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C-reactive protein and its relation to high blood pressure in overweight or obese children and adolescents

Proteína C-reativa e sua relação com pressão arterial elevada em crianças e adolescentes com sobrepeso ou obesidade

Proteína C-reactiva y su relación con la presión arterial elevada en niños y adolescentes con sobrepeso u obesidad

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ABSTRACT

Objective: To investigate the association between C-reactive protein (CRP) and high blood pressure (BP) in overweight or obese children and adolescents.

Methods: Cross-sectional study with 184 overweight or obese children and adolescents aged from two to 18 years old, from April, 2009 to April, 2010. The classification of nutritional status used the body mass index (BMI). Based on the Centers for Disease Control and Prevention curve, individuals were classified as: overweight (BMI between the 85th–95th percentiles), obesity (BMI between 95th–97th percentiles) and severe obesity (BMI >97th percentile). Abnormal values were considered for systolic BP (SBP) and/or diastolic (DBP) if ≥90th percentile of the BP curve recommended for children and adolescents in the V Brazilian Guidelines on Hypertension, for waist circumference (WC) if ≥90th percentile of the curve established by the National Cholesterol Education Program, and for high sensitive CRP (hs-CRP) if >3mg/dL. To evaluate the association of inadequate values of CRP and the studied groups, chi-square test and analysis of variance were applied, using the Statistical Package for the Social Sciences version 17.0 and adopting a significance level of 5%.

Results: Among the evaluated sample, 66.3% were female, 63.5%, non-white, 64.1% had severe obesity, 78.3% had altered WC and 70.6% presented high BP. There was a significant association of CRP high levels with altered WC and BMI ≥97th percentile. In adolescents, high CRP was related to high SBP. CRP mean values were higher in individuals with elevated SBP.

Conclusions: Inadequate values of hs-CRP were associated with severe obesity and high SBP in the studied population. These markers can be used to identify children and adolescents at higher risk for developing atherosclerosis.

Key-words: arterial pressure; C-reactive protein; obesity; cardiovascular diseases; child; adolescent.

RESUMO

Objetivo: Verificar a associação entre proteína C-reativa (PCR) e pressão arterial (PA) elevada em crianças e adolescentes com sobrepeso ou obesidade.

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Métodos: Estudo transversal, realizado de abril de 2009 a abril de 2010, com 184 crianças e adolescentes de dois a 18 anos, obesos ou com sobrepeso. Realizou-se a classificação do estado nutricional por meio do índice da massa corpórea (IMC). Adotou-se a curva do *Centers for Disease Control and Prevention*, classificando-se os indivíduos em: sobrepeso (IMC entre percentil 85–95), obesidade (IMC entre percentil 95–97) e obesidade grave (IMC>percentil 97). Consideraram-se alterados os valores de PA sistólica (PAS) e/ou diastótica (PAD) ≥percentil 90, conforme curva de classificação da PA para crianças e adolescentes nas V Diretrizes Brasileiras de Hipertensão Arterial, circunferência abdominal (CA) ≥percentil 90 de acordo com a curva do *National Cholesterol Education Program*, e PCR ultrassensível (PCR-us) >3mg/dL. Para avaliar a associação de valores inadequados de PCR entre os grupos, utilizaram-se o teste do qui-quadrado e análise de variância. As análises foram realizadas na versão 17.0 do programa *Statistical Package for the Social Sciences*, adotando-se nível de significância de 5%.

Resultados: Dos avaliados, 66,3% eram do sexo feminino, 63,5%, não brancos, 64,1% tinham obesidade grave, 78,3% apresentavam CA alterada e 70,6%, PA elevada. Verificou-se associação significante dos níveis aumentados de PCR com CA alterada e IMC ≥percentil 97. Nos adolescentes, a PCR aumentada associou-se à PAS elevada. Os valores médios da PCR foram superiores nos indivíduos que apresentaram PAS elevada.

Conclusões: Valores inadequados da PCR-us associaram-se à obesidade grave e à PAS elevada na população estudada. Tais marcadores podem ser utilizados para identificar crianças e adolescentes com maior risco de desenvolver aterosclerose.

