ANDRÉA HARUMI HIROTA

IMPORTÂNCIA DO DIAGNÓSTICO DA SÍNDROME METABÓLICA NA DETERMINAÇÃO DO RISCO CARDIOVASCULAR EM PACIENTES HIPERTENSOS

Tese apresentada à Universidade Federal de São Paulo – Escola Paulista de Medicina para a Obtenção de Título de Mestre em Ciências

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De tudo na vida

ficaram três coisas:

A certeza de que estamos sempre começando...

A certeza de que precisamos continuar...

A certeza de que seremos interrompidos antes de terminar...

Portanto, devemos:

Fazer da interrupção um caminho novo...

Da queda, um passo de dança...

Do medo, uma escada...

Do sonho, uma ponte...

Fernando Pessoa

Dedico esse trabalho

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ÍNDICE

CONSIDERAÇÕES INICIAIS

O termo Síndrome Metabólica (SM) consiste em um conjunto de fatores de risco cardiovasculares. Por muito tempo a doença cardiovascular (DCV) foi considerada a maior causa de morbimortalidade em paises do 1º mundo [1]. Durante esse período houve preocupação em identificar os fatores que contribuíam para isso.

Embora essas anormalidades metabólicas tenham sido reconhecidas antes de 1923 [2], somente em 1988 Reaven [3] definiu a Síndrome X, caracterizada pela presença de resistência a insulina, hiperglicemia, hipertensão, diminuição de HDL e aumento de triglicérides. Reaven e cols não incluíram a obesidade abdominal, mas atualmente ela é reconhecida como um componente essencial da síndrome. Os autores postularam que a resistência à insulina e a hiperinsulinemia compensatória predispõe os pacientes a hipertensão arterial, dislipidemia e Diabetes Mellitus tipo 2 (DM2), resultando em alta incidência de doença cardiovascular [4,5].

A resistência à insulina foi considerada a alteração metabólica primária e todas as demais seriam dela decorrentes. Posteriormente, o próprio autor, em outros trabalhos, ampliou o conceito de síndrome, sugerindo então a inclusão de outras manifestações clínicas, como a hiperuricemia, aumento dos níveis de PAI-1 e a obesidade abdominal [6]. O reconhecimento desse conjunto de alterações metabólicas foi ao longo do tempo recebendo inúmeras denominações, como Síndrome de Reaven, quarteto mortal, Síndrome da resistência a insulina, Síndrome da obesidade-dislipidemia ou Síndrome Plurimetabólica, para chegar finalmente a ser denominada Síndrome Metabólica pela Organização Mundial da Saúde.

Os componentes da síndrome têm sido reconhecidos como fatores de risco cardiovasculares. Portanto é compreensível que a própria síndrome constitua por si mesma um fator de risco cardiovascular muito importante. No contexto da SM, ainda não estão totalmente esclarecidos todos os caminhos metabólicos que associam resistência à insulina e seus demais elementos às complicações inerentes, porém evidências tornam-se mais claras a exemplo do

papel da obesidade central nas doenças cardiovasculares que desponta atualmente como elemento diagnóstico [6].

Devido ao grande risco de morbidade e mortalidade cardiovascular associado com a SM, é importante identificarmos quais pacientes são de risco. No entanto a identificação de pacientes com a síndrome é dificultada pela ausência de consenso na sua definição e nos pontos de cortes de seus componentes.

A WHO (World Health Organization) definiu SM em 1988 [7] e tem como ponto de partida a avaliação da resistência à insulina ou do distúrbio do metabolismo da glicose, o que dificulta a sua utilização. Mais recentemente o ATP III-NCEP [8] definiu SM pela presença de três ou mais critérios que se seguem: Hipertensão Arterial (PA $\geq$ 130/85), circunferência da cintura > 102 cm para homens e > 88 cm para mulheres, valores de Triglicérides plasmáticos > 150 mg/dl, valores de HDL-Colesterol < 40 mg/dl em homens e < 50 mg/dl em mulheres, valores de Glicemia > 100 mg/dl. Os critérios utilizados pelo NCEP foram propostos para tornar mais fácil a identificação de pacientes com SM na prática clínica [9].

Em 2005, a Federação Internacional de Diabetes (IDF) definiu SM [10] pela presença de cintura abdominal $\geq$ 94 cm em homens e $\geq$ 80 cm em mulheres, mais a presença de 2 ou mais fatores: Hipertensão Arterial (PA $\geq$ 130/85 mmHg), valores de triglicérides plasmáticos $\geq$ 150 mg/dl, valores de HDL colesterol < 40 mg/dl em homens e < 50 mg/dl em mulheres, valores de glicemia > 100mg/dl. Devido a grande associação de obesidade abdominal e SM, o consenso proposto pelo IDF identifica a cintura abdominal como um componente essencial para o diagnóstico de SM. Atualmente estima-se que a prevalência de SM seja de 6,7% em indivíduos de 20-29 anos e 43,5% naqueles entre 60-69 anos [1].

Independente do critério usado sabe-se que o diagnóstico de SM aumenta o risco de DCV [11]. Pacientes com SM têm incremento de 2 vezes na mortalidade e incidência 3 vezes maior de doença cardiovascular ou AVC do que pessoas sem SM [5]. Além disso, pacientes com SM têm risco 5 vezes maior de desenvolver DM2 [12]. Por isso, a importância de se identificar SM precocemente é

fundamental para promover intervenções no estilo de vida e tratar precocemente pacientes com SM, evitando assim DCV.

