Relationship of C-Reactive Protein to Adiposity, Cardiovascular Risk Factors, and Subclinical Atherosclerosis in Healthy Children

Mónica Acevedo,[a] Pilar Arnáiz,[a,b] Salesa Barja,[b] Claudia Bambs,[a] Ximena Berríos,[c] Beatriz Guzmán,[c] Jacqueline Carvajal,[a] Berta Cassis,[b] and Carlos Navarrete[a]

[a]Departamento de Enfermedades Cardiovasculares, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
[b]Departamento de Pediatría, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
[c]Departamento de Salud Pública, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

Introduction and objectives. In adults, C-reactive protein is a marker of cardiovascular risk. It is associated with both classical and metabolic risk factors and is a predictor of cardiovascular events. The aim was to investigate the relationship of the C-reactive protein concentration to classical cardiovascular risk factors, measures of adiposity subclinical atherosclerosis in children.

Methods. The values of traditional risk factors, anthropometric parameters, fasting lipids, glucose and C-reactive protein levels were recorded. In addition, the carotid artery intima-media thickness was measured, and brachial artery endothelial function was assessed using flow-mediated dilation.

Results. The study included 112 children (58 male) with a mean age of 11.3 (1.9) years. The mean C-reactive protein concentration was 0.9 (1.5) mg/L. In males, there were significant direct correlations between the C-reactive protein concentration and body mass index, total fat mass, central adiposity, waist circumference, and low-density lipoprotein (LDL) cholesterol level. In females, C-reactive protein was associated with only body mass index. Boys in the highest C-reactive protein tertile had a significantly higher body mass index, total fat mass, LDL cholesterol level, and waist circumference. In the whole group, the best predictor of an elevated ultrasensitive C-reactive protein concentration was the body mass index (odds ratio 2.04 [1.30-3.21]). No relationship was found between the C-reactive protein concentration and the percentage flow-mediated dilation of the brachial artery or the carotid intima-media thickness.

Conclusions. The results indicate that, in children, there is a significant direct relationship between the ultrasensitive C-reactive protein concentration and measures of adiposity, particularly body mass index. However, no relationship between C-reactive protein and subclinical atherosclerosis was observed.

Key words: *C-reactive protein. Risk factors. Adiposity. Children. Obesity.*

Proteína C reactiva y su relación con adiposidad, factores de riesgo cardiovascular y aterosclerosis subclínica en niños sanos

Introducción y objetivos. En adultos, la proteína C reactiva es un marcador de riesgo cardiovascular que se asocia a los factores de riesgo tradicionales y metabólicos y predice eventos cardiovasculares.

Métodos. Estudiamos la concentración de proteína C reactiva ultrasensible para establecer su relación con medidas de adiposidad, factores de riesgo tradicionales y aterosclerosis subclínica en niños. El objetivo ha sido la evaluación de factores de riesgo clásicos, antropometría, lípidos, glucemia y proteína C reactiva en ayunas, junto con evaluación de la función endotelial mediada por flujo en la arteria braquial y el grosor intimomedial de la arteria carótida.

Resultados. Se estudió a 112 niños (58 varones) con una media ± desviación estándar de edad de 11,3 ± 1,9 años. La media de proteína C reactiva del grupo fue 0,9 ± 1,5 mg/l. En los varones, la proteína C reactiva se correlacionó en forma directa y significativa con el índice de masa corporal, la masa grasa total, la grasa troncal y la cintura y el colesterol de las lipoproteínas de baja densidad (cLDL). En las mujeres, se asoció sólo al índice de masa corporal. Los varones en el tercil superior de proteína C reactiva presentaron mayor índice de masa corporal, grasa total, cintura y cLDL. El factor que mejor determinó una proteína C reactiva ultrasensible elevada en el grupo total fue el índice de masa corporal (*odds ratio* [OR] = 2,04 [1,30-3,21]). No se demostró asociación entre proteína C reactiva y porcentaje de dilatación de la arteria braquial mediada por flujo o grosor de la carótida.

Conclusiones. Este estudio indica que la proteína C reactiva ultrasensible se asocia en forma directa y significativa al grado de adiposidad, especialmente el índice de masa corporal, pero no a marcadores de aterosclerosis subclínica en niños.

Palabras clave: *Proteína C reactiva. Factores de riesgo. Adiposidad. Niños. Obesidad.*

Correspondence: Dr. M. Acevedo.
Departamento de Enfermedades Cardiovasculares.
Pontificia Universidad Católica de Chile.
Lira 85, 1.er piso. Santiago. Chile.
E-mail: macevedo@med.puc.cl

Received January 2, 2007.
Accepted for publication June 22, 2007.

