ORIGINAL ARTICLE

C-Reactive Protein: A Biomarker Associated with the Metabolic Syndrome and Abdominal Obesity

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ABSTRACT

Clinical and biochemical parameters including high sensitivity C-reactive protein of an Argentine population of 467 adult patients from both sexes were evaluated in a cross-sectional study in order to analyze the distribution of high sensitivity C-reactive protein and to study the association of this biomarker with the metabolic syndrome and its components. The median value of high sensitivity C-reactive protein in the population was of 1.3 mg/L and there were no significant differences between both sexes. Subjects with metabolic syndrome had higher levels of high sensitivity C-reactive protein compared to those without metabolic syndrome, 3.1 and 1.1 (p = 0.000), respectively. Abdominal obesity, low HDL-C levels according to sex and blood pressure ≥ 130/85 mm Hg were independent variables associated with CRP > 3 mg/dl (OR 3.0 p = 0,000, OR 2.5 p = 0,000 and OR 2.1 p = 0.005, respectively). After adjusting for confounders, the relative likelihood of presenting high sensitivity C-reactive protein > 3.0 mg/L was 4.8 times greater in subjects with metabolic syndrome compared to those without metabolic syndrome. These results show a strong relation between adipose tissue, cardiovascular disease and inflammation.

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Key words > C-Reactive Protein - Obesity - Inflammation - Cardiovascular Diseases

Abbreviations >

BAHA	American Heart Association	**BMI**	Body mass index
WC	Waist circumference	**IR**	Insulin resistance
CDC	Centers for Disease Control	**NHLBI**	National Heart, Lung, and Blood Institute
HDL-C	High density lipoprotein-cholesterol	**BP**	Blood pressure
DM2	Type 2 diabetes mellitus	**CRP**	C-reactive protein
CVD	Cardiovascular disease	**hsCRP**	High sensitivity C-reactive protein
HT	Hypertension	**MS**	Metabolic syndrome
IDF	International Diabetes Federation	**TNF-α**	Tumor necrosis factor-α
IL-6	Interleukin-6		

BACKGROUND

The metabolic syndrome (MS), also known as plurimetabolic syndrome or X syndrome, is a controversial clinical condition. It is not a disease in itself but an association of metabolic disorders caused by the combination of genetic factors and factors related with lifestyle, particularly overnutrition and sedentary life. The metabolic disorders included in the MS are impaired glucose tolerance [type 2 diabetes mellitus (DM2), impaired glucose tolerance or impaired fasting glucose], insulin resistance (IR), central obesity, dyslipidemia, hypertension (HT), vascular inflammation and prothrombotic state; all these conditions are risk factors for cardiovascular disease (CVD) (1)

The MS has several definitions. Although all the classifications include the fundamental components of the syndrome, some include different factors which are sometimes difficult to measure. (2) The most common definitions used are those developed by the International Diabetes Federation (3) and the Adult Pannel Treatment III (ATP-III) of the National Cholesterol Education Program. (4)

The joint statement of the International Diabetes Federation (IDF), the National Heart, Lung, and Blood Institute (NHLBI) and the American Heart Association has produced a new definition of the MS adequate for medical practice worldwide. (5)

The presence of MS produces a five-fold increase

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in the risk of DM2 and a two-fold increase in the risk of CVD; (1) therefore, the importance of the diagnosis of MS is to identify persons with high risk of CVD. In Argentina, the prevalence of MS ranges between 20% and 30%, depending on age, gender and criteria used in the definition. (1, 5, 6)

The risk of CVD associated with MS is greater than the risk produced by the combination of its components. Epidemiological studies demonstrate that the risk increases in an exponential fashion. (2)

The evolution of the MS is progressive, beginning with the presence of certain causal factors (central adiposity and insulin resistance, as well as genetic factors). These give rise to the metabolic abnormalities (HT, dyslipidemia, and glucose metabolism disorders) which in turn are followed by the development of vasculopathy. This is initially subclinical but finally atherothrombotic complications develop. (2)

Inflammation has proved to play a crucial role in the development of atheromatosis and CVD, which is associated with DM2, central obesity and dyslipidemia, all components of the MS. Therefore, MS is an inflammatory process associated with elevated plasma levels of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). (7)

C-reactive protein, an acute-phase reactant which is the prototypical marker of inflammation, plays a key role in the pathophysiology of atherosclerotic disease, with active participation in the development and rupture of atheromatous plaque. (8) High sensitivity C-reactive protein (hsCRP) is a relevant biomarker of subclinical inflammation.

