High-sensitivity c-reactive protein epidemiological behavior in adult individuals from Maracaibo, Venezuela

De alta sensibilidad la proteína C reactiva epidemiológica comportamiento en los individuos adultos de Maracaibo, Venezuela

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Abstract

Objectives: High-sensitivity C-Reactive Protein (hs-CRP) is one of the most applied inflammation markers; therefore, the main objective of this research is to evaluate its epidemiological behavior in adult subjects of the Maracaibo City, Venezuela.

Materials and Methods: A total of 1,422 subjects, 704 women (49.5%) and 718 men (50.5%), were enrolled in the Maracaibo City Metabolic Syndrome Prevalence Study. The results were expressed as medians and inter-quartile ranges (p25-p75). Differences were determined through the Mann-Whitney U test and one-way ANOVA test with the Bonferroni adjustment. A multiple logistic regression model was designed for the analysis of the main factors associated with high serum hs-CRP levels.

Results: Overall hs-CRP median was 0,.372 mg/L (0.126-0.765 mg/L), 0,382 mg/L (0.122-0.829 mg/L) for women and 0.365 mg/L (0.133-0.712 mg/L) for men; p=0.616. An increasing pattern was observed in hs-CRP concentrations through age, BMI, waist circumference and HOMA2-IR categories. After adjusting for independent variables, a greater risk for elevated hs-CRP levels was observed with female gender, hypertriacylglyceridemia, obesity, diagnosis of metabolic syndrome and very large waist circumference values.

Conclusions: Elevated hs-CRP levels are related to the metabolic syndrome but not with each of their separate components, being a greater waist circumference one of the more important risk factors, but only at values much higher than those proposed for our population.

Key Words: Cardiovascular disease, low-grade inflammation, risk factors, metabolic syndrome.

Introducción

Cardiovascular Disease (CVD) is currently considered a true global epidemic[1], constituting the main cause of morbid-mortality in the adult population at a worldwide, national and regional level[2-4]. In 2004, 17.3 millions of people reportedly died worldwide due to this cause, and it has been predicted that by 2030, yearly global deaths due to CVD will have reached 23.5 million of people[2]. Likewise, in our country in 2009, 20.30% of all deaths were attributed to heart disease[3], whereas in the Zulia State 23.4% of all deceases were caused by CVD in the year 2008[4]. As a consequence, these pathologies represent a problem for

public health systems due to the large economic and human resource burdens involved in its prevention, management and rehabilitation[5].

Traditionally, these entities have been associated with risk factors such as dyslipidemia, high blood pressure (HBP), obesity and insulin resistance[6]. Moreover, it is widely accepted that an inflammatory component plays a preponderant role not only in the development of these risk factors, but also in the initiation and progression of atherosclerosis, the principal physiopathologic element of CVD[7]. Hence, numerous studies have focused on the search of inflammatory biomarkers which would allow the early detection of this process, improving the prediction of cardiovascular events. In the clinical field, the molecule with the greatest acceptance in the clinical field for this purpose is the high-sensitivity C-Reactive Protein (hs-CRP)[8], an acute-phase reactant belonging to the pentraxin family, highly sensitive for the detection of inflammatory processes[9].

In effect, current evidence[10] shows that local microenvironment in an atherosclerotic plaque represents more than a simple lipidic infiltration and that the inflammatory process at this stage is more complex than thought decades ago, where CRP, more than a simple observant, is an active molecule with direct participation at the endothelium[11]. Nevertheless, the relationship between hs-CRP levels and cardiovascular morbimortality has not been sufficiently clarified[12]. Thus, numerous techniques have been described for the quantification of plasmatic CRP levels; however, because the standard methods for its determination lose sensitivity with serum levels lower than 3 mg/L, the detection of low-grade inflammation states is not viable[13]. The first-rate test used for the identification of these states is the determination of high-sensitivity CRP (hs-CRP), as this technique allows for the precise measuring of serum values as low as 0.05 mg/L, showing much more sensitivity than other methods[14]. Through the application of this technique, the interpretation of CRP levels for the prediction of CVD risk becomes a possible endeavor[15].

