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C-reactive protein and cardiometabolic risk factors in overweight or obese children and adolescents[1]

Proteína C-reativa e fatores de risco cardiometabólicos em crianças e adolescentes sobrepeso ou obesidade

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ABSTRACT

Objective

To investigate the relationship between ultrasensitive C-reactive protein and cardiometabolic risk factors in overweight or obese childrenand adolescents.

Methods

Cross-sectional study conducted at the Center for Childhood Obesity in the period from April 2009 to April 2010, involving 185 overweight children and adolescents aged 2 to 18 years. Measures of ultrasensitive C-reactive protein according to age, nutritional status, gender, race, cardiometabolic risk factors (waist circumference, lipid profile, impaired fasting glucose, high blood pressure and presence of insulin resistance) were compared through the Chi-square test and analysis of variance. All analyses were performed using the Statistical Package for the Social Sciences software version 17.0, adopting a significance level of 5%.

[1] Article based on the master's thesis of AS CARDOSO intitled "*Proteína C-reativa e fatores de risco cardiometabólicos em crianças e adolescentes com excesso de peso*". Universidade Estadual da Paraíba; 2012.

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Results

Altered high-density lipoprotein was the most frequent cardiometabolic risk factor, and there was a significant association between altered ultrasensitive C-reactive protein values and severe obesity (p=0.005), high waist circumference (p<0.001), hypertriglyceridemia (p=0.037) and insulin resistance (p=0.002), as well as significantly higher body mass index (p=0.000), waist circumference (p=0.001), insulin (p=0.005) and index of glucose homeostasis values(p=0.005).

Conclusion

High prevalence of altered ultrasensitive C-reactive protein and significant association with severe obesity, waist circumference, hypertriglyceridemia and insulin resistance were observed.

Indexing terms: C-reactive protein. Cardiovascular diseases. Obesity. Risk factors.

R E S U M O

Objetivo

Verificar a relação existente entre a proteína C-reativa ultrassensível e fatores de risco cardiometabólicos em crianças e adolescentes com sobrepeso e obesidade.

Métodos

Estudo transversal realizado no Centro de Obesidade Infantil, no período de abril/2009 a abril/2010, envolvendo 185 crianças e adolescentes entre 2 e 18 anos com excesso de peso. Foram comparadas as medidas de proteína C-reativa ultrassensível de acordo com a faixa etária, estado nutricional, sexo, raça, fatores de risco cardiometabólicos (circunferência abdominal, perfil lipídico, glicemia de jejum alterada, pressão arterial elevada e presença de resistência insulínica) através do teste do Qui-quadrado e da análise de variância. Todas as análises foram realizadas com a versão 17.0 do programa Statistical Package for the Social Sciences*, adotando-se o nível de significância de 5%.*

Resultados

A lipoproteína de alta densidade alterada foi o fator de risco cardiometabólico mais frequente; houve uma associação significativa entre os valores da proteína C-reativa ultrassensível alterada e obesidade acentuada (p=0,005), circunferência abdominal elevada (p<0,001), hipertrigliceridemia (p=0,037) e resistência insulínica (p=0,002), bem como com valores significativamente mais elevados do índice de massa corporal (p=0,000), circunferência abdominal (p=0,001), insulina (p=0,005) e Modelo de Avaliação da Homeostase (p=0,005).

Conclusão

Observou-se uma alta prevalência da proteína C-reativa ultrassensível alterada e uma associação significativa com obesidade acentuada, circunferência abdominal elevada, hipertrigliceridemia e resistência insulínica.

Termos de indexação: *Proteína C-reativa. Doenças cardiovasculares. Obesidade. Fatores de risco.*

I N T R O D U C T I O N

The changing epidemiological, demographic and nutritional profile characterized by reduced incidence of infectious or communicable diseases followed by increased incidence of non-communicable chronic diseases among children and adolescents has set new challenges in the fields of health care, research, and management of resources related to health in this age group[1].

The increased consumption of highly caloric foods and decreased physical activities have contributed to the increased prevalence of obesity and overweight in the population, especially in children and adolescents, causing the emergence of ever earlier complications, such as systemic hypertension, Type-2 Diabetes *Mellitus*, dyslipidemia, obstructive sleep apnea and some cancers[2,3]. Due to its negative effects on cardiovascular structure and function, obesity also has a major impact on Cardiovascular Diseases (CVD) such as atherosclerosis[4].

