Evaluation of the Degree of Vascular Inflammation in Patients with Metabolic Syndrome

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Summary

Background: Metabolic Syndrome (MS) is defined as a set of cardiovascular risk factors related to visceral obesity and insulin resistance that lead to an increase in general mortality, especially cardiovascular. The inflammatory markers are considered emergent risk factors and can be potentially used in the clinical stratification of cardiovascular diseases, establishing prognostic values.

Objective: This study aims at evaluating which components of the MS present an increase of IL-6 and hs-CRP, identifying the marker that better expresses the degree of inflammation and which isolate component presents a higher degree of interference on the studied inflammatory markers, in order to identify other important risk factors when determining arterial inflammation.

Methods: A total of 87 hypertensive, diabetic and dyslipidemic patients were selected, aged 26 to 85 years, who met the necessary criteria for the positive diagnosis of MS. The patients were assessed through 24-hour ambulatory blood pressure monitoring (ABPM) and underwent hs-CRP and IL-6 measurements, among other metabolic variables.

Results: The patients that presented CRP > 0.3mg/dL showed a significant correlation (P<0.05) with abdominal perimeter >102/88 cm in 83.7%, glycemia > 110mg/dL in 88% and BMI > 30kg/m² in 60.5% of the studied individuals.

Conclusion: We concluded that the CRP was the inflammatory marker with the highest expression regarding the studied variables, with smoking, albuminuria, previous personal history of cardiopathy, BMI, abdominal perimeter and hyperglycemia being the ones with the highest statistical significance. Interleukin-6 did not present a correlation with any of the studied variables. (Arq Bras Cardiol 2009; 93(3) : 334-339)

Key Words: Metabolic Syndrome; C-Reactive Protein; Interleukin-6.

Introduction

The Metabolic Syndrome is a frequent entity in developed countries, as well as in our country. It is defined as a set of cardiovascular risk factors related to visceral obesity and insulin resistance that lead to an increase in the general mortality, especially that of cardiovascular origin[1]. This final consensus has been broadly discussed and it has gone through several definitions based on large-scale studies. During decades, different criteria were adopted to define the Metabolic Syndrome (MS), taking into account the presence of dyslipidemia, SAH, insulin resistance, abdominal circumference measurements and BMI, in addition to the presence of dysglycemia or diabetes mellitus, in their several associations[2,3]. As it is a syndrome that comprehends several aggregated components that vary according to ethnicity, sex, dietary habits, life styles, phenotypes and geographical location, it becomes difficult to establish a single classification for MS.

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In clinical practice, some inflammatory factors, albeit unspecific, such as C-reactive protein (CRP) and interleukin-6 (IL-6) have demonstrated an established predictive and prognostic role or great clinical relevance in several types of cardiovascular disease (CVD)[4].

Initially, the CRP was used in the diagnosis of joint processes. The role of the highly sensitive C-Reactive Protein (hs-CRP) currently attracts a large amount of attention as a risk marker of clinical usefulness in an assortment of patients that have the potential to develop atherosclerotic disease[5]. This marker has a higher prognostic value for cardiac events when compared to other emergent risk markers, such as homocysteine and lipoprotein A or Lp(a)[6]. Interleukin-6 (IL-6) is a multifunctional cytokine that acts like an inflammatory mediator, increasing in response to stress and being elevated in MS and insulin resistance. Based on these observations and considering the importance of controlling risk factors and their stratification regarding the association among SAH, diabetes mellitus or insulin resistance, dyslipidemia and visceral obesity, it becomes necessary to promote greater efforts to outline the prognostic factors, adopting them as a practical tool used for the prevention and progression of cardiovascular disease in our services.

Methods

This is an observational, cross-sectional study focused mainly on the assessment of the degree of inflammation, according to the CRP and IL-6, related to the components of the MS and other cardiovascular risk factors. The study was designed according to the Guidelines and Norms Regulating Research Involving Human Beings (Decree 196/1996 of the National Health Council) and was approved by the Ethics Committee of the Universidade Federal Fluminense.