The clinical utility of hs-CRP is a currently widely discussed aspect; not only in regard of its usefulness in the prediction of cardiovascular events, but also in account of the potential validity of its interpretation in other clinical scenarios[16]. Consequently, experimental studies are necessary for the clarification of its true role as a cardiovascular risk factor, as well as population describing the behavior of hs-CRP values. Nonetheless, studies on hs-CRP are scarce both nationally and in Latin America in general, particularly in respect of its relationship to CVD, obesity, dyslipidemia, insulin resistance and other cardiometabolic factors. Accordingly, the main objective of this research is the evaluation of the epidemiological behavior of serum hs-CRP concentrations in adult individuals of the Maracaibo City, Venezuela.

Materiales y Métodos

Sample Selection

The Maracaibo Metabolic Syndrome Prevalence Study (MMSPS)[17] was a cross-sectional research study which took place in the city of Maracaibo-Venezuela, with the purpose of identifying and evaluating metabolic syndrome and cardiovascular risk factors in the adult population of the Maracaibo municipality. There were 2,230 subjects enrolled as previously described, out of which 1,422 were selected based on hs-CRP measurement and exclusion based on personal history of autoimmune disease and/or chronic inflammatory disease, as well as individuals with an active infectious disease at the moment of evaluation. All participants signed a written consent before being interrogated and physically examined. The study was approved by the Ethics Committee of the Endocrine and Metabolic Diseases Research Center.

Subject Evaluation

A full medical history was obtained using the Venezuelan Popular Powers Health Ministry approved medical, filled out by trained personnel. Socioeconomic status[18] and ethnic background were also assessed. The International Physical Activity Questionnaire (IPAQ)[19] was used for the evaluation of physical activity. For the statistical analysis only the leisure time subsphere was taken into account, because of the overestimation of global physical activity in our population when all 4 IPAQ spheres (Work, Active Transportation, Home, Leisure Time) are assessed through the IPAQ Scoring protocol. Accordingly, our population was classified based on the degree of physical activity performed exclusively during leisure time, in 3 groups: a) Sufficiently Active Subjects, who perform vigorous physical activity for ≥20 minutes at least 3 days a week, or moderate physical activity ≥30 minutes at least 5 days a week; b) Insufficiently Active Subjects, those who performed some physical activity but did not achieve the previous recommendations for vigorous and moderate physical activity; and c) Inactive Subjects, which comprises all individuals who do not perform any of physical activity, or lowers degrees than previously described.

Blood Pressure

For the quantification of Blood Pressure (BP), the auscultatory method was used, employing a calibrated and adequately validated sphygmomanometer. Subjects were sitting and at rest for a minimum of 15 minutes, with their feet on the ground and the arm used for the measurement at the level of the heart. Diagnostic criteria proposed by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) were used for the definition of subjects as hypertensive or non-hypertensive[20].

Anthropometry

Waist circumference was measured using calibrated measuring tapes in accordance to the anatomical landmarks proposed by the USA National Institutes of Health pro-

tocol[21]: midpoint between the lower border of the rib cage and the iliac crest, taking the length at the end of expiration, with participants standing and wearing only undergarments. For its analysis, the obtained data were divided on quartiles for each gender, obtaining the following classification: For women: Q1 (<81.35 cm); Q2 (81.35-90.99 cm); Q3 (91-99.99 cm) and Q4 (≥100 cm); and for men: Q1 (<88 cm); Q2 (88-97.99 cm); Q3 (98-107.11 cm) and Q4 (≥107.12 cm). Weight was determined using a digital weighing scale, while height values were obtained with a vertical tape measure calibrated in centimeters and millimeters; subjects had their feet bare and all clothing which could alter the determinations were removes. For the quantification of the Body Mass Index (BMI)[22], the [Weight/Height^2] formula was applied. The obtained values were grouped in 3 categories: Normal weight Subjects (<24.99 kg/m^2), Overweight Subjects (25-29.99 kg/m^2) and Obese Subjects (≥30 kg/m^2).