ABBREVIATIONS

BMI: body mass index
CRPus: ultrasensitive C-reactive protein
FMD: flow-mediated dilation (of the brachial artery)
IMT: intima-media thickness (of the carotid artery)
PCp50: percentage of the 50th percentile (for waste circumference)

INTRODUCTION

The available evidence suggests that the pathogenesis of atherosclerosis begins in childhood. Anatomic pathology studies have shown the presence of early precursors of atherosclerosis, such as fatty streaks or intimal thickening, in the arteries of children.[1] Currently, the guidelines for primary prevention in children and adolescents published by the American College of Cardiology and the American Heart Society include the study of the traditional risk factors, based on the idea that these continue into adulthood and are related to atherosclerotic changes during this stage of life.[2]

It is now known that atherosclerosis is an inflammatory disease.[3] C-reactive protein (CRP), an acute phase protein, is a highly sensitive marker of general inflammation. Experimental studies have detected the presence of CRP in arteries with atherosclerotic lesions. It has also been shown that CRP induces the production of inflammatory cells and that it reduces the expression of nitric oxide synthetase.[4] Thus, from a biological point of view, CRP participates in the atherogenic process. In adults, CRP detected with ultrasensitive techniques (ultrasensitive CRP or CRPus) is associated with traditional risk factors and its concentration predicts cardiovascular events. Few studies have been performed, however, on the concentration of CRPus and its relationship with classical risk factors, adiposity variables, endothelial function, and carotid thickness in children. From a biological point of view, the advantage of studying children is that established coronary artery disease, a confounding factor of great importance in adults can be ruled out.

The aim of the present study was to determine the CRPus concentration of healthy children and to seek possible correlations with anthropometric variables such as adiposity, cardiovascular risk factors, and endothelial function (estimated by flow-mediated dilation of the brachial artery [FMD] and the intima-media thickness [IMT] of the carotid artery).

METHODS

The study subjects were the children or grandchildren of adults who took party in an epidemiological study performed by the *Departamento de Salud Pública* (Dept. of Public Health) of our university in 2004. These adult subjects belonged to nuclear families residing in different neighborhoods of Santiago; all answered a questionnaire regarding their cardiovascular risk factors, and all underwent tests to determine their lipid profile, blood sugar level, blood pressure, and CRPus concentration. The different neighborhoods were randomly selected by multistage sampling and their inhabitants stratified by age, gender, and socioeconomic level. The children and grandchildren of the healthy adults in this earlier study (ie, those with no cardiovascular risk factors nor atherosclerotic disease, and who had a normal CRPus concentration) were invited to take part in the present study, which was undertaken between October 2005 and December 2006. Thus, the same type of sampling method was used to obtain a representative sample of the children from these neighborhoods. All those enrolled were aged between 6 and 13 years. The adults legally in charge of these children all gave their signed, informed consent for their charges to take part. The study was approved by the University's ethics committee.

A nurse contacted the selected children by telephone to invite them to take part and to arm their parents or grandparents with some general recommendations. These included: *a)* that the children should always come to the hospital accompanied by an adult, *b)* that they should have fasted for at least 12 h before tests, *c)* that a child not attend an appointment if he/she had been ill between 1 day and 2 weeks prior to the appointment date, and *d)* that no medications be taken for at least 12 h before attending an appointment.

Data Collection

All the children underwent testing between 8.00 h and 10.00 h. All answered questionnaires to record their demographic data, clinical history, physical activity, and nutritional background. Information on the risk factors affecting the parents or grandparents were also recorded. Children with high blood pressure, hypercholesterolemia, or who suffered a metabolic or inflammatory disease were excluded.

All the children were examined physically by a pediatric cardiologist. Two cardiologists and a nurse trained in vascular ultrasonography recorded the subjects' FMD and IMT data. Blood samples were collected after these echographic studies were completed.

Anthropometric Measurements and Pubertal Development

A pediatric nurse recorded the weight and height of the children (barefoot, dressed in their underwear, and covered by a robe) using a lever balance and a SECA® stadiometer respectively. Height/age (H/A) and weight/height (W/H) ratios were then calculated, along

with the body mass index (BMI) (weight in kg/height in meters squared), and expressed as percentiles and z values (z=value recorded–median/1 standard deviation). The NCHS-CDC[5] curves for the year 2000 were used as references and obesity defined as BMI ≥p95, overweight or risk of obesity as p85 to p94, eutrophy between p10 and p84, and underweight as below p10. The BMI was expressed as a z value to transform it into a continuous variable adjusted for age and sex. Since body composition changes during childhood, the same NCHS-CDC[5] reference was used.