Palavras-chave: pressão arterial; proteína C-reativa; obesidade; doenças cardiovasculares; criança; adolescente.

RESUMEN

Objetivo: Verificar la asociación entre proteína C-reactiva (PCR) y presión arterial (PA) elevada en niños y adolescentes con sobrepeso u obesidad.

Métodos: Estudio transversal, realizado de abril de 2009 a abril de 2010, con 184 niños y adolescentes de 2 a 18 años, obesos o con sobrepeso, atendidos en el Centro de Obesidad Infantil. Se realizó la clasificación del estado nutricional por medio del índice de masa corporal (IMC). Se adoptó la curva del *Centers for Disease Control and Prevention*, clasificándose a los individuos en: sobrepeso (IMC entre percentil 85–95), obesidad (IMC entre percentil 95–97) y obesidad grave (IMC >percentil 97). Se consideraron alterados los valores de PA sistólica (PAS) y/o diastólica (PAD) ≥percentil 90 - conforme curva de clasificación de la PA para niños y adolescentes recomendada en las V Directrices Brasileñas de Hipertensión Arterial, circunferencia abdominal (CA) ≥percentil 90 - conforme a la curva establecida por el *National Cholesterol Education Program*, y PCR ultrasensible (PCR-us) >3mg/dL. Para evaluar la asociación de valores inadecuados de PCR entre los grupos, se utilizaron la prueba del chi-cuadrado y análisis de variancia. Los análisis fueron realizados en la versión 17.0 del programa *Statistical Package for the Social Sciences*, adoptándose nivel de significancia de 5%.

Resultados: De los evaluados, el 66,3% eran del sexo femenino, el 63,5% no blancos, el 64,1% tenían obesidad grave, el 78,3% presentaban CA alterada y el 70,6%, PA elevada. Se verificó la asociación significante de los niveles aumentados de PCR con CA alterada e IMC ≥percentil 97. En los adolescentes, la PCR aumentada se asoció a la PAS elevada. Los valores medianos de la PCR fueron superiores en los individuos que presentaron PAS elevada.

Conclusiones: Valores inadecuados de PCR-us se asociaron a la obesidad grave y a la PAS elevada en la población estudiada. Es posible utilizar esos marcadores para identificar a niños y adolescentes con mayor riesgo de desarrollar aterosclerosis.

Palabras clave: presión arterial; proteína C-reactiva; obesidad; enfermedades cardiovasculares; niño; adolescente.

Introduction

Obesity is closely associated with cardiovascular diseases, since excess body fat may predispose the individual to multiple comorbidities, such as hypertension and dyslipidemia[1,2]. Scientific evidence indicates that obesity is associated with a subclinical inflammatory process, as the adipose tissue secretes substances such as tumor necrosis factor-alpha (TNFα), interleukin 6 (IL-6), adiponectin, and resistin, acting on the vascular endothelium and metabolism of glucose and lipids, contributing to the pathophysiology of cardiovascular diseases[3,4].

The concentration of the C-reactive protein (CRP) has a direct relationship with the severity of obesity in childhood, being used as an inflammatory marker of accelerated progression of atherosclerosis[5]. The determination of ultra-sensitive CRP (us-CRP) is a relatively moderate predictor of cardiovascular events and hypertension, as it is associated with changes in fibrinolysis and components of the metabolic syndrome (MS), such as systemic arterial hypertension (SAH)[6-8].

Few studies have evaluated the relationship between inflammatory biomarker levels (us-CRP) and high blood pressure (BP) in children and adolescents[6]. High BP is considered an independent predictor of increased CRP levels, leading to the hypothesis that arterial hypertension in adults leads to atherosclerosis, partly due to chronic inflammatory diseases[9]. Moreover, there is an association between family history of hypertension with HBP in children and those with hypertension or prehypertension have higher levels of subclinical inflammation, measured by CRP[10].

Due to the impact caused by high BP on health in a population and the observed association between CRP and hypertension — besides the limited understanding of this connection in childhood, especially in individuals who are overweight —, this study aimed to verify the relationship between the inflammatory biomarker (Us-CRP) and high BP in overweight children and adolescents from 2 to 18 years, treated at a Child Obesity Center.

