C-reactive Protein and Metabolic Syndrome in Youth: A Strong Relationship?

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Objective: Metabolic syndrome (MS) is on the rise in youth. As high-sensitivity C-reactive protein (hs-CRP) is associated with cardiovascular/metabolic disorders, we evaluated the association between MS and its components and hs-CRP in a sample of Brazilian overweight and obese youth.

Methods and Procedures: A total of 407 students (229 girls, 273 with excessive weight, 11.3 ± 3.2 years) were evaluated. Measurement included BMI, waist circumference (WC), blood pressure, lipids, insulin, and hs-CRP. Excessive weight was defined using BMI *z*-score; MS by the modified National Cholesterol Education Program—Adult Treatment Panel III.

Results: Subjects were classified into two groups: with MS ($n = 72$) and without ($n = 335$). hs-CRP means and medians were higher in MS group (1.41 mg/l vs. 1.06 mg/l, $P < 0.001$; 2.21 mg/l vs. 1.23 mg/l, $P < 0.001$). Associations between hs-CRP quartiles and insulin resistance (IR) ($P < 0.001$), MS ($P < 0.001$), WC ($P < 0.000$), BMI *z*-score ($P < 0.001$), hypertension ($P < 0.001$), hypertriglyceridemia ($P < 0.001$), and low HDL-c ($P = 0.023$) were significant; adjustment of hs-CRP for BMI *z*-score eliminated the previous association, except for the number of MS components (nMSc) ($P < 0.001$). Adjusting for homeostasis model assessment method of IR (HOMA-IR) did not eliminate the relation between hs-CRP and MS components. Furthermore, increases in BMI *z*-score and nMSc were associated with an increased hs-CRP. Excessive weight (odds ratio (OR), 7.9; confidence interval (CI), 4.7–13.4; $P = 0.000$), hypertension (OR, 2.3; CI, 1.3–4.2; $P = 0.003$), and hypertriglyceridemia (OR, 2.3; CI, 1.5–3.7; $P < 0.001$) were independently associated with hs-CRP.

Discussion: In youth, hs-CRP is strongly related with MS and its components, and is also determined by the body composition. This association indicates a precocious proinflammatory state.

Obesity (2008) **16,** 1094–1098. doi:10.1038/oby.2008.43

INTRODUCTION

The prevalence of metabolic syndrome (MS), a clustering of cardiovascular risk factors, is on the increase among adults and children (1,2) with the background of obesity (2–4). The strong association between MS and the development of diabetes mellitus, cardiovascular disease (CVD) (5), and a chronic low-grade inflammatory state (6) may explain the linkage between MS and cardiovascular mortality (7).

Elevated high-sensitivity C-reactive protein (hs-CRP) concentration has emerged as an independent predictor of CVD development (5). However, this issue has received limited attention in youth, in spite of the data concerning Native Canadian subjects aged 1–19 years old, in which the relationship between this inflammatory marker and the traditional cardiovascular risk factor was strongly demonstrated (8).

It is already known that atherosclerosis begins early in life (9) and the cardiovascular risk factors in childhood track into adulthood and can predict future CVD (10). Thus, the inclusion of a screening test to evaluate the atherosclerotic inflammatory response in children and adolescents at risk of CVD may reduce cardiovascular morbidity. The aim of this study was to evaluate the association between MS and its components and hs-CRP in a large sample of northeastern Brazilian children and adolescents.

METHODS AND PROCEDURES

Study participants and measurements

The study was conducted in the public and private schools of Feira de Santana, Bahia, Brazil. The sample comprised healthy subjects ranging from 4 to 18 years old, enrolled during the period of 1 year (from May 2004 to June 2005); 407 students (229 girls; 273 with excessive weight; mean age ± s.d., 11.3 ± 3.2 years) were included in the protocol.

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Received 24 May 2007; accepted 6 September 2007; published online 6 March 2008. doi:10.1038/oby.2008.43

The exclusion criteria were smoking, acute illnesses, or any treatment of inflammatory or chronic infectious disease during the previous 3 months.

The students attended the clinic initially to undergo a clinical and anthropometric examination. A standard 2-h oral glucose tolerance test was performed, in accordance with the American Diabetes Association guidelines (11). Blood samples were withdrawn for the fasting measurement of glucose, insulin, high-density lipoprotein cholesterol (HDL-c), triglycerides (TG), uric acid, and hs-CRP and at 120 min, to measure glucose.