Central obesity was determined by measuring the waist with a non-stretch plastic tape; the mean of 2 measurements was recorded. As a reference, a percentile distribution for a multiracial child population[6] was used, with waste circumference values expressed in terms of the percentage of the 50th percentile (PCp50), ie, (true measurement/p50)×100. Percentile distributions for the waist were used given the changes that occur in body shape and composition with age and development.

Finally, the thicknesses of four skin folds were measured the biceps, triceps (TC), subscapular (SS), and suprailiac folds–using Lange® calipers, along with the brachial circumference. All measurements were made following international norms.[7] The SS/TC ratio was used as an indirect indicator of trunk fat.[8] The percentage total fat mass was determined using the formulae of Slaughter[9] (which require TC and SS values be known).

The sexual maturity of each subject was determined using the Tanner index.[6]

Blood Pressure

Blood pressure was measured with subjects in the supine position following a 10 min rest period in a temperature-controlled room. All measurements were taken on the right arm using a Dynamap Pro 100 (Criticon®) device with an adult and pediatric cuff. Three measurements were made at intervals of 5 min and the mean calculated. High blood pressure was defined as a systolic or diastolic pressure ≥p95 for the subject's sex, age, and height, according to international standards (NIH, 1996).

Blood Tests

All blood samples were obtained by venipuncture after a 12 h fast. Ultrasensitive C-reactive protein was determined by nephelometry using a Dade Behring BN II nephelometer (detection limit 0.1 mg/L). Total cholesterol, high density lipoprotein cholesterol (HDL-C) and triglycerides were determined by standard enzymatic methods using a Yaci analyzer. Low density lipoprotein cholesterol (LDL-C) was determined using the Friedewald formula, and blood sugar by the glucose oxidase method.

Assessment of Subclinical Atherosclerosis

For the measurement of IMT and FMD a Hewlett Packard Sonos 5500 apparatus with a high frequency (5-13 MHz) linear transducer was used. The operator remained blinded to the blood test results during these determinations.

Carotid Intima-Media Thickness

This was measured according to the 2004 Mannheim consensus.[10] The image was centered on the posterior wall of each common carotid artery, and a 1 cm segment selected near the bifurcation. Measurements were made using software that automatically detected the carotid borders (M'Ath® Std). All measurements were made off-line at the end of diastole. The highest IMT value measured on either the right or left side was used in statistical analyses. The intraoperator coefficient of variation was 3.8%.

Endothelial Function

This was determined according to the 2002 recommendations of the International Brachial Artery Reactivity Task Force.[11] The child assumed the supine position and a blood pressure cuff was placed on the non-dominant forearm. The brachial artery was explored at the elbow fold, and its baseline diameter recorded. The cuff was then inflated to a pressure at least 50 mm Hg above that of the child's resting (5 min) systolic blood pressure (hyperemic phase); it was then deflated and the posthyperemic response measured. Both diameter measurements (baseline and posthyperemic) were made during diastole over 3 cardiac cycles, involved intima-intima measurements, and were taken using an electronic caliper. The FMD value was calculated as the percentage change in the posthyperemic diameter compared to baseline. Nitric oxide-independent dilation with nitroglycerine was not performed given the age of the children and the danger of inducing low blood pressure.

Statistical Analysis

The results are expressed as means (standard deviation). The distribution of the CRPus values was markedly symmetrical; this variable was therefore presented in terms of medians and interquartile ranges. In all analyses involving the CRPus values in continuous form, log(CRPus) values were used to correct the asymmetry and stabilize the variance. The associations between the log(CRPus) and all other variables were determined by Pearson correlation coefficient analysis, using multiple linear regression models adjusted for age and sex. Logistic regression models adjusted for age and sex were used to calculate odds ratios (OR), using a CRPus concentration

of >0.43 mg/L (the sample median) for all analyses. A *P* value less than .05 was considered significant.

RESULTS

The study sample (n=112) was composed of 58 boys and 54 girls; 30% of the boys and 55% of the girls were prepubertal (*P*<.01, Fisher exact test; such a difference might be expected in a representative population of children of this age). According to their BMI, 65% of the children were eutrophic, 22% were overweight, 10% obese, and 3% underweight; this is comparable to the distribution for the Chilean school-age population.[8] Only 1 girl had a high CRPus concentration (14.7 mg/L), a sign of an infection; she was excluded from the analysis. In 9 children the images of the brachial artery obtained in FMD analysis were unsatisfactory and excluded from analysis.

