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C-reactive protein important biomarker of cardiometabolic risk in childhood obesity

Proteína C reactiva importante biomarcador de riesgo cardiometabólico en la obesidad infantil

Proteína C reativa importante biomarcador de risco cardiometabólico na obesidade infanto-juvenil

ABSTRACT
To establish the importance of evaluating ultrasensitive C-reactive protein (hs-CRP) as a biomarker in an obese pediatric group, detecting possible cardiometabolic complications early. This is a case-control study involving 342 children and adolescents, from the Preventive Medicine Service, Aracaju-Sergipe, Brazil. 235 obese and 107 controls participated in the study. The CR-P-us showed a mean value of 2.36 ± 1.28 mg / dL in the obese group and 0.01 ± 0.1 mg / dL in the control group. There was a significant correlation between the increase in hs-CRP in the obese group and biochemical and anthropometric findings such as: reduced HDL, elevated triglycerides and with the highest indicators of body mass index and abdominal circumference. Homocysteine proved to be a poorly specific biomarker in this study. Therefore, ultrasensitive C-reactive protein has been shown to be a biomarker of cardiometabolic risk, presenting high sensitivity in our pediatric population with obesity.
DESCRIPTORS: C-Reactive Protein; Obesity; Pediatrics.

RESUMEN
Establecer la importancia de evaluar la proteína C reactiva ultrasensible (hs-PCR) como biomarcador en un grupo pediátrico obeso, detectando precozmente posibles complicaciones cardiometabólicas. Se trata de un estudio de casos y controles que involucró a 342 niños y adolescentes, del Servicio de Medicina Preventiva, Aracaju-Sergipe, Brasil. 235 obesos y 107 controles participaron en el estudio. El CRP-us mostró un valor medio de 2,36 ± 1,28 mg / dL en el grupo de obesos y 0,01 ± 0,1 mg / dL en el grupo control. Hubo una correlación significativa entre el aumento de hs-PCR en el grupo de obesos y hallazgos bioquímicos y antropométricos como: HDL reducido, triglicéridos elevados y con los mayores indicadores de índice de masa corporal y circunferencia abdominal. La homocisteína demostró ser un biomarcador poco específico en este estudio. Por tanto, la proteína C reactiva ultrasensible ha demostrado ser un biomarcador de riesgo cardiometabólico, presentando una alta sensibilidad en nuestra población pediátrica con obesidad.
DESCRIPTORES: Proteína C-Reactiva; Obesidad; Pediatría.

RESUMO
Estabelecer a importância da avaliação da proteína C reativa ultrassensível (PCR-us) como biomarcador em um grupo pediátrico obeso, detectando precocemente possíveis complicações cardiometabólicas. Trata-se de estudo caso-controle envolvendo 342 crianças e adolescentes, do Serviço de Medicina Preventiva, Aracaju-Sergipe, Brasil. Participaram do estudo 235 obesos e 107 controles. A PCR-us apresentou valor médio de 2,36 ± 1,28 mg/dL no grupo obeso e 0,01 ± 0,1 mg/dL no grupo controle. Observou-se correlação significativa do aumento de PCR-us no grupo obeso com achados bioquímicos e antropométricos como: redução do HDL, elevação de triglicérides e com os maiores indicadores de índice de massa corporal e da circunferência abdominal. A homocisteína demonstrou ser um biomarcador pouco especifico neste estudo. Portanto, a proteína C reativa ultrassensível demonstrou ser um biomarcador de risco cardiometabólico, apresentando alta sensibilidade em nossa população pediátrica com obesidade.
DESCRITORES: Proteína C-Reativa; Obesidade; Pediatria.