Sera were stored at −70 °C until they were analyzed. Plasma glucose, HDL-c, TG, and uric acid concentrations were measured by automated enzymatic photometry; serum insulin levels by radioimmunoassay unit (Linco Laboratories); hs-CRP by fixed time nephelometry (reporting range 0.2–10 mg/l, coefficient of variation <7%) (Dade Behring, Deerfield, IL). The population was classified into two groups: with (group 1) and without (group 2) MS. The local Human Research Ethics Committee reviewed and approved the study and written informed consent/assent was obtained from guardians and children/adolescents.

Definitions

In accordance with the criteria of the National Cholesterol Education Program—Adult Treatment Panel III (12) modified for age, the MS was diagnosed by the concomitant presence of at least three of the following five clinical features: waist circumference (WC) >75th percentile (13); fasting plasma glucose ≥100 mg/dl, or 2-h glucose post challenger between 140 and 199 or ≥200 mg/dl (11); TG >100 and >130 mg/dl for younger than 10 years and between 10 and 19 years, respectively (14); high-density lipoprotein cholesterol <40 and <35 mg/dl for younger than 10 years and between 10 and 19 years, respectively (14); and arterial systolic/diastolic blood pressure (BP) ≥95th percentile by height percentile for age and gender (15).

To compare BMI across different ages and in both boys and girls, BMI *z*-score was calculated and a threshold of ≥1.5 s.d. defined excessive weight. The subjects were then classified as overweight (*z*-score of 1.5–2.0 s.d.) or obese (*z*-score >2.0 s.d.).

The WC was measured using the methodology described by the National Center of Health Statistics (16) and the BP according to the Task Force on Blood Pressure Control in Children (17). The anthropometric measurements were taken in triplicate by a trained team formed by three nursery education students, coordinated by one of the authors, and the mean value was used.

The homeostasis model assessment method of insulin resistance (HOMA-IR) based on serum fasting glucose and insulin levels (product of glucose concentrations (expressed as milligrams per deciliter) and insulin (expressed as microunits per milliliter) divided by a constant (405)) was used as a measure of insulin resistance (IR) (18). The cutoff used was 3.16, as described by Keskin *et al.* (19).

Statistical analysis

Because the distribution of CRP was highly skewed, this variable was natural log-transformed for the analyses. Quartiles of concentration of CRP were computed and the subjects were classified into these quartiles. Differences among quartiles were tested with ANOVA for continuous variables and by the χ^2-test for proportions. A descriptive analysis was performed, continuous variables being expressed as mean values ± s.d., except for CRP where median values were showed. Categorical variables were expressed as frequencies and proportions. The χ^2 or the Fisher's exact tests were used whenever appropriate. Student's *t*-test or the Wilcoxon's rank-sum tests were performed to compare continuous variables between groups with and without the MS. Linear models assuming normal errors (20) were used to summarize log (CRP) among subjects grouped according to the presence of MS. Logistic regression was used to model categorized CRP. SPSS (Statistical Packard for Social Sciences) for Windows statistical software version 10.0 was used for all calculations. A *P* value <0.05 defined statistical significance.

RESULTS

Demographic and metabolic variable

The sample was classified into two groups: 1 ($n = 72$), with MS and 2 ($n = 335$), without this syndrome. Baseline demographic and metabolic variables for these groups are shown in Table 1. The frequency of MS was 17.4% and a WC >75th percentile was found in 100.0%, high TG in 84.7%, low HDL-c in 80.6%, and high BP in 50.0% of youth with MS. No case of diabetes mellitus, impaired glucose tolerance, or impaired fasting glucose was diagnosed. In the whole population, ~29.7% (121) of subjects met only one criterion for MS, 27.0% (110) met two, 14.7% (60) met three, and 3.0% (12) met four. None of the subjects met the five criteria.

As reported in Table 1, there were significant differences between the groups in age ($P = 0.042$) and gender ($P = 0.013$) but not in ethnic group ($P = 0.277$). In addition, all subjects with MS had diagnoses of excessive weight (overweight/obese) and central obesity, determined by high WC. In the group without MS, 60.0% had excessive weight and 58.2% had high WC.