Once considered mere deposit of fat, the adipose tissue is now seen as an active endocrine

and paracrine organ producer of several inflammatory cytokines. In the last two decades, the remarkable development in the field of vascular biology has clarified that atherosclerotic lesions are indeed a series of highly specific and dynamic cellular and molecular responses mainly inflammatory in nature[5].

The importance of recognizing obesity as an inflammatory state is due to the possibility of inflammation being one of the links between obesity, insulin resistance, high blood pressure (hypertension) and cardiovascular disease[6].

The C-Reactive Protein (CRP) is a non-glycosylated polymer composed of five identical subunits. It is produced by the liver in order to combat invading antigens. Its synthesis by the liver is triggered by the release of some types of cytokines by inflammatory cells, particularly Interleukin-6[7].

The relationship of CRP to plasma lipoproteins has been known for over 60 years, but the first suggestion of a possible association with atherosclerosis came with the observation that the protein selectively binds to Low Density Lipoprotein (LDL)[7]. Since then, several studies have demonstrated the relationship between CRP levels and morbidity and mortality associated with CVD[8].

It has been speculated that CRP may have significant pro- inflammatory effects and, upon binding to molecules exposed on the cells (resulting from infection, inflammation, ischemia, and other disorders) and triggering the activation of the complement, it may exacerbate tissue damage[9]. Elevated CRP levels may reflect increased formation of atherosclerotic plaques, higher tendency to plaque rupture and thrombosis[3].

Based on the strong correlation between anthropometric parameters, lipid profile, CRP and cardiovascular risk widely described in the adult population, this study aims to assess the relationship between CRP and cardiometabolic risk factors in overweight children and adolescents.

METHODS

This is a cross-sectional study conducted at the Center for Childhood Obesity (COI) from April 2009 to April 2010. The COI is the reference service in obesity of *Campina Grande* (PB) with a multidisciplinary team composed of endocrinologists, nutritionists, psychologists, nurses, pharmacists, social worker and physical trainer and treatsoverweight children and adolescents referred by Basic Health Units.

This study was approved by the research ethics committee of the *Universidade Estadual da Paraíba* (UEPB) through CAAE 0040.0.133.000-08 on August 30, 2008, and all participants signed the Free and Informed Consent Form prior to their inclusion in the sample.

The sample size was calculated considering the juvenile population of the city of *Campina Grande* (PB) of 65,890 children and adolescents aged from 2 to 18 years registered in December 2008 in the *Sistema de Informação de Atenção Básica* (SIAB, Primary Care Information System). The study also considered prevalence of overweight and obesity of 25%[10] and metabolic syndrome of 42% in Brazilian children and adolescents with this condition[11], for a total of 200 children and adolescents after addition of 20% of eventual losses. Of these, two were excluded due to the use of corticosteroids and two were considered as loss for not attending blood collection. For purposes of statistical analysis, 11 were excluded for showing CRP equal or greater than 10 mg/dL, and the final sample was composed of 185 children and adolescents.

A questionnaire including socioeconomic personal and family history issues was applied and anthropometric measurements and laboratory tests were performed.

Anthropometric data (weight, height and waist circumference) were recorded in duplicate, using the mean value of the two measurements. Weight was measuredusing a platform-type Welmy® digital scale with capacity of 150 kg and precision of 0.1 kg. Height was measured using a

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Tonelli® stadiometer to the nearest 0.1 cm and Waist Circumference (WC) was measured with inelastic Cardiomed® measure tape with precision of 0.1 cm at the midpoint between the top edge of the iliac crest and the last costal margin. During the measurement, the individual should be wearing light clothing and procedures recommended by World Health Organization[10] were followed.

For classification of the nutritional status, Body Mass Index (BMI) was calculated as recommendations of the Centers of Disease Control and Prevention, and the following categories were used: overweight (85 ≤BMI <95) and obesity (≥95th percentile)[11].

Blood pressure was measured three times with rest intervals of approximately two minutes according to method established in the "VI Brazilian Guidelines on Blood Hypertension"[12], with Tycos® mercury sphygmomanometer using cuffs of appropriate sizes. The average of the last two systolic and diastolic pressure measurements was considered.