Neste contexto, o presente estudo analisou a associação entre a ocorrência da SM, definida pelos dois critérios, e a ocorrência de doença cardiovascular estabelecida, em uma população de indivíduos com pelo menos 1 componente da SM sobre o risco cardiovascular. A interação entre a ocorrência de DCV e a SM foi estudada em função da presença ou não de DM nesta população.

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IMPORTANCE OF THE DIAGNOSIS OF METABOLIC SYNDROME IN DETERMINING CARDIOVASCULAR RISK IN HYPERTENSIVE PATIENTS

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ABSTRACT

We evaluated the significance of a diagnosis of metabolic syndrome (MetS), as defined by the National Cholesterol Education Program (NCEP) and by the International Diabetes Federation (IDF), in the evaluation of cardiovascular risk in hypertensive patients. The patients were evaluated to identify MetS and any history of cardiovascular disease (CVD). This was a cross-sectional study involving 638 patients, of which 202 (31.7%) had diabetes. The prevalence of MetS was 54.7% when the IDF criteria were used, compared with 45.5% when the NCEP criteria were used ($p < 0.05$). Using either set of criteria, MetS was associated with type 2 diabetes mellitus (T2DM) (NCEP,OR: 6.8; 95% CI: 4.7-10 and IDF, OR: 8.4; 95% CI: 5.4-13; $p < 0.05$ for both). We found that, regardless of the diagnostic criteria used, MetS correlated significantly with the risk and history of CVD (NCEP, OR: 2.04; 95% CI: 1.2-3.4; $p < 0.05$; and IDF, OR: 2.68; 95% CI: 1.5-4.8; $p < 0.05$), partially caused by the inclusion of patients with diabetes in the sample. In patients without diabetes, MetS diagnosed using the IDF criteria alone was associated with a history of CVD (OR: 2.4; 95% CI: 1.1-5.2; $p = 0.029$ vs. NCEP criteria, OR: 1.99; 95% CI: 0.9-4.3, p = NS). In patients with T2DM, MetS was not associated with CVD, regardless of the criteria used. We conclude that, among individuals without diabetes, an IDF criteria-based diagnosis of MetS is useful in identifying those at greater risk for cardiovascular disease. Among patients with diabetes, a diagnosis of MetS, regardless of the criteria used, is of little utility in assessing cardiovascular risk. However, a diagnosis of MetS, using either set of criteria, is useful for identifying individuals more likely to develop T2DM.

Keywords:

Metabolic Syndrome; Cardiovascular Disease, Cardiovascular Risk Factors.

INTRODUCTION

Cardiovascular disease (CVD) is the principal cause of death in various populations, being responsible for 37.7% of all deaths in the American population [1]. Various risk factors for CVD have been identified, among which are smoking, type 2 diabetes mellitus (T2DM), systemic arterial hypertension, dyslipidemia and visceral obesity [2]. There has been a consistent increase in the prevalence of visceral obesity, which has attenuated the increase in life expectancy. According to the World Health Organization (WHO), the number of overweight and obese individuals worldwide will reach 1.5 billion by 2015 [1].

Visceral obesity is intimately linked to metabolic syndrome (MetS), which is a disorder involving cardiovascular risk factors that are typically associated with insulin resistance [3]. Various studies have demonstrated that MetS correlates with an increase in the number of cardiovascular events and in the occurrence of T2DM [4-6]. The 2006 prevalence of MetS was estimated to range from 6.7% (in the 20-29 age bracket) to 43% (in the 60-69 age bracket) [1].

Due to the high cardiovascular morbidity and mortality associated with MetS [6-18], the appropriate characterization of the syndrome is extremely relevant. Among individuals with MetS, the mortality rate is twice as high as in those without. In addition, the incidence of CVD and cerebral vascular accident is three-times higher in individuals without MetS than in those without [5]. Furthermore, the risk of developing T2DM is five-times greater among patients with MetS than among those without [19]. However, the lack of a universal standard for MetS criteria hinders understanding of the magnitude of its impact on the occurrence of these events. The definition of MetS proposed by the WHO [20] was based on clinical and laboratory data that would indicate insulin resistance, thereby making it difficult to apply in clinical practice. In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) proposed a new definition [21], which considered the following components: blood glucose; blood pressure; serum levels of high-density lipoprotein (HDL) cholesterol and triglycerides; and waist circumference. Although the NCEP ATP III criteria are easier to apply, evidence suggests that cardiovascular risk is increased at blood glucose and waist circumference values lower than those initially

recommended [22,23]. Therefore, in 2005, the International Diabetes Federation (IDF) reformulated the criteria for the classification of MetS and designated waist circumference as an essential component of the definition, as well as establishing specific cut-off points for individuals of various ethnicities [24].

The aim of the present study was to analyze the association between a diagnoses of MetS, defined using either set of criteria, and the presence of an established CVD, in a population of individuals presenting hypertension. The interaction between the presence of CVD and MetS was studied in relation to the presence or absence of T2DM in this population.

METHODS

Patients were selected from among those treated at the Integrated Center for Hypertension and Cardiovascular Metabolism of the *Universidade Federal de São Paulo* (UNIFESP, Federal University of São Paulo) with the following inclusion criteria: at least 18 years old, patients presenting at least one component of MetS and wash-out of one month from lipid modifying agents. The study protocol was approved by the UNIFESP Ethics in Research Committee. All individuals participating in the study gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki and with Brazilian National Ministry of Health Resolution CNS 196/96.