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INTRODUCTION

Childhood obesity is considered a worldwide growth epidemic, due to the strong environmental, behavioral and genetic influence, which contribute to the accumulation of fat and therefore, in body composition. [1,2] This marked increase in obesity in this period may be responsible for the early onset of cardiometabolic disorders. [2]

The global trend regarding the increase in the body mass index (BMI) demonstrated in the infantile phase a global increase of this indicator per decade of 0,32 kg/m² in girls and 0,40 kg/m² in boys. This resulted in an increase in childhood obesity from 0,7% to 5,6% and from 0,9% to 7,8% for women and men respectively during this period. [3] However, there is a stabilization of the growth of childhood obesity in developed countries and its maintenance in developing countries. [4,5] In Brazil, the Family Budget Survey (POF - Pesquisa de Orçamentos Familiares), in partnership with the Ministry of Health (MH), showed that 33,5% of children aged 5-9 years were overweight and among them 16,6% of boys and girls 11,8% of the girls were obese; in the 10-19 year age group, overweight was 21,7% in males and 19,4% in females, with the southeastern region corresponding to the area with the highest presentation of child overweight. [6,7]

Obesity is considered a complex and multifactorial chronic disease, resulting from a long period of positive energy balance, in which genetic and environmental factors are involved, as well as the association of a low-grade inflammatory process.[8,9] Currently, there is evidence that the adipose tissue not only serves as an energy reservoir, but also acts as an active endocrine organ, which acts in different ways in the organic systems, contributing to the inflammatory process in obese individuals. The abnormal values of metabolites such as lipids, fatty acids and cytokines released by adipose tissue act by activating M1 macrophages and increasing the inflammatory response, by increasing the secretion of cytokines, which stimulate macrophages and adipocytes to produce pro-inflammatory adipokines, such as tumor necrosis factor alpha (TNF-alpha), interleukin-1 (IL-1), interleukin-6 (IL-6) and procoagulant substances. [10,11] Among these, a highlight is IL-6, which stimulates the liver to produce C-reactive protein (CRP). On the other hand, the subcutaneous adipose tissue produces adiponectin, a hormone that antagonically to other adipokines increases insulin sensitivity in tissues and acts as an anti-inflammatory, anti-adipogenic and anti-atherogenic protein hormone. [10]

Various clinical conditions, such as infection, trauma and inflammation, result in significant direct and indirect systemic changes culminating in the elevation of C-reactive protein (CRP). In this process, there is a regulation of the production of nitric oxide (NO), an increase in low-density lipoprotein (LDL-c), facilitation of the action of pro atherosclerotic genes, inhibition of adiponectin, vasoconstriction and stimulating platelet adhesion and activation, causing occlusion and thrombus formation. Thus, CRP, in addition to being an inflammatory marker of atherosclerosis and coronary events, is also a mediator of disease due to its contribution to the formation of lesions. [8,10,12]

Once the role of inflammation in the development of obesity and atherosclerotic disease has been determined, different inflammatory biomarkers were researched and identified in order to add prognostic value to cardiovascular risk even in the pediatric group. However, the world literature is not unanimous regarding the correlation between ultrasensitive CRP (CRP-us) and cardiometabolic risk in childhood and juvenile obesity. [13]

Therefore, this study aimed to establish the importance of evaluating CRP-us in our pediatric group with obesity and to demonstrate its importance as a biomarker, whose aim is to detect possible cardiometabolic complications early in this age group.

MATERIAL AND METHODS

Sample

This is a case-control study with a sample of 342 individuals aged between 6 and 18 years, with 235 obese children and adolescents (128 males and 107 females) and 107 in the control group, composed of children and adolescent controls (52 males and 55 females). Due to the heterogeneity of the sample, we divided individuals into three age groups according to the International

Diabetes Federation (FID): 6-10 years, 10-16 years and over 16 years.

The study was developed at the Preventive Medicine Service (SEMPER) in Aracaju-Sergipe, Brazil. The study was approved by the Research Ethics Committee of the State University of Santa Cruz (UESC), via Plataforma Brasil and informed the study consent on the number 04065412.600005526.