Table 1 Baseline anthropometric, clinical, and metabolic characteristics by metabolic syndrome

Variables	Metabolic syndrome—yes ($n = 72$)	Metabolic syndrome—no ($n = 335$)	*P* value
Age (years)	10.5 ± 3.2	11.4 ± 3.1	0.042*
Gender (boys)	41 (56.9)	137 (40.9)	0.013*
Ethnic group (white)	35 (48.6)	132 (39.4)	0.277
Height (cm)	148.1 ± 18.0	147.2 ± 16.0	0.899
Weight (kg)	63.95 ± 27.0	49.39 ± 19.3	<0.001*
BMI (*z*-score)	2.18 ± 0.4	0.8 ± 1.3	<0.001*
Waist circumference (cm)	91.3 ± 14.4	78.1 ± 15.2	<0.001*
Systolic blood pressure (mm Hg)	118.8 ± 17.5	104.0 ± 15.1	<0.001*
Diastolic blood pressure (mm Hg)	73.4 ± 12.2	65.3 ± 11.8	<0.001*
Fasting plasma glucose (mg/dl)	76.1 ± 10.7	74.8 ± 10.0	0.347
Triglycerides (mg/dl)	159.9 ± 66.2	95.2 ± 56.5	<0.001*
HDL-cholesterol (mg/dl)	32.6 ± 5.4	42.1 ± 8.7	<0.001*
Fasting plasma insulin (μU/ml)	23.1 ± 16.6	15.7 ± 13.6	<0.001*
TG/HDL-c ratio	5.1 ± 2.5	2.3 ± 1.3	<0.001*
Mean HOMA-IR	4.3 ± 3.0	2.9 ± 2.6	<0.001*
CRP (geometric mean) (mg/l)	1.41	1.06	<0.001*
Median CRP (mg/l)	2.21	1.23	<0.001*
MS components (*n*)	3.1 ± 0.3	1.0 ± 0.8	<0.001*

Data are means ± s.e., *n* (%) or geometric means. **P* based on Wilcoxon's rank-sum test for continuous variables and χ^2-test for dichotomous variables. CRP, C-reactive protein; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment method of insulin resistance; MS, metabolic syndrome; TG, triglycerides.

In group 1 (MS), their systolic BP (SBP), diastolic BP (DBP), TG, and fasting insulin were higher and they were more insulin resistant than those in group 2, as expected. A lower level of HDL-c was also observed. There was no significant difference in fasting plasma glucose ($P = 0.347$). The hs-CRP geometric means (1.41 vs. 1.06, $P < 0.001$) and medians (2.21 vs. 1.23, $P < 0.001$) were higher in the MS group.

Selected quartile values of hs-CRP in the whole sample are presented in **Table 2**. There was a tendency toward higher values by analyzing BMI *z*-score, WC, SBP, DBP, TG, TG/HDL-c ratio, fasting insulin, and HOMA-IR as well as the presence or IR, MS, and number of MS components (nMSc).

In the whole sample, using linear regression adjusting for age, gender, and ethnic group, there was a relationship between hs-CRP and WC ($P < 0.001$), SBP ($P < 0.001$), DBP ($P < 0.001$), TG ($P < 0.001$), HDL-c ($P < 0.001$), TG/HDL-c ($P < 0.001$), insulin ($P < 0.001$), HOMA-IR ($P < 0.001$), and nMSc ($P < 0.001$). As expected from data presented earlier, there was a positive and significant association between hs-CRP and all of these variables. After adjustment for age, gender, ethnicity, and BMI *z*-score, the statistical significance of the association between hs-CRP and WC ($P = 0.069$), SBP ($P = 0.459$), DBP ($P = 0.574$), TG ($P = 0.781$), HDL-c ($P = 0.289$), TG/HDL-c ($P = 0.909$), insulin ($P = 0.369$), and HOMA-IR ($P = 0.528$) was weakened or eliminated, however it remained unchanged for the nMSc, as shown in **Figure 1**. Adjustment for HOMA-IR did not abolish the significant association between hs-CRP and WC ($P < 0.001$), SBP ($P = 0.002$), DBP ($P = 0.021$), HDL-c ($P = 0.025$), and nMSc ($P < 0.001$), but did it for TG ($P = 0.104$) and TG/HDL-c ratio ($P = 0.168$).

In a linear regression analysis, adjusted for age, gender, and ethnic group, a progressive BMI *z*-score was associated with an increase in hs-CRP ($P = 0.000$), and the nMSc was also positively associated with an increase in hs-CRP ($P = 0.000$).