Laboratory Analysis

After overnight fasting, serum levels of glucose, total cholesterol, TAG and HDL-C were determined employing commercial enzymatic-colorimetric kits (Human Gesellshoft Biochemica and Diagnostica MBH) and specialized computerized equipment. LDL-C levels were calculated through Friedewald's formula[23]. Serum hs-CRP levels were quantified employing immunoturbidimetric essays (Human Gesellshoft Biochemica and Diagnostica MBH); and basal insulin levels utilizing International Inc. USA. New Jersey DRG insulin kits. For the evaluation of Insulin Resistance (IR), the HOMA2-IR model proposed by Levy et al.[24] was used, calculated through the HOMA-Calculator available at http://www.dtu.ox.ac.uk/homacalculator/index.php from the Oxford Centre for Diabetes, Endocrinology and Metabolism (http://www.dtu.ox.ac.uk/). For statistical analyses, these values were distributed into quartiles: Q1 (<1.3); Q2 (1.3-1.89); Q3 (1.9-2.69) and Q4 (≥2.7). For the diagnosis of Metabolic Syndrome (MS), the criteria from the IDF/AHA/NHLBI/WHF/IASO 2009 consensus were applied[25], after the determination of elevated waist circumference (≥80cm for females and ≥90cm for males), blood pressure, serum levels of triacylglycerides (TAG), high-density lipoprotein (HDL-C) and basal glycemia on all subjects.

Statistical Analysis

Qualitative variables were expressed in absolute and relative frequencies, evaluating association through the χ^2 test. Normal distribution of variables was assessed through the Kolmogorov-Smirnov and Geary tests according to the sample size. Variables with non-normal distribution were expressed in medians and interquartile ranges. Quantitative variables which showed a normal behavior, or those with a non-normal distribution which were normalized after applying a logarithmic transformation, were expressed as arithmetic mean±SD (standard deviation), utilizing the T-Student test for comparisons between 2 groups. High sensitivity-CRP values were expressed as medians and interquartile ranges (p25-p75), applying Mann-Whitney's U Test for comparisons between 2 groups, and One-Way ANOVA test with the Bonferroni adjustment for comparisons among 3 or more groups. Likewise, logistic regression models were designed, estimating Odds Ratios (IC 95%) for elevated hs-CRP (defined as hs-CRP ≥0.765 mg/L, 75th percentile for our population), adjusted by gender, age groups, BMI categories, elevated waist circumference (specific for each model), diagnosis of MS, and high serum TAG (≥150mg/dL). Data were analyzed with Statistical Product and Service Solutions (SPSS) v.19 (SPSS IBM Chicago, IL), and the R Project for Statistical Computing, developed at Bell Laboratories, available at http://www.r-project.org/, considered significant when p<0.05.

Resultados

Characteristics of the Population

A total of 1,422 subjects were studied, of which 49.5% (n=704) corresponded to the female gender, and 50.5% (n=718) to the male gender. General characteristics of the studied population are presented in Table 1, while anthropometric and laboratory variables are observed in Table 2. The overall median for hs-CRP was 0.372 mg/L (0.126-0.765 mg/L); percentile distribution for serum hs-CRP concentrations in the main population, as well as by sex, is presented in Table 3.

Serum hs-CRP, sociodemographic characteristics and cardiometabolic diagnoses

The analysis of hs-CRP serum levels in our population by sociodemographic variables is shown in Table 4. When compared by genders, hs-CRP concentrations were greater in women than in men, 0.382 vs. 0.365 mg/L, p=0.616. High-sensitivity-CRP serum concentrations showed an ascending trend as age increased, displaying significant difference between subjects aged 20-29 and 40-49 years: 0.299 (0.090-0.644) mg/L vs. 0.471 (0.170-0.874) mg/L, respectively; p=0.003. On the other hand, when assessing the behavior of serum hs-CRP concentrations by ethnic groups, no significant differences were detected (p=0.214). Similar results were witnessed when contrasting serum hs-CRP levels among the diverse socioeconomic statuses (p=0.139). On the contrary, serum hs-CRP concentrations were significantly greater in hypertensive subjects vs. non-hypertensive subjects ($p=1.88x10^{-5}$), as well as in diabetics vs non-diabetics (p=0.0006), and in individuals with a diagnosis of MS vs those without such diagnosis ($p=3.29x10^{-17}$).

