



ASSOCIATION BETWEEN C-REACTIVE PROTEIN AND METABOLIC SYNDROME IN THE POPULATION OF PERU IN THE PERU MIGRANT STUDY

ASOCIACIÓN ENTRE LA PROTEÍNA C REACTIVA Y EL SÍNDROME METABÓLICO EN LA POBLACIÓN PERUANA DEL ESTUDIO PERU MIGRANT

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ABSTRACT

Introduction: Metabolic syndrome (MetS) is a group of cardiovascular risk factors characterized by the presence of low-grade chronic inflammation. Among all the inflammatory biomarkers associated with MetS, the best characterized and well standardized is C-Reactive protein (CRP). **Objectives:** To evaluate the association between C-Reactive protein and metabolic syndrome in the Peruvian population of the PERU MIGRANT study. **Methods:** Secondary database analysis of the PERU MIGRANT study. MetS was considered according to the Harmonizing the Metabolic Syndrome criteria. For CRP, a cutoff point of ≥ 3 mg/L was established. **Results:** We worked with a total of 958 subjects. The prevalence of MetS was 24.53%. In the simple regression analysis, it was found that people with high CRP levels had a 75% higher frequency of having MetS, compared to those who did not present high CRP levels (PR = 2.21, 95% CI: 1.40 - 2.18). In multiple regression, it was observed that patients with high CRP levels had a 31% greater frequency of having MetS, compared to those with normal CRP levels; adjusting for the rest of the covariates (PR = 1.31, 95% CI: 1.05 - 1.62). **Conclusions:** Plasma CRP was positively associated with MetS. This suggests that a low-grade inflammatory process may be related to the presence of MetS. Against this, physicians should pay attention to glucose, lipid profile, and central obesity in patients with elevated plasma CRP levels.

Key words: Metabolic Syndrome; C-Reactive Protein; Inflammation Mediators (source: MeSH NLM).

RESUMEN

Introducción: El síndrome metabólico (MetS) es un grupo de factores de riesgo cardiovascular que se caracteriza por la presencia de inflamación crónica de bajo grado. Entre todos los biomarcadores inflamatorios asociados al MetS, el mejor caracterizado y bien estandarizado es la proteína C-Reactiva (PCR). **Objetivo:** Evaluar la asociación entre la proteína C-Reactiva y el síndrome metabólico en la población peruana del estudio PERU MIGRANT. **Métodos:** Estudio transversal analítico. Análisis de base de datos secundario del estudio PERU MIGRANT. Se consideró MetS según los criterios de Harmonizing the Metabolic Syndrome. Para la PCR, se dispuso un punto de corte ≥ 3 mg/L. Se usó modelos lineales generalizados de familia de Poisson para hallar la razón de prevalencias cruda y ajustada. **Resultados:** Se trabajó con un total de 958 sujetos. La prevalencia de MetS fue de 24,53%. En el análisis de regresión simple, se encontró que las personas con niveles altos de PCR tenían 75% mayor frecuencia de tener MetS, en comparación a quienes no presentaban niveles altos de PCR (RP=2,21, IC95%: 1,40 – 2,18). En la regresión múltiple, se observó que los pacientes con niveles altos de PCR tenían 31% mayor frecuencia de tener MetS, respecto a quienes presentaban niveles normales de PCR; ajustando por el resto de covariables (RP=1,31, IC95%: 1,05 – 1,62). **Conclusiones:** La PCR plasmática se asoció positivamente con MetS. Ello sugiere que un proceso inflamatorio de bajo grado puede estar relacionado con la presencia de MetS.

Palabras clave: Síndrome metabólico; Proteína C-Reactiva; Mediadores de Inflamación (fuente: DeCS BIREME).

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INTRODUCTION

Metabolic syndrome (MetS) is a group of cardiovascular risk factors characterized by abdominal obesity, hypertension, and dyslipidemia⁽¹⁾. The prevalence of metabolic syndrome has increased throughout the world and has become a major public health problem recently⁽²⁾. Almost half of the American adults have MetS, and the prevalence increases with age⁽³⁾. In the case of the Peruvian population, according to the criteria used, the prevalence fluctuates between 25 and 45%⁽⁴⁾.

