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Significant associations between C-reactive protein levels, body adiposity distribution and peripheral blood cells in school-age children.

Aralia Berenice Salgado-Bernabé[1], Luz Elena Ramos-Arellano[1], Iris Paola Guzmán-Guzmán[1], José Francisco Muñoz-Valle[2], Natividad Castro-Alarcón[1], Amalia Vences-Velázquez[1], Lorenzo Salgado-Goytia[1] and Isela Parra-Rojas[1].

[1]Unidad Académica de Ciencias Químico Biológicas, Universidad Autónoma de Guerrero, Chilpancingo, Guerrero, México.
[2]Instituto de Investigación en Ciencias Biomédicas, Departamento de Biología Molecular y Genómica, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Jalisco, México.

Key words: C-reactive protein; obesity; children; inflammation; blood cells.

Abstract. Obesity is associated with a state of chronic low-grade inflammation. Generally, there are significant correlations between body mass index and increased C-reactive protein levels. We investigated the relationship of high sensitivity C-reactive protein (hsCRP) levels with body adiposity distribution and blood cell count in obese children. A cross-sectional study was performed in 225 Mexican children. In the study were included 106 obese and 119 normal-weight children, aged 6-13 years old. The body composition was evaluated by BMI, body circumferences and skinfold thickness. hsCRP levels and hematological parameters were analyzed in all children. The hsCRP levels were higher in obese children than in the control group (1.5 and 0.41 mg/L respectively, P<0.001). Interestingly, hsCRP levels >3 mg/L were associated with the increase of circumferences of the waist, hip and arms (ORs= 9.08, 6.78 and 8.73, respectively, P<0.001), and a higher thickness of triceps, subscapular and suprailiac skinfolds (ORs= 4.73, 6.39 and 5.26, respectively, P=0.001), as well as a higher leukocyte and platelet counts. The data suggest that hsCRP levels are associated with skinfold thickness and body circumferences, and a moderate relationship was found with leukocyte and platelet counts in the studied children.

Corresponding author: Isela Parra Rojas, Laboratorio de Investigación en Obesidad y Diabetes, Unidad Académica de Ciencias Químico Biológicas, Universidad Autónoma de Guerrero, Chilpancingo, Guerrero 39090, México. E-mail: iprojas@yahoo.com.

Asociaciones significativas entre los niveles de proteína C reactiva, distribución de la adiposidad corporal y células sanguíneas periféricas en niños escolares.

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Palabras clave: proteína C reactiva; obesidad; niños; inflamación; células sanguíneas.

Resumen. La obesidad se asocia con un estado de inflamación crónica de bajo grado. Generalmente, hay correlaciones significativas entre el índice de masa corporal y el incremento en los niveles de la proteína C reactiva (CRP). Se investigó la relación de los niveles de CRP de alta sensibilidad (hsCRP) con la distribución de la adiposidad corporal y la cuenta de las células sanguíneas en niños obesos. Se realizó un estudio transversal en 225 niños mexicanos. En el estudio se incluyeron 106 niños obesos y 119 con peso normal, edad de 6-13 años. La composición corporal fue evaluada por IMC, circunferencias corporales y grosor de pliegues cutáneos. Los niveles de la hsCRP de alta sensibilidad y los parámetros hematológicos fueron analizados en todos los niños. Los niveles de la hsCRP presentaron un incremento en los niños obesos con respecto al grupo control (1,5 y 0,41 mg/L respectivamente, P<0,001). Es interesante que los niveles de hsCRP>3 mg/L se asociaron con mayor circunferencia de cintura, cadera y brazo (ORs= 9,08, 6,78 y 8,73, respectivamente, P<0,001) y mayor grosor de los pliegues como tríceps, subescapular y suprailiaco (ORs= 4,73, 6,39 y 5,26, respectivamente, P=0,001), así como con el aumento en la cuenta de leucocitos y plaquetas. Los datos sugieren que los niveles de la hsCRP se asocian con el grosor de los pliegues cutáneos y las circunferencias corporales y fue encontrada una relación moderada con las cuentas de leucocitos y plaquetas en los niños estudiados.

