.0 ± 2.1	12.3 ± 1.9	NS
Pubertal stage				
Prepubertal	8	37	1	NS
Pubertal	8	35	11	NS
Young adult	11	19	2	NS
BMI (kg/m^2)	24.3 ± 2.8	30.3 ± 3.9	31.0 ± 3.3	<0.0001
BMI (*Z* score)	1.0 ± 0.6	3.2 ± 1.0	3.2 ± 0.7	<0.0001
Systolic blood pressure (mmHg)	113.5 ± 13	118.5 ± 11	120.5 ± 17	NS
Diastolic blood pressure (mmHg)	67.5 ± 9.9	69.8 ± 9.9	68.0 ± 15	NS
Waist circumference (cm)	78.7 ± 9.2	90.0 ± 11.8	97.0 ± 10.9	<0.0001
Hip circumference (cm)	97.1 ± 8.9	105.5 ± 11.9	112.2 ± 10.4	<0.0001
Waist-to-hip ratio	0.81 ± 0.05	0.85 ± 0.07	0.86 ± 0.06	0.03
Fasting glycemia (mg/dl)	85.0 ± 11.4	81.5 ± 9.4	84.1 ± 9.9	NS
Fasting insulin (mU/l)	15.7 ± 9.8	20.8 ± 11.2	27.4 ± 15.7	0.006
HOMA	3.3 ± 2.2	4.2 ± 2.5	5.9 ± 4.3	0.002
QUICKI	0.331 ± 0.03	0.319 ± 0.02	0.306 ± 0.02	0.03
Triglycerides (mg/dl)	74.2 ± 35.3	93.4 ± 43.6	145.3 ± 122.6	0.006
Cholesterol (mg/dl)	157.4 ± 21.1	158.1 ± 32.0	146.5 ± 18.1	NS
LDL cholesterol (mg/dl)	93.1 ± 21.4	91.2 ± 27.4	81.9 ± 25.3	NS
HDL cholesterol (mg/dl)	49.2 ± 10.7	46.1 ± 8.3	42.4 ± 12.2	0.03
Apolipoprotein B (mg/dl)	69.6 ± 14.5	75.6 ± 19.5	72.3 ± 24.0	NS

Data are mean ± SD or *n*. HOMA, homeostasis model assessment; QUICKI, quantitative insulin sensitivity check index.

0.20; $P < 0.01$), plasma triglycerides ($r = 0.25$; $P < 0.001$), and VLDL cholesterol ($r = 0.37$; $P < 0.001$). A negative bivariate correlation was observed with quantitative insulin sensitivity check index ($r = -0.18$; $P < 0.05$), insulinogenic index ($r = -0.20$; $P < 0.01$), and total ($r = -0.22$; $P < 0.01$), LDL ($r = -0.24$; $P < 0.001$), and HDL ($r = -0.32$; $P < 0.001$) cholesterol.

CONCLUSIONS — Plasma IL-6 levels increased in parallel with obesity and glucose intolerance, showing a positive correlation with fasting insulin and homeostasis model assessment index in a similar way to that observed in adult subjects (11). Although a pathophysiological role cannot be deduced with this study design, the association between circulating IL-6 and several anthropometric and metabolic markers linked to insulin resistance (BMI, waist-to-hip ratio, and triglycerides) points to a participation of this cytokine in childhood insulin resistance, as has been seen in adults. IL-6, a pleiotropic circulating cytokine, is reported to have multiple effects, ranging from inflammation to host defense and tissue injury. It is secreted by many cell types, including immune cells, fibroblasts, endothelial cells, skeletal muscle, and adipose tissue. High IL-6 levels are predictive of type 2 diabetes and myocardial infarction in adults (18); however, to date, little is known on its role in younger subjects.

In conclusion, IL-6 appears to be involved in glucose metabolism, insulin resistance, and dyslipidemia in obese children and adolescents with glucose intolerance. Although the present data suggest that plasma IL-6 values could be used in the identification of glucose intolerance in the obese pediatric population, wider studies should determine whether IL-6 may be an early metabolic marker of metabolic and lipid alterations associated with obesity in children and adolescents.

Acknowledgments— This study was supported by grants from the "Fondo de Investigaciones Sanitarias " (04-0377 and 05-1994) and CIBER CB06/03 ICSIII.

We are grateful to the nurses of our pediatric endocrine functional studies unit, Eulalia Armengol and Milagros Losada for their collaboration in the study, and to Christine O'Hara for her useful English manuscript corrections.

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