Patients presenting active infectious or inflammatory diseases were excluded, as were pregnant/breastfeeding patients and HIV-infected patients. The use of the following medications was discontinued in the four weeks preceding inclusion in the study: 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins); cholesterol absorption inhibitors such as ezetimibe; probucol; cholestyramine; niacin; fibric acid derivates (fibrates); and drugs for treating obesity (orlistat and sibutramine). Temporary discontinuation of medications that alter the lipid profile was aimed at facilitating the appropriate characterization of MetS.

The patients were submitted to anamnesis and physical examination, in which weight, height, blood pressure (BP) and waist circumference were determined. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared (kg/m^2). Blood pressure was obtained by a trained operator in the sitting position after five minutes of rest. A mercury sphygmomanometer was used according to a standard protocol and BP was calculated as the average after excluding the first of four measurements [25].

For analysis of the metabolic profile, 30 mL of blood were collected from each participant after a 12-h fast. Fasting glycemia, serum levels of uric acid, total cholesterol and triglycerides were determined using an automated enzymatic-colorimetric method. Fractions of HDL-cholesterol were measured using enzyme homogeneous colorimetric method and LDL-cholesterol was calculated using the Friedewald formula. The analyzer used was the Roche Hitachi 912 (Roche Hitachi, Montreal, Quebec). Serum levels of C-reactive protein (CRP) were determined using chemiluminescence immunoassay (Diagnostic Products Corporation, Los Angeles, CA, USA), with an analytical sensitivity of 0.01 mg/dL, intra-assay variability of 4.2-6.4% and inter-assay variability of 4.8-10%.

The glomerular filtration rate (GFR) was estimated using the equations described in the MDRD study [26]. The diagnosis of T2DM was made based on fasting glycemia and the need for treatment with hypoglycemic agents. Patient presenting angina were classified as having CVD, as were those with a confirmed history of acute myocardial infarction (MI), stroke, peripheral arterial obstruction or aortic aneurysm.

The patients were classified according to a diagnosis of MetS, based on the NCEP and IDF criteria. The NCEP criteria define MetS as the presence of three or more of the following factors: elevated blood pressure ≥ 130/85 mmHg; waist circumference > 102 cm for men and > 88 cm for women; plasma triglycerides ≥ 150 mg/dL; HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in women; and blood glucose ≥ 110 mg/dL. The guidelines proposed by the IDF identify waist circumference (≥ 94 cm for men and ≥ 80 cm for women) as an essential component for the diagnosis of MetS. Therefore, in order to meet the IDF criteria for MetS, an individual must present a large waist circumference, as well

as at least two of the following factors: elevated blood pressure ≥ 130/85 mmHg; plasma triglycerides ≥ 150mg/dL; HDL-cholesterol < 40 mg/dL in men and < 50 mg/dL in women; and blood glucose ≥ 100 mg/dL.

For those patients with primary prevention, cardiovascular risk was calculated using the Framingham score, which establishes the absolute 10-year risk of coronary artery disease (CAD) by sex. The risk factors employed are as follows: age; smoking; family history of CVD, HDL and systolic blood pressure. The score for each risk factor is calculated and associated with the absolute risk of CAD according to the percentage risk (low, medium or high).

Data are expressed as means and standard deviations for variables with regular distribution and as medians for nonparametric variables. To test the differences found between patients with T2DM and those without diabetes in terms of the various variables analyzed, the Student's t-test (for parametric variables) and the chi-square test (for nonparametric variables) were used. The groups were divided according to the presence or absence of T2DM, as well as to the presence or absence of MetS. The chi-square test was carried out with the aim of determining whether MetS correlated with CVD. Two models of binary logistic regression were employed, using CVD as a dependent variable. In one model, we included the following as independent variables: sex; age; creatinine clearance; serum levels of CRP; smoking; microalbuminuria; and a diagnosis of MetS according to NCEP criteria. In the second model, the independent variables included were as follows: sex; age; creatinine clearance, serum levels of CRP, smoking, microalbuminuria and a diagnosis of MetS according to IDF criteria. A receiver operating characteristic curve was constructed, and the area under the curve (AUC) was used in order to evaluate the value of a diagnosis of MetS, as defined using the NCEP criteria, the IDF criteria and the Framingham Score, in predicting a history of CVD. In all tests, the level of statistical significance required to reject the null hypothesis was set at 5% The statistical analysis was conducted using the Statistical Package for the Social Sciences, version 15.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

The sample consisted of patients, but 26 of them were excluded because they did not fulfill the hypertension criteria. Females accounting for 66.8% (426 patients). The mean age was 57.7 ± 5.7 years and was similar for males and females. There were 202 patients with T2DM (31.7%). Of the 638 patients evaluated, 68 (10.7%) were smokers, and 64 (10.1%) had a history of CVD. Of the 426 women in the sample, 334 (78.6%) were postmenopausal, and 12 (3.5%) of those were under hormone replacement therapy. In the sample as a whole, 262 (41.1%) of the patients were overweight (BMI ≥ 25 kg/m^2 and < 30 kg/m^2) and 263 (41.2%) were obese (BMI ≥ 30 kg/m^2). (Table 1). There were 23.2% patients with low HDL (< 40 mg/dl in men and < 50 mg/dl in women) and 40.3% of the patients have elevated triglycerides.

According to the criteria defined by the IDF, 349 (54.7%) of the patients presented MetS, compared with only 290 (45.5%) according to the NCEP criteria ($p < 0.05$).