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INTRODUCTION

Increasing evidence indicates that adipose tissue is an important source of cytokines and that adiposity contributes to a proinflammatory state (1). Circulating levels of cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and acute phase proteins, such as C-reactive protein (CRP) are increased in obesity, insulin resistance syndrome and type 2 diabetes (T2D) (2, 3).

Recently, C-reactive protein has been recognized as a strong risk factor for the development of cardiovascular disease (4). In adults, plasma CRP levels are significantly associated with body fat as well as specific components of the metabolic syndrome, including systolic blood pressure, fasting plasma insulin levels, triglycerides and HDL-cholesterol (5, 6). Another inflammation marker is the white blood cell count (WBC), this marker has been found to correlate with metabolic syndrome, type 2 diabetes, dyslipidemia and cardiovascular disease (7).

Other factors such as smoking (8) and hormone replacement therapy (9) have been associated with elevated CRP concentrations in mi-

ddle-aged and elderly subjects. Female gender (5) and African American ethnicity (10) also have been related with CRP levels.

Several studies in children suggest that adiposity is the major determinant of CRP levels (11, 12). Similarly, another study showed that elevated systolic blood pressure (SBP), Hispanic ethnicity and obesity were associated with increased CRP levels (13). Other studies have been conducted to know CRP levels in children with and without obesity. In Mexican healthy children, the high sensitivity C-reactive protein (hsCRP) median was of 0.3 mg/L and it was positively and significantly correlated with BMI and LDL-C (14). In Brazilian adolescents, hs-CRP levels were increased in the obese group compared to the eutrophic group, and hsCRP levels correlated with BMI, arm and waist circumferences, total colesterol, LDL-C and anti-oxLDL (15). In another study in Chilean children, the mean C-reactive protein concentration was 0.9±1.5 mg/L. In males, there were significant direct correlations between the CRP concentration and BMI, total fat mass, central adiposity, waist circumference, and LDL cholesterol level. In females, CRP was associated with only BMI (16).

In a sample of Spanish adolescents, the hs-CRP mean was of 1.137 mg/L, and a statistically significant association was also found between CRP concentration and the nutritional status and waist to hip ratio values (17).

In the present study we investigated the relationship between hsCRP levels with body fat distribution in obese and normal-weight children. Further, we studied whether the hsCRP levels >3 mg/L considered to high cardiovascular risk in adults are associated with measures of body fat and blood cells.

PATIENTS AND METHODS

Participants

All children were from the State of Guerrero, and recruited from three primary schools in Chilpancingo city, localized in southern Mexico. There were 225 participant children, 108 girls and 117 boys, with an age range of 6-13 years. None of the participants had symptoms of infection during the 2 weeks before of the study. The control children were apparently healthy and not coursing with infectious diseases or under any regular medication.

The parents or guardians were provided with a description of the study, informed consent forms, and a family history/lifestyle questionnaire. If willing to participate, parents/guardians were then asked to sign the informed consent form and complete the questionnaire. Approval for the study was obtained from the Research Ethics Committee of the University of Guerrero.

Anthropometrical measurements

Body weight was determined in light clothes and without shoes using a Tanita body composition monitor (Tanita BC-553, Arlington, USA) and height was measured to the nearest 0.1 cm using a stadiometer (Seca, Hamburg, Germany). From these measurements, body mass index was calculated (BMI= weight/height^2, kg/m^2). Body circumferences were measured twice using a diameter tape (Seca 201, Hamburg, Germany) accurate to within ± 0.1 cm. The thickness of four skinfolds was measured twice to the nearest 0.1 mm using a skinfold caliper (Dynatronics Co, Salt Lake City, USA): triceps, biceps, subscapular and suprailiac. The duplicate measures were averaged. The classification of obesity was made using the 2000 Center for Disease Control and Prevention growth charts, y and defined as normal-weight 5th-85th percentiles and obesity ≥95th percentile (18); overweight children were not included in the study.

