0021-7557/07/83-05/477
Jornal de Pediatria

C-reactive protein as an indicator of low intensity inflammation in children and adolescents with and without obesity

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Abstract

Objectives: To determine the levels of high sensitivity C-reactive protein (hsCRP) in children/adolescents with and without obesity and their correlation with body mass index (BMI) and clinical and laboratory variables.

Methods: A cross-sectional study comparing two parallel groups, one a group of overweight or obese children/adolescents (obesity group, n = 131) and the other a control group of children/adolescents without obesity (control group, n = 114). High sensitivity nephelometry was used to determine hsCRP concentrations.

Results: The obesity group exhibited greater hsCRP concentrations than the control group ($p < 0.0005$). There were relationships between hsCRP and BMI ($p < 0.0001$) and hsCRP and triglycerides ($p = 0.05$). The relationship between hsCRP and triglycerides was attenuated by adjustment for BMI, losing its statistical significance ($p = 0.10$).

Conclusions: The hsCRP concentrations increased as BMI increased. The majority of individuals who were not overweight exhibited hsCRP concentrations of less than 2 mg/L.

J Pediatr (Rio J). 2007;83(5):477-480: Obesity, overweight, inflammation, C-reactive protein.

Introduction

The association between obesity, cardiovascular disease and diabetes has been demonstrated in several different studies, although without defining its causality. Recent research has identified that the inflammatory reaction is a factor common to these diseases.[1,2] Adipose tissues secrete substances (tumor necrosis factor-α interleukin-6, adiponectin, resistin) that affect the vascular endothelium and glucose and lipid metabolism.[3,4]

C-reactive protein (CRP) is produced in the liver in response to stimulus by inflammatory cytokines. Since 1970 CRP assays have been used to diagnose inflammatory and infectious states.[5] Recently, epidemiological studies have found evidence that discrete elevations in CRP concentrations, even when within the normal reference range, may predict the appearance of cardiovascular diseases[6,7] and diabetes.[8]

Since 1999, when Visser et al.[9] published the first paper relating obesity with CRP, a great deal of research has been undertaken in order to elucidate the association. There is speculation whether, in the adult population, the increase in CRP is a consequence or if it is directly involved in the pathophysiology of chronic diseases. Since the prevalence of degenerative diseases is low in childhood, research into the markers of inflammation in this age group is of great value to understanding these questions.

In this study we assayed CRP concentrations in children and adolescents with and without obesity and investigated its

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Dade Behring supplied the kit for ultrasensitive PCR.

Suggested citation: Brasil AR, Norton RC, Rossetti MB, Leão E, Mendes RP. C-reactive protein as an indicator of low intensity inflammation in children and adolescents with and without obesity. J Pediatr (Rio J). 2007;83(5):477-480.

Manuscript received Dec 13 2006, accepted for publication May 30 2007.

doi 10.2223/JPED.1690

correlation with body mass index (BMI). The CRP concentrations of overweight and obese children and adolescents were also related to clinical and laboratory variables frequently associated with cardiovascular diseases and diabetes.

Methods

This was a comparative cross-sectional study of parallel groups; one a group of children/adolescents with overweight or obesity (obesity group) and a control group of children/adolescents who were not obese (control group). The sample was calculated for a level of confidence of 95% and statistical power of 80%, resulting in 224 patients in order to contemplate sample size estimation (112 per group). The obesity group comprised 131 children/adolescents referred for assessment for overweight (BMI = weight/height^2 – between the 85th and 95th percentiles) or obesity (BMI over the 95th percentile - NCHS-2000 reference values) during 2004 (January to December) who took a high sensitivity CRP test (hsCRP). The control group was made up of 114 children/adolescents with BMI below the 85th percentile, who had blood taken at the Central Laboratory of the HC-UFMG or volunteers.

The study was carried out at the Nutritional Diseases Clinic at the Hospital das Clínicas at the Universidade Federal de Minas Gerais (HC-UFMG) and was approved by the council of the Pediatrics Department at the Medical Faculty of the UFMG and by the Research Ethics Committee at the UFMG. The parents/guardians and children/adolescents were informed of the importance of the research, its objectives and the guarantee of anonymity by means of an informed consent form.

Children/adolescents were excluded from the study if the had with cardiac, renal, rheumatic, neurological, respiratory, infectious, endocrinal or metabolic diseases, if they had secondary obesity or were using anti-inflammatories (steroidal or non-steroidal) or estatins. Patients were also excluded if their hsCRP concentration was over 10 mg/L, since this level is suggestive of active inflammation or infection.