Method

This was a cross-sectional study, with a quantitative approach, performed between April 2009 and April 2010, as part of a larger study entitled "Prevalence of cardiometabolic risk factors among obese or overweight children and adolescents" (*Prevalência de fatores de risco cardiometabólicos entre crianças e adolescentes obesos ou com sobrepeso)*, approved by the Research Ethics Committee of Universidade Estadual da Paraíba, under n. 0040.0.133.000-08. The study was developed at the Child Obesity Center (COC), at Instituto de Saúde Elpídio de Almeida (ISEA), in the municipality of Campina Grande, state of Paraíba, specifically to meet the demands of this research. The Child Obesity Center is formed by researchers and a multidisciplinary team, composed of endocrinologists, nutritionists, psychologists, nurses, pharmacists, social workers, and physical instructor.

The sample was selected by convenience sampling and included children and adolescents from 2 to 18 years old who were overweight or obese. However, to verify the representativeness of the number, the ideal sample size was calculated with StatCalc with Epi-Info. Therefore, there was initially a population between 2 and 19 years registered in the Primary Care Information System (PCIS) in 2008, which amounted to 65,980[11]. The prevalence of overweight and obesity was of 25%[12] and of systemic arterial hypertension (SAH), 37.5%[13]. For 5% error, the sample size would result in 160 individuals. However, the study included a higher number, due to greater recruitment of subjects for the study.

Children and adolescents were recruited by the advertising of the research in the Basic Health Units in the municipality, performed by the Department of Health. Individuals who presented the inclusion criteria for the study were invited to participate and referred to the COC. In this period, 200 children and adolescents attended the Child Obesity Center, and those presenting one of the following complications were excluded: chronic disease, such as secondary hypertension, type 1 diabetes, inflammatory process, alcoholism, smoking, or using medications that interfered in lipid or glucose metabolism. Two individuals were excluded by the use of steroids and 14 by presenting values of us-CRP higher than 10mg/dL; then, a total of 184 individuals were analyzed. After explanation of the goals, methods and procedures to be followed, parents or guardians who agreed to participate in the study signed an informed consent form.

Initially, a form was administered with clinical (gender and age) and anthropometric (weight, height, body mass index – BMI, and waist circumference) variables, then BP was measured by previously trained students, and laboratory tests were scheduled to determine the concentrations of Us-CRP.

Anthropometric variables weight and height were collected in duplicate, based of the standardized criteria recommended by the World Health Organization (WHO). It was considered the mean of the two measures. To obtain weight, a Welmy digital scale (platform type) was used with a capacity of 150kg and accuracy of 0.1kg, children were barefoot, wearing light clothes and positioned in the center of the scale platform. Height was measured by stadiometer (Toneli), accurate to 0.1cm, with children barefoot, in upright position, arms at the sides, feet together, knees straight, head held in the Frankfurt plane, after deep inspiration[14]. Waist circumference was measured by an inelastic tape with accuracy of 0.5cm, at the midpoint between the top edge of the iliac crest and the last coastal rib, with the patient in upright position, unclothed, with arms positioned along the body and in the expiration phase of breathing[15]. Values above the 90th percentile were considered increased, but with a maximum limit of 88cm for girls and 102cm for boys, as recommended by the curve adopted by the National Cholesterol Education Program (NCEP)[16].

For the classification of nutritional status, BMI was calculated and, as recommended by the curve adopted by the Centers for Disease Control and Prevention (CDC)[17], individuals were classified into the following categories: overweight (BMI between percentile 85 and 95), obesity (BMI between percentile 95 and 97) and severe obesity (BMI ≥percentile 97).

BP was measured three times, with rest intervals of about 2 minutes, according to the method established in the V Brazilian Guidelines of Arterial Hypertension[18], with a mercury sphygmomanometer (Tycos), using appropriate cuff sizes. The mean of the last two measurements was considered as systolic and diastolic blood pressure. Since BP was measured only once, and according to the recommendation of the V Brazilian Guidelines of Arterial Hypertension[18] — to confirm the diagnosis of systemic arterial hypertension it is necessary to repeat the measurement of BP after 2 weeks in asymptomatic individuals —, we chose to adopt the nomenclature "high BP". Values of SBP or DBP for sex, age, and stature, were considered normal when <90th percentile, borderline between the 90th and 95th percentile, and high ≥95th percentile, according to the classification curve of BP for children and adolescents adopted at the V Brazilian Guidelines of Hypertension[18], and re-categorized as normal BP, when <90th percentile, and abnormal, if ≥90th percentile for sex, age and height, for purposes of statistical analysis.

