Metabolic Syndrome and Insulin Resistance in Normal Glucose Tolerant Brazilian Adolescents With Family History of Type 2 Diabetes

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Metabolic syndrome increases risk for cardiovascular disease (1,2). The diagnosis of metabolic syndrome in patients might hold promise for enhanced prevention of cardiovascular disease. Currently, there is no consensus on the diagnosis of metabolic syndrome in children and adolescents, with variable prevalence of metabolic syndrome from 4.2 to 32% in several populations (3–5). The highest rates of metabolic syndrome were found in adolescents with Latino or African backgrounds (3,6). However, this racial/ethnic predisposition to metabolic syndrome is not well defined. The Brazilian population has a high degree of miscegenation that includes a mix of indigenous people, Afro- and Euro-Brazilians, and a widespread Latin ancestry. We do not know if this genetic and environmental diversity can modify the prevalence of metabolic syndrome or its relationship to obesity. In this study, we determine the prevalence of metabolic syndrome in a group of Brazilian adolescents with a family history of type 2 diabetes.

RESEARCH DESIGN AND METHODS

— Inclusion criteria were age between 10 and 19 years, good health, and family history of type 2 diabetes. The São Paulo Federal University Ethics Committee reviewed and approved the study. Informed consent and assent were obtained from all participants or relatives. BMI cut points for overweight and obesity by sex and age in children were defined as 25 and 30 kg/m^2, respectively, at age 18 years. These criteria were chosen because of the inclusion of Brazilian children and adolescents in the original study (7). The adolescents were stratified into three groups: G_0 (normal), G_1 (overweight), and G_2 (obese) according to the above criteria. Blood pressure was measured on the right arm using a mercury-gravity manometer with proper cuff size. Children whose systolic blood pressure (SBP) or diastolic blood pressure exceeded the 95th percentile for age and sex (8) were considered to have hypertension (high blood pressure). After a 12-h overnight fast, baseline samples were obtained for measurements of plasma glucose, lipids (total, HDL, and LDL cholesterol and triglycerides), and serum insulin. Thereafter, an oral glucose load (1.75 g/kg body wt [up to a maximum of 75 g]) was given, and after 2 h, plasma glucose and serum insulin were measured. Glucose tolerance was classified according to American Diabetes Association criteria (9). Metabolic syndrome was devised as a child-specific definition, by the presence of at least three of the following factors: BMI 97th percentile for age/sex, high blood pressure and hypertriglyceridemia (≥130 mg/dl) (10), low HDL cholesterol (≤35 mg/dl) (10), insulin resistance (defined as homeostasis model assessment [HOMA] of insulin resistance [HOMA-IR] >2.5), impaired glucose tolerance, impaired fasting glucose, or type 2 diabetes (4). Our study was based on a child-specific definition, although we used the cutoff for obesity as the equivalent to a BMI of 30 kg/m^2 at age 18 years (7). HOMA, β-cell function, and insulin sensitivity were calculated by the HOMA Model Program (University of Oxford, Oxford, U.K.). HOMA-IR was calculated as (fasting serum insulin [μU/ml]) × (fasting plasma glucose [mmol · l^{-1} · dl^{-1}])/22.5 (11). Values are expressed as means ± SD, and when not normally distributed, they were ln transformed for analysis (version 1.0, SigmaStat; Systat Software). P values <0.05 were considered statistically significant.

RESULTS

— Characteristics of adolescents are presented in Table 1. There was no significant difference in birth weight, age, sex, height, Tanner stage, and physical activity among the three groups. HOMA-IR, in the whole group (n = 99), was found to be correlated with BMI (r = 0.46, P < 0.001), visceral obesity (waist) (r = 0.52, P < 0.001), SBP (r = 0.29, P < 0.005), triglycerides (r = 0.35, P < 0.005), 2-h plasma glucose (r = 0.28, P < 0.05), and 2-h serum insulin (r = 0.47, P < 0.001) on an oral glucose tolerance test. The 2-h plasma glucose, also in the whole group, was correlated with total cholesterol (r = 0.25, P < 0.05), LDL cholesterol (r = 0.25, P < 0.05), and 2-h serum insulin (r = 0.41, P < 0.005). Forward stepwise regression analysis was conducted to examine the effect of the following variables on HOMA-IR in the whole group: BMI, waist, triglycerides, SBP, 2-h plasma glucose, and 2-h serum insulin. The variables that remained significant were waist (R^2 = 0.275, P < 0.005) and 2-h serum insulin (R^2 =