Laboratory measurements

A fasting blood sample was obtained from each child for the measurement of the following parameters. Peripheral blood cell counts were

determined by ADVIA®60 (Bayer Corporation, Tarrytown, New York, USA). High sensitivity C-reactive protein (hsCRP) was analyzed using an assay where serum CRP causes agglutination of the latex particles coated with anti-human CRP. The agglutination of the latex particles is proportional to the CRP concentration and can be measured by turbidimetry in the analyzer A25 (Biosystems S.A., Barcelona, España). The intra- and interassay coefficient of variation (CV) were <3% and <5%, respectively, and the detection limit was 0.06 mg/L.

TABLE I
DEMOGRAPHIC, CLINICAL AND HEMATOLOGICAL VARIABLES BY GROUP

	Control (n=119)	**Obesity (n=106)**	***P* value**
Age (years)*	9(6-12)	9(6-11)	0.70
Sex (%)**			0.19
Boys	57(47.9)	60(56.6)	
Girls	62(52.1)	46(43.4)	
Weight (kg)*	27.8(19.2-39.9)	42.5(27.4-63.9)	<0.001
Height (cm)*	129.6(114-148.4)	135(118-158)	<0.001
BMI (kg/m^2)*	16.3(13.9-19.1)	23.1(18.8-29.1)	<0.001
Waist circumference (cm)*	62.0(52-73)	79.0(64.5-94)	<0.001
Hip circumference (cm)*	70.0(61-82)	84.0(69.5-99)	<0.001
Waist-to-hip ratio*	0.87(0.8-0.96)	0.9(0.8-1.0)	<0.001
Arm circumference (cm)*	19.0(15-22)	24.5(20.5-30.5)	<0.001
Biceps skinfold (mm)*	13.5(6.0-20.5)	17.5(12-24.5)	<0.001
Triceps skinfold (mm)*	12.0(8-18)	18.0(11.5-22)	<0.001
Subscapular skinfold (mm)*	10.0(5-18)	18.0(11.5-24.5)	<0.001
Suprailiac skinfold (mm)*	15.0(8.0-22.5)	21.5(15.0-29.5)	<0.001
hsCRP (mg/L)*	0.41(0.1-6.0)	1.5(0.16-8.4)	<0.001
Leukocytes count (10^3/μL)*	7.0(4.7-12.3)	8.1(5.8-12.7)	<0.001
Erythrocytes count (10^6/μL)*	5.23(4.61-5.71)	5.35(4.81-5.98)	<0.001
Platelets count (10^3/μL)*	302(202-410)	319(235-415)	0.02

BMI: body mass index; hsCRP: high sensitivity C-reactive protein.
* Median (5-95th percentile), Mann Whitney U test.
** n (%), chi square test.

Statistical methods

The statistical analysis was performed using the chi-square test for categorical variables, median and 5th to 95th percentiles for non-symmetrical variables. The significance of differences between groups was determined using the Mann Whitney U test. Spearman's correlation coefficients were computed to assess the associations between CRP levels and some variables in all children. A multiple regression analysis was used to determine the odds ratios for hs-CRP >3 mg/L levels with respect to clinic and hematological variables (all measurements were grouped into tertiles and were analyzed used the 1st tertile as a reference). Statistical analysis was performed with STATA software (V.9) and a value P<0.05 was considered as statistically significant.

RESULTS

The study groups were similar in age and gender; the children had a median of nine years, with significant differences in all anthropometric, hematological and inflammatory measurements between control and obesity groups (Table I). All body circumferences and skinfold thickness were significantly larger in children with obesity in comparison with normal the weight group. Obese children had higher hsCRP levels than the control group (P<0.001). Similarly, high blood cell counts were determined in the group with obesity compared with normal weight group. Thus, significant differences in leukocyte (P<0.001), erythrocyte (P<0.001), and platelet counts (P=0.02), were found.