Table 1 shows the demographic, anthropometric, and biochemical results for the children studied; the mean age of the subjects was 11.3 (1.9) years. No differences were seen between the boys and girls in terms of demographic variables. The SE/TC ratio of the girls was significantly higher (*P*<.01). The median CRPus value was 0.43 mg/L (interquartile interval, 0.69 mg/L). No significant differences were seen between the CRPus of boys and girls. Table 2 shows the Pearson correlation coefficients between CRPus concentration and the anthropometric, biochemical, and subclinical atherosclerotic variables for the sample as a whole. A separate analysis of the boys and girls revealed a positive correlation between CRPus concentration and BMI, total fat mass, waist circumference, the SE/TC ratio, and LDL-C level in the boys, both pubertal and prepubertal. In the girls, a significant relationship was found between CRPus concentration and BMI, zBMI, total fat mass, and PCp50–always in those who were pubertal. No association was found between CRPus and age, total cholesterol, HDL-C, or triglyceride levels, blood pressure, blood sugar, IMT, or FMD, either in boys or girls.

Log(CRPus) was significantly associated with BMI, zBMI, total fat mass, waist circumference, and blood sugar, after adjusting for age and sex. No significant associations were seen with cholesterol or triglyceride levels, blood pressure, IMT or FMD. Table 3 shows the values of these variables with respect to the CRPus concentration divided into tertiles.

The risk factors associated with an elevated CRPus concentration (CRPus >0.43 mg/L, the sample median) were identified by logistic regression adjusted for age and sex. Significant associations were found with BMI (OR=1.28; 1.1-1.5), zBMI (OR=2.04; 1.3-3.2), total fat mass (OR=1.1; 1.04-1.15), and waste circumference (OR=1.09; 1.03-1.14) (Table 4).

DISCUSSION

The results indicate that the CRPus concentration is directly and significantly associated with anthropometric indicators of adiposity, but not with subclinical atherosclerosis indicators in healthy children.

TABLE 1. **Demographic and Analytical Variables**[a]

Variable	Boys (n=58) Mean (SD)	Girls (n=54) Mean (SD)	Total Sample (n=112) Mean (SD)
Age, mean (SD), y	11.3 (1.9)	11.1 (1.8)	11.2 (1.9)
BMI	19 (3)	19 (3)	19 (3)
zBMI	0.46 (0.95)	0.54 (0.99)	0.50 (0.96)
Waist circumference, cm	69 (9)	70 (11)	70 (10)
PCp50, %	106 (12)	108 (16)	107 (14)
TFM, %	23 (10)	26 (9)	25 (9)
SE/TC, mm[b]	0.76 (0.22)	0.88 (0.28)	0.82 (0.26)
SBP, mm Hg	102 (7)	101 (9)	102 (8)
DBP, mm Hg	55 (5)	56 (6)	55 (5)
CRPus, mg/L[c]	0.38 (0.6)	0.55 (0.8)	0.43 (0.69)
log CRPus	–0.74 (1)	–0.6 (1.08)	–0.67 (1.04)
Blood sugar, mg/dL	86 (5)	83 (6)	85 (5)
Total cholesterol, mg/dL	146 (23)	153 (26)	149 (24)
HDL-C, mg/dL	56 (11)	56 (11)	56 (11)
LDL-C, mg/dL	76 (23)	83 (19)	80 (22)
Triglycerides, mg/dL	64 (31)	68 (33)	66 (32)
Maximum IMT, mm	0.65 (0.06)	0.64 (0.07)	0.64 (0.06)
Mean IMT, mm	0.51 (0.03)	0.51 (0.04)	0.51 (0.04)
FMD, %	9.4 (4.4)	9.8 (3.8)	9.6 (4.1)

[a]HDL-C indicates high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; FMD, flow-mediated dilation of the brachial artery; BMI, body mass index; IMT, carotid intima-media thickness; TFM, total fat mass; DBP, diastolic blood pressure; SBP, systolic blood pressure; PCp50, percentage of the 50th percentile for waste circumference; CRPus, ultrasensitive C-reactive protein; SE/TC, ratio of subscapular/triceps skin fold thickness; zBMI, z value for BMI.
[b]Significant difference between sexes (*P*<.01).
[c]Median and interquartile range.