A diagnosis of MetS was associated with a greater than 20% 10-year risk of CAD, and this was true for the use of the NCEP criteria and the IDF criteria (OR: 5.98; 95% CI: 4.2-8.6 vs. OR: 5.84; 95% CI: 4.0-8.6, $p < 0.05$ for both). The use of the NCEP criteria to define MetS was found to have a sensitivity of 72.7% and a specificity of 69.1% for identifying patients with a greater than 20% 10-year risk of CAD. The use of the IDF criteria to define MetS was found to have a sensitivity of 80.3% and specificity of 58.8% for identifying such patients. A diagnosis of MetS was associated with CVD using the NCEP criteria or the IDF criteria (OR: 2.04; 95% CI: 1.2-3.4 vs. OR: 2.68; 95% CI: 1.5-4.8, $p < 0.05$ for both.) We also observed that a high risk of CAD correlated significantly with a history of CVD (OR: 3.9; 95% CI: 2.3-6.7, $p < 0.05$).

An NCEP or IDF criteria-based diagnosis of MetS was also associated with the development of T2DM (OR: 6.8; 95% CI: 4.7-10.0 vs. OR: 8.4; 95% CI: 5.4-13.0, $p < 0.05$ for both). The table 2 discriminates the antihypertensive agents taken by the patients either with or without MetS (NCEP and IDF).

When the population was subdivided into patients with T2DM and those without diabetes, the correlation between the diagnoses of MetS, using either set of criteria, and a history of CVD began to differ. In the group without diabetes (Table 3), the association between an NCEP criteria-based diagnosis of MetS and a history of CVD ceased to exist (OR: 1.99; 95% CI: 0.9-4.3, p = NS). However, the correlation between an IDF criteria-based diagnosis of MetS and a history of CVD remained significant (OR: 2.4; 95% CI: 1.1-5.2; p = 0.029). The sensitivity and specificity of an IDF criteria-based diagnosis of MetS for identifying a history of CVD were 60.7% and 60.8%, respectively.

The 202 patients with T2DM (Table 4) accounted for 31.7% of the sample, and 120 (59.4%) of those patients were female. Within this subgroup, already considered high risk, 16 (7.9%) were smokers and 39 (19.3%) had a history of CVD (OR: 3.7; 95% CI: 2.2-6.2, p < 0.05 vs. a history of CVD in patients without diabetes). The use of NCEP criteria in patients with T2DM resulted in a 75.7% prevalence of MetS, compared with 85.1% when the IDF criteria were used. However, a diagnosis of MetS presented no association with a history of CVD, whether MetS was defined using the NCEP criteria (OR: 0.8; 95% CI: 0.4-1.7; p = 0.54) or the IDF criteria (OR: 0.9; 95% CI: 0.4-2.5, p = 1.0).

The logistic regression model included the presence of CVD as a dependent variable and the following as independent variables: sex; age; serum levels of uric acid; microalbuminuria; serum levels of CRP; smoking; creatinine clearance, as calculated using the modification of diet in renal disease method, and a diagnosis of MetS. Using this model, only an IDF criteria-based diagnosis of MetS and uric acid were found to be predictors of a history of CVD.

When only non-classical cardiovascular risk factors (microalbuminuria, creatinine clearance, serum levels of uric acid and serum levels of CRP) were included as independent variables, a greater than 20% 10-year risk of CAD (as determined using the Framingham score) and serum levels of uric acid were shown to be predictors of a history of CVD. The AUC for the power of a diagnosis of MetS to predict a history of CVD was greater when the IDF criteria were used (AUC = 0.724; 95% CI: 0.66-0.789) than when the NCEP criteria were

used (AUC = 0.703; 95% CI: 0.634-0.776; p < 0.05) or when the Framingham score was used (AUC = 0,659; 95% CI; p < 0.05).

The stratification of all patients due to the number of MetS components defined by both NCEP and IDF criteria was similar, and most patients presented two MetS components.

We found that the number of MetS components, as defined using either criteria, correlated positively with the percentage of patients with CVD, as well as with serum levels of CRP. We found a greater proportion of patients with CVD and higher mean serum levels of CRP in those with more MetS components.

DISCUSSION

In the present study, we evaluated a final sample of 638 patients with hypertension and found the prevalence of MetS to be 45.5% when patients were analyzed according to NCEP criteria, compared with 54.7% when IDF criteria were applied.

Our results show that the prevalence of MetS in this population with the inclusion of patients with essential hypertension, was similar to that reported by the American Heart Association Statistics Committee and Stroke Statistics Subcommittee [(1)], which found the prevalence of MetS, according to NCEP criteria, to be 43.5% in the American population between 60-69 years of age. In contrast, Ford et al. [(27)] evaluated 20,050 American noninstitutionalized individuals over the age of 20 in the Third National Health and Nutrition Examination Survey (NHANES III, conducted under the auspices of the National Centers for Disease Control and Prevention) and found the NCEP criteria-based prevalence of MetS to be 23.9%. The higher prevalence of MetS in our sample can be attributed to the inclusion of a greater number of older patients, as well as to the fact that our sample was composed of patients with at least one MetS component.

Comparing the two sets of criteria, the prevalence of MetS was higher when the IDF criteria were used than when the NCEP criteria were used. Our data are in accordance with the results of Lorenzo et al. (28), who demonstrated a higher prevalence of IDF criteria-based MetS than of NCEP criteria-based MetS. The author compared American individuals of two ethnicities (Hispanics and Caucasians), and, in both groups, more patients with MetS were identified when the IDF criteria were used. In addition, in a recent analysis involving 20,789 outpatient evaluations conducted as part of the NHANES between 1999 and 2002, Katzmarzyk et al. demonstrated that the prevalence of MetS according to IDF criteria was 50% greater that that determined using the NCEP criteria [29].