Blood collection was performed after a 12-hour fasting period at the Clinical Laboratory of the UEPB. Total Cholesterol (TC), High Density Lipoprotein-cholesterol (HDL-c), Triglycerides (TG) and blood glucose were assessed by the enzymatic colorimetric method in automatic equipment (Model BioSystems® 310), according to recommendations of the Labtest® kit manufacturer. To calculate LDL-c, the Friedewald's formula was used: LDL-c= TC-HDL-c-TG/5, which is valid for TG levels lower than 400 mg/dL. Values adopted in the "I Guideline for Prevention of Atherosclerosis in Childhood and Adolescence" were considered as reference[13].

Insulin and us-CRP values were determined by chemiluminescence on an outsourced laboratory with quality seal, the latter being measured in Immulite 1000 automated equipment (Siemens®). Us-CRP values (dependent variable) greater than 3 mg/L were considered high, and those with us-CRP values greater than or equal to 10 mg/L were excluded for suggesting acute infectious or inflammatory process[14].

As a criterion for the diagnosis of insulin resistance, the Homeostatic Model Assessment - Insulin Resistance (HOMA-IR) index described by Matthews *et al*.[15] and validated by several authors for epidemiological studies was used, which is the product of fasting insulin (μUI/mL) and fasting glucose (mmol/L) divided by 22.5[16,17]. As cutoff, HOMA-IR ≥2.5 was used[18].

The following cardiometabolic risk factors were considered: WC ≥90th percentile, with maximum limit of 88 cm for girls and 102 cm for boys[19]; Systolic and/or diastolic blood pressure ≥90th percentile; TC ≥170 mg/dL , LDL-c ≥130 mg/dL, TG ≥130 mg/dL and HDL-c <45 mg/dL; fasting glucose ≥100 mg/dL; HOMA-IR ≥2.5.

The sample was described by absolute and relative frequency of variables. The evaluation of the association between CRP with socio-demographic variables (gender, race, maternal education, age group) and cardiometabolic risk factors was performed using the Chi-square test. The comparison of the average CRP according to the presence of cardiometabolic risk factors was assessed by analysis of variance. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) software version 17.0 and significance level of 5% was adopted.

RESULTS

Of the 185 children and adolescents that composed the sample, most were female (67.6%), belonged to the adolescent age group (62.6%) and had income equal to or less than 2 minimum wages (59.4%). Regarding nutritional status, prevalence of severe obesity (65.4%) was observed.

It was found that low HDL was the most common cardiometabolic risk factor (81.6%), followed by high WC (79.5%). Regarding systemic blood pressure, Diastolic Blood Pressure (DBP) showed higher levels compared with Systolic

Table 1. C-reactive protein in overweight children and adolescents according to socio-demographic, anthropometric and metabolic variables. Centre for Childhood Obesity, *Instituto Saúde Elpídeo de Almeida*, *Campina Grande* (PB), Brazil, 2008-2010.

Variables	CRP				*p*
	High		Normal		
	n	%	n	%	
Gender					0.784
Male	18	30.0	42	70.0	
Female	40	32.0	85	68.0	
Age group					0.388
Childhood (2-9 years)	19	27.5	50	72.5	
Adolescence (10-18 years)	39	33.6	77	66.4	
Nutritional status					**0.005**
Obesity	55	35.5	100	64.5	
Overweight	3	10.0	27	90.0	
Income					0.869
≤2 MW	31	30.7	70	69.3	
>2 MW	22	31.9	47	68.1	
WC					<0.001*
High	56	38.1	91	61.9	
Normal	2	5.3	36	94.7	
SBP					0.099
SBP ≥P90	27	38.6	43	61.4	
SBP <P90	31	27.0	84	73.0	
DBP					0.919
DBP ≥P90	37	31.1	82	68.9	
DBP <P90	21	38.1	45	68.2	
TG					**0.037**
High	29	40.3	43	59.7	
Normal	29	25.7	84	74.3	
HDL-c					0.277
Reduced	50	33.1	101	66.9	
Normal	8	23.5	26	76.5	
LDL-c					0.571
High	10	35.7	18	64.3	
Normal	47	30.3	108	69.7	
TC					0.659
High	22	29.3	53	70.7	
Normal	35	32.4	73	67.6	
Blood glucose					1.00*
High	1	33.3	2	66.7	
Normal	57	31.3	125	68.7	
Insulin resistance					**0.002**
Present	34	43.6	44	56.4	
Absent	23	21.9	82	78.1	

Note: *p Fischer. The highlighted numbers represent the associations between the variables (p<0.05).