TABLE II
CORRELATIONS BETWEEN HIGH SENSITIVITY C- REACTIVE PROTEIN LEVELS AND CLINICAL AND HEMATOLOGICAL VARIABLES

Variables	R*	*P* value
BMI (kg/m^2)	0.4348	<0.001
Weight (kg)	0.2971	<0.001
Waist (cm)	0.3934	<0.001
Hip (cm)	0.3452	<0.001
Waist to hip ratio	0.3173	<0.001
Arm circumference (cm)	0.3981	<0.001
Biceps skinfold (mm)	0.3013	<0.001
Triceps skinfold (mm)	0.4457	<0.001
Subscapular skinfold (mm)	0.4659	<0.001
Suprailiac skinfold (mm)	0.3996	<0.001
Leukocytes count (10^3/μL)	0.3985	<0.001
Erythrocytes count (10^6 μL)	0.0304	NS
Platelets count (10^3/μL)	0.2427	0.009

* Spearman's correlation coefficient, calculated in all children.

Table II show Spearman's correlation coefficients between hsCRP levels and anthropometric and hematological variables. CRP was significantly correlated with all parameters analyzed except erythrocyte count. The peripheral adiposity determined by the skinfolds thickness, and central adiposity evaluated by waist and hip circumferences were positively and similarly correlated with hsCRP levels. Furthermore, both leukocyte and platelet counts were significantly correlated with hsCRP levels (P<0.001 and P=0.009, respectively).

Multiple regression models were performed to analyze the relation between hsCRP levels and some parameters studied. The hsCRP levels >3 mg/L correspond to high risk cardiovascular factor in adults (19), as this cut-off has not been established in children, the same value was considered. A total of 41 children had hsCRP levels >3 mg/L. After adjustment for age and gender, the hsCRP levels >3 mg/L were strongly associated to waist, hip and arm circumferences 3rd tertiles (P=0.01). In addition, triceps skinfold 3rd tertile (P=0.001), subscapular skinfold 3rd tertile (P<0.001), and suprailiac skinfold 3rd tertile (P=0.001) showed a significant association with high hsCRP levels. However, moderate association was observed with leukocyte and platelet counts 3rd tertiles (P<0.001 and P=0.02; respectively) (Table III).

Statistical analysis was performed to determine the association between leukocyte types and C-reactive protein levels, but not statistically significant differences were found, which were not included in the results.

DISCUSSION

Here the main findings were that obese children showed high hsCRP levels, and higher leukocyte, erythrocyte and platelet counts than those of normal weight. Moreover, hsCRP levels were associated with overall, central and peripheral adiposity, as well as leukocyte and platelet counts. These important results in obese children may suggest a state of low-grade systemic inflammation in which the prevalence of any confounding subclinical disease is very low.

A positive association between BMI and CRP levels has been repeatedly observed in adults (6, 8, 20). The study found an association in children between hsCRP levels with central and peripheral adiposity. Therefore, we used three anthropometric measurements of body fat: the BMI as an indicator of overall body fat; waist circumference and waist-to-hip ratio as markers of central adiposity, and skinfold thickness as indicators of peripheral body fat. Similarly, in another study in Mexican children, it was found that obese children had a significantly higher level of C-reactive protein compared with children with a normal percentage of fat mass and modest correlations were identified between serum levels of C-reactive protein and body mass index (r=0.39, p=0.001); triceps skinfold (r=0.36, p=0.002); and subscapular skinfold (r=0.405, p<0.001). No correlation was found between adiposity and serum tumor necrosis factor-alpha (21).

Also it has been shown that CRP levels may be predictive of obesity. Children with high baseline levels of hsCRP had a greater increase in BMI z-score and central adiposity over time and were at higher risk of developing becoming overweight/obese during growth (22).

Our results are consistent with previous studies that shown that adiposity is the major determinant of CRP levels in children and have speculated that cytokines secreted from adipocytes may be responsible for the relationship between serum CRP concentrations and adiposity (11, 12). Recently, it was reported that portal IL-6 levels are higher than peripheral levels, and that visceral fat was identified as an important site for IL-6 secretion (23). Thus, portal IL-6 from visceral fat might directly induce the production of CRP in the liver. Approximately 30% of basal circulating IL-6 originates in human adipose tis-