Anthropometric and biochemical assessments

Initially, the following anthropometric parameters of the individuals were evaluated: weight, height, BMI, waist circumference (WC) and blood pressure (BP). To check the weight, an anthropometric scale (Filizola®, Brazil) was used. The characterization of obesity was based on the BMI tables of the World Health Organization (WHO), following the comparison between gender and age. 30 The individuals were considered obese when the BMI value was above the 97th percentile or the calculation of the Z-BMI score is greater than +2. Abdominal circumference was measured at the midpoint between the lower costal margin and the highest elevation of the iliac crest and blood pressure was measured using cuffs with the appropriate circumference and width for the referred age group.

Subsequently, the groups were evaluated biochemically through the measurements of FG (fasting glucose), insulin, Homeostasis model assessment of insulin resistance (HOMA-IR), AST (aspartate aminotransferase), ALT (alanine aminotransferase), GT range (glutamyl transferase range), uric acid, total cholesterol (TC), low-density lipoprotein (LDL-c), high-density lipoprotein (HDL), triglycerides (TG), complete blood count, TSH (thyroid-stimulating hormone), free T4 (free thyroxine) , IGF-1 (insulin-like growth factor), urinary cortisol, in addition to the homocysteine and CRP-us biomarkers.

Laboratory measurement of cardiometabolic risk biomarkers

The hs-CRP was measured by the immunoturbidimetry method using the Immage device (BeckmanCoulter, USA). The values used for cardiovascular risk stratification (CVR) were: low CVR: <0,1 mg/dL, average CVR: 0,1 - 0,3 mg/dL and high CVR:> 0,3 mg/dL.

Total plasma homocysteine was determined using the chemiluminescence method, with a reference value less than 15 mcmol/L. Plasma insulin was also determined by the chemiluminescence method, the reference value being less than 28,4 mU/mL. HOMA-IR was calculated by multiplying fasting insulin (mU/mL) x fasting glucose (mg/dL)/405. The cut-off value used to characterize insulin resistance was greater than or equal to 3,16.

Statistical analysis

The results were analyzed statistically by the Mann Whitney test, adopting a p <0,05 as the level of significance. The results were obtained through the mean, the standard error of the mean and the confidence interval. For statistical analysis, the GraphPad Prisma software version 5.1 was used.

RESULTS

342 children and adolescents were evaluated, 235 from the obese group (128 males and 107 females), and 107 individuals from the non-obese control group (52 males and 55 females). The average interval of chronological ages was 10 ± 2,3 years for both groups.

The anthropometric and biochemical data of the obese male group compared to the control according to the age group are shown in Table 1. It is observed that, in all the age groups evaluated, obese individuals showed significant changes in the anthropometric parameters, with an increase in the BMI and increased AC compared to the control group (6 to 16 years old p <0,0001> 16 years old p <0,001). In addition, it was found that these individuals showed a significant increase in TC (p <0,001) in all age groups, an increase in LDL-c, TG and a reduction in HDL-c, these differences being more prominent in the age group up to 16 years (p <0,001). Regarding the glycemic profile, individuals over 16 years of age had fasting blood glucose above the control group (p <0,05). The results also revealed that the hs-CRP was increased in all groups evaluated (p <0,0001).

TABLE 1. Anthropometric and biochemical data in a group of male children and adolescents according to age group, control group (n=52) and with obesity (n=128).