Serum hs-CRP concentration and Physical Activity

The behavior of serum hs-CRP concentrations in the general population according to the degree of leisure-time physical activity performed is depicted in Figure 1, where a decrease in serum hs-CRP proportions is evidenced as the degree of physical activity increased, displaying values of 0.404 (0.144-0.840) mg/L for Inactive Subjects and 0.285 (0.058-0.576) mg/L for Sufficiently Active Subjects.

After making comparisons through the One-Way ANOVA test with Bonferroni adjustments (significance when p<0.016), significant differences were found between the levels of serum hs-CRP displayed by Inactive Subjects and those of the Sufficiently Active Subjects (p=0.001). In spite of this, no statistically significant differences were ascertained regarding the serum hs-CRP concentrations of Insufficiently Active vs. Sufficiently Active subjects (p=0.047), nor between those of Inactive vs. Insufficiently Active subjects (p=0.474).

Serum hs-CRP concentration and BMI

A progressive increase in serum hs-CRP values is observed contingent upon an increase in BMI, with values of 0.309 (0.084-0,623) mg/L for Normal weight Subjects and 0.539 (0.200-1.109) mg/L for Obese individuals. Significant differences are evidence when contrasting Normal weights and Obese subjects ($p=5.78x10^{-8}$), as well as Overweight and Obese subjects ($p=4.02x10^{-9}$) (Figure 2).

Serum hs-CRP concentration and waist circumference

Serum hs-CRP levels show an upwards tendency through waist circumference quartiles for each gender as the latter values increase, with concentrations of 0.279 (0.063-0.577) mg/L and 0.297 (0.065-0.575) mg/L in the first quartile; and of 0.586 (0.228-1.241) mg/L and 0.474 (0.188-1.290) mg/L in the fourth quartile, for females and males, respectively (Figure 3). Significant differences were found among females when comparing Q4 vs. Q1 (p=0.001) and Q4 vs. Q2 (p=0.001); as were encountered among males when contrasting Q4 vs. ($p=3.26x10^{-5}$), Q4 vs. Q2 (p=0.002) and Q4 vs. Q3 (p=0.001).

Serum hs-CRP concentration and insulin resistance

In the same vein, when categorizing the population in HOMA2-IR quartiles, an ascending trend is exposed in serum hs-CRP values regarding these groups as the degree of insulin resistance escalates (Figure 4). Values of 0.28 (0.066-0.565) mg/L were found for the first quartile; and of 0.466 (0.179-1.071) mg/L for the fourth quartile; significant differences were detected between individuals of Q4 vs Q1 ($p=2.37x10^{-8}$), Q4 vs Q2 ($p=1.07x10^{-6}$) and Q4 vs Q3 ($p=1.84x10^{-4}$).

Risk Factors for elevated serum hs-CRP in Maracaibo

Risk factors for the presence of increased serum hs-CRP concentrations in our population are shown in Table 4. In the first logistic regression model, it was evidenced that subjects with hypertriacylglyceridemia had the greatest levels of hs-CRP (OR=2.06, CI95%=1.48-2.86; p<0.01); however, no significant p values were observed in those with central obesity. In the second model, higher cut-off points for waist circumference (females: ≥88cm; males: ≥102 cm) were employed for the definition of abdominal obesity, without achieving to show any significant evidence that the risk for presenting high serum hs-CRP levels would increase at these points either. In the final third model, where higher cut-off points were utilized (females: ≥125cm; males: ≥140cm), these subjects were found to be twice as prone to display elevated hs-CRP levels with statistical significance. It is noteworthy to highlight that in the women`s group, obesity and the diagnosis of MS are conditions which increase the risk for exhibiting low-grade inflammation.

Table 1. General characteristics of the population, evaluated by gender. The Maracaibo City Metabolic Syndrome Prevalence Study, 2013.