Adult patients older than 18 years, with a mean age of 62.2 years were selected, with 75.9% being females and 24.1 males. The subjects were known hypertensive, type-2 diabetic and dyslipidemic patients that met the necessary criteria for the positive diagnosis of metabolic syndrome. All analyzed patients presented arterial hypertension diagnosed through casual measurements of blood pressure (BP >130/85 mmHg, in at least two different occasions), Diabetes mellitus (fasting glycemia ≥ 126mg/dl in two distinct previous measurements) and previously diagnosed dyslipidemia, undergoing or not treatment with anti-hypertensive, hypolipemiant and/or hypoglycemiant drugs, recruited from the Ambulatories of Cardiology of Hospital de Saracuruna/RJ and from the Universidade Estadual do Rio de Janeiro. After being instructed on the research, they answered an anamnesis questionnaire, underwent a clinical examination and were asked about the willingness and availability to participate in the study, signing a Free and Informed Consent Form. All principles present in the Declaration of Helsinki were followed.

All results were delivered to the participants and all questions raised on any doubts involving the research were clarified for posterior referral to the assistant physician.

Individuals without a previous diagnosis of systemic arterial hypertension (SAH) and type-2 diabetes mellitus (DM2) or that did not met the minimum classical criteria for the diagnosis of SM, individuals treated with steroidal and non-steroidal anti-inflammatory drugs, patients that had undergone recent trauma, patients with a history of active infectious processes or history of neoplasia and those who did not agree with the complementary examinations were excluded from the study. Patients undergoing treatment with aspirin at platelet antiaggregant doses remained in the study.

Anamnesis data that were relevant for the study were years of life, time of SAH and DM2 in years, in addition to abdominal perimeter and body mass index (BMI) measurements. The time of SAH and DM2 were counted as years of life. The BMI was calculated using the formula: weight in kilograms divided by the square height in meters (weight Kg/height m^2).

The patients were, then, referred to the Laboratory Dr. Sergio Franco to undergo the complementary laboratory assessment and evaluation of the BP behavior through 24-hr Ambulatory Blood Pressure Monitoring (ABPM).

The standardization of the BP values was carried out through the use of the V Guideline of Arterial Hypertension of the Brazilian Society of Cardiology (SBC/2006), which classifies SAH as stages 1, 2 and 3 and isolated systolic[7]. The patients were evaluated through ABPM for a period of 24 hours (24-hour ABPM), according to the recommendations of the IV Guideline of ABPM of SBC/2005. We evaluated blood pressure through oscillometric measurement, using a Spacelab's equipment, model 90207. A minimum percentage of 80% of the total measurements performed was accepted. The tensional analysis used mean values of the systolic (SAP) and diastolic (DAP) arterial pressure measurements obtained during alertness and sleep, the quantification of the systolic and diastolic nocturnal dip and the calculation of the systolic-diastolic pressure loads in these periods.

We considered as altered variables: systolic and diastolic pressure loads > 50% during alertness, as well as sleep; absence of satisfactory nocturnal dip (decrease < 10% for systolic and diastolic pressures in comparison to the period of alertness); SAP > 135 mmHg and PAD > 85 mmHg for the alertness period; SAP > 120mmHg and PAD > 70 mmHg for the sleep period; and BP > 130 x 80 mmHg at the 24-h monitoring. The patients whose activities were carried out during the night were excluded from the study.

In the present study, almost all measurements were performed at the same laboratory and on a single day, with the blood collection being collected in the morning, after a 12-hour fast and a previous one-hour rest. The laboratory measurements of relevance in the present study were carried out as they presented correlation with the assessment of the metabolic behavior and pressure dynamics as a whole, such as urea, serum and urinary creatinine, glycemia, glycated hemoglobin, total cholesterol and fractions, triglycerides, renin, urinary albumin, CRP, IL-6 and uric acid.