Regardless of the criteria used, MetS contains variables which increase the risk of CVD [15,23]. Despite this fact, not all studies associate MetS with a risk of CVD. The INTERHEART study [2] was a case-control study involving 262 treatment facilities in 52 countries and evaluating the principal predictive factors of cardiovascular events. The study identified the variables responsible for 95% of the risk of CVD, especially MI. In the subanalysis of that study, a diagnosis of MetS, as defined by NCEP criteria, was not predictive of CVD. In the present study, a diagnosis of MetS, regardless of the set of criteria used, was clearly associated with CVD. However, this association seemed to be at least partially dependent upon the inclusion of patients with T2DM. In fact, when patients with T2DM were excluded, the correlation between MetS and CVD remained significant only when the IDF criteria were used. It could be a result of high prevalence of MetS in patients with diabetes.

Our results are in accordance with those of Lakka et al. and Eckel et al [4,30], who demonstrated a correlation between an NCEP criteria-based diagnosis of MetS and CVD, as well as with those of Nisson et al. [31], who showed that an IDF criteria-based diagnosis of MetS correlates with a significant increase in the occurrence of CVD. In fact, among individuals without diabetes, the mortality rate and incidence of CVD/CVA are two times and three times higher, respectively, for those with an IDF criteria-based diagnosis of MetS than for those without MetS. In addition, the risk of developing T2DM is five times greater for individuals with

MetS [19]. It is possible that the elevated prevalence of CVD associated with MetS is due to insulin resistance [32], which is associated with endothelial dysfunction and the atherosclerosis process.

Due to a strong association between larger waist circumference and insulin resistance, the IDF definition of MetS includes, as an obligatory criterion, a larger waist circumference, with cut-off values determined by gender and ethnicity [33]. On the basis of epidemiological data, the waist circumference cut-off point has been reduced for various ethnic groups [34-38]. Tan et al. [39] studied 4723 individuals of different ethnicities in Singapore and observed that when MetS was defined using lower values of waist circumference (< 80 cm in women and < 90 cm in men, values similar to those proposed by the IDF), it was possible to identify patients at risk for CVD with greater reliability than when NCEP values were used. In this context, the characterization of waist circumference by ethnic group has its relevance, since the definition established by the NCEP criteria, when applied to Asian and European populations might underestimate the prevalence of MetS and, consequently, fail to identify individuals with risk of CVD. Tan et al. did not evaluate the risk of CVD in the population of patients with and without diabetes.

The impact that a diagnosis of MetS has on the incidence of CVD in patients with diabetes is not well established yet. Haffner et al. showed that the presence of T2DM increases the risk of CAD, making it similar to that of individuals without diabetes who have already suffered a coronary event [40]. The authors found that the incidence of MI in individuals with T2DM and no history of CVD was similar to that of those without diabetes and with a history of MI. Therefore, they dubbed T2DM a CAD risk 'equivalent'. The Framingham study had already called the attention to the fact that T2DM doubles the risk of CVD in men and triples it in women. In a recent evaluation of MetS sponsored by the American Association of Diabetes and the European Association for the Study of Diabetes, Bruno et al. [41] found that, in patients with diabetes, a diagnosis of MetS has little or no value in determining CVD mortality risk [42]. The study involved 1565 patients with diabetes in outpatient treatment for 8 years. The authors found the prevalence of MetS to be 76%, and the relative risk for all-cause mortality, as well as for cardiovascular mortality, in the group with MetS was similar to that of patients with

T2DM without MetS. Similarly, Lorenzo et al. showed that MetS was not predictive of CVD in patients with a history of CVD or equivalent ischemic vascular events [43]. In addition, a retrospective analysis conducted by Carole et al., involving data from the United Kingdom Prospective Diabetes Study, provided a better evaluation of the association between MetS and CVD in patients with diabetes through the simultaneous analysis of different definitions of MetS in a more than 50,000 person-years of follow-up evaluation. In that analysis, there was a considerable superimposition in the estimate of risk of CVD in 10 years between T2DM patients with and without MetS, and the authors attributed limited clinical value to the diagnosis of MetS for the stratification of cardiovascular risk in patients with T2DM. Our data are in accordance with those cited, since we did not find a correlation between MetS and CVD when we evaluated patients with T2DM, regardless of the criteria used to define MetS. However, in patients without diabetes, a diagnosis of MetS based solely on the IDF criteria was associated with a higher frequency of CVD.

In summary, we can affirm that the prevalence of MetS, at least in patients without diabetes, depends on the criteria applied. In the patients without diabetes, MetS defined by IDF criteria alone was associated with a higher frequency of CVD. In patients with T2DM, a diagnosis of MetS, regardless of the criteria adopted, was not associated with CVD. A diagnosis of MetS, regardless of the diagnostic criteria applied, showed a strong association with the occurrence of T2DM.

We conclude that, in patients without diabetes, a diagnosis of MetS according to IDF criteria is useful in identifying individuals with a higher probability of presenting CVD. In patients with diabetes, a population already considered at high risk for CVD, a diagnosis of MetS, regardless of the criteria used, has no impact on prognosis. Nevertheless, in patients without diabetes, a diagnosis of MetS, regardless of the criteria used, can identify individuals more likely to develop T2DM.

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Table 1: Demographic characteristics and biochemical evaluation of patients with and without metabolic syndrome according to the two sets of criteria.