	Females (n=704)		Males (n=718)		Total (n=1422)	
	n	%	n	%	n	%
Age Group (%)						
18-19	60	8.5	52	7.2	112	7.9
20-29	148	21.0	223	30.9	370	26.0
30-39	111	15.8	136	18.9	247	17.4
40-49	175	24.9	125	17.4	300	21.1
50-59	126	17.9	118	16.6	245	17.2
≥60	74	11.9	64	8.9	184	10.4
Ethnic Group(%)						
Mixed Race	528	75.0	558	77.7	1086	76.4
Hispanic Whites	110	15.6	105	14.6	215	15.1
Afro-Venezuelas	20	2.8	22	3.1	42	3.0
American-Indians	41	5.8	33	4.6	74	5.2
Others	5	0.7	0	0	5	0.4
Socioeconomic Status (%)						
Stratum I: High Class	7	1.0	10	1.4	17	1.2
Stratum II: Upper-Middle Class	117	16.6	141	19.6	258	18.1
Stratum III: Middle Class	247	35.1	300	41.8	547	38.5
Stratum IV: Working Class	287	40.8	245	34.1	532	37.4
Stratum V: Lower – Extreme Poverty	46	6.5	22	3.1	68	4.8
Physical Inactvity[a] (%)	521	74.0	398	55.4	919	64.6
Obesity [b] (%)	213	32.7	232	35.7	445	34.2
Insulin Resistance[c] (%)	331	49.9	340	48.8	671	49.3
Type 2 Diabetes mellitus [d] (%)	45	6.4	49	6.8	94	6.6
HBP [d] (%)vv	128	18.2	195	27.2	323	22.7
MS (%)	279	39.6	322	44.8	601	42.3
Total (%)	704	49.5	718	50.5	1422	100

[a] <10 minutes/week of moderate physical activity
[b] Body Mass Index ≥30Kg/m^2.
[c] HOMA2-IR ≥2.
[d] Personal history

Table 2. Clinical and biochemical variables, evaluated by gender. The Maracaibo City Metabolic Syndrome Prevalence Study, 2013.

	Females (n=704)	Males (n=718)	*p**
Age (Years)	41±16	38±15	0.0007
BMI (kg/m^2)	28.1±6.4	28.9±6.3	0.006
Waist Circumference (cm)	91.7±14.2	99.1±16.2	$1.05x10^{-20}$
HOMA2-IR	2.3±1.4	2.3±1.5	0.281
Basal Glycemia (mg/dL)	97.6±29.9	99.1±36.5	0.747
Insulin (UI/ml)	15.2±10.1	15±9.8	0.206
TAG (mg/dL)	116.3±84.5	149.2±122.9	$1.37x10^{-11}$
Total Cholesterol (mg/dL)	193.7±46.0	185.7±48.8	0.0002
HDL-C (mg/dL)	46.6±11.7	40.0±9.6	$2.32x10^{-30}$
LDL-C (mg/dL)	122.9±38.9	116.3±38.0	0.003
SBP (mmHg)	117.6±17.2	121.9±16.1	$1.3x10^{-7}$
DBP (mmHg)	75.4±10.7	78.8±11.8	$3.3x10^{-8}$

*t-Student test. Statistically significant differences (p<0.05).
TAG=Triacylglyceridos; BMI=Body Mass Index; HDL-C=High-Density Lipoprotein; LDL-C=Low-Density Lipoprotein; SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure

Table 3. Percentile distribution of serum hs-CRP concentrations in the general population and by gender. The Maracaibo City Metabolic Syndrome Prevalence Study, 2013.

	hs-CRP concentration (mg/L)						
	p25	p50	p75	p90	p95	p97.5	p99
Females	0.122	0.381	0.829	1.490	2.073	2.995	5.557
Males	0.133	0.365	0.712	1.519	2.165	3.020	5.170
Total	**0.126**	**0.372**	**0.765**	**1.490**	**2.105**	**2.995**	**5.170**

Tabla 4. Serum hs-CRP concentrations by sociodemographic variables and cardiometabolic profiles in the general population. The Maracaibo City Metabolic Syndrome Prevalence Study, 2013.