TABLE 2. **Correlation Between Ultrasensitive C-Reactive Protein and Anthropometric, Biochemical, and Subclinical Atherosclerotic Variables in Children**[a]

Variable	Boys (n=58), *r*	Girls (n=54), *r*	Total Sample (n=112), *r*	*P*[b]
Age, mean (SD), y	–0.04	–0.2	–0.12	NS
Weight, kg	0.27	0.14	0.2	.031
BMI	0.37	0.29	0.33	<.001
zBMI	0.29	0.43	0.37	<.001
Waist circumference, cm	0.41	0.2	0.3	<.01
PCp50, %	0.47	0.3	0.38	<.001
TFM, %	0.49	0.22	0.37	<.001
SE/TC, mm	0.33	0.14	0.24	.012
Blood sugar, mg/dL	–0.28	–0.24	–0.26	<.01
Total cholesterol, mg/dL	0.26	–0.05	0.1	NS
HDL-C, mg/dL	0.005	–0.11	–0.05	NS
LDL-C, mg/dL	0.28	–0.013	0.15	NS
Triglycerides, mg/dL	–0.09	0.02	–0.03	NS
SBP, mm Hg	0.02	0.03	0.02	NS
SBP, mm Hg	–0.02	–0.1	–0.06	NS
Mean IMT, mm	–0.01	–0.008	–0.01	NS
FMD, %	0.04	0.14	0.09	NS

[a]HDL-C indicates high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; FMD, flow-mediated dilation of the brachial artery; BMI, body mass index; IMT, carotid intima-media thickness; TFM, total fat mass; NS, *P*>.1; DBP, diastolic blood pressure; SBP, systolic blood pressure; PCp50, percentage of the 50th percentile for waste circumference; *r*, Pearson correlation coefficient, not adjusted; SE/TC, ratio of subscapular/triceps skin fold thickness; zBMI, z value for BMI.
[b]*P* for the entire sample.

TABLE 3. **Distribution of Anthropometric Measurements, Lipids, Blood Pressure, Intima-Media Thickness, and Flow-Mediated Dilation of the Brachial Artery by Tertiles of Ultrasensitive C-Reactive Protein**[a]

Variable	CRPus <0.27 mg/L (n=35) Mean (SD)	CRPus 0.27-0.66 mg/L (n=37) Mean (SD)	CRPus >0.66 mg/L (n=39) Mean (SD)	*P*[b]
BMI	18 (3)	19 (3)	20 (3)	<.01
zBMI	0.14 (1.1)	0.37 (0.9)	0.9 (0.8)	<.01
Total fat mass, %	22 (9)	22 (9)	30 (9)	<.01
Waist circumference, cm	67 (8)	68 (9)	74 (11)	<.01
PCp50, %	102 (11)	105 (11)	114 (16)	<.01
Total cholesterol, mg/dL	149 (24)	145 (24)	152 (25)	NS
LDL-C, mg/dL	79 (19)	75 (20)	84 (24)	NS
HDL-C, mg/dL	57 (11)	58 (13)	55 (9)	NS
Triglycerides, mg/dL	70 (37)	61 (29)	68 (31)	NS
SBP, mm Hg	101 (7)	103 (9)	101 (8)	NS
DBP, mm Hg	55 (4)	57 (6)	54 (6)	NS
FMD, %	9 (3)	10 (4)	10 (5)	NS
Mean IMT, mm	0.50 (0.03)	0.51 (0.04)	0.51 (0.04)	NS

[a]HDL-C indicates high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; FMD, flow-mediated dilation of the brachial artery; BMI, body mass index; IMT, carotid intima-media thickness; DBP, diastolic blood pressure; SBP, systolic blood pressure; PCp50, percentage of the 50th percentile for waste circumference; zBMI, z value for BMI.
[b]Value of *P* trend for response of log(CRP) adjusted for age and sex; NS, *P*>.10.

Knowledge of CRPus levels in children is being seen as increasingly important, although only recently have studies on the relationship of this marker with cardiovascular disease begun in children and adolescents. The CRPus concentrations of the children in the present study were significantly lower than those seen in adults.[12] In healthy children the median CRPus concentration ranges from 0.2 to 0.5 mg/L.[12] The present results are comparable to those of Ford et al[13] who examined 3348 children in the NHANES study in 2003; the median CRPus reported was 0.4 mg/L with no significant difference between boys and girls.