The parameters used to allocate the diabetic patients and those with MS were based on the I Brazilian Guideline for the Diagnosis and Treatment of Metabolic Syndrome/2005, which establishes as normoglycemic the patients with a fasting glycemia of up to 99mg/dl, glucose-intolerant as those whose glycemia varied between 100 and 125 mg/dl and as diabetic the ones that presented two or more serum measurements of glucose > 126 mg/dl. The fasting glycemia measurements were considered altered for the present study when they were ≥ 110 mg/ dL, according to the aforementioned guideline[8].

The quantitative C-reactive protein (CRP) was measured by the nephelometric method (ultra-sensitive), in isolated blood samples, and the reference value considered normal was up to 0.3mg/dl. Interleukin-6 was measured using an Immulite IL-6 Kit (DPC), with quantitative serum measurement. The normal reference value was up to 5.0 pg/ml.

With the objective of verifying whether there was a significant association between the risk factors and the inflammatory markers, CRP and IL-6, the following methods were applied:

- to compare quantitative data between two groups, we used the Student's *t* test for independent samples or the Mann-Whitney test (non-parametric);
- to compare proportions (qualitative data) we used the Chi-square test (χ^2) or Fisher's exact test, when χ^2 could not be evaluated;

The non-parametric method was used, as some variables did not present a normal distribution (Gaussian distribution),

due to the dispersion of data and/or lack of symmetry of the distribution. The level of significance was established as 5%.

Results

We found elevated hs-CRP levels, with values of 0.7mg/dL, with minimum values of 0.3mg/dL and maximum values of 4.4mg/dL, suggesting the presence of vascular inflammation. When analyzing extreme values of CRP (<0.3mg/dL or > 0.3mg/dL), we observed that the group of patients with CRP > 0.3mg/dL presented a significantly higher (p = 0.010) proportion of smokers (23.8%) than the group with CRP ≤ 0.3mg/dL (4.6%), that is, patients that smoked present more vascular inflammation that non-smokers, as shown in Chart 1. Patients with CRP > 0.3mg/dL presented a significantly higher (p = 0.042) proportion of personal history of cardiopathy (25.6%) when compared with the group with CRP ≤ 0.3mg/dL (9.1%), as shown in Chart 2. These facts mean that a previous personal history of cardiopathy presented a higher correlation with the development of vascular inflammation.

Regarding the visceral obesity, during the quantitative analysis, the group of patients with CRP > 0.3mg/dL presented a proportion of BMI > 30Kg/m² (60.5%) that was significantly higher (p = 0.024) than the group with CRP ≤ 0.3mg/dL (34.1%) Chart 3.

When analyzing quantitatively the studied risk factors according to the hs-CRP, we observed that the group of patients with CRP > 0.3mg/dL presented a significantly higher (p = 0.007) mean BMI (31.2 ± 4.2Kg/m²) than the group with CRP ≤ 0.3mg/dL (28.6 ± 4.7Kg/m²), as evaluated by the abovementioned calculations and demonstrated by the previous charts (Chart 3).

Approximately 83.7% of the patients with elevated serum levels of hs-CRP (>0.3mg/dl) presented an abdominal perimeter >102/88cm, demonstrating a significant correlation at the level of 0.011% when compared to patients with CRP < 0.3mg/dL (59.1%), as shown in Chart 4.

Patients with elevated glycemia (>110mg/dL) presented a significantly higher (p = 0,05) CRP > 0.3mg/dL (88.6%) than the group with CRP ≤ 0.3mg/dL (72.1%), corroborating what the medical literature present in evidence.

Patients with elevated CRP (> 0.3mg/dL) presented median urinary albumin levels (20mg/L) that were significantly higher (p = 0.05) than the group with CRP ≤ 0.3mg/dL (11.7mg/L).

There was no significant association between CRP and the other risk factors, at the level of 5%. We also analyzed, both qualitatively and quantitatively, interleukin-6 (IL-6) levels, with the objective of verifying whether the two groups (IL-6 > 5.0 and IL-6 ≤ 5.0 pg/dL) were statistically different under the point of view of the studied risk factors.

Regarding the analysis of the IL-6, it was observed that there was no significant association between this marker and the qualitative risk factors.