TABLE III
ASSOCIATION OF hsCRP >3 mg/L WITH CLINIC AND HEMATOLOGICAL VARIABLES

	Model without adjusted		Model adjusted	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P*** value**
Subject with obesity (BMI ≥95th percentile)	2.60 (1.27-5.32)	0.009	2.73 (1.32-5.64)	0.006
Waist circumference 3rd tertile (>74 cm)	5.08 (2.00-12.89)	0.001	9.08 (3.11-26.42)	<0.001
Hip circumference 3rd tertile (>81 cm)	3.32 (1.43-7.71)	0.005	6.78 (2.40-19.15)	<0.001
Arm circumference 3rd tertile (>23 cm)	5.05 (1.98-12.89)	0.001	8.73 (3.01-25.31)	<0.001
Biceps skinfold 3rd tertile (>17.5 mm)	2.29 (0.95-5.50)	0.06	2.37 (0.97-5.76)	0.05
Triceps skinfold 3rd tertile (>17 mm)	4.52 (1.75-11.65)	0.002	4.73 (1.81-12.34)	0.001
Subscapular skinfold 3rd tertile (>17 mm)	6.17 (2.41-15.76)	<0.001	6.39 (2.47-16.52)	<0.001
Suprailiac skinfold 3rd tertile (>20 mm)	5.15 (1.91-13.83)	0.001	5.26 (1.94-14.23)	0.001
Leukocytes count 3rd tertile (>8.46 $10^3/\mu L$)	1.38 (1.17-1.63)	<0.001	1.39 (1.17-1.64)	<0.001
Erythrocytes count 3rd tertile (>5.42 $10^6/\mu L$)	1.56 (0.55-4.44)	0.39	1.68 (0.58-4.83)	0.33
Platelets count 3rd tertile (>334.3 $10^3/\mu L$)	1.006 (1.001-1.01)	0.01	1.006 (1.00-1.01)	0.02

*Adjusted by age and gender.

sue (24) with production in intra-abdominal fat three times that of subcutaneous fat (25). Some cross-sectional studies demonstrate stronger associations of IL-6 and TNF-α with abdominal circumference or visceral fat area than BMI (26).

Interestingly, in the present study an association between the peripheral adiposity evaluated by the skinfolds thickness and hsCRP levels was found, suggesting that in children the peripheral adipose tissue, rather than central fat, may contribute to basal hsCRP levels. In the same way, Pou et al, recently reported that CRP was positively and similarly correlated with both subcutaneous and visceral adipose tissue volumes (27). In addition, CRP mRNA has been detected in human subcutaneous abdominal adipose tissue (28), suggesting that adipose tissue itself may contribute to basal plasma CRP levels. These results indicate that in childhood there exists a certain level of inflammation in relation with the increase of body fat. Therefore, anthropometric measurements of both central and peripheral adiposity may be important predictors of subclinical inflammation in children.

Peripheral white blood cell count is a marker of systemic inflammation and it is included in the blood tests for routine health examinations, but together with fibrinogen and CRP are useful indicators of cardiovascular disease (29). Furthermore, white blood cell count has been shown to be associated with insulin resistance, type 2 diabetes, diabetes micro- and macrovascular complications, and a cluster of components of the metabolic syndrome (30). Interestingly, in this study, an association was observed between CRP levels and both leukocyte and platelet counts. The possible explanation could be related with the increase IL-6 production by adipose tissue, and consequently these cytokine induce the hepatic synthesis of CRP. IL-6 is also known to stimulate the production of platelets, as well as leukocytes (20, 31).

It has also been shown that myeloperoxidase and CRP levels are early biomarkers of inflammation associated with CVD risk in obese children at the prepubertal age (32). In addition those hsCRP concentrations increased proportionally with the degree of abdominal obesity in healthy prepubertal children (33). In another study, the obese women had higher hsCRP levels ($p= 0.001$) compared with normal-weight women and there was a relation between serum hsCRP levels and insulin resistance (34). Therefore, the increase of hsCRP levels in obese children, together with leukocyte and platelet counts, suggest that blood cell counts may be of clinical importance as markers of low-grade systemic inflammation, and as predictors of insulin resistance, type 2 diabetes and metabolic syndrome in children.

In conclusion, it was found that obese children had higher hsCRP levels and blood cell counts than normal-weight children, and that hsCRP levels were associated with greater body circumferences and skinfold thickness, and a moderate relationship with leukocyte and platelet counts.

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