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Abbreviations: HOMA, homeostasis model assessment; HOMA-IR, HOMA of insulin resistance; SBP, systolic blood pressure.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Characteristics of normal BMI (G_0), overweight (G_1), and obese (G_2) groups*

	G_0	G_1	G_2
n	46	30	23
Age (years)	14.4 ± 2.7	15.7 ± 2.6	14.3 ± 2.7
Sex (% male)	52.0	46.7	43.5
Race (% white)	63.0	63.0	56.5
Weight (kg)*	50.2 ± 12.3	66.5 ± 10.0	81.6 ± 14.4
Height (cm)	158.3 ± 11.4	160.4 ± 10.5	159.3 ± 9.6
BMI (kg/m^2)*	19.7 ± 2.7	25.6 ± 1.7	32.0 ± 4.3
Tanner (median)	5.0	5.0	5.0
SBP (mmHg)†	113.8 ± 11.5	117.5 ± 13.2	130.6 ± 15.3
DBP (mmHg)	74.3 ± 12.5	77.2 ± 9.0	82.8 ± 11.9
Acanthosis nigricans (%)¶	8.7	16.7	65.2
Waist (cm)*	72.7 ± 9.3	88.8 ± 8.9	106.2 ± 8.6
Birth weight (g)	3,121.5 ± 651.3	3,450.0 ± 737.7	3,633.4 ± 992.7
Total cholesterol (mg/dl)	147.1 ± 30.2	157.2 ± 29.6	160.6 ± 35.1
HDL cholesterol (mg/dl)	43.6 ± 6.0	43.3 ± 7.2	41.5 ± 7.0
LDL cholesterol (mg/dl)	88.0 ± 25.8	98.6 ± 24.4	99.2 ± 31.2
Triglycerides (mg/dl)†	76.5 ± 34.0	75.9 ± 26.8	100.0 ± 39.1
Uric acid (mg/dl)‡	4.2 ± 1.0	4.9 ± 1.3	5.4 ± 1.6
Fasting glucose (mg/dl)	79.7 ± 9.7	81.3 ± 9.8	81.1 ± 11.7
2-h blood glucose (mg/dl)	84.6 ± 19.2	91.5 ± 16.8	88.7 ± 15.5
Fasting serum insulin (μU/ml)‡	7.3 ± 3.6	10.0 ± 4.6	13.9 ± 6.7
2-h serum insulin (μU/ml)‡	33.7 ± 26.6	50.1 ± 41.6	70.1 ± 41.1
β-Cell function (%)§	104.2 ± 36.7	158.1 ± 168.0	173.5 ± 89.2
Insulin sensitivity (%)‡	161.2 ± 103.2	101.8 ± 44.8	90.4 ± 77.0
HOMA-IR‡	1.5 ± 0.8	2.0 ± 1.0	2.8 ± 1.5

Data are means ± SD unless otherwise indicated. *$P < 0.05$ for G_0 vs. G_1, G_0 vs. G_2, and G_1 vs. G_2; †$P < 0.05$ for G_2 vs. G_0 and G_2 vs. G_1; ‡$P < 0.05$ for G_0 vs. G_2 and G_0 vs. G_1; §$P < 0.05$ for G_2 vs. G_0. DBP, diastolic blood pressure.

0.365, $P < 0.005$). The same was conducted to 2-h plasma glucose (variables: total cholesterol, LDL cholesterol, and 2-h serum insulin). Variables selected in the mode were LDL cholesterol ($R^2 = 0.172$, $P < 0.05$) and 2-h serum insulin ($R^2 = 0.212$, $P < 0.005$).

The overall prevalence of metabolic syndrome was 6% (95% CI 5.9–6.1). In G_0 and G_1, none of the subjects had metabolic syndrome, while in G_2 the prevalence was 26.1% (8.2–45.6). In the whole group, the characteristics of metabolic syndrome included obesity (23.4%), HOMA-IR ≥2.5 (22.2%), high blood pressure (18.2%), hypertriglyceridemia (8.1%), and low HDL cholesterol (8.1%). In G_0, the highest prevalence was high blood pressure (13%), followed by insulin resistance (10.9%), high triglycerides (6.5%), and low HDL cholesterol (4.3%). In G_1, the more prevalent characteristic was insulin resistance (23%), followed by high blood pressure (10%), high triglycerides (6.7%) and low HDL cholesterol (6.7%). In G_2, where all of the individuals were obese, the prevalence was insulin resistance (43.5%), high blood pressure (39.1%), low HDL cholesterol (17.4%), and high triglycerides (13%).