The American College of Cardiology and the AHA address measurement of hsCRP for CVD risk assessment in intermediate-risk adults. (9) The levels of hsCRP strongly correlate with MS and increased cardiovascular risk (10) yet the precise mechanisms for this increased propensity remain to be elucidated. (11) Among other factors, central adiposity plays a key role. (12)

The evidence suggests that the association of CRP with MS is stronger in women. (13) CRP levels vary among different populations and differ by gender and other factors such as obesity, smoking, alcohol consumption, and physical activity. No data have been published in Argentina.

The AHA and the Centers for Disease Control (CDC) have issued specific recommendations that pertain to the laboratory aspect of CRP and defined cut-points for clinical interpretation; CRP concentrations <1 mg/L are considered low, 1–3 mg/L average, and >3 mg/L high relative risk. (14)

High sensitivity CRP levels easily detect subclinical and clinical inflammation. Subclinic inflammation suggests a greater risk of suffering cardiovascular events; thus, its early identification allows the implementation of therapeutic and prophylactic measures. (15) In this sense, the determination CRP has important advantages as it identifies those subjects with greater cardiovascular risk; however, the causes of the underlying inflammatory state cannot be elucidated.

The goal of this study was to analyze the distribution of hsCRP in a population of the province of Buenos Aires, Argentina, and to study the association of this biochemical parameter with obesity and the MS.

METHODS

Study design

We conducted an observational and descriptive cross-sectional epidemiological study.

Inclusion and exclusion criteria

The study included 467 healthy adults (286 men and 181 women) between 18 and 67 years of age. The participants were selected from a population attending a public hospital in the province of Buenos Aires between 2009 and 2011. Patients with hsCRP > 10.0 mg/L suggestive of a relevant inflammatory condition, those with inflammations or infections, therapy with anti-inflammatory agents, pregnancy and those who had developed prior intense physical activity were excluded from the study.

Clinical data and definitions

The following data were recorded: age, gender, smoking habits. The anthropometric measurements as weight, height and waist circumference (WC) were obtained by trained staff, according to standardized procedures. (16) Body mass index (BMI) was calculated using the formula weight (kg)/ height (m)2.

The WC (cm) was determined at the midpoint between the lower rib margin and the level of the anterior superior iliac spine using a non-stretchable measuring tape, with the patient in the standing position. Blood pressure (BP) was measured (mm Hg) using a sphygmomanometer.

The MS was defined according to the AHA/NHLBI criteria (7) as the presence of three or more of the following risk factors: abdominal obesity with WC ≥102 cm in men and ≥88 cm in women; triglycerides ≥150 mg/dL or on drug treatment for elevated triglycerides; high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL in men and < 50 mg/dL in women or on drug treatment for reduced HDL-C; elevated blood pressure ≥130 mm Hg systolic blood pressure or ≥85 mm Hg diastolic blood pressure or on antihypertensive drug treatment and fasting glucose ≥100 mg/dL or on drug treatment for elevated glucose.

Biochemical determinations

Blood samples were obtained in the morning after a 12-hour fast by antecubital vein puncture and were drawn into heparin tubes. A Siemens ADVIA 1200 autoanalyzer with biochemistry analyzer reagents was used for biochemical determinations of hsCRP with immunoturbodimetric assay (CV: 2.0%), blood glucose levels, total cholesterol and triglycerides with enzymatic colorimetric assay method, and HDL-C was detected using direct method.

Statistical Analysis

Statistical analysis was performed using SPSS 15.0 statistical package for Windows (SPSS Inc, Chigago, Ill, USA).

Normality of distribution of variables was assessed using the Kolmogorov-Smirnov test and the Shapiro-Wilk test.

Mean and standard deviation were used for parametric variables and median and interquartile range for non-parametric variables. Analysis of the variance and the Mann-Whitney test were used to analyze parametric and non-parametric variables, respectively.

Proportions were compared with the chi square test with a 95% confidence interval.

Spearman's rank correlation coefficient was applied to analyze the relation between the different variables and hsCRP.

A multivariate analysis was then carried out to estimate the strength of the association between the components of the MS and hsCRP levels > 3.0 mg/dL by means of a multivariate regression model using forward stepwise Wald option and the OR (odds ratio) concept with its corresponding 95% confidence interval (CI) that associates the predictive variable studied with the outcome.

A p value < 5% was considered statistically significant. (18-20)

Ethical considerations

This study was approved by the Committee on Ethics of the Hospital Municipal de Agudos de Bahía Blanca. All the participants gave their informed consent.

RESULTS

The clinical characteristics of the participants are shown in Table 1. Levels of C-HDL were higher and glucose, triglycerides, BP and WC were lower in women compares to men.