	Diagnosis of MetS using NCEP criteria			**Diagnosis of MetS using IDF criteria**		
	Yes n (%)	**No n (%)**	**p***	**Yes n (%)**	**No n (%)**	**p***
n	290 (45%)	348 (55%)		349 (54.7%)	289 (45.3%)	
Female, n (%)	205 (70.7)		ns	242 (96.3%)		ns
Age (years)	57.9 ± 9.5	57.6 ± 10.5	ns	57.9 ± 9.5	57.6 ± 11.0	ns
BMI (kg/m^2)	32.1 ± 4.7	27.5 ± 4.6	<0.05	31.4 ± 4.9	27.5 ± 4.7	<0.05
SBP (mmHg)	139 ± 19	136 ± 20	<0.05	138 ± 19	136 ± 21	ns
DBP (mmHg)	86 ± 11	84 ± 11	ns	86 ± 11	85 ± 11	ns
Waist circumference (cm) men	105.8 ± 10	94.1 ± 8.5	<0.05	105.1 ± 8.4	92.3 ± 9.1	<0.05
Waist circumference (cm)women	101.3 ±10	90.0 ±12	<0.05	99.3±11	90.9±12	<0.05
TC (mg/dL)	213.5 ± 45	209.2 ± 37	ns	213.2 ± 44	209.2 ± 37	ns
HDL-C (mg/dL)	50.8 ± 13	61.9 ± 15	<0.05	52.3 ± 13	62 ± 16	<0.05
LDL-C (mg/dL)	123.9 ± 38	123.2 ± 33	ns	124.5 ± 37	122.4 ± 34	ns
TG (mg/dL)	197.8 ± 111	120.5 ± 62	<0.05	186.7 ± 107	118.2 ± 61	<0.05
Blood glucose (mg/dL)	117.8 ± 49	93.1 ± 34	<0.05	115.1 ± 46	91.3 ± 37	<0.05
Uric acid (mg/dL)	6.0 ± 1.6	5.2 ± 1.6	<0.05	5.9 ± 1.6	5.3 ± 1.6	<0.05
Creatinine (mg/dL)	1.0 ± 0.3	1.0 ± 0.2	ns	1.0 ± 0.2	1.0 ± 0.2	ns
Creatinine clearance (ml/min/1.73m^2)	68.8 ± 15	71.5 ± 12.8	<0.05	69.5 ± 14	71.2 ± 13	ns
Potassium (mEq/L)	4.4 ± 0.4	4.5 ± 0.5	ns	4.4 ± 0.4	4.5 ± 0.5	ns
Microalbuminuria (µg/min)	62.8 ± 233	18.6 ± 118	<0.05	45.6 ± 175	30.2 ± 187	ns
CRP (mg/dL)	0.7 ± 0.8	0.5 ± 0.6	<0.05	0.7 ± 0.7	0.5 ± 0.6	<0.05
Framingham score	15 ± 3.7	13 ± 4.3	<0.05	14.7 ± 3.7	13.1 ± 4.5	<0.05

MetS: metabolic syndrome; NCEP: National Cholesterol Education Program; IDF: International Diabetes Federation; ns: not significant; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglycerides; CRP: C-reactive protein.

*vs. patients without MetS.

Table 2: discriminates the stratification of MetS components as well as the antihypertensive agents taken by the patients either with or without MetS (NCEP and IDF)

	TOTAL		NCEP		IDF	
	N	%	N	%	N	%
DIURETICS	350	54,9	179	61,7	266	76,2
ACEi/ARB	414	64,9	221	76,2	211	60,5
CCB AGENTS	179	28,1	89	30,7	103	29,5
BETA BLOCKING AGENTS	118	18,5	52	17,9	66	18,9
OUTROS	27	4,2	15	5,1	16	4,6

ACEi: Angiotensina-Conveting Enzime inhibitor; ARB: Angiotensin II Receptor blocking; CCB: calcium channel blocking.

Table 3: Demographic characteristics and biochemical evaluation of patients without diabetes (with and without metabolic syndrome according to the two sets of criteria).

	Diagnosis of MetS using NCEP criteria			**Diagnosis of MetS using IDF criteria**		
	Yes n (%)	**No n (%)**	**p***	**Yes n (%)**	**No n (%)**	**p***
n	137 (31.4%)	298 (68.3%)		177 (40.6%)	285 (59.2%)	
Female, n (%)	104 (75.9%)		ns	129 (72.9%)		ns
Age (years)	56.1 ± 9.4	57.2 ± 10.8	ns	56.3 ± 9.3	57.2 ± 11.0	ns
BMI (kg/m^2)	32.2 ± 5.0	27.8 ± 4.7	<0.05	31.3 ± 5.2	27.7 ± 4.7	<0.05
SBP (mmHg)	139 ± 19	137 ± 20	ns	138 ± 19	137 ± 20	ns
DBP (mmHg)	88 ± 11	85 ± 11	<0.05	87 ± 11	85 ± 11	<0.05
Waist circumference (cm) men	104.3±9	94.6 ± 9	<0.05	103.5 ± 6.1	93.3 ±9.8	<0.05
Waist circumference (cm) women	101.3±10.6	90.45±11.8	<0.05	99.1±11.4	90.5±12	<0.05
TC (mg/dL)	218.9 ± 42	211.3 ± 36	ns	218.5 ± 41	210.4 ± 36	<0.05
HDL-C (mg/dL)	48.1 ± 10	62.2 ± 15	<0.05	50.2 ± 11	63.0 ± 15	<0.05
LDL-C (mg/dL)	130.6 ± 37	124.6 ± 33	ns	130.4 ± 36	124.0 ± 33	ns
TG (mg/dL)	204.4 ± 85	122.3 ± 59	<0.05	195.44 ± 85	115.8 ± 53	<0.05
Blood glucose (mg/dL)	88.8 ± 12	84.2 ± 10	<0.05	89.5 ± 12	83 ± 9	<0.05
Uric acid (mg/dL)	6.1 ± 1.5	5.3 ± 1.5	<0.05	6.0 ± 1.5	5.2 ± 1.5	<0.05
Creatinine (mg/dL)	1.0 ± 0.2	1.0 ± 0.2	ns	1.0 ± 0.2	1.0 ± 0.2	ns
Creatinine clearance (ml/min/1.73m^2)	69.7 ± 14	71.1 ± 13	ns	70.1 ± 13	71± 13	ns
Potassium (mEq/L)	4.4 ± 0.4	4.5 ± 0.5	ns	4.4 ± 0.4	4.5 ± 0.5	<0.05
Microalbuminuria (µg/min)	29.8 ± 107	12.7 ± 57	<0.05	25.1 ± 95	13.7 ± 60	ns
CRP (mg/dL)	0.7 ± 0.7	0.5 ± 0.6	<0.05	0.7 ± 0.7	0.5 ± 0.6	<0.05
Framingham score	15 ± 3.7	13 ± 4.5	<0.05	14.7 ± 3.7	13.2 ± 4.6	<0.05