CONCLUSIONS — We present data on metabolic syndrome in the adolescent population not well described previously, with most of the present literature focusing on the U.S. or Europe. The prevalence of metabolic syndrome was 6% in the whole group, and 24.2% of these adolescents had at least one feature of metabolic syndrome. In the obese adolescents (G_2), the prevalence of metabolic syndrome was 26.1%. Similar metabolic syndrome prevalence has been shown in diverse populations (3–5,12), despite limitations of comparison. Insulin resistance and obesity have been identified as main features of metabolic syndrome in our normal glucose tolerant adolescents. The regression analysis has shown that visceral obesity (waist) and 2-h serum insulin were the main factors for HOMA-IR and LDL cholesterol and 2-h serum insulin for 2-h plasma glucose. HOMA-IR was also correlated with triglycerides, similar to what was found in the Bogalusa Heart Study from a biracial community (13). This last study showed that blood pressure has a positive correlation with fasting insulin (even after adjustment for BMI) at as early as 5 years of age (14). The prevalence of high blood pressure in our adolescents was higher compared with other studies (15).

In summary, we show that the prevalence of metabolic syndrome in a group of normal glucose tolerant Brazilian adolescents with family history of type 2 diabetes is similar to several studies conducted in the U.S. and Europe, although there are differences in the metabolic syndrome characteristics among all groups.

References

1. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahiti K, Nissén M, Taskinen M-R, Groop L: Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 24:683–689, 2001
2. Ford ES, Giles WH, Dietz WH: Prevalence of the metabolic syndrome among US adults: findings from the Third National Health and Nutrition Examination Survey. *JAMA* 287:356–359, 2002
3. Cruz ML, Weigensberg MJ, Huang TT-K, Ball G, Shaibi GQ, Goran MI: The metabolic syndrome in overweight Hispanic youth and the role of insulin sensitivity. *J Clin Endocrinol Metab* 89:108–113, 2004
4. Invitti C, Maffeis C, Gilardini L, Pontiggia B, Mazzilli G, Morabito F, Viberti G: Prevalence of metabolic syndrome in obese children: an analysis using children-specific criteria (Abstract). *Diabetes* 52 (Suppl. 1):A70, 2003
5. Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH: Prevalence of a metabolic syndrome phenotype in adolescents: findings from the Third National Health and Nutrition Examination survey, 1988–1994. *Arch Pediatr Adolesc Med* 157:821–827, 2003
6. Klein DJ, Friedman LA, Harlan WR, Barton BA, Schreiber GB, Cohen RM, Harlan LC, Morrison JA: Obesity and the development of insulin resistance and impaired fasting glucose in black and white adolescent girls: a longitudinal study. *Diabetes Care* 27:378–383, 2004
7. Cole TJ, Bellizi MC, Flegal KM, Dietz WH: Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 320:1–6, 2000
8. Hypertension Brazilian Society, Brazilian Society of Cardiology, Brazilian Society of Nephrology: *IV. Brazilian Guidelines to Arterial Hypertension.* São Paulo, SP, Brazil, 2002

9. Summary of revisions for the 2004 Clinical Practice Recommendations. *Diabetes Care* 27(Suppl. 1):S3, 2004
10. Brazilian Society of Cardiology: *III. Brazilian Guidelines to Dyslipidemia.* São Paulo, SP, Brazil, 2001
11. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
12. Csábi G, Török K, Jeges S, Molnar D: Presence of metabolic cardiovascular syndrome in obese children. *Eur J Pediatr* 159: 91–94, 2000
13. Jiang X, Srinivasan SR, Webber LS, Wattigney WA, Berenson GS: Association of fasting insulin level with serum lipid and lipoprotein levels in children, adolescents, and young adults: the Bogalusa Heart Study. *Arch Intern Med* 155:190–196, 1995
14. Jiang X, Srinivasan SR, Bao W: Association of fasting insulin with blood pressure in young individuals: the Bogalusa Heart Study. *Arch Intern Med* 153:323–328, 1993
15. Oliveira RG, Lamounier JA, Oliveira ADB, Castro MDR, Oliveira JS: Arterial hypertension in children and adolescents: the Belo Horizonte City Study. *J Pediatr (Rio J)* 75:256–266, 1999