	hs-CRP concentration (mg/L)		
	Median	p25-p75	*p*
Gender			[a]**0.616**
Females	0.381	0.122-0.829	
Males	0.365	0.133-0.712	
Age Groups (Years)			[c]**8.12x10^{-45}**
18-19	0.213	0.044-0.547	
20-29*	0.299	0.090-0.644	
30-39	0.448	0.093-0.898	
40-49*	0.471	0.170-0.874	
50-59	0.402	0.167-1.030	
≥60	0.447	0.216-0.954	
Ethnic Groups			[b]**0.214**
Mixed Race	0.366	0.108-0.750	
Hispanic Whites	0.400	0.184-0.797	
Afro-Venezuelas	0.337	0.176-0.880	
American-Indians	0.447	0.170-1.012	
Others	0.572	0.318-0.668	
Socioeconomic Status (%)			[b]**0.139**
Stratum I: High Class	0.174	0.051-0.342	
Stratum II: Upper-Middle Class	0.338	0.126-0.644	
Stratum III: Middle Class	0.377	0.134-0.720	
Stratum IV: Working Class	0.397	0.105-0.862	
Stratum V: Lower – Extreme Poverty	0.465	0.226-0.794	
High Blood Pressure			[a]**1.88x10^{-5}**
Non-Hypertensives	0.348	0.104-0.692	
Hypertensives	0.466	0.189-0.943	
Type 2 Diabetes Mellitus			[a]**0.006**
Non-Diabetics	0.363	0.123-0.741	
Diabetics	0.561	0.216-1.086	
Metabolic Syndrome			[a]**3.29x10^{-17}**
Present	0.309	0.083-0.591	
Absent	0.504	0.207-1.079	

Mann-Whitney's U Test [a] Statistically significant differences (p<0.05)
One-Way ANOVA with Bonferroni adjustment: Statistically significant differences: [b](p<0.01) ot [c](p<0.0083)
* Statistically significant difference between age groups 20-29 vs 40-49 (p=0.003)

Table 5. Logistic regression models of risk factors for elevated hs-CRP in adult individuals. The Maracaibo City Metabolic Syndrome Prevalence Study, 2013.

	Model 1*				Model 2**		Model 3***	
	Crude Odds Ratio (IC 95%[a])	*p*[b]	Adjusted Odds Ratio[c] (IC 95%[a])	*p*[b]	Adjusted Odds Ratio[c] (IC 95%[a])	*p*[b]	Adjusted Odds Ratio[c] (IC 95%[a])	*p*[b]
Gender								
Males	1.00	-	1.00	-	1.00	-	1.00	-
Females	1.23 (0.97 - 1.56)	0.09	1.50 (1.15 - 1.96)	< 0.01	1.42 (1.08 - 1.86)	0.01	1.48 (1.14 - 1.92)	< 0.01
Metabolic Syndrome								
Absent	1.00	-	1.00	-	1.00	-	1.00	-
Present	3.05 (2.38 - 3.91)	< 0.01	1.84 (1.27 - 2.67)	< 0.01	1.72 (1.20 - 2.47)	< 0.01	1.68 (1.17 - 2.41)	< 0.01
Hypertriacylgliyceridemia[d]								
Absent	1.00	-	1.00	-	1.00	-	1.00	-
Present	3.06 (2.38 - 3.94)	< 0.01	2.06 (1.48 - 2.86)	< 0.01	2.07 (1.49 - 2.88)	< 0.01	2.18 (1.56 - 3.05)	< 0.01
Elevated Waist Circumference[e]								
Absente	1.00	-	1.00	-	1.00	-	1.00	-
Presente	3.06 (2.38 - 3.94)	< 0.01	0.80 (0.51 - 1.25)	0.32	1.20 (1.49 - 2.88)	0.34	2.39 (1.02 - 5.56)	0.04
Age Groups (Years)								
< 20	1.00	-	1.00	-	1.00	-	1.00	-
20-29	1.26 (0.70 - 2.29)	0.44	0.92 (0.60 - 2.05)	0.73	1.06 (0.57 - 1.95)	0.86	1.07 (0.58 - 1.96)	0.84
30-39	2.60 (1.43 - 4.71)	< 0.01	1.88 (0.90 - 3.18)	0.10	1.59 (0.85 - 2.99)	0.15	1.62 (0.86 - 3.04)	0.13
40-49	2.22 (1.23 - 3.99)	< 0.01	1.11 (0.59 - 2.11)	0.75	1.02 (0.54 - 1.92)	0.96	1.06 (0.56 - 1.99)	0.86
50-59	2.59 (1.43 - 4.70)	< 0.01	1.28 (0.67 - 2.45)	0.46	1.17 (0.61 - 2.23)	0.64	1.21 (0.64 - 2.30)	0.56
≥60	2.27 (1.20 - 4.31)	0.01	1.02 (0.50 - 2.05)	0.97	0.93 (0.46 - 1.87)	0.84	0.98 (0.49 - 1.97)	0.96
BMI (Kg/m^2)								
≤ 24.9	1.00	-	1.00	-	1.00	-	1.00	-
25 – 29.9	1.16 (0.83 - 1.61)	0.39	0.92 (0.62 - 1.37)	0.67	0.79 (0.54 - 1.16)	0.23	0.84 (0.59 - 1.21)	0.33
≥ 30	2.72 (1.99 - 3.70)	< 0.01	1.88 (1.24 - 2.84)	< 0.01	1.47 (0.93 - 2.33)	0.09	1.63 (1.14 - 2.33)	< 0.01