CRP: C-Reactive Protein; MW: Minimum Wages; WC: Waist Circumference; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; TG: Triglycerides; HDL-C: High Density Lipoprotein-Cholesterol; LDL-C: Low Density Lipoprotein-Cholesterol; TC: Total Cholesterol.

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Blood Pressure (SBP) (64.3, 37.8%, respectively). Insulin resistance was diagnosed in 42.6% of overweight children and adolescents. Furthermore, over half of them already had 3 or more cardiometabolic risk factors.

CRP was greater than 3 mg/L in 31.4% of children and adolescents. There was a significant association between high CRP values and obesity (p=0.005), elevated WC (p<0.001), high triglyceride levels (p=0.037) and insulin resistance (p=0.002) (Table 1).

In the analysis of variance to compare the means of anthropometric and metabolic variables, significantly higher BMI (p<0.001), WC (p=0.001), TG (p=0.008), SBP (p=0.009), insulin (p=0.005), HOMA-IR values (p=0.005) and lower HDL values(p=0.008) were observed in those with elevated CRP levels (Table 2).

DISCUSSION

In the present study, a high frequency of altered CRP was observed. Norton *et al.*[20] in a study with 131 obese or overweight children and adolescents showed similar results (26.7%) of us-CRP >3 mg/dL.

Although no significant association of CRP with gender and age was observed, there was a higher prevalence of high CRP among females and adolescents,which corroborateda study conducted with 164 adolescents in two schools in England that showed no significant differences in the CRP concentrations among boys and girls[21].

Prevalence of severe obesity among children and adolescents was observed,since the health service in which this study was conducted is reference for the population of overweight children and adolescents.

Low High Density Lipoprotein-cholesterol was the most frequent cardiometabolic risk factor. Other authors[3,22] also found that low HDL values, regardless of nutritional status, questioned whether the cutoff would be ideal for this population or such outcomes would already be indicative of a serious public health problem.

The relationship of CRP with other cardiometabolic risk factors showed a significant association between elevated CRP values and

Table 2. Mean values and standard deviation of CRP according to clinical variables and cardiometabolic risk factors in 185 overweight children and adolescents. Centre for Childhood Obesity, *Instituto Saúde Elpídeo de Almeida*, Campina Grande (PB), Brazil. 2008-2010.

Variables	CRP				*p*
	High		Normal		
	Mean	SD	Mean	SD	
Age (years)	11.48	3.48	11.09	3.78	0.508
WC (cm)	90.48	12.71	83.61	12.24	0.001
BMI (kg/m²)	29.38	4.85	26.25	4.02	<0.001
TG (mg/dL)	149.88	78.69	121.53	60.27	0.008
SBP(mmHg)	111.04	11.02	106.24	11.73	0.009
DBP (mmHg)	72.94	9.39	72.02	9.80	0.551
Blood glucose (mg/dL)	82.10	8.27	80.85	7.42	0.306
Insulin (mg/dL)	14.88	9.53	11.14	7.69	0.005
HOMA-IR	3.04	1.98	2.26	1.58	0.005
TC	163.49	39.76	164.06	35.70	0.923
LDL-c	97.22	30.45	100.40	29.81	0.505
HDL-c	35.83	7.41	39.30	8.52	0.008

Note: CRP: C-Reactive Protein; WC: Waist Circumference; BMI: Body Mass Index; TG: Triglycerides; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HOMA-IR: Index of Glucose Homeostasis; TC: Total Cholesterol; LDL-C: Low Density Lipoprotein-Cholesterol; HDL-C: High Density Lipoprotein-Cholesterol; SD: Standard Deviation.

severe obesity, WC, insulin resistance and hypertriglyceridemia.

In the Cardiovascular Health Study, CRP was also positively correlated with BMI, indicating that, although there is no single cut off for CRP, children and adolescents included in the study showed a subclinical inflammation process associated with obesity[23].

Obesity is a potent risk factor for metabolic and cardiovascular disease at population level. At individual level; however, the correlation between BMI and cardiovascular disease is not always simple due in part to differences in the fatty tissue deposits, overall rate of adipocyte dysfunction, tissue vascularity, and local level of inflammation[21].