		6 TO 10 YEARS	10 TO 16 YEARS	> 16 YEARS
BMI (Kg/m2)	Control	17,74 ± 0,99	19,92 ± 0,60	18,75±0,19
	Obese	26,21 ± 0,49***	29,11 ± 0,59***	33,90±1,37**
AC (cm)	Control	64,39 ± 1,28	67,30 ± 0,72	70,5 ± 0,5
	Obese	84,00 ± 1,17***	96,07 ± 1,83***	105,8 ± 3,92**
FG (mg/dL)	Control	85,78 ± 1,57	84,90 ± 1,18	88,25 ± 2,75
	Obese	86,92 ± 1,23	87,61 ± 1,25	99,90 ± 1,18*
TC (mg/dL)	Control	157,0 ± 5,13	156,7 ± 5,56	126,8 ± 16,2
	Obese	180,1 ± 4,29**	175,4 ± 3,45**	211,3 ± 8,59**
LDL (mg/dL)	Control	92,72 ± 4,55	102,4 ± 7,10	93,75 ± 6,25
	Obese	109,1 ± 4,31***	110,8 ± 4,04***	138,8 ± 14,3**
HDL (mg/dL)	Control	49,61 ± 1,81	45,30 ± 1,85	47,50 ± 2,5
	Obese	39,02 ± 1,22***	37,98 ± 1,15***	37,10 ± 0,86**

TG (mg/dL)	Control	77,11 ± 6,72	90,40 ± 10,5	71,00 ± 6,0
	Obese	147,0 ± 1,96***	136,7 ± 7,7***	235,5 ± 27,5**
PCR-us (mg/dL)	Control	0,06 ±0,01	0,06 ± 0,01	0,01 ± 0,01
	Obese	1,43 ± 0,12***	2,33 ± 0,17***	2,82 ± 0,35***

Source: Study authors
BMI: Body mass index; AC: abdominal circumference; FG: Fasting glycemia; TC: total cholesterol; LDL-c (low density lipoprotein), HDL: high density lipoprotein), TG (triglycerides). *p<0,05, **p<0,001 e ***p<0,0001compared to the control group.

TABLE 2: Anthropometric and biochemical data in a group of children and adolescents of the female sex, control (n=55) and with obesity (n=107).

		6 TO 10 YEARS	10 TO 16 YEARS	> 16 YEARS
BMI (Kg/m2)	Control	17,99 ± 0,84	17,91 ± 0,41	22,5 ± 0,1
	Obese	25,39 ± 0,45***	29,11 ± 0,71***	30,40±1,13*
AC (cm)	Control	62,27 ± 2,01	65,75 ± 1,01	70,0 ± 0,1
	Obese	82,97 ± 1,29***	90,02 ± 1,33***	96,50 ± 3,17*
FG (mg/dL)	Control	83,93 ± 2,07	85,67 ± 1,54	88,5 ± 0,1
	Obese	84,74 ± 1,35	87,38 ± 1,03	96,00 ± 2,04*
TC (mg/dL)	Control	128,1 ± 4,37	141,5 ± 3,80	120,2 ± 0,1
	Obese	172,7 ± 4,35***	168,8 ± 4,45**	182,3 ± 4,23
LDL (mg/dL)	Control	99,73 ± 7,11	96,00 ± 3,52	99,0 ± 0,1
	Obese	110,7 ± 4,04*	104,1 ± 3,68	107,3 ± 5,4
HDL (mg/dL)	Control	58,87 ± 2,33	45,76 ± 1,41	48,0 ± 0,1
	Obese	39,0 ± 0,96***	38,2 ± 1,20*	39,75 ± 0,5
TG (mg/dL)	Control	74,93 ± 4,04	81,95 ± 3,21	110 ± 2,0
	Obese	152,4 ± 8,67***	158,9 ± 8,8***	159,0 ± 7,4
PCR-us (mg/dL)	Control	0,039 ±0,009	0,04 ± 0,009	0,02 ± 0,1
	Obese	1,85 ± 0,15***	2,27 ± 0,37***	2,92 ± 0,14*

Source: Study authors
BMI: Body mass index; AC: abdominal circumference; FG: Fasting glycemia; TC: total cholesterol; LDL-c (low density lipoprotein), HDL: high density lipoprotein), TG (triglycerides). *p<0,05, **p<0,001 e ***p<0,0001compared to the control group.

TABLE 3: Biochemical and hormonal data from a group of children and adolescents of both sexes, control (n=107) and with obesity (n=235).