In the group with MS, also using linear regression, adjusting for age, gender, and ethnicity, there was a relationship between hs-CRP and WC ($P = 0.004$), BMI *z*-score ($P < 0.001$), HDL-c ($P = 0.055$), and fasting insulin ($P = 0.058$). After adjustment for age, gender, ethnic group, and BMI *z*-score, the relationship between this marker and WC ($P = 0.884$), HDL-c ($P = 0.211$), and fasting insulin ($P = 0.752$) was eliminated; in spite of this, an adjustment for HOMA-IR did not abolish the

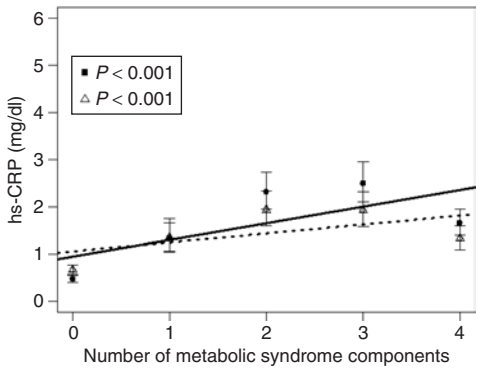

Figure 1 Relationship, in the whole sample, between number of metabolic syndrome components and high-sensitivity C-reactive protein (hs-CRP) adjusted for BMI *z*-score as well as age, sex, and ethnicity. The trend line describing the relationships adjusted for age, sex, and ethnicity is illustrated as the line with rectangles while the one adjusted for BMI *z*-score, age, sex, and ethnicity is shown as the line with triangles. Data are geometric means (95% confidence interval).

Table 2 Association between hs-CRP quartiles and demographic and clinical variables

	Quartiles of hs-CRP (mg/dl)*				
Variables	Q1 ($n = 103$)	Q2 ($n = 101$)	Q3 ($n = 102$)	Q4 ($n = 101$)	*P* value
Age (years)	11.3 ± 3.1	11.0 ± 3.1	11.5 ± 3.0	11.1 ± 3.4	0.752
BMI *z*-score	0.21± 1.36	0.97 ± 1.39	1.54 ± 1.11	1.73 ± 0.95	<0.001*
WC (cm)	70.9 ± 12.9	78.2 ± 15.1	85.0 ± 13.7	87.9 ± 16.0	<0.001*
SBP (mm Hg)	101.2 ± 14.1	104.8 ± 15.7	109.2 ± 16.4	111.2 ± 18.0	<0.001*
DBP (mm Hg)	62.8 ± 10.0	64.8 ± 11.3	68.9 ± 12.4	70.4 ± 13.8	<0.001*
TG (mg/dl)	87.1 ± 45.3	103.4 ± 54.3	123.5 ± 82.7	112.8 ± 59.1	<0.001*
HDL-c (mg/dl)	43.1 ± 9.6	39.4 ± 8.1	40.0 ± 9.8	39.3 ± 7.8	0.006*
TG/HDL-c ratio	2.19 ± 1.55	2.82 ± 1.89	3.37 ± 2.57	2.94 ± 1.47	<0.001*
Fasting glucose (mg/dl)	76.5 ± 10.1	73.8 ± 10.8	76.1 ± 9.7	73.8 ± 9.5	0.098
Fasting insulin (μU/ml)	9.7 ± 8.4	15.4 ± 11.3	21.4 ± 15.7	20.6 ± 17.1	<0.001*
HOMA-IR	1.8 ± 1.5	2.8 ± 2.1	4.1 ± 3.2	3.7 ± 3.0	<0.001*
Insulin resistance, *n* (%)	12 (15.0)	32 (36.0)	48 (49.5)	47 (49.5)	<0.001*
Metabolic syndrome, *n* (%)	7 (6.8)	14 (13.9)	26 (25.5)	24 (23.8)	<0.001*
Number of MS components	0.6 ± 0.9	1.3 ± 1.1	1.6 ± 1.0	1.8 ± 0.9	<0.001*

Data are means ± s.e. for continuous variables and *n* (%) for categorical. **P* based on ANOVA for continuous variables and χ^2-test for dichotomous variables.
DBP, diastolic blood pressure; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment method of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; MS, metabolic syndrome; Q1, first quartile; Q2, median; Q3, third quartile; Q4, fourth quartile; SBP, systolic blood pressure; TG, triglycerides; WC, waist circumference.

relationship between hs-CRP and WC ($P = 0.024$) and BMI z-score ($P = 0.004$). In the same group, an increase in BMI z-score was associated with an increase in hs-CRP ($P < 0.001$).

Using a logistic regression analysis, adjusting for age, gender, and ethnicity, high BMI z-score (odds ratio (OR), 7.9; confidence interval (CI), 4.7–13.4; $P < 0.000$), high BP (OR, 2.3; CI, 1.3–4.2; $P = 0.003$), and high TG (OR, 2.3; CI, 1.5–3.7; $P < 0.001$) were the covariates independently associated with hs-CRP above median.