a Confidence Interval (95%); **b** Level of Sgnificance; **c** Adjusted for: Gender, Age Groups, presence or not of Metabolic Syndrome, hypertriacylglyceridemia, BMI and Elevted Waist Circumference; **d** Triacylglycerides ≥150 mg/dL; **e** Specific cut-off point for each model

* **Model 1**: Elevated Waist Circumference: Females: ≥80cm; Males: ≥90cm

** **Model 2**: : Elevated Waist Circumference: Females: ≥88cm; Males: ≥102 cm

*** **Model 3**: : Elevated Waist Circumference: Females: ≥125 cm; Males ≥140 cm

Discusión

The fundamental role played by inflammation in the initiation and evolution of atherosclerosis, the common physiopathologic element of all CVD, is widely recognized[26]. Therefore, one of the main research objectives in the cardiovascular field is the identification of biomarkers for the early detection of this low-grade inflammatory component underlying the atherosclerotic process, for the prediction of future cardiovascular events. For this purpose, hs-CRP prevails over several other markers, by virtue of its greater sensitivity to detect low-grade inflammatory processes[13] with the best cost-benefit relationship[27]. Moreover, CRP exhibits great structural stability, a lengthy half-life, and it does not require special collection or conservation techniques for its quantification[28,29], favoring its routine utilization in the everyday clinical scenario. These features, along with the standardization of all techniques for its determination, guarantee low variability in results, independently of the method employed[30]. Nevertheless, controversy still surrounds the use of hs-CRP in clinical settings and primary prevention; and despite the high prevalence of CVD a scarcity remains of epidemiologic studies assessing the behavior of hs-CRP and its relationship with phenotypic and cardiometabolic qualities endogenous to our demography.

At first instance, when comparing hs-CRP values between genders, no statistically significant differences were found, diverging from previously reported results[31,32]. Women may manifest more substantial concentrations of inflammatory markers than men due to events inherent to female physiology, such as ovulation and menstruation in fertile women[33] and the dwindling of estrogen concentrations in postmenopausal women[34]; in both contexts, adiposity seems to be the magnifying factor of all low-grade inflammation states[35]. Nonetheless, the apparent parallelism of serum hs-CRP levels for both sexes in our population may stem from the lack of significant differences in the proportions of adipose mass between female and male subjects.

When arranging subjects by age groups, serum hs-CRP concentrations appear to rise as age increases, particularly in the group of 30-year-olds and onwards (Table 4), a picture resembling data described by Woloshin et al.[36] in American individuals. This behavior is tightly associated with metabolic changes typical of aging, which favor not only the enhancing of visceral adipose tissue accumulation, but also the development of a pro-oxidative environment, contributing to a chronic inflammatory state; particularly through the activation of NF-κB[37]. Furthermore, the longer time of exposure to proinflammatory environmental stimuli, such as smoke and infections, poses a notorious factor in the fundament of this relationship[38]. Prominently, in our population, values of waist circumference, HOMA2-IR, total cholesterol, TAG, systolic blood pressure and diastolic blood pressure showed a similar increasing pattern though age groups. An important effect over serum hs-CRP levels has also been conceded to ethnic origin[39]. In spite of this, no sign of this association is found in our population, ostensibly because of the extended proportion of subjects of mixed race in our study, and the deep-rooted crossbreeding backdrop inherent to our demography[40].