Median hsCRP in the general population was of 1.3 mg/L.

Plasma levels of hsCRP were higher in women; however, this difference was not statistically significant (see Table 1).

The prevalence of MS was 18% (n = 85) and elevated hsCRP was present in 24.4% of the study population. Fifty three percent of patients with MS had hsCRP > 3.0 mg/L.

Median hsCRP in subjects with MS was higher compared to those without MS (3.1 and 1.1, p = 0.000, respectively) (Figure 1).

Figure 2 shows that hsCRP levels raised as the number of components of the metabolic syndrome increased.

As shown in Table 2, Spearman's correlation coefficients between the variables included in the MS and hsCRP were statistically significant, yet the correlation was poor for systolic BP, diastolic BP, glucose, triglycerides and LDL-C and more intense between hsCRP and WC.

Table 3 describes the characteristics of the subjects according to hsCRP level > 3.0 mg/L (hsCRP+) or hsCRP 3.0 mg/L (hsCRP-). Subjects with MS with hsCRP+ had greater values of BP, BMI and WC.

Logistic regression analysis identified WC > 102 cm in men and > 88 cm in women and BP > 130/85 mm Hg, low LDL-C level according to gender and BP > or = 130/85 as predictors of de hsCRP > 3.0 mg/L [OR 3.0 (95% CI 1.8-5.0), p = 0.000; OR 2.5 (95% CI 1.5-4.0), p = 0.000 and OR 2.1 (95% CI 1.3-3.6), p = 0.005, respectively] after adjusting for age, gender, smoking habits, elevated triglycerides and blood glucose ≥ 100 mg/dL.

In patients with MS, the odds of having hsCRP > 3.0 mg/L was of 4.8 (I95% CI 2.7-8.3; p = 0.000) in a model that adjusted for gender, age, cholesterol and smoking.

The average increase in hsCRP in patients with MS was of 0.3 mg/dL after adjusting for gender, cholesterol and smoking habits.

DISCUSSION

High-sensitivity CRP levels were lower in the study population compared to those reported for other American populations. (21)

In our study, median CRP levels in women (1.4 mg/L) are similar to those reported by Kelley-Hedgepeth et al. in white women enrolled in the Study of Women's Health Across the Nation (SWAN) (1.5 mg/L) but are different from the values reported in other populations: African-American women had 3.2 mg/L, Hispanic 2.3 mg/L, Chinese 0.7 mg/L, and Japanese 0.5 mg/L. (22)

There were no significant differences in hsCRP

Table 1. Epidemiological characteristics of the population divided by gender

Variable	Total (n = 467)	Men (n = 286)	Women (n = 181)	p
Age (years)	37 ± 13	38 ± 13	37 ± 12	0.707
SBP (mm Hg)	114 ± 19	117 ±19	108 ± 17	0.000
DBP (mm Hg)	71 ± 13	74 ± 14	67 ± 11	0.000
BMI (kg/m2)	28 ± 6	29 ± 5	27 ± 7	0.016
WC (cm)	88 ± 16	92 ± 14	80 ± 16	0.000
Blood glucose (mg/dl)	93 ± 22	95 ± 26	89 ± 14	0.002
Triglycerides (mg/dl)*	95 (1,023)	106 (1,023)	85 (378)	0.000
HDL cholesterol (mg/dl)	53 ± 15	48 ± 12	60 ± 13	0.000
Total cholesterol	188 ± 38	190 ± 40	186 ± 34	0.225
hsCRP (mg/L)*	1.3 (9.9)	1.2 (9.8)	1.4 (9.9)	0.227
Current smokers, n (%)**	159 (34)	106 (22.7)	53 (11.3)	0.084
Diabetics, n (%)**	18 (3.9)	14 (3.0)	4 (0.9%)	0.142
Hypertension, n (%)**	94 (20.1)	69 (14.8)	25 (5.4)	0.007
Dyslipidemia, n (%)**	188 (40.3)	98 (21.0)	286 (61.3)	0.012

SBP: Systolic blood pressure.DBP: Diastolic blood pressure. BMI: Body mass index. WC: Waist circumference. hsCRP: High sensitivity C-reactive protein.
p value: Differences between men and women. Data are shown as mean ± standard deviation median an interquartile* range or as numbers and percentages**.