Although the individual components of MetS contribute independently to the further development of cardiovascular diseases (CVD) and type 2 diabetes mellitus (DM2), overall, the risk increases exponentially^(5,6). The precise mechanisms for this greater propensity lie in the presence of low-grade chronic inflammation^(7,8). Among all the inflammatory biomarkers associated with evaluating their value in the prediction of CVD, the best characterized and well standardized is C-Reactive protein (CRP).

CRP is an acute phase reactant produced by hepatocytes, and its production is regulated by interleukin-6 and other inflammatory cytokines^(9,10). Classically, plasma PCR is used as a test for the detection and activity of inflammatory diseases, such as rheumatological diseases⁽¹¹⁾. However, plasma CRP levels have also been shown to reflect the course of certain chronic diseases, including MetS⁽¹²⁻¹⁴⁾. Given these observations found, some investigators have suggested that CRP should be added as a clinical criterion for MetS.

Although several countries have studied the relationship between plasma CRP and metabolic syndrome, it has not been thoroughly investigated in the Peruvian population. For this reason, the present study aims to evaluate the association of C-reactive protein in metabolic syndrome in the Peruvian population of the PERU MIGRANT study.

METHODS

Design and study area

The present study had a cross-sectional analytical observational design. It was a secondary database analysis of the PERU MIGRANT study. This research work was designed to evaluate the magnitude of the differences between rural groups, rural to urban migrants, and urban ones in relation to specific

cardiovascular risk factors⁽¹⁵⁾.

Population and sample

The PERU MIGRANT study (primary study) considered two different settings. The first was San José de Secce, a village located in Ayacucho, which was selected as the rural study site. The second was the area "Las Pampas de San Juan de Miraflores" in Lima, selected as the urban area for the study. Study groups were defined by a single random sampling of participants aged 30 years or older from the rural site of Ayacucho, the urban site of Lima, and migrants from the countryside to the city of Ayacucho who now reside in Lima.

Ayacucho was chosen for this study because it was one of the most affected areas during the conflict period in Peru, resulting in 50% of the deaths. For the period 1988-1993, 50.7% of the total emigrants from Ayacucho moved to Lima, making Ayacucho the main source of emigrants to Lima.

Additional information on the selection criteria, sample size, and participation rates have been published elsewhere. (fifteen).

Of the total number of participants recruited in the primary study, 989 people were evaluated. In the present study, all subjects with the variables of interest were included, and all subjects with a diagnosis of DM2 were excluded. Finally, there were a total of 958 subjects.

With a sample size of 958 subjects, with an expected proportion of subjects with high MetS and CRP of 44.5%; and an expected proportion of subjects with MetS without high CRP of 55.5; and with a confidence level of 95%, a statistical power of 92.6% was calculated.

Variables and instruments

The dependent variable was the MetS diagnosis. MetS was considered according to the Harmonizing the Metabolic Syndrome criteria⁽¹⁶⁾, presenting three or more of the following alterations: Waist circumference ≥ 80 cm for women or ≥ 94 cm for men; triglycerides ≥ 150 mg / dl; fasting glucose ≥ 100 mg / dl (or if they receive treatment to lower glucose levels); systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg (or receive treatment to lower blood pressure levels); HDL-cholesterol <50 mg / dl in women or <40 mg / dl in men.

Our main exposure variable was plasma ultrasensitive CRP levels. In this study, a cut-off point was

established where CRP was considered high ≥ 3 mg / L. The American Heart Association and the Center for Disease Control recognized that people with CRP above this value are a high-risk group for CVD⁽¹⁷⁻¹⁹⁾.