TESTS	CONTROL	OBESE
Leukocytes (mm3)	6900 ± 600	7600 ± 450
PCR- us (mg/dL)	0,01± 0,1	2,36±1,28***
Uric acid (mg/dL)	4,6 ± 1,05	5,85 ± 1,14***
Insulin (UI/ml)	14,9 ± 6,2	18,9 ± 5,4***
HOMA-IR	2,0	3,96***
TC (mg/dL)	170 ± 36	237 ± 34***
HDL (mg/dL)	44 ± 9,3	38 ± 7,9***
LDL (mg/dL)	94 ± 19	154 ± 39**
FG (mg/dL)	111 ± 60	180 ± 13***
AST (U/L)	21 ± 2,07	32 ± 2,7***
ALT (U/L)	23 ± 1,6	37 ± 1,3***

The anthropometric and biochemical variables of the groups with female obesity compared to the control according to the age group are shown in Table 2. It is noted that the anthropometric parameters BMI and WC were significantly elevated in the groups of children with obesity in relation to the control group, with greater differences in the age groups up to 16 years (p <0,0001). Regarding the lipid profile, the CT of the obese group was elevated in individuals aged 6 to 10 years (p <0,0001) and 10 and 16 years (p <0,001) and LDL increased only in the obese group of 6 to 10 years (p <0,05). HDL was reduced in the group with obesity in the age groups of 6 to 10 (p <0,0001) and 10 to 16 years (p <0,05), triglycerides were shown to be elevated in obese individuals under 16 years of age (P <0,0001). Similar to the male gender, increased blood glucose levels were only observed in obese individuals over 16 years of age with p <0,05. The CRP-us was found to be elevated in all age groups in the obese group in relation to the control group, with greater differences in those under 16 years old (p <0,0001).

The results regarding the laboratory evaluation of the obese group in relation to the control of the entire study sample are shown in Table 3. The group with obesity presented changes in the biochemical variables analyzed, such as uric acid, insulin, HOMA-IR, TC, HDL, LDL , TG, AST, ALT, GGT. On the other hand, there was no difference in hormonal dosage between the obese and control groups, in addition to the leukogram not showing any significant difference in the groups evaluated.

The levels of CRP and homocysteine in the obese and control group, depending on the age group and sex, are shown in Figure 1. The results revealed that the obese group has higher levels of CRP in all age groups and in both sexes when compared to the control group. Such statistical differences were quite significant in males aged less than 16 years (p <0,0001). It was not possible to

GGT (U/L)	29 ± 12	54 ± 9,2***
TSH (mUI/ml)	1,10 ± 1,19	2,07 ± 1,16
T4 livre (ng/dL)	1,07 ± 0,2	1,03 ± 0,29
Cortisol urinário (ug/dL)	9,78 ± 4,75	9,38 ± 4,88
IGF-1 (ng/ml)	231 ± 83	245 ± 111

Source: Study authors
FG: fasting glycemia; HOMA-IR: Homeostasis of the class of insulin resistance, TC: total cholesterol; HDL: high density lipoprotein, LDL-c: low density lipoprotein, TG: triglycerides, AST: aspartateaminotransferase, ALT: alanineaminotransferase, GGT: gamma glutamyl transferase, TSH: thyroid-stimulating hormone, free T4: free thyroxine, IGF-1: insulin-like growth factor, hs-CRP: high-sensitivity C-reactive protein.
* p <0,05, ** p <0,001 and *** p <0,0001 compared to the control group.

Figure 1. Representation of the behavior of C-reactive protein (hs-CRP) and homocysteine in relation to the obese and male (A and C) and female (B and D) control groups in the studied age groups. *p< 0,05, **p<0,01, *** p<0,0001.