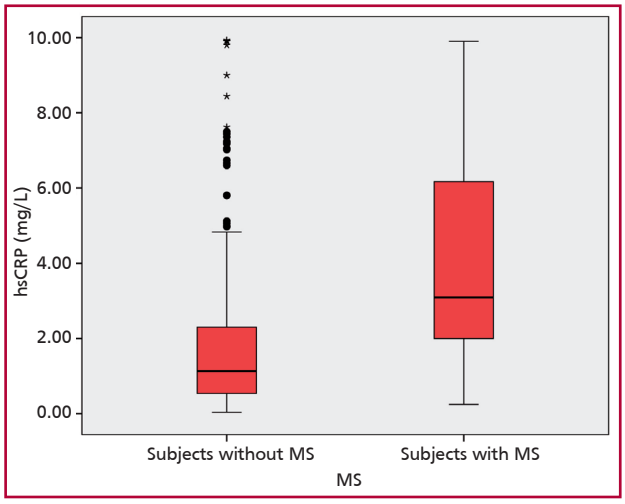

Fig. 1. Median C-reactive protein in the population with or without metabolic syndrome. hsCRP: High sensitivity C-reactive protein. MS: Metabolic syndrome.

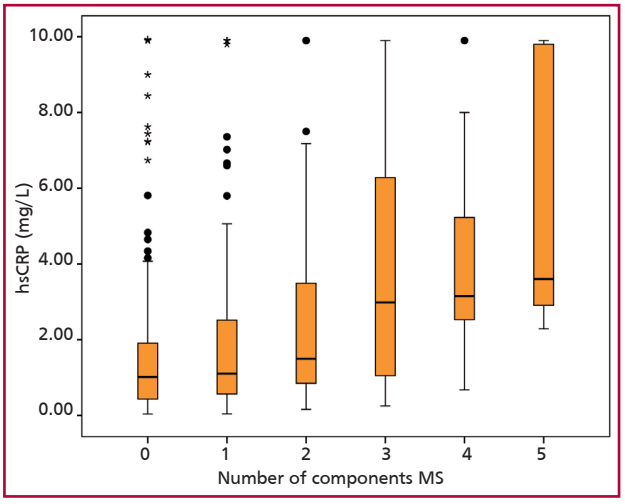

Fig. 2. Median concentration of high sensitivity C-reactive protein according to the number of components of the metabolic syndrome. hsCRP: High sensitivity C-reactive protein. MS: Metabolic syndrome.

Table 2. Spearman's correlation coefficient between the variables included in the metabolic syndrome criteria and high sensitivity C-reactive protein

Variable	Spearman's correlation coefficient	p
SBP (mm Hg)	0.193	0.000
DBP (mm Hg)	0.157	0.000
WC (cm)	0.480	0.000
Blood glucose (mg/dl)	0.103	0.000
Triglycerides (mg/dl)	0.123	0.008
HDL cholesterol (mg/dl)	0.137	0.003

SBP: Systolic blood pressure. DBP: Diastolic blood pressure. WC: Waist circumference.

Table 3. Characteristics of the subjects with metabolic syndrome stratified according to hsCRP level > 3.0 mg/L (hsCRP+) or hsCRP ≤ 3.0 mg/L (hsCRP-)

Variable	hsCRP+ n = 45	hsCRP- n = 40	p
Age (years)	47 ± 10	48 ± 11	0.786
SBP (mm Hg)	143 ± 21	131 ± 21	0.013
DBP (mm Hg)	90 ± 12	84 ± 14	0.034
BMI (kg/m2)	38 ± 6	32 ± 4	0.000
WC (cm)	112 ± 12	101 ± 10	0.000
Blood glucose (mg/dl)	110 ± 35	120 ± 47	0.301
Triglycerides (mg/dl)	142 (781)	157 (980)	0.117
HDL cholesterol (mg/dl)	44 ± 12	44 ± 8	0.906
Total cholesterol (mg/dl)	199 ± 36	210 ± 41	0.178
Current smokers, n (%)	12 (14.1)	17 (20)	0.124
Diabetics, n (%)	6 (7.1)	10 (11.8)	0.170
Hypertension, n (%)	37 (43.5)	25 (29.4)	0.041
Dyslipidemia, n (%)	41 (48.2)	38 (44.7)	0.485

SBP: Systolic blood pressure. DBP: Diastolic blood pressure. BMI: Body mass index. WC: Waist circumference. hs CRP: high sensitivity C-Reactive Protein

levels between genders. The information available from different parts of the world is controversial. While Rifai et al. did not find differences in an American population, Khera et al. found differences between men and women of the same race. (21, 22)

As other authors have reported and in other populations, (13) all the components of the MS had a significant correlation with hsCRP. Yet, only WC has a more intense correlation with certain clinical relevance. Patients with MS had higher levels of hsCRP compared to those without MS.. However, it should be noted that, as shown in the frequency graph and box diagram, a group of patients without MS presented elevated hsCRP levels which might be due to the presence of subclinical inflammation or be an eventual value. High-sensitivity CRP levels were not measured at a second occasion due to the characteristics of the study.