Abdominal adipose tissue verified by high WC has been considered a predictor of elevated us-CRP concentrations due to significant expression of this protein in the deposits of abdominal, visceral and subcutaneous fat. Although the relationship between CRP and various cardiometabolic risk factors is well documented in adults but not in adolescents, Denney-Wilson *et al.*[24] recently reported that obesity and elevated WC levels in adolescents were associated with CRP.

The understanding of the relationship between inflammation process and the pathophysiology of insulin resistance in the context of cardiometabolic risk factors is based on the abdominal adipose tissue, proven in animal models submitted to surgical removal of the omentum, which showed the remission of all risk factors. The importance of removing the omentum to improve the metabolic profile was also observed in humans according to the best results found in patients with level 3 obesity undergoing gastroplasty associated with the removal of the greater omentum compared to those who underwent only gastroplasty[21].

In this sense, other studies with children and adolescents found that the accumulation of abdominal fat and hyperinsulinemia are associated with a thrombogenic and inflammatory profile. Cameron *et al.*[25] used data from three cohorts and showed that the abdominal waist circumference can predict the outbreak of four to five other cardiometabolic risk factors, indicating that visceral obesity plays a central role in the development of the metabolic syndrome and seems to precede the onset of other risk factors such as elevated CRP.

Studies have suggested the occurrence of increased cardiovascular risk from obesity (identified by either BMI or waist circumference), followed by subclinical inflammation (defined by CRP), dyslipidemia, and insulin resistance. A case-control study with children and adolescents found that obese individuals with IR have 10 times higher CRP levels than control subjects[3].

A study conducted with 209 Chilean children reported that CRP is able to predict the presence of a greater number of cardiometabolic components that lead to faster development of atherosclerosis in adulthood[26].

Children and adolescents in this study had an overall mean CRP of 2.6 mg/dL. In the analysis of variance, it was observed that the mean BMI, WC, insulin and HOMA values were significantly higher in those with altered CRP.

The significantly higher BMI values (severe obesity) during childhood and adolescence and increased inflammation can promote the activation of mechanisms related to the onset of the atherosclerotic process[26]. Serrano *et al.*[27] also found higher mean insulin and HOMA values among overweight adolescents, although no significant correlation with any of the variables (weight, height, BMI, body fat percentage, waist circumference, hip circumference and waist-hip ratio) was found.

It was observed that in addition to the mean BMI, WC and HOMA values, triglycerides also arise as a factor associated with high CRP concentrations.

The increase in the amount of adipose tissue is directly related to hypertriglyceridemia and hypercholesterolemia. Some studies have

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indicated that excess weight is the risk factor most strongly associated with dyslipidemia and this is due to multiple metabolic causes: insulin resistance, hyperinsulinemia, hyperglycemia, increased protein transferring cholesterol esters secreted by adipocytes, among others[28].

The relationship between triglyceride concentrations and CRP was also observed by Simões[29]. According to the author, this association suggests that an unfavorable lipid profile leads to increased inflammatory activity.

Although it is well established that overweight prospectively leads to chronic inflammation, it is also plausible that inflammation may precede overweight.

Thus, one limitation of this study is its cross-sectional nature, in which there is no way to determine the direction of the association between inflammatory markers and overweight; moreover, it is important to observe that among the studies conducted in Brazil, the amount of longitudinal designs with children and adolescents is still reduced.

It is known that the concept of "sum of cardiometabolic components" is more important from the predictive point of view than the absolute definition "presence-absence" of the metabolic syndrome[30].

Few studies have shown a precise relationship between obesity and inflammatory markers, especially in the age range evaluated here. Therefore, this study aims at detecting factors associated with cardiometabolic alterations, allowing early identification and intervention and the consequent reduction in morbidity and mortality rates for cardiovascular and metabolic diseases.

CONCLUSION

A high frequency of high us-CRP and a significant association with severe obesity, elevated WC, hypertriglyceridemia and insulin resistance were observed. Considering these findings and demonstratingthat CVD may have their origin in childhood and adolescence, us-CRP levels should be used in screening for the assessment of cardiometabolic risks, thereby contributing to early and possibly more effective intervention on these factors, reducing morbidity and mortalityin the near future.

CONTRIBUTORS

AS CARDOSO participation in project design, data analysis and final review of the manuscript. RO OLIVEIRA formatting and final review of the manuscript. DF CARVALHO final review of the manuscript. N COLLET final review of the manuscript. CCM MEDEIROS participation in project design, data analysis and final review of the manuscript.

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