From a clinical point of view the importance of clarifying the pathogenic role of CRPus in children lies in its relationship with atherosclerotic lesions established in children before the age of 15, independent of other risk factors.[14] In adults it is accepted that CRPus has a pathogenic role in the formation of atherosclerotic

TABLE 4. **Risk of Elevated CRPus According to Anthropometric and Lipid Variables, Blood Pressure, Blood Sugar, and Carotid Intima-Media Thickness[a]**

Variable	OR[b]	*P*
BMI	1.28 (1.10-1.5)	<.01
zBMI	2.04 (1.3-3.21)	<.01
Total fat mass, %	1.10 (1.04-1.15)	<.001
Waist circumference, cm	1.09 (1.03-1.14)	<.01
PCp50, %	1.12 (1.07-1.16)	<.01
Total cholesterol, mg/dL	1 (0.99-1.02)	NS
LDL-C, mg/dL	1.01 (0.99-1.03)	NS
HDL-C, mg/dL	0.99 (0.96-1.03)	NS
Triglycerides, mg/dL	0.99 (0.98-1.01)	NS
SBP, mm Hg	1.04 (0.98-1.09)	NS
DBP, mm Hg	0.98 (0.91-1.05)	NS
Blood sugar, mg/dL	0.94 (0.87-1.02)	NS
Mean IMT, mm	1.49 (0.10-9)	NS
FMD, %	1.10 (0.99-1.22)	NS

[a]HDL-C indicates high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; FMD, flow-mediated dilation of the brachial artery; BMI, body mass index; IMT, carotid intima-media thickness; OR, odds ratio; DBP, diastolic blood pressure; SBP, systolic blood pressure; PCp50, percentage of the 50th percentile for waste circumference; zBMI, z value for BMI.
[b]OR for CRPus >0.43 (sample median) adjusted for age and sex by independent logistic regression; NS, *P*>.1.

plaques: among other properties it seems able to activate complement and endothelial cells,[15,16] alter the production of nitric oxide,[17] and mediate the production of tissue fluid.[18] Currently, the American College of Cardiology and the American Cardiology Society recommend the measurement of CRPus in adults to improve the prediction of cardiovascular risk in persons with an intermediate risk (10%-20%) according to the Framingham scale.[19]

The most important determinants in the CRPus values of the present subjects were BMI, zBMI, and other clinical indicators of adiposity such as the percentage total fat mass, the waist circumference, and the SS/TC ratio (an indicator of trunk obesity).

Few studies have investigated the relationship between the CRPus concentration and the traditional risk factors and anthropometric variables in "healthy" children. However, the present results agree with those of these studies.[20-22] Cook et al[20] reported the ponderal index to be the major factor determining the CRPus concentration, both in girls and boys, while Ford[21] found this to be the BMI. In the present study, the magnitude of the correlation coefficients between the CRPus concentration and the adiposity variables were similar to those published by these other authors. The fact that this magnitude is low is explained in that healthy children have fewer risk factors and low CRPus concentrations.

The supposed relationship between the CRPus concentration and adiposity is based on numerous studies in adults that have shown obese and overweight individuals acquire a proinflammatory status.[23] It is currently thought that their higher CRPus concentrations are due to the increased expression of interleukin-6 or tissue necrosis factor in the intra-abdominal tissue. This would explain the close, significant relationship between BMI or zBMI and CRPus, both in adults[23] and in overweight and obese children.[24-26] It has recently been reported that CRPus is also a marker of insulin resistance and diabetes in adults.[27,28] Finally, obesity is associated with high concentrations of leptin and low concentrations of adiponectin (an anti-inflammatory and anti-atherogenic protein),[29] both of which are produced exclusively by adipose tissue. Thus, a state of chronic inflammation (high CRPus concentrations) along with low adiponectin concentrations and a greater prevalence of metabolic risk factors could favor the development of atherosclerosis in obese adults and children.

Unlike in adults, no relationship has been consistently shown between the CRPus concentration and dyslipidemia in children. In the present sample, the CRPus concentration was only significantly associated with the LDL-C level in boys; no such relationship was seen with other plasma lipids. This finding is interesting from a pathophysiological point of view since it has been shown that CRPus mediates the capture of LDL-C by macrophages in atherosclerotic plaques, and is thus involved in the development of atherosclerosis.[17] Unlike that which occurs in adults, the lack of correlation between CRPus and other risk factors (eg, blood pressure or blood sugar) seen in the present study shows that this association may begin to appear later in life or require more inflammation for it to become manifest.