Probably, the most relevant finding of this study is that CRP levels were higher when the number of components of the MS increased, suggesting a greater association between inflammation and the MS and a better interpretation of increased cardiovascular risk observed in these patients. The risk of cardiovascular events is greater as the number of components of the MS increases, reflected by the inflammatory state in subjects with hs CRP.

Obesity is an inflammatory condition. Abdominal adipose tissue produces cytokines and adipokines which promote recruitment of monocytes and activation of macrophages which is essential for the expression of TNF and IL-6 and for increasing liver CRP

production. Although insulin may inhibit this mechanism, in the presence of an IR state, as in diabetics and in subjects with MS, this control mechanism fails and liver CRP production increases. (23, 24) Adipose tissue has been associated with CRP secretion, and the relation between abdominal obesity and subclinical inflammation might have an anatomic cause. (23)

Elevated WC is a marker of central obesity and a diagnostic criterion for the diagnosis of MS according to the AHA/NHLBI statement. This investigation team has previously observed that WC in the best anthropometric measurement that discriminates between the presence and the absence of cardiovascular risk after analyzing its association with the cardiometabolic risk and comparing it with the BMI (unpublished data).

This study showed that WC had a significant and independent association with elevated hsCRP, which was also independent of confounders (such as age, gender and smoking habits) in subjects with MS, demonstrating that central obesity is the main contributor to elevated CRP plasma levels.

Hypertension and DM2 are associated with high levels of CRP, (23) sharing pathophysiological mechanisms which have been previously mentioned. The present study demonstrated the independent association between BP ≥ 130/85 mm Hg, glucose ≥ 100 mg/dL with elevated hsCRP.

As mentioned before, several mechanisms have been proposed to explain the relation between the components of MS and subclinical elevation of CRP.

Hypertension and dyslipidemia may produce endothelial dysfunction and subclinical atherosclerosis, leading to an inflammatory state and increasing CRP levels. (23)

The study also showed that hsCRP was higher when the number of components of the MS increased. The goal of the diagnosis of patients with MS is to establish the risk of developing CVD, as it is well known that the risk produced by the combination of the MS components increases geometrically. Therefore, it might be assumed that in the studied population elevated hsCRP implies greater cardiovascular risk.

Study limitations

A cause and effect relationship between the MS and hsCRP was not established due to the cross-sectional design of the study, and only the association between both parameters was verified.

Despite the CDC/AHA statement recommends that hsCRP should be measures twice with an interval of at least two weeks to establish individual CVD risk, we could only perform one determination

CONCLUSIONS

Determination of hsCRP is simple and available for medium complexity laboratories for evaluating cardiovascular risk and may be useful to apply prevention and treatment strategies which help to control DM 2 and CVD epidemics affecting the world population.

Conflicts of interest

None declared

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RESUMEN

Proteína C reactiva: un marcador bioquímico asociado con el síndrome metabólico y la obesidad abdominal

Con el objetivo de analizar la distribución de proteína C reactiva de alta sensibilidad en una población argentina y estudiar la asociación de este parámetro bioquímico con el síndrome metabólico y con los componentes que lo conforman, se realizó un estudio transversal que incluyó 467 pacientes adultos de ambos sexos en los que se evaluaron parámetros clínicos y bioquímicos, incluida la proteína C reactiva de alta sensibilidad. El valor de la mediana de proteína C reactiva de alta sensibilidad en la población fue de 1,3 mg/L y no se observaron diferencias entre sexos. Los sujetos con síndrome metabólico presentaron niveles superiores de proteína C reactiva de alta sensibilidad respecto de aquellos sin síndrome metabólico, 3,1 y 1,1 (p = 0,000), respectivamente. Las variables asociadas en forma independiente con una PCR > 3 mg/dl fueron la obesidad abdominal, el C-HDL bajo según el sexo y la presión arterial ≥ 130/85 mm Hg (OR 3,0 p = 0,000, OR 2,5 p = 0,000 y OR 2,1 p = 0,005, respectivamente). La probabilidad relativa de que los individuos con síndrome metabólico presentaran proteína C reactiva de alta sensibilidad > 3,0 mg/L fue 4,8 veces mayor respecto de aquellos sin síndrome metabólico luego de ajustar por variables confundidoras. Los resultados obtenidos evidencian la fuerte relación existente entre tejido adiposo, enfermedad cardiovascular e inflamación.

Palabras clave > Proteína C reactiva - Obesidad - Inflamación - Enfermedades cardiovasculares

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