Patients in the obesity group were seen by a pediatrician who took their history and anthropometric data and performed a physical examination and puberty stage assessment. Patients at sexual maturity stage 1 were defined as prepubescent and those above Tanner stage 2 were classified as pubescent.

Tests were carried out by the Central Laboratory at the HC-UFMG. For the obesity group, tests were performed to assay patients' total cholesterol and fractions (esterase oxidase, Johnson Vitros 750 XRC), triglycerides (Roche Cobas Mira/Mira Plus), fasting glycemia (oxidase, Johnson Vitros 750 XRC), fasting insulinemia (chemiluminescence), thyroid stimulating hormone (Quimioluminescence-DPC) and hsCRP. The hsCRP assays were carried out by nephelometry, with a Dade Behring kit that detects levels above 0.16 mg/L. Undetectable levels were defined as being 0.15 mg/L. Samples for the tests were taken after 12 hours' fasting.

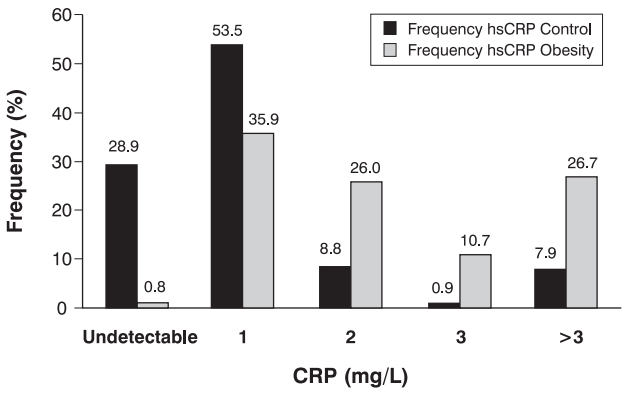

Figure 1 - Distribution of hsCRP concentrations for control and obesity groups

Members of the control group only underwent the hsCRP test, with no need for fasting.

Since hsCRP and insulin results did not exhibit normal distribution, they were log-transformed for comparison of means.

Data were analyzed using Epi-Info and Minitab. Categorical variables were subjected to the chi-square test, means were compared with Student's *t* test, and correlations between variables were analyzed with Pearson's coefficient and simple linear regression.

Results

The age range of the study sample was from 2.3 to 19 years. The mean BMI percentile was 93.2±4.5 in the obesity group, and 39.0±24.9 in the control group ($p < 0.0005$). There was not difference of statistical significance between the obesity group and the control group in terms of sex (48.9 and 57.9% males) or mean age (10.3±3.5 and 10.21±4.0 years). The obesity group had significantly higher concentrations of hsCRP (1.43±2.74 mg/L) than the control group (0.42±2.83 mg/L).

In the control group 33 (28.9%) individuals had hsCRP levels below the detectable limit (< 0.16 mg/L), and 104 (91.2%) had concentrations of less than 2 mg/L. Just one (0.8%) child in the obesity group had an undetectable hsCRP level, and 82 (62.7%) were below 2 mg/L (Figure 1).

Neither of the groups exhibited differences in mean hsCRP concentrations between sexes (males: 0.80 mg/L; females: 0.81 mg/L; $p = 0.92$). In the obesity group there were no differences in mean hsCRP concentrations related to puberty stage (prepubescent 1.82 mg/L; pubescent 1.40 mg/L; $p = 0.14$).

Table 1 - Clinical characteristics of the patients in the obesity group

	n	mean	Normal* n (%)	Abnormal n (%)
Total cholesterol	108	161±26 mg/dL	99 (91.7%)	9 (8.3%)
LDL	107	99±24 mg/dL	94 (87.9%)	13 (12.1%)
HDL	107	41±12 mg/dL	71 (66.4%)	36 (33.6%)
Triglycerides	109	107±52 mg/dL	73 (67.0%)	36 (33.0%)
Fasting glycemia	105	79±6.5 mg/dL	105 (100.0%)	0
Fasting insulinemia	106	9.3±1.9 µUI/mL	103 (97.2%)	3 (2.8%)
Diastolic pressure	116	65±10 mmHg	104 (89.7%)	12 (10.3%)
Systolic pressure	116	110±17 mmHg	95 (81.9%)	21 (18.1%)

*Normal values[10]: total cholesterol < 200 mg/dL; LDL < 130 mg/dL; HDL ≥ 40 mg/dL in the under-10s and ≥ 35 mg/dL in over-10s; triglycerides < 100 mg/dL in the under-10s and < 130 in over-10s. Glycemia < 110 mg/dL, insulinemia ≤ 27 µUI/mL. Arterial blood pressure: values ≤ 90th percentile for age and sex[11].