In the Chilean setting, evidence exists that metabolic complications accompany childhood obesity–associations once believed to exist only in adults.[8,30] Our concern for studying these variables in children came about because of these reports and because some 38% of the Chilean school-age population is overweight. As reported by Freedman et al[14] in follow-up investigations associated with the Bogalusa Study, there is a high probability that these children will continue to be obese and develop cardiovascular risk factors as they approach adulthood.[31,32] Juonala et al[33] have recently reported that, in addition to traditional risk factors, childhood CRPus concentrations tend to be retained into adult life. In a recent study on 51 healthy Spanish children and adolescents, all the offspring of at least 1 hypertensive parent, it was reported that all their CRPus values were high,[34] perhaps indicating a genetic effect. As in the present study, a significant relationship was also found between obesity markers and the CRPus concentration. If it is confirmed that subclinical inflammation is a predictor of cardiac events, as it is for diabetes mellitus type II, knowledge of the behavior of this marker in childhood would gain in clinical importance.

Finally, no association was found between the CRPus concentration and the subclinical atherosclerotic variables studied. In contrast, Järvisalo et al,[22] who studied

79 Finnish children, showed an elevated CRPus concentration to be associated with abnormal endothelial functioning and carotid thickening. It is hard to offer an explanation for the differences between this and the present study since the values for CRPus, FMD, and other risk factors were very similar. One explanation might be the existence of protective genetic factors in our population. Certainly, the scarcity of publications regarding the association between the CRPus concentration and vascular anatomy and function in healthy children shows there is still much work to be done. What has been shown is that, compared to eutrophic children, children with morbid obesity show a relationship between the CRPus concentration and changes in the dilation of the brachial artery and the IMT. However, the information currently available is insufficient to be able to say for certain whether these arterial abnormalities in obese children are caused by the inflammation present alone, or whether they are the consequence of a greater risk factor load with the degree of inflammation being a mere epiphenomenon.

The present results should stimulate the development of new programs focused on the prevention of and early intervention in childhood obesity. Physical activity could be the "ideal medication" - one that should be used from infancy to old age.[35]

Study Limitations

The present study suffers the following limitations: *a)* small sample size; *b)* the fact that this was a cross sectional study makes it impossible to establish cause-effect relationships; prospective studies are therefore essential; and *c)* given the small sample size, the lack of correlation between age and the CRPus concentration may be subject to some error.

CONCLUSIONS

This study provides evidence of a close relationship between the CRPus concentration (a marker of subclinical inflammation) and clinical markers of obesity. Only the follow-up of these children can clarify whether the CRPus concentration is the cause or consequence of the atherogenic process, and whether damage is reversible. The relationship between this marker and adipose variables in children shows it is necessary to investigate its relationship with metabolic variables that might increase the risk of diabetes or other chronic diseases of adult life.

REFERENCES

1. Zieske AW, Tracy RP, McMahan CA, Herderick EE, Homma S, Malcom G, et al. Elevated serum C-reactive protein levels and advanced atherosclerosis in youth. Circulation. 2005;25:1237-43.
2. Kavey REW, Daniels SR, Lauer RM, Atkinns DL, Hayman LL, Taubert K. American Heart Association guidelines for primary prevention of atherosclerotic cardiovascular disease beginning in chilhood. Circulation. 2003;107:1562-6.
3. Ross R. Mechanisms of disease: Atherosclerosis — An inflammatory disease. New Engl J Med. 1999;340:115-26.
4. Lagrand WK, Visser CA, Hermens WT, Niessen HW, Verheugt FW, Wolbink GJ, et al. C-reactive protein as a cardiovascular risk factor: more than an epiphenomenon? Circulation. 1999;100: 96-102.
5. National Health and Nutrition Examination Survey. Anthropometry Procedures Manual 2002. Available from: http//www.cdc. gov/nchs/ data/nhanes/bm.pdf
6. Fernández J, Redden D, Pietrobelli A, Allison D. Waist circumference percentiles in nationally representative samples of african-american, european-american an mexican-american children and adolescents. J Pediatr. 2004;145:439-44.
7. Moran A, Jacobs DR, Jr, Steinberger J, Hong CP, Prineas R, Luepker R, et al. Insulin resistance during puberty: results from clamp studies in 357 children. Diabetes. 1999;48:2039-44.
8. Barja S, Arteaga A, Acosta AM, Hodgson MI. Resistencia insulínica y otras expresiones del síndrome metabólico en niños obesos chilenos. Rev Med Chile. 2003;131:259-68.
9. Slaughter MH, Lohman TG, Boileau RA. Skinfold ecuation for estimation of body fatness in children and youth. Human Biology. 1998;60:709-23.
10. Touboul P, Hennerici MG, Adams H, Amarenco P, Desvarieux M, Ebrahim S, et al. Mannheim Intima-Media Thickness Consensus. Cerebrovasc Dis. 2004;18:346-9.
11. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery. A report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol. 2002;39:257-65.
12. Ridker PM, Rifai N. In: MediEdition, editor. C-reactive protein and cardiovascular disease. Boston: MediEdition; 2006.
13. Ford ES, Wayne HG, Myers GL, Rifai N, Ridker PM, Mannino M. C-reactive protein concentration distribution among US children and young adults: Findings from the National Health and Nutrition Examination Survey, 1999-2000. Clin Chem. 2003;49:1353-7.
14. Freedman DS, Kettel L, Dietz W, Srinivasan S, Berenson GS. Relationship of childhood obesity to coronary heart disease risk factors in adulthood: the Bogalusa Heart Study. Pediatrics. 2001;108:712-18.
15. Pasceri V, Cheng JS, Willerson JT, Yeh ET. Modulation of C-reactive protein-mediated monocyte chemoattractant protein-1 induction in human endothelial cells by anti-atherosclerosis drugs. Circulation. 2001. 103:2531-4.
16. Pasceri V, Willerson JT, Yeh ET. Direct proinflammatory effect of C-reactive protein on human endothelial cells. Circulation. 2000;102:2165-8.
17. Zwaka TP, Hombach V, Torzewski J. C-reactive protein-mediated low density lipoprotein uptake by macrophages. Circulation. 2001;103:1194-7.
18. Du Clos TW. Function of C-reactive protein. Ann Med. 2000;32: 274-8.
19. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, et al; Centers for Disease Control and Prevention, American Heart Association. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003;107:499-511.
20. Cook DG, Mendall MA, Whincup PH, Carey IM, Ballam L, Morris JE, et al. C-reactive protein concentration in children: relationship to adiposity and other cardiovascular risk factors. Atherosclerosis. 2000;149:139-50.
21. Ford ES. C-reactive protein concentration and cardiovascular disease risk factors in children. Circulation. 2003;108:1053-8.