The other variables of the analysis were age, gender (male or female), group according to migration (urban, rural or migrant), smoker status, alcohol drinker and physical activity. Excessive alcohol consumption was defined as low or high alcohol consumption. Smoking was defined in three categories: if you have not smoked (never), have stopped smoking 6 months ago (old) or if you have smoked in the last 6 months (current). Physical activity levels were defined according to the International Physical Activity Questionnaire (IPAQ) protocol. The categorical physical levels were coded based on the total number of days of physical activity and the metabolic equivalent in minutes/week three categories: high, medium and low.

To collect all the variables of the primary study, a team of community health workers with previous experience in fieldwork was trained in-home visits to enroll the participants and carry out the questionnaires. All laboratory evaluations were performed by trained personnel on venous samples taken in the morning after a minimum of 8 hours of fasting.

Procedures

The database of the primary study is freely accessible, without restrictions. The researchers accessed the scientific information, the variables that were of interest to the study were taken and the present manuscript was prepared.

Statistical analysis

Statistical analysis was performed with STATA v16.0 software. For descriptive analysis, the qualitative variables were summarized in proportions. The quantitative variables were presented as the mean and the standard deviation. For the bivariate analysis, the chi-square test was performed for the categorical variables, and the Student's T test and Wilcoxon were chosen for the numerical variables, according to the normality distribution of the variables.

Subsequently, a generalized linear model of the

Poisson family (crude and adjusted) with robust variance was made. The variables included in the adjusted model were age, gender, group (urban, rural or migrant), state of smoker, alcohol drinker and physical activity. The measure of association was the prevalence ratio (PR) with its respective 95% confidence interval (CI).

Ethical considerations Ethical

Approval for the primary study was obtained from the Universidad Peruana Cayetano Heredia's ethics committees in Peru and the London School of Hygiene and Tropical Medicine in the UK. The purpose of the study was explained to each of the study participants and informed consent was obtained, following international standards for ethical research in developing countries.

This is secondary data analysis, so no contact was made with human subjects. In this sense, the possible risks for the subjects of the analysis are minimal.

In turn, it is worth clarifying that the database is freely accessible to the general public.

Finally, during the study's implementation, the ethical principles outlined in the Declaration of Helsinki were respected.

RESULTS

Of 958 participants selected for this research, the prevalence of MetS was 24.53%. It was found that the majority were female (52.92%) and belonged to the migrant group (59.71%). The mean age was 47.83 years. Almost half practiced high physical activity (44.84%). 11.17% were current smokers, and 7.31% reported high alcohol consumption. The fourth part (25.47%) presented high levels of CRP.

Patients with high CRP levels had a 15.48% higher frequency of being metabolic syndrome than those with normal CRP levels (56.60% vs. 25.59%; $p < 0.001$). It was found that women had an 18.28% greater frequency of having MetS, compared to men (33.14% vs. 14.86%; $p < 0.001$). Finally, age was significantly associated with having MetS ($p = 0.005$). Only the smoker state did not show proportional statistical differences in relation to presenting MetS. Table 1.



Table 1. Important characteristics of the Peruvian population of the PERU MIGRANT study based on metabolic syndrome

Characteristics	Total n (%)	Metabolic Syndrome		p*
		No (n=723) n (%)	Yes (n=235) n (%)	
Gender				< 0.001
Female	507 (52.92)	339 (66.86)	168 (33.14)	
Male	451 (47.08)	384 (85.14)	67 (14.86)	
Age (years) *	47.83 (± 12.05)	47.20 (± 12,58)	49.76 (± 10.02)	0.005¥
Group				< 0.001
Rural	197 (20.56)	179 (90.86)	18 (9.14)	
Migrant	572 (59.71)	421 (73.60)	151 (26.40)	
Urban	189 (19.73)	123 (75.47)	66 (34.92)	
Physical Activity				
Low	246 (25.89)	176 (71.54)	70 (28.46)	0.002
Moderate	278 (29.26)	195 (70.14)	83 (29.86)	
High	426 (44.84)	344 (80.75)	82 (19.25)	
Smoking status				0.265
Never	789 (82.36)	594 (75.29)	195 (24.71)	
Old	62 (6.47)	43 (69.35)	19 (30.65)	
Current	107 (11.17)	86 (80.37)	21 (19.63)	
Alcohol consumption				< 0.001
Low	888 (92.36)	662 (74.55)	226 (24.45)	
High	70 (7.31)	61 (87.14)	9 (12.86)	
High CRP				< 0.001
No	714 (74.53)	567 (79.41)	147 (20.59)	
Yes	244 (25.47)	156 (63.93)	88 (36.07)	

* Obtained with the Chi square test

* Mean ± standard deviation.