The patients in the obesity group exhibited abnormalities in terms of metabolism and arterial blood pressure, as shown in Table 1.

There was a relationship between hsCRP and BMI ($r = 0.29$, $p < 0.0001$) and between hsCRP and triglycerides concentration ($r = 0.18$, $p < 0.05$), but not with the other variables. After adjustment for BMI, the relationship between hsCRP and triglycerides was attenuated, losing its statistical significance ($p = 0.10$).

Discussion

In this study, comparing a group of overweight children/adolescents with a group without overweight, hsCRP concentrations were higher in the group with overweight or obesity. The majority of individuals in the control group had hsCRP concentrations lower than 2 mg/L. The hsCRP values increased in line with BMI, as has been demonstrated in several studies.

In 2000, Cook et al.[12] carried out research with children (9-11 years old) to evaluate CRP concentrations and their relationship with adiposity and cardiovascular risk factors. There was a robust relationship between CRP concentration and ponderal index. There was also a strong relationship between CRP and fibrinogen and inverse relationships with HDL and heart rate. Other cardiovascular risk factors (cholesterol, triglycerides, glucose, insulin, arterial pressure) were not related to CRP or were attenuated after adjustment for adiposity.

In 2001, Visser et al.[13] assessed CRP concentration in 3,512 children/adolescents (8-16 years) who had taken part in the Third National Health and Nutrition Examination Survey (NHANES III) (1988-1994). They observed a greater prevalence of elevated CRP results (> 2.2 mg/L) among overweight or obese children/adolescents, when compared with those whose BMI was below the 85th percentile. Among those children/adolescents whose BMI was above the 85th percentile, 20.6% of the males and 18.7% of the females exhibited elevated CRP values.

In 2001, Ford et al.[14] published their analysis of the data from NHANES III (1988-1994), on 5,305 individuals aged 6 to 18 years, finding that 90% of them had CRP concentrations < 2.1 mg/L. The percentage of participants with CRP > 2.1 mg/L increased to the extent that the BMI increased. There were no associations with age, sex, race or puberty stage.

In addition to inflammation, the overweight children/adolescents in this study also exhibited arterial hypertension, elevated triglyceride levels, reduced HDL levels and hyperinsulinemia; as was also demonstrated in another Brazilian study.[15] The hsCRP levels did not exhibit any statistical relationship with these risk factors, in common with the results of a study by Weiss et al.[16]

In a study comparing 100 obese children with 50 not obese children, Iannuzzi et al.[17] demonstrated that, compared to the control group, the obese children had higher levels of arterial pressure, triglycerides, glycemia, insulinemia, insulin resistance and CRP (4.5±2.4 and 3.5±0.3 mg/L; $p < 0.001$).

Other research into the pediatric population also detected associations between CRP and cardiovascular risk factors, but this relationship was attenuated after adjustment by adiposity indices. Research with adults has demonstrated associations between CRP and high triglyceride, LDL and insulin concentrations, low HDL concentrations and arterial hypertension.

The inflammation may be an initial factor responsible for the comorbidity associated with obesity. Large quantities of inflammatory cytokines, released by the adipose tissue,

stimulate production of CRP in the liver and may be associated with the development of cardiovascular diseases and diabetes by means of a variety of mechanisms: altered sensitivity to insulin, increased liberation of adhesion molecules by endothelium, increase in hepatic production of fibrinogen and platelet coagulation factor.

It is even more important to prevent childhood obesity, since this unfavorable metabolic/inflammatory state can persist year after year, resulting in serious consequences in adulthood. Early treatment of overweight individuals can reduce the incidence of comorbidities in adulthood. Further research is needed in order to demonstrate the association of inflammatory markers and cardiovascular risk factors related to obesity during childhood and adolescence. It is also necessary to establish a safe cutoff point for CRP concentration in for the prediction of complications.

Acknowledgments

We are grateful to the pathologists at the Central Laboratory, Hospital das Clínicas/Universidade Federal de Minas Gerais, carrying out the hsCRP assays.

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