DISCUSSION

CVD represents a significant cause of mortality, and a better understanding of the linkage between cardiovasucular risk factors and inflammatory markers is necessary to reduce cardiovascular morbidity, especially in youth (21,22). Recent studies provide evidence that inflammation might play a role in the development of CVD (5,23), with some inflammatory cytokines being regarded as markers and risk factors for subclinical atherosclerosis (9,24) and MS (8).

In this study of Brazilian overweight and obese children and adolescents, a group at risk of CVD (25–28), it was demonstrated that factors such as, high WC, high TG, low HDL, and hypertension were very frequent in the MS patients and clearly related to IR. Furthermore, the high cardiovascular risk profile of this population is also demonstrated by a strong association between the presence of MS and increasing hs-CRP levels. It is interesting to note that even in the early stages of life, the presence of MS is linked to a subclinical inflammatory stage.

The high prevalence of MS (17.7%) according to the modified National Cholesterol Education Program—Adult Treatment Panel III (12) is not surprising, as all of the patients were overweight or obese and had high WC. The link between excessive weight, abdominal fat, and the MS has previously been shown (29,30). In the adult population, WC is considered to be the most accurate anthropometric indicator of CVD risk (23). Similar results in this study indicate that this measurement may be a useful tool in children and adolescents as well. The finding of high WC in 100% of the subjects with MS indicated the necessity of this clinical marker being included in the routine pediatric examination.

Data from clinical series support the contention that hs-CRP is associated with total and abdominal adiposity (31,32), IR (5), and MS and its components (33), which has been confirmed in this study, by a clear tendency toward higher values of BMI z-score, WC, SBP, DBP, TG, TG/HDL-c ratio, fasting insulin, HOMA-IR, and nMSc following the increasing levels of this inflammatory marker. Moreover, the majority of MS subjects were in the high quartiles of hs-CRP, even after careful checking for diseases and other factors known to influence CRP concentrations.

The finding of a high OR linking excessive weight and increased hs-CRP levels, and the fact that patients with MS presented the highest CRP levels confirm (i) the hypothesis that the adipose tissue plays a significant role in the inflammatory process and (ii) suggest that a clustering of MS components increases the proinflammatory state associated with a more severe adipose tissue dysfunction.

It is noteworthy that the only MS component not related to hsCRP in this study was fasting glucose. One possible explanation for this finding is that obesity and increase in hs-CRP concentrations precede the disturbance in glucose metabolism, differently from other parameters, such as high BP, which is also a determinant of the low-grade chronic inflammation present in MS (34), and hypertriglyceridemia, which is an early consequence of IR and obesity in children (35). Thus, the relationship between hs-CRP and each MS component appeared to be largely dependent on the body weight and it is strengthened by the nonsignificant association after adjusting for BMI z-score. These findings are very consistent with data in adults, which demonstrated that obesity and body composition with the background of adipocytokines production are a great determinant of CRP levels in both obese and MS subjects (34,36,37).

The crude association between hs-CRP and fasting insulin and HOMA-IR, reflects a relationship between this marker and IR. The continuing significance of WC after adjustment for HOMA-IR suggests once again that abdominal obesity may be the cause, not the consequence of IR in youth and needs early diagnosis through a practical and available tool.

The strong relationship between BMI and hs-CRP in the whole sample and in the group with MS is incontestable especially within the higher degrees of obesity. The BMI was the best predictor of hs-CRP above median even though hypertriglyceridemia was also related to this inflammatory marker. Moreover, the association between high BP and high levels of hs-CRP may reflect endothelial dysfunction. Taken together, these findings indicate that MS is involved in the precocious development of the atherogenic process in the young.

In conclusion, we have demonstrated that in overweight and obese children and adolescents, in whom there is no confounding effect of other factors known to influence CRP concentrations, IR and MS are strongly associated with increased inflammation even in the early stages of life. Body composition plays a role in mediating these effects and probably represents a marker of dysfunctional adipose tissue, and is of central importance in clinical diagnosis. However IR does not appear to be a precocious determining factor for increased hs-CRP levels. These findings suggest that, in groups at risk, measurement of hs-CRP may be useful on a large scale and in clinical practice for recognition of early stages of CVD in order to predict cardiovascular events and improve outcomes.

ACKNOWLEDGMENTS

We thank the children, parents, teachers, and school authorities from Feira de Santana, Bahia, Brazil, for their cooperation. This study was supported by the Research Foundation of Bahia (FAPESB), Bahia, Brazil. This article is part of A.C.O.'s M.Sc. Thesis of the Bahian School of Medicine and Public Health Post Graduate Course.

DISCLOSURE

The authors declared no conflict of interest.

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