Discussion

When the components of the MS associated among them are evaluated with all the causes of death, it is observed that the trinomial increased abdominal perimeter associated to elevated glycemia, arterial hypertension or hypertriglyceridemia, or the combination of these four factors is more significant than other associations. In a large proportion of the middle-aged population, four specific components of the MS are associated to a much higher risk of mortality. This evidence represents a relevant impact on the detection of high-

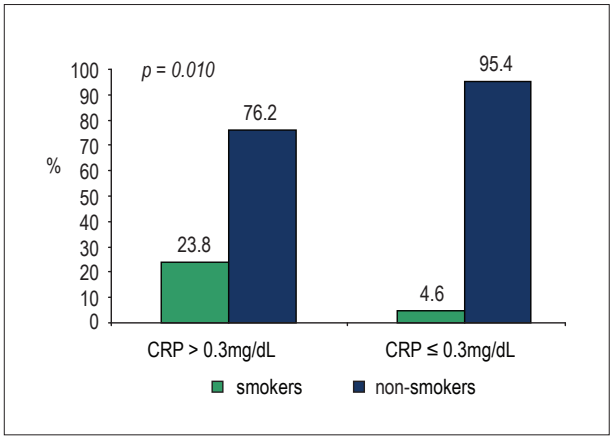

Chart 1 - *Smoking versus CRP*

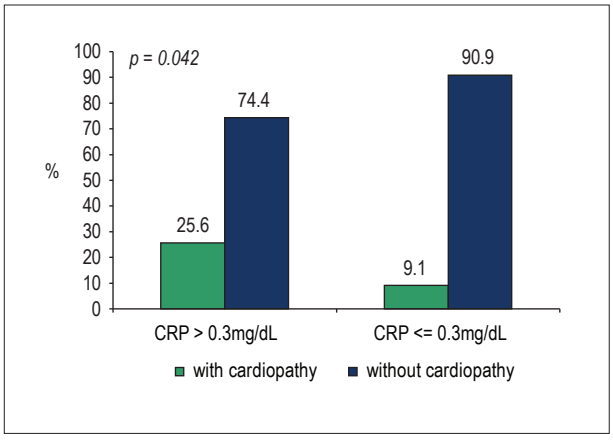

Chart 2 - *Personal history of cardiopathy versus CRP.*

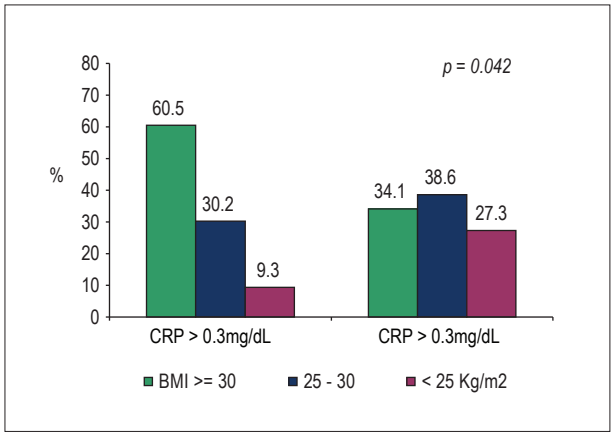

Chart 3 - *Body Mass Index versus CRP.*

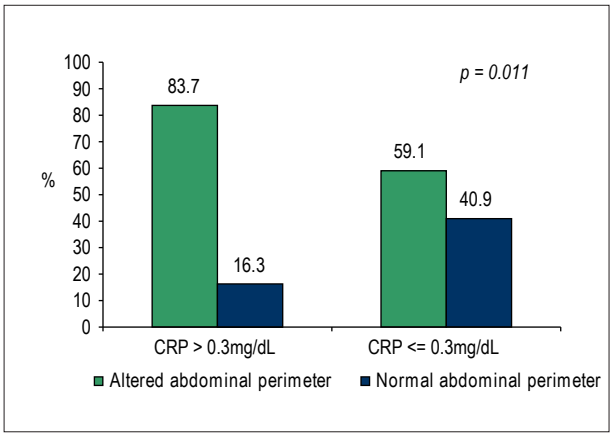

Chart 4 - Abdominal Perimeter versus CRP.

risk patients with metabolic disorders and suggests that the metabolic syndrome does not have a homogenous behavior profile, as recently observed by Guize L. et al[9].