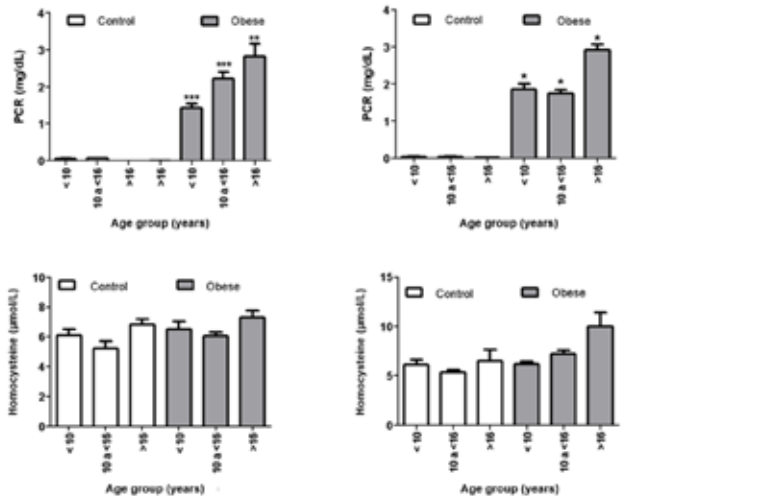
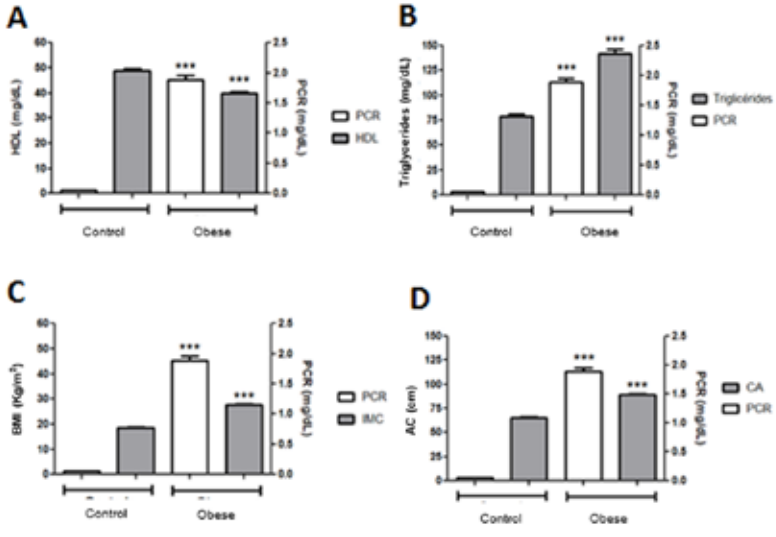


Figure 2. Representation of the behavior of C-reactive protein (CRP-us) compared to the variables HDL (A), triglycerides (B), BMI (C) and AC (D) in the obese and control groups (n=342, *** p <0,0001).



detect a statistical difference in homocysteine levels between the obese and control groups.

A comparison between anthropometric variables, BMI and WC and laboratory variables, triglycerides and HDL, of both groups in the sample is shown in Figure 2. The representation shows significant differences in the values of hs-CRP in the obese group with a reduction in HDL (p = 0,001), with an increase in triglycerides (p=0,001), a higher degree of BMI (p=0,001) and an increase in WC (p=0,001).

DISCUSSION

A biomarker is an indicator of a normal biological process, a pathogenic process or a pharmacological response to treatment [13], being a quantifiable measure of biological homeostasis that defines what is normal and provides subsidies to predict or detect changes. It is used to identify patients at increased risk of unfavorable outcomes according to Marshall et al. [13] When dealing with obesity in the pediatric age group, there is no consensus in the world literature regarding the presence of a biomarker of cardiometabolic comorbidities, although, in the adult population, this correlation is already well-founded. [14] However, studies have shown that hs-CRP already has high levels in children and adolescents with obesity. [15,16,17] This shows the relationship between obesity and the onset of the inflammatory process in the pediatric population that is obese in relation to those with normal weight. [15,16,17] The results of this study corroborate these findings, however, this increase was more expressive in both genders in individuals with obesity in the age group above 16 years when compared to non-obese controls, as shown in figure 1. This fact is probably due to the highest degree of obesity and, consequently, to the highest BMI, since the literature relates the elevation of C-reactive protein being directly proportional to the degree of BMI.[18] In a study conducted by Kitsios et al[19], CRP