The us-CRP was assessed by chemiluminescence with automatic IMMULITE 1000 (SIEMENS®). The individuals who presented values of CRP ≥10mg/dL were excluded, once, in these cases, it is recommended to repeat the exam[6,18]. Values of CRP ≤3mg/L (low risk for cardiovascular events) and CRP >3mg/L (high risk for cardiovascular events) were considered as cutoff values[6].

Data were presented by means of proportion, mean, and standard-deviation (SD). The association between BP and the groups (age range, sex, and nutritional status) was verified by the Persons' chi-square test or Fisher's exact test, as appropriate. For the comparison of means, the one-way ANOVA was used. All analyses were performed with the Statistical Package for the Social Sciences version 17.0 (SPSS Inc., Chicago, EUA). Significance was established at $p<0.05$.

Results

The present study analyzed 184 children and adolescents; 66.3% were female, 63.5% non-white, 64.1% had severe obesity and 78.3% had abnormal waist circumference (WC). Abnormal BP was present in 70.6% of the sample. There was no association of high BP, SBP and DBP with sex, age range, us-CRP, BMI and WC (Table 1).

Table 2 shows that abnormal CRP was associated with high WC ($p<0.001$) and severe obesity (BMI≥97) ($p=0.005$). The chance of having increased CRP levels

Table 1 - Distribution of abnormal blood pressure by gender, age range, nutritional status, waist circumference and C-reactive protein in children and adolescents with excess weight at the Child Obesity Center, Campina Grande, Paraíba, 2009–2010

	BP≥p90 n (%)	*p*-value	SBP≥p90 n (%)	*p*-value	DBP≥p90 n (%)	Total	*p*-value
Sex							0.243
Male	45 (72.6)	0.682	22 (35.5)	0.687	44 (71.0)	62	
Female	85 (69.7)		47 (38.5)		76 (62.3)	122	
Age range							0.395
Adolescent	82 (70.7)	0.988	48 (41.4)	0.156	73 (62.9)	116	
Childhood	48 (70.6)		21 (30.9)		47 (69.1)	68	
Nutritional status							0.104
BMI≥97th percentile	89 (75.4)	0.057	48 (40.7)	0.234	82 (69.5)	118	
BMI<97th percentile	41 (62.1)		21 (31.8)		38 (57.6)	66	
WC							0.683
>90th percentile	104 (72.)	0.375	59 (41.0)	0.065	95 (66.0)	133	
≤90th percentile	26 (65.0)		10 (25.0)		25 (62.5)	51	
CRP							0.966
>3mg/L	43 (71.7)	0.833	27 (45.0)	0.144	39 (65.0)	60	
≤3mg/L	87 (70.2)		42(33.9)		81 (65.3)	124	
Total	130 (70.6)		69 (37.5)		120 (65.2)	184	

CRP: C-reactive protein; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; WC: waist circumference

Table 2 - Distribution of CRP by gender, age, nutritional status and waist circunference in overweight or obese children and adolescents, Child Obesity Center, Campina Grande, Paraíba, 2009–2010

	CRP >3mg/L n (%)	CRP ≤3mg/L n (%)	*p*-value	Total	PR (95%CI)
Sex					
Male	42 (67.7%)	20 (32.3%)	0.942	62	–
Female	82 (67.2%)	40 (32.8%)		122	
Age range					
Adolescence	76 (65.5%)	40 (34.5%)	0.479	116	–
Childhood	48 (70.6%)	20 (29.4%)		68	
Nutritional status					
BMI ≥97th percentile	47 (39.8%)	71 (60.2%)	0.005	118	2.70 (1.33–5.49)
BMI <97th percentile	13 (19.7%)	53 (80.3%)		66	
WC					
>90th percentile	57 (39.6%)	87 (60.4%)	< 0.001	133	8.08 (2.38–27.45)
≤90th percentile	3 (7.5%)	37 (92.5%)		51	