Patients with 4 or 5 MS components have a higher risk of developing cardiovascular disease. It is worth mentioning that the risk of developing diabetes is even more significant, compared to the patients without any metabolic component. The CRP provides prognostic information in both cases[10].

Therefore, the CRP inflammatory marker is associated to long-term cardiovascular morbidity, being strongly related to the number of components of the MS. There is, however, a stronger correlation with adiposity than with insulin sensitivity or glycemic control, observed in a study carried out through the "ADOPT Study Group, 2006" (A Diabetes Outcomes Progression Trial). Hence, obesity is the most determinant direct association factor between serum levels of CRP and MS, in patients with DM2, a fact also demonstrated in the objectives of the present study[11].

The mean BMI of our participants was at the overweight range (29.9kg/m^2), with 47.1% of the individuals presenting BMI > 30kg/m^2. This variable significantly correlated with C-reactive protein (p = 0.024).

According to the analyzed studies and the results obtained at the statistical analysis of patients with MS, we observed that the most relevant component of this syndrome, and which had the most significant association with the inflammatory markers, is closely related to visceral obesity, expressed as the high BMI and increased abdominal perimeter. In the present study, the group of patients with CRP > 0.3mg/dL presented significantly higher proportions of abdominal perimeter >102/88cm than the group with low CRP levels (p=0.011).

A recent study by Saijo et al[12] investigated the association between the CRP levels, visceral obesity parameters, insulin resistance syndrome and carotid atherosclerosis in healthy eastern patients that had a lower BMI than western patients, calculated through anthropometric values, bioimpedance analysis (BIA), abdominal computed tomography (CT) and hs-CRP. The associations with MS components, IL-6, tissue necrosis factor alpha (TNF-α), and medial-intimal thickening of the common carotid artery (CCA) were assessed by ultrasonography in 116 healthy patients.

A significant association was found between the CRP and the parameters of visceral obesity at the crude regression analyses. After adjustments for age, sex and smoking status, the association of high levels of CRP was even more significant with the visceral obesity parameters (waist circumference, waist-hip ratio and accumulation of visceral adipose tissue) than with other parameters of obesity (weight). The eastern study did not show a direct association between IL-6 and CRP; however, BP and metabolic variables were significantly correlated with CRP, as in the present study. After adjustments for age, sex, smoking status and BMI, BP and HDL-cholesterol showed to be significantly associated[12].

Therefore, we concluded that elevated CRP levels are associated with the accumulated visceral adipose tissue, more significantly with the components of insulin resistance syndrome. These data suggest that there is a possible role of the visceral adipose tissue in the genesis of atherosclerosis. Thus, obesity, insulin resistance syndrome and atherosclerosis are closely related and can be determinants of a vascular inflammation increased response.

In the present study, we observed that elevated CRP levels presented a negative association when analyzed in patients with low BMI, suggesting a lower inflammatory effect in non-obese patients. Another important study also evaluated the association between CRP, obesity measures, metabolic syndrome variables and medial-intimal thickening of common carotids in 186 healthy middle-aged women selected from the general population, through regression analysis[13]. The CRP was strongly associated with the BMI, waist circumference and other metabolic syndrome variables, including BP, insulin, HDL-cholesterol, triglycerides, apolipoprotein A1 (inverse), plasminogen activator inhibitor antigen and tissue plasminogen activator antigen. The associations between CRP and the insulin resistance syndrome variables disappeared after adjustment for the BMI. The association between CRP and the medial-intimal thickness was weak and limited to smokers; BMI correlated in 29.7% of the patients in relation to the CRP variation, whereas the carotid medial-intimal thickness did it in only 3.7% of them.