22. Järvisalo MJ, Harmoinen A, Hakanen M, Paakkunainen U, Viikari JSA, Hartiala J, et al. Elevated C-reactive protein levels and early arterial changes in healthy children. Arterioscler Thromb Vasc Biol. 2002;22:1323-8.
23. Visser M, Bouter LM, McQuillan G, Wener M, Harris T. Elevated C-reactive protein levels in overweight and obese adults. JAMA. 1999;282:2131-5.
24. Wu DM, Chu NF, Shen MH, Chang JB. Plasma C-reactive protein levels and their relationship to anthropometric and lipid characteristics among children. J Clin Epidemiol. 2003;56:94-100.
25. Valle M, Martos R, Gascón F, Cañete R, Zafra MA, Morales R. Low-grade systemic inflammation, hypoadiponectinemia and a high concentration of leptin are present in very young obese children, and correlate with metabolic syndrome. Diabetes Metab. 2005;31:55-62.
26. Visser CA, Bouter LM, McQuillan G, Wener M, Harris T. Low grade systemic inflamation in overweight children. Pediatrics. 2001;107:e13.
27. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and the risk of developing type 2 diabetes mellitus. JAMA. 2001;286:327-34.
28. Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB, Wilson PWF. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. Circulation. 2004;110:380-5.
29. Pischon T, Rimm EB. Adiponectin: A promising marker for cardiovascular disease. Clin Chem. 2006;52:797-9.
30. Burrows R, Gattas V, Leiva L, Barrera G, Burgueño M. Biological, familial and metabolic characteristics of infantile and juvenile obesity. Rev Med Chile. 2001;129:1155-62.
31. Raitakari OT, Juonala M, Kähönen M, Taittonen L, Laitinen T, Mäki-Torko N, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood. The Cardiovascular Risk in Young Finns. JAMA. 2003;290:2277-83.
32. Davis PH, Dawson JD, Ryley WA, Lauer RM. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: The Muscatine Study. Circulation. 2001;104:2815-9.
33. Juonala M, Viikari JSA, Ronnemaa T, Taittonen L, Marniemi J, Raitakari OT. Childhood C-reactive protein in predicting CRPand carotid intima-media thickness in adulthood. The Cardiovascular Risk Risk in Young Finns Study. Arterioscler Thromb Vasc Biol. 2006;26:1883-8.
34. Diaz JJ, Arguelles J, Malaga I, Perillán C, Vijande M, Malaga S. C-reactive protein is elevated in the offspring of parents with essential hypertension. Arch Dis Child. 2007;92:304-8.
35. Elosua R. Actividad física. Un eficiente y olvidado elemento de la prevención cardiovascular, desde la infancia a la vejez. Rev Esp Cardiol. 2005;58:887-90.