¥ Performed with the Student's T test

In the simple regression analysis, it was found that people with high levels of CRP had a 75% higher frequency of having MetS, compared to those who did not present high levels of CRP (PR = 2.21, 95% CI: 1.40-2.18). Then, in the multiple regression, the observed association in terms of direction and magnitude was

preserved. It was observed that patients with high CRP levels had a 31% higher frequency of having MetS, compared to those with normal CRP levels; adjusting for the confounding covariates of gender, age, group, smoking status, alcohol drinker and physical activity (PR = 1.31, 95% CI: 1.05 - 1.62). Table 2.

Table 2. Crude and adjusted Poisson regression model to evaluate the association between plasma fibrinogen and metabolic syndrome.

Characteristics	Crude			Analysis Adjusted Analysis *		
	RP	IC 95%	p	RP	95% CI	p
high CRP						
No	Ref			Ref		
Yes	1.75	1.40 – 2.18	< 0.001	1.31	1.05 – 1.62	0.015

* Adjusted for age, gender, group (urban, rural or migrant), status of smoker, alcohol drinker and physical activity.

DISCUSSION

Given the long-term implications of MetS on cardiovascular alterations, and the possible role that the pro-inflammatory state would play in this process, the present work aimed to evaluate the association between CRP and MetS. After performing the analysis adjusted for the most important covariates, we found a close relationship between both variables of interest.

Our results indicate that elevated CRP concentrations are associated with a higher prevalence of MetS. This result is supported by several epidemiological studies. The association between MetS and elevated CRP levels has been demonstrated in non-diabetic Cuban-Americans aged ≥ 30 years⁽²⁰⁾. A study of 5,728 subjects showed that subjects with three, four, or five MetS features were more likely to increase CRP compared to subjects without any MetS features⁽²¹⁾. In Korea, research concluded that people with normal plasma CRP levels are less likely to have MetS, as opposed to those with high levels⁽²²⁾.

In a more recent publication, they found that CRP screening could identify a larger group of people who might be at high risk for MetS, regardless of their weight⁽²³⁾. Finally, one study observed that CRP was a useful and effective variable in predicting the risk of developing MetS. The connection of this variable and the number of criteria for MetS was also clear because CRP levels increased in the presence of more MetS factors, and CRP levels in normal individuals

decreased⁽²⁴⁾.

The pathophysiological role of CRP in MetS is through its participation in the process of atherosclerosis, through several potential mechanisms: 1) CRP can bind to oxidized LDL; 2) CRP can decrease nitric oxide production and inhibit angiogenesis; 3) the synergy between CRP and inflammatory mediators could play a role in the pathogenesis of atherosclerosis; and 4) PCR can also activate complement^(10,25,26).

Several limitations of this study are worth mentioning. The present analysis was based on a primary study where a single measurement of the CRP level was performed without repeating the tests; however, a first shot already brings us closer to the state of the subject under study. The population of this study was only carried out in two cities of the country and not nationally, so it is possible that this population does not represent the entire Peruvian population; however, given the characteristics that they may have in common, a certain inference could finally be made.

CONCLUSION

Plasma CRP was positively associated with MetS in the Peruvian population of the PERU MIGRANT study. The results of this study suggest that a low-grade inflammatory process may be related to the presence of MetS. Against this, physicians should pay attention to glucose, lipid profile, and central obesity in patients with elevated plasma CRP levels.



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