The results of the present study indicated that adiposity is strongly associated with CRP in healthy middle-aged women. In this population, the BMI showed to be significantly associated with CRP and other MS variables; however, further studies must determine whether the weight loss can improve the inflammatory state.

Few studies have presented a precise association between obesity and inflammatory markers in patients with MS. Individuals with abdominal obesity presented significantly higher serum levels of hs-CRP and IL-6 than non-obese patients, as demonstrated and recently published by Nishida and cols. In the present study, we found a significant association between BMI and increased abdominal perimeter when compared with the CRP, with a p value of 0.024 and 0.011, respectively. When the statistical analysis was applied to the IL-6, we did not observe a statistically significant difference[14].

Regarding dyslipidemia, the present study did not demonstrate a relevant correlation with the analyzed inflammatory variables, CRP and IL-6. However, the statistical analysis showed a slight tendency of significant correlation, with a p value of 0.082,

with HDL-cholesterol levels of 43.3mg/dl and CRP >0.3mg/dl. Although 68.2% of the participants of the present study had elevated LDL-cholesterol, that is, LDL-c > 100mg/dl, no significant correlation was found between this variable and the inflammatory markers at the statistical analysis.

Smoking is an important modifiable risk factor and has a consistent epidemiological association with CVD, both in men and women. Approximately 50% of the middle-aged patients with cardio-circulatory disease are smokers or ex-smokers. The vascular alterations caused by smoking involve endothelial dysfunction, alterations of blood coagulation and abnormalities of the lipid metabolism. The contribution of the vascular inflammation to atherosclerotic disease in patients that smoked was demonstrated in studies that evaluated the serum levels of CRP in smokers and non-smokers in the "Women's Health Study"[15]. In the smoker's group, the serum levels of CRP were significantly higher than those in the non-smoker's group. Similar results were observed among a population of physicians, in which the CRP was sued as an inflammation marker. The association between the CRP levels and smoking is proportional to the number of smoked cigarettes. The study by Mendall and cols. showed that the increase in serum levels of CRP and IL-6 in men was directly proportional to the number of smoked cigarettes[16].

Some recent studies have suggested an association between arterial hypertension and IL-6 levels, so that SAH seems to be a predictor of IL-6 levels in women, but not in men[17], which was not demonstrated in the present study.

Altered glycemic levels are generally present in metabolic disorders, vascular and renal lesions. In our sample, 80.5% of the patients presented elevated levels of fasting glycemia, with mean values of 154.5 mg/dl. This variable was significantly correlated with the CRP inflammatory marker (p=0.05), but it did not present the same association with IL-6, confronting the literature findings.

According to Laaksonen et al[18], patients with CRP levels > 3mg/l present a higher risk of developing SM or diabetes than those with CRP levels < 1.0mg/l. After adjustments for lifestyle and factors related to insulin resistance, the risk of the onset of diabetes mellitus is still high in patients with elevated CRP levels; however, the association with the MS becomes not so significant. Low-degree inflammation can increase the risk of MS and diabetes in middle-aged patients, but this risk is, in part, mediated by obesity and factors related to insulin resistance[18].

The analysis of the data presented in the present study corroborates the literature and shows a significant correlation between dysglycemia and CRP, that is, in 88.6% of the studied patients with glycemia levels ≥ 110 mg/d L, the CRP levels were > 0.3 mg/d L. Altered glycemic levels are usually present in metabolic disorders, vascular and renal lesions. In our sample, 80.5% of the patients presented high fasting glycemia levels and this variable was significantly correlated with the CRP inflammatory marker.

In this context, the presence of microalbuminuria, that is, increased urinary excretion of albumin above the desired levels is one of the predisposing factors of insulin resistance, metabolic syndrome and CVD (main cause of death among patients with type 2 diabetes[19]. For this reason, the World Health Organization recommends its measurement in patients that fit this clinical profile.