CRP: C-reactive protein; PR: prevalence ratio; 95%CI: 95% confidence interval; BMI: body mass index; WC: waist circumference

Table 3 - Distribution of mean values and standard deviation of C-reactive protein according to normal, borderline, or high SBP and DBP in children and adolescents with excess weight, Child Obesity Center, Campina Grande, Paraíba, 2009–2010

		CRP		
		n	Mean (SD)	*p*-value
BP	Normal	54	2.84 (2.07)	0.193
	Borderline	72	2.32 (2.05)	
	High	58	3.02 (2.71)	
SBP	Normal	115	2.45 (2.04)	0.013
	Borderline	39	2.54 (2.12)	
	High	30	3.81 (3.05)	
DBP	Normal	64	2.96 (2.18)	0.489
	Borderline	76	2.50 (2.41)	
	High	44	2.64 (2.25)	

CRP: C-reactive protein; SD: standard deviation; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure

was higher in the groups with high WC (Prevalence Ratio PR=8.08) and severe obesity (PR=2.70). The mean values of CRP were higher in the individuals who presented high SBP (p=0.013), a fact that was not observed in relation to DBP (Table 3). There was a significant association between increased CRP levels and high SBP (p=0.031) only in adolescents. Bivariate analysis between the outcomes high BP, SBP, and DBP and the studied factors was not statistically significant. Stratification by age group showed an association (p=0.013), indicating that adolescents with high CRP have twice the chance of presenting abnormal SBP than those with normal CRP [PR=2.35 (95%CI 1.07–5.14)] (Table 4).

Discussion

The importance of recognizing obesity as an inflammatory state is because of the possibility that inflammation may be one of the links among obesity and insulin resistance, hypertension, and cardiovascular disease[19].

In this study a high prevalence of high BP in overweight and obese children and adolescents was found. This is worrying, since the early risk for cardiovascular diseases may be enhanced at younger ages simply by the presence of excess body weight[20]. As obesity in childhood and adolescence predisposes to obesity in adult life, the high prevalence of high BP found in this research, in all age groups, represents an alert for the health conditions of these individuals[21].

The high BP was more prevalent in males, adolescents, and severely obese individuals, supporting the study performed by Costanzi *et al*[22] with 1,413 children between 7 and 12 years old, students of public and private schools. In this study, there was a prevalence of high BP of 13.8%, being twice this value in those with obesity or overweight. In a study conducted in the state of Paraíba with 674 adolescents in public and private schools, the prevalence of high BP was of 7.4%, being higher in boys (10.2%) than in girls[23].

The risk of BP reaching high values varies according to the duration and intensity of obesity. One cannot say that the high BP increased with advanced age — since there was no longitudinal follow-up of patients, but it was more frequent in the older age group, i.e., in adolescence. It is also possible that the time period in which these individuals were exposed to excess adipose tissue may have contributed to the elevation in blood pressure values[24].

Table 4 - Bivariate analysis of normal and high blood pressure according to age range and C-reactive protein in children and adolescents with excess weight treated at the Child Obesity Center, Campina Grande, Paraíba, Brazil, 2009–2010

CRP	BP		*p*-value	SBP		*p*-value	DBP		*p*-value
	≥90th percentile	<90th percentile		≥90th percentile	<90th percentile		≥90th percentile	<90th percentile	
Adolescence									
>3mg/L	30 (75.0%)	10 (25.0%)	0.459	22 (55.0%)	18 (45.0%)	0.031	26 (65.0%)	14 (35.0%)	0.738
≤3mg/L	52 (68.4%)	24 (31.6%)		26 (34.2%)	50 (65.8%)		47 (61.8%)	29 (38.2%)	
Childhood									
>3mg/L	13 (65.0%)	7 (35.0%)	0.514	5 (25.0%)	15 (75.0%)	0.498	13 (65.0%)	7 (35.0%)	0.635
≤3mg/L	35 (72.9%)	13 (27.1%)		16 (33.3%)	32 (66.7%)		34 (70.8%)	14 (29.2%)	

CRP: C-reactive protein; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure

In this study, there was no association between high BP and nutritional status or WC, as well as in a study conducted with Chilean children, in which no direct association was found between children with high blood pressure and the degree of obesity[10].