Regarding psychobiological behaviors, physical activity appears to play a relevant part in the prevention of chronic proinflammatory states. The minimizing impact of physical activity over serum concentrations of inflammatory markers, including hs-CRP, is a widely recognized consideration[41,42]. Our findings offer substance to this assertion; with hs-CRP values decreasing with greater degrees of physical activity in our population, as has been reported beforehand[43,44]. Aerobic physical activity prevents and aids in the management of pathologies such as obesity, HBP, insulin resistance and hypertriacylglyceridemia[45], all of which encompass an underlying inflammatory component in their physiopathology[46]. In consequence, it is important to promote physical activity for the primary or coadjutant therapy of these entities, as it also diminishes the magnitude of chronic inflammatory states, translated in the lowering of hs-CRP concentrations, and reduction of CVD risk.

The importance of obesity in the development of low-grade inflammatory states becomes evident when assessing serum hs-CRP levels based on waist circumference values for both genders, where the analyses unveiled significantly greater concentrations in subjects included in the fourth quartile of waist circumference values, harmonizing with the results portrayed by Sorensen et al. in Siberian subjects[47]. This highlights meaningfulness of visceral adipose tissue, typical of the abdominal region, in the systemic inflammation found in obesity[48]. Notwithstanding the undisputed role of chronic inflammation in the development of obesity, and by consequence, of insulin resistance[49], population studies assessing these elements through hs-CRP and HOMA2-IR are scarce. The assertions stated by Bangqiong et al.[50] on 587 Chinese subjects concur with our findings, reporting significantly higher serum hs-CRP concentrations in individuals pertaining to the fourth quartile of HOMA2-IR values, which also possesses the highest BMI and waist circumference values in our population. Increased adiposity, both visceral and subcutaneous, are associated with the chronic secretion of proinflammatory cytokines and greater hs-CRP levels, factors which have been implicated in the evolution of insulin resistance, as they interfere with insulin signaling and the synthesis of glucose transporters in insulin-dependent tissues[51,52]. As expected on the basis of prior discussion, serum hs-CRP levels were significantly greater in subjects with type 2 diabetes mellitus, in agreement with previous studies[53,54].

Another widely discussed concept is the link between inflammation and HBP[55]. In harmony with the reports of the MESA study, our findings reflect significantly higher hs-CRP values in hypertensive individuals than in non-hypertensive subjects[56]. CRP flaunts a relevant role in the pathogenesis of HBP by inhibiting the activity of Endothelial Nitric Oxide Synthase, and in consequence, diminishing the endothelial vasodilatory capacity[57]. In addition, angiotensin II can enhance this effect not only through its classic hypertensive effects, but also by upregulating the synthesis of numerous inflammatory markers through the activation of NF-Kb, equally exacerbating the underlying chronic inflammatory process[58].

In the same way, and as claimed beforehand in our continent[59], subjects with a diagnosis of MS displayed greater levels of hs-CRP, as well as a greater risk of exhibiting elevated hs-CRP in the multivariate analysis. This analysis also revealed that in our population, only abdominal obesity and hypertriacylglyceridemia represent risk factors for low-grade inflammation, results differing from those ascertained by Tamakoshi et al.[60] who found an association with each of the separate components of MS.

Finally, the analysis of serum hs-CRP levels has allowed for the recognition of its behavior in our population, illustrating the need for the proposal of adequate reference intervals which would enable the categorization of patients in distinct risk levels. This would also allow for the comparison of these cut-off points with those established by the CDC and other worldwide population studies, with the objective of formulating management guidelines based on these values.

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Disclosure

The authors have are no conflicts of interest to disclose.

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