levels were significantly higher in the obese and overweight groups compared to the control group. Suhet et al[20], when evaluating 350 children, they reported a significant association between overweight CRP-us, believing that the increase in CRP-us could be a potential mediator between obesity and the onset of childhood atherosclerosis. A relevant fact of our study was the use of the sample pairing the sexes with the chronological age according to the International Diabetes Federation. This enabled greater clarity on the importance of this biomarker in obesity, even in a pediatric group.

CRP-us is an inflammatory biomarker validated as a predictor of cardiovascular risk in apparently healthy adult individuals. The Center for Chronic Disease Control (CDC) and the American Heart Association (AHA) classify, in relation to the category of relative risk cardiometabolic, the following levels of hs-CRP into: low cardiac risk (<0,1 mg/dL), average cardiac risk (0,1-0,3 mg/dL) and high cardiac risk (> 0,3 mg/dL). These values were considered for the American and European population. [21] Using these criteria in this study, it appears that children and adolescents with obesity had elevated CRP in all age groups. This result made it possible to adopt dietary and behavioral measures to change the life of obese individuals. [30] For that, it was necessary the effort of a multiprofessional team composed of an endocrinologist, a physical educator, a nutritionist and a psychologist who stimulated the children's weight loss and changes in the habits of the whole family. [30] This proposal was also adopted by Isasi et al. [22]

With regard to homocysteine, this cardiometabolic biomarker did not show to have a good correlation with obesity in the sample evaluated. This fact corroborates that described by Anderson et al [23], With regard to homocysteine, this cardiometabolic biomarker did not show to have a good correlation with obesity in the sample evaluated. This fact corroborates that described by Anderson et al. [24] Currently, there are few reports in the literature showing the importance of this biomarker as a tool for the prognosis of cardiometabolic risk in obesity.

CRP-us is an inflammatory biomarker validated as a predictor of cardiovascular risk in apparently healthy adult individuals.

Regarding the lipid profile, there were higher statistically significant values in the obese group when compared to controls, with an increase in total cholesterol, LDL-c, triglycerides and a reduction in HDL. This fact is of paramount importance for metabolic bias, as these children and adolescents with this lipid profile may already have streaks of fatty plaques at the coronary and carotid levels, associated with increased CRP-us. [25] Suhet et al [20] observed an association between hs-CRP and low HDL. In a research carried out with 124 children, Muramoto et al [26] reported that, for each 1 mg/L increase in the serum concentration of CRP, there was a reduction of 0,072 mg/dL of HDL, but when the LDL rises, it infiltrates the arterial endothelium, producing fatty streaks early-around the first and second decade of life. The progression of this dyslipidemia contributes for several subgroups of white cells to infiltrate the vascular wall and secrete inflammatory cytokines, oxidative molecules and result in the inflammatory state. This mixed dyslipidemia, with subsequent atheromatous plaque, was seen in Mexican children described by Enriquez et al. [27]

According to Weiss et al [28], there is a positive association between the incidence of obesity and dyslipidemia in children and adolescents. A prevalence of approximately 50% of dyslipidemia was found in children with high BMI, associated with a greater abdominal circumference, with later accumulation of visceral fat and non-alcoholic liver steatosis. Therefore, excess weight is considered a criterion for screening the lipid profile in obese children and adolescents, as directed by the Brazilian Society of Pediatrics. [29] On the other hand, dyslipidemia in childhood may be associated with the early development of cardiometabolic risk with an increase in CRP-us, as observed in other populations of children and adolescents with obesity and also in our study population. [28]

Therefore, we can conclude that ultra-sensitive C-reactive protein can be used early as an important biomarker of cardiometabolic risk even in pediatric groups with obesity. ■

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