MetS: metabolic syndrome; NCEP: National Cholesterol Education Program; IDF: International Diabetes Federation; ns: not significant; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglycerides; CRP: C-reactive protein.

*vs. patients without MetS.

Table 4: Demographic characteristics and biochemical evaluation of patients with diabetes (with and without metabolic syndrome according to the two sets of criteria).

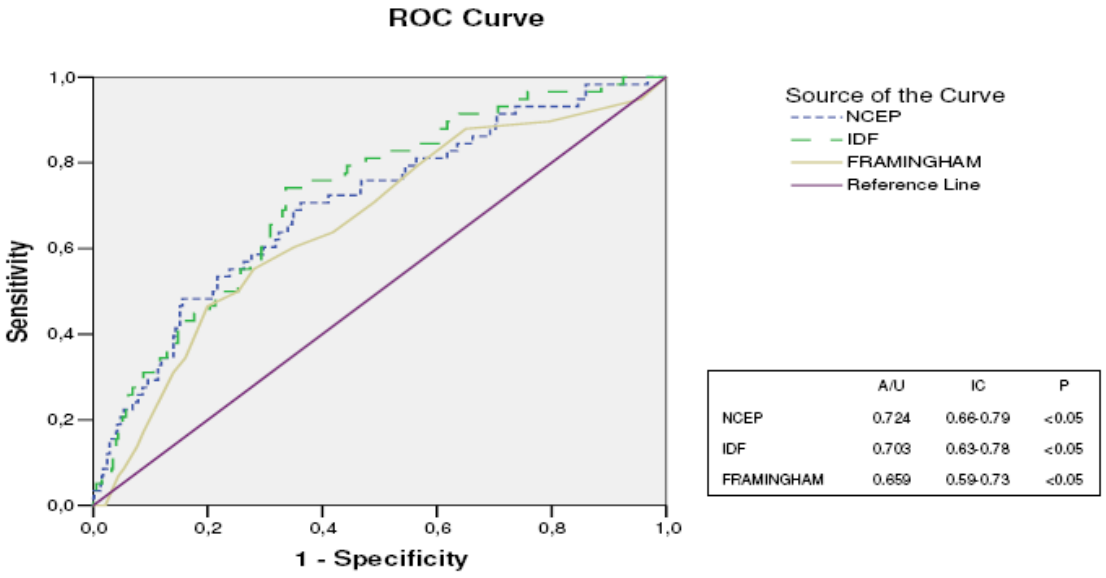
	Diagnosis of MetS using NCEP criteria			**Diagnosis of MetS using IDF criteria**		
	Yes n (%)	**No n (%)**	**p***	**Yes n (%)**	**No n (%)**	**p***
n	153 (75.7%)	49 (24.3%)		172 (85.1%)	30 (14.9%)	
Female, n (%)	113 (65.7%)		<0.05	101 (66%)		<0.05
Age (years)	59.5 ± 9.4	60.5 ± 8.5	ns	57.5 ± 9.3	60.8 ± 8.5	ns
BMI (kg/m^2)	32.0 ± 4.5	26.2 ± 3.7	<0.05	31.5 ± 4.6	25.7 ± 4.6	<0.05
SBP (mmHg)	139 ± 18	127 ± 17	<0.05	138 ± 18	124.7 ± 17	<0.05
DBP (mmHg)	85 ± 11	79.7 ± 8	<0.05	84 ± 11	80 ± 9	ns
Waist circumference (cm) men	106.6 ± 11	92.6 ±6.4	<0.05	106.4 ± 9.7	88.8 ± 5	<0.05
Waist circumference (cm) women	101.3±9.5	85.4±13.3	<0.05	99.5±10.5	87.9±22.5	<0.05
TC (mg/dL)	208.6 ± 48	196.2 ± 41	ns	207.7 ± 47	193.9 ± 45	ns
HDL-C (mg/dL)	53.1 ± 15	59.6 ± 17	<0.05	54.5 ± 15	55.9 ± 20	ns
LDL-C (mg/dL)	117.8 ± 38	114.8 ± 35	ns	118.3 ± 37	110.1 ± 38	ns
TG (mg/dL)	192.0 ± 130	109.57 ± 73	<0.05	177.6 ± 126	139.8 ± 106	ns
Blood glucose (mg/dL)	143.8 ± 55	147.5 ± 66	ns	141.5 ± 52	163.0 ± 82	ns
Uric acid (mg/dL)	6.0 ± 1.7	5.2 ± .21	<0.05	5.8 ± 1.7	5.7 ± 2.5	ns
Creatinine (mg/dL)	1.1 ± 0.3	1.0 ± 0.2	ns	1.0 ± 0.3	1.1 ± 0.3	ns
Creatinine clearance (ml/min/1.73m^2)	68 ± 16	74.4 ± 14	<0.05	69.9 ± 15	73.3 ± 16	ns
Potassium (mEq/L)	4.4 ± 0.5	4.6 ± 0.5	ns	4.5 ± 0.5	4.6 ± 0.6	ns
Microalbuminuria (µg/min)	92.7 ± 303	53.2 ± 276	ns	66.7 ± 228	176.5 ± 542	ns
CRP (mg/dL)	0.7 ± 0.8	0.4 ± 0.6	<0.05	0.7 ± 0.7	0.5 ± 0.7	ns
Framingham score	14.8 ± 3.7	13 ± 3.2	<0.05	14.6 ± 3.7	12.9 ± 3.0	<0.05