The measure of WC in adults is accepted as an important tool to assess the risk of diseases, especially atherosclerosis. In childhood and adolescence, however, the lack of long-term prospective studies does not allow the mere extrapolation of this knowledge. Furthermore, as this measure presents variation due to physical growth, it results in different cutoff points for each age range[25].

Higher levels of us-CRP were found among individuals who were obese and in the preschool and school age ranges. The values of CRP rose as BMI increased, with severe obese having a prevalence of high CRP three times higher. The levels of high CRP were more frequent in individuals with high WC. Many studies performed with children and adolescents suggest that the concentration of us-CRP is strongly related to the ponderal index[26].

Junqueira, Romêo Filho and Junqueira[27] state that high levels of CRP are associated with the accumulation of visceral adipose tissue and metabolic syndrome components. These data suggest a possible role of the visceral adipose tissue in the pathogenesis of arteriosclerosis. Therefore, obesity, metabolic syndrome, and arteriosclerosis are closely related and can de determinants of a vascular inflammation increased response.

Because of the easy measurement of serum concentration, the low cost, and better clinical-epidemiological correlation when compared to other inflammatory markers such as IL-6 and TNFα, the CRP is of particular interest, given the possibility of elucidating new pathways for prevention and treatment of diseases of high prevalence, morbidity, and mortality[28]. Studies have shown that individuals with normal levels of us-CRP and BP have higher survival free from cardiovascular events compared to those with high levels[28]. These findings suggest that inflammation and hypertension may act together to promote atherosclerosis[9].

Studies from the National Health and Nutrition Examination Survey (NHANES) found that adiposity was the best predictor of high levels of us-CRP[29]. Thus, among those who were overweight, the higher the concentration of us-CRP, the greater the number of metabolic anomalies found[30]. When analyzing SBP as a continuous variable, it was independently associated with the levels of us-CRP in girls from 12 to 17 years old. In the present study, there was association of abnormal SBP values and us-CRP in adolescence, and the CRP had a significantly higher mean value in those who presented high SAH.

Clinical and anatomopathological studies suggest that atherosclerosis can develop in adolescents, being more prevalent in those with high BP[6]. Such findings, together with the role of chronic inflammation in the pathogenesis of atherosclerosis, have led researchers to study the relationship between high us-CRP, levels of BP, and other cardiovascular risk factors in children and adolescents. The measurement of us-CRP only in children and adolescents with excess weight and the cross-sectional design are limitations of this study; therefore, causality was unclear, which indicates that further studies with a longitudinal design are needed to better understand this relationship. A better understanding of the determinants of systemic inflammation at early ages may have important implications for primary prevention of many diseases related to chronic inflammation[3].

Another limitation of the study was the measurement of BP in a single visit, which cannot be used to characterize arterial hypertension. This measure should be used as a risk indicator of hypertension for cross-sectional comparisons in epidemiological studies conducted with children and adolescents. The literature shows that the prevalence of high blood pressure can vary depending on the population

studied, the cutoffs adopted (desirable or normal values), as well as educational, cultural, and genetic variables. These findings refer to a limitation of this study, which lies in the fact that the different criteria adopted, as well as the different populations studied hinder comparisons. However, it is important to highlight that no studies were found in the literature involving children and adolescents with excess weight that have included the number of cases and the wide age range that was analyzed in the present work.

Thus, the present study demonstrated a high prevalence of abnormal BP in children and adolescents who are overweight or obese, and a significant association of us-CRP with severe obesity, increased waist circumference, and SBP, so these markers can be used to identify children and adolescents with higher risk for development of atherosclerosis.

The prevention of obesity from an early age can prevent the metabolic/inflammatory unfavorable condition from remaining over the years, causing serious consequences in adulthood. Early treatment of children and adolescents with excess weight can decrease the incidence of comorbidities in adulthood. Further research is needed to demonstrate the association of inflammatory markers and comorbidities related to obesity in childhood and adolescence, which is currently one of the major public health problems.

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