Considering that the urinary loss of protein is one of the first manifestations of renal lesion, either secondary to diabetic nephropathy or hypertensive nephropathy, the urinary albumin is then measured with a cutoff of 20mg/L. Although levels of renal protein loss are graded as micro and macroalbuminuria, respectively 20 to 350mg/l and >350mg/l, we chose to classify the observed values as normal (<20mg/l) or altered (>20mg/l). Considering that they are common clinical manifestations in patients with SAH and diabetes, entities that make up the diagnosis of MS, we observed a correlation between a median urinary albumin of 20mg/l and elevated CRP, at the level of significance of p=0.05, when compared to CRP values <0.3mg/dl (11.7mg/l), that is, the group with elevated CRP levels presented a significantly higher median albuminuria than the group with low CRP levels.

Microalbuminuria is currently considered an independent risk factor for atherosclerosis and CVD, premature mortality in type-1 and type-2 diabetic patients, patients with SAH, as well as in the general population[20].

According to Lin, Klausen and Choi, (2007) the microalbuminuria is strongly associated to the metabolic syndrome, with a significant association between the number of components and the prevalence of renal lesion[21].

We believe that the association between albuminuria, MS components and inflammatory markers can be even more significant, according to the reviewed literature, in larger samples, when the statistical tests become more sensitive.

Considering the current knowledge, it becomes obvious to recommend that medical researches on MS be intensified and encouraged, considering that there are still much controversy about the strict definitions and criteria used to establish the unified diagnosis of this entity, which is so important in the present and in the future. It is a concern the fact that the life style adopted by our population has been augmenting the onset of multiple diseases that comprise the components of this syndrome. In this context, medical evidence has demonstrated the need for an early diagnostic approach, establishment of preventive measures and specific therapies, with the objective of having an important impact on the decrease of the morbimortality of our patients.

Conclusion

A well-established definition of the Metabolic Syndrome has yet to be attained, but there is a consensus indication that the increase in arterial pressure, metabolic disorders of lipids and glycids and excess weight are definitely associated to the increase in cardiovascular morbimortality, a fact observed not only in developed countries, but also, and disturbingly so, in developing countries[2].

Due to elevated degree of injury that the metabolic alterations confer to the body, it becomes essential to recognize the modifiable risk factors and adopt behavioral changes, as well as measure the abdominal circumference, arterial pressure, lipid profile and fasting glycemia levels, in order to outline the cardiovascular risk of the patient. The

prevention and the continuing efforts in the early detection of these alterations are fundamental in the global endeavor to revert the obesity epidemics.

The inflammatory markers are considered emergent risk factors and can be potentially used in the clinical stratification of CVD, establishing prognostic values. The high-sensitivity C-reactive protein (hs-CRP) was proposed as an inflammatory marker that can be used in the early detection of atherosclerotic diseases[5]. The analysis of the correlations between serum variations of inflammatory markers in the particular group of patients, more specifically CRP and IL-6, can suggest two early indicators of target-organ lesions, benefiting the patient by providing a more incisive prevention[22]. In the present study, we concluded that the inflammatory marker with the highest expression was the hs-CRP, correlating especially with BMI, abdominal perimeter and elevated fasting glycemia, corroborating the medical literature. However, IL-6 did not show a significant correlation with any of the metabolic components or other studied risk factors. Considering the other analyzed risk factors, we obtained a significant correlation between hs-CRP and smoking, elevated median urinary albumin and personal history of cardiopathy.

Despite the known importance of the conventional risk factors that have been described and the role of atherosclerosis as a substrate for cardiopathies, it becomes important to search for other factors that can play a relevant role in the stratification and development of cardiovascular disease, in order to attain a more effective prevention.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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References

1. Sociedade Brasileira de Cardiologia. I Diretriz brasileira de diagnóstico e tratamento da síndrome metabólica. Arq Bras Cardiol. 2005; 84 (supl I): 3-28.
2. Reaven GM. The metabolic syndrome or the insulin resistance syndrome? Different names, different concepts, and different goals. Endocrinol Metab Clin North Am. 2004; 33: 283-303.
3. Vidal J, Morinigo R, Codoceo VH, Casamitjana R, Pellitero S, Gomis R. The importance of diagnostic criteria in the association between the metabolic syndrome and cardiovascular disease in obese subjects. Int J Obes Relat Metab Disord. 2005; 29: 668-74.
4. da Luz PL, Laurindo FRM. Inflamação e aterosclerose. In: Nobre F, Serrano Jr, CV (eds). Tratado de Cardiologia SOCESP. São Paulo: Manole; 2005. p. 369-80.
5. Ridker PM. High sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation. 2001; 103 (13): 1813-8.
6. Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB, Wilson PW. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. Circulation. 2004; 110 (4): 380-5.
7. Sociedade Brasileira de Cardiologia. V Diretrizes brasileiras de hipertensão arterial. Arq Bras Cardiol. 2007; 89 (3): 24-7.
8. Sociedade Brasileira de Cardiologia. I Diretriz brasileira de diagnóstico e tratamento da síndrome metabólica. Arq Bras Cardiol. 2005; 84 (supl I): 3-38.
9. Guize L, Thomas F, Pannier B, Bean K, Jego B, Benetos A. All-cause mortality associated with specific combinations of the metabolic syndrome according to recent definitions. Diabetes Care. 2007; 30: 2381-7.
10. Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly DS, Haffner SM, et al. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. Circulation. 2003; 108: 414-9.
11. Kahn SE, Zinman B, Haffner SM, O'Neill MC, Kravitz BG, Yu D, et al. Obesity is a major determinant of the association of C-reactive protein levels and the metabolic syndrome in type 2 diabetes. Diabetes. 2006; 55: 2357-64.
12. Saijo Y, Kiyota N, Kawasaki Y, Miyazaki Y, Kashimura J, Fukuda M, et al. Relationship between C-reactive protein and visceral adipose tissue in healthy Japanese subjects. Diabetes Obes Metab. 2004; 6 (4): 249-58.
13. Hak AE, Stehouwer CD, Bots ML, Polderman KH, Schalkwijk CG, Westendorp IC. Associations of C-reactive protein with measures of obesity, insulin resistance, and subclinical atherosclerosis in healthy, middle-aged women. Arterioscler Thromb Vasc Biol. 1999; 8: 1986-91.
14. Nishida M, Moriyama T, Sugita Y, Yamauchi T, Kihara K. Abdominal obesity exhibits distinct effect on inflammatory and anti-inflammatory proteins in apparently healthy Japanese men. Cardiovasc Diabetol. 2007; 6: 27.
15. Bermudez EA, Rifai N, Buring JE, Manson JE, Ridker PM. Relation between markers of systemic vascular inflammation and smoking in women. Am J Cardiol. 2002; 89: 1117-9.
16. Mendall MA, Patel P, Ballam L, Strachan D, Northfield TC. C-reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. Br Med J. 1996; 312: 1061-5.
17. Chen J, Muntner P, Hamm LL, Jones DW, Batuman V, Fonseca V, et al. The metabolic syndrome and chronic kidney disease in U.S. adults. Ann Intern Med. 2004; 140: 167-74.
18. Laaksonen DE, Niskanen L, Nyyssönen K, Punnonen K, Tuomainen TP, Valkonen VP, et al. C-reactive protein and the development of the metabolic syndrome and diabetes in middle-aged men. Diabetologia. 2004; 47 (8): 1403-10.
19. Gross JL. Microalbuminúria e a síndrome metabólica. Arq Bras Endrocrinol Metab. 2003; 47: 109-10.
20. Hadi HA, Suwaidi JA. Endothelial dysfunction in diabetes mellitus. Vasc Health Risk Manag. 2007; 3: 853-76.
21. Lin CC, Liu CS, Li TC, Chen CC, Li CI, Lin WY. Microalbuminuria and the metabolic syndrome and its components in the chinese population. Eur J Clin Invest. 2007; 37: 783-90.
22. Ridker PM, Rifai N, Clearfield M, Downs JR, Weis SE, Miles JS. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. N Engl J Med. 2001; 344: 1959-65.