MetS: metabolic syndrome; NCEP: National Cholesterol Education Program; IDF: International Diabetes Federation; ns: not significant; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglycerides; CRP: C-reactive protein.

*vs. patients without MetS.

FIGURE LEGENDS

Figure 1: Receiver operating characteristic (ROC) curve: cardiovascular disease in relation to the Framingham Score, as well as to metabolic syndrome according to the National Cholesterol Education Program (NCEP) and International Diabetes Federation (IDF) criteria, in the population studied



	A/U	IC	P
NCEP	0.724	0.66-0.79	<0.05
IDF	0.703	0.63-0.78	<0.05
FRAMINGHAM	0.659	0.59-0.73	<0.05

ANEXOS

ANEXO 1: Termo de consentimento livre e esclarecido

Hospital do Rim e Hipertensão

Disciplina de Nefrologia

Universidade Federal de São Paulo – UNIFESP

Polimorfismo de Genes de Citocinas: Impacto nas Subfrações de Lipoproteínas em Hipertensos Estratificados de Acordo com os Componente da Síndrome Metabólica

TERMO DE CONSENTIMENTO

Proposta do estudo: Eu entendo que está sendo solicitada a minha participação, como voluntário(a), em uma Pesquisa que irá estudar o polimorfismo (estudo genético) das citocinas (grupos moleculares responsáveis pela resposta inflamatória do corpo humano) e o perfil das lipoproteínas (lipídeos do sangue) em pacientes portadores de hipertensão arterial, comparando-os a um grupo de indivíduos sem doença.

Importância do estudo: Pacientes com hipertensão arterial têm maior risco de doença coronariana que indivíduos sem doença. Dados de pesquisas anteriores já demonstram estreita relação entre a ateosclerose, a dislipidemia e os processos inflamatórios crônicos. Estudos mais recentes demonstram que também na hipertensão arterial a resposta inflamatória está envolvida na ocorrência de doenças cardiovasculares (infarto, angina e acidentes vasculares cerebrais). A análise genética, através do estudo do polimorfismo das citocinas, tem proporcionado grande avanço no entendimento das doenças cardiovasculares. De maneira semelhante, a hipertensão arterial ocasiona alteração do perfil lipídico, com aumento do nível de triglicérides e redução dos níveis de HDL, o que facilita a ocorrência de doença coronariana. Este Estudo proporcionará melhor avaliação deste fatores de risco (redução do HDL e aumento do triglicérides) em pacientes com hipertensão arterial analisados sob a ótica da inflamação.

População do estudo: Eu entendo que, para participar deste Estudo, devo ter idade maior que 18 anos e devo preencher os critérios científicos estabelecidos pelos pesquisadores. Eu não poderei participar do estudo se estiver recebendo qualquer medicação para tratar dislipidemia.

Procedimento: Será solicitada a minha presença no Ambulatório de Hipertensão da Disciplina de Nefrologia da Universidade Federal de São Paulo para que eu seja submetido(a) a coleta de 40 ml de sangue para a mensuração de perfil lipídico e estudo dos genes envolvidos na inflamação (citocinas). Entendo que parte da amostra de sangue coletada poderá ser utilizada em futuros estudos de genes envolvidos na inflamação e doença cardiovascular. Eu entendo que, ao me apresentar para a coleta de sangue, deverei estar em jejum (incluindo qualquer tipo de líquido) nas 12 horas precedentes.

Risco do procedimento: Eu entendo que não há maior risco ou perigo relacionado à minha participação no estudo. Também entendo que a coleta de sangue poderá ocasionar pequeno desconforto no local da punção bem como eventual formação de hematoma.

Benefícios: Eu entendo que não haverá benefício direto, nem compensação financeira, relacionados à minha participação neste Estudo. No entanto, esta pesquisa poderá proporcionar novas e relevantes informações dos fatores de risco para doença coronariana relacionados à inflamação e à hipertensão arterial. Eu entendo que posso desistir de participar deste Estudo quando for da minha vontade sem que isso afete qualquer tratamento médico futuro nesta Instituição.

Confidencialidade: Eu entendo que toda informação produzida por este Estudo será confidencial e privada. Se esta informação for utilizada para publicação em literatura médica ou com finalidade de ensino, não será fornecida a identidade dos participantes. Os arquivos derivados deste Estudo serão mantidos confidenciais e só serão liberados por força da lei.

Eu fui orientado(a), em caso de qualquer dúvida, procurar o seguinte pesquisador:

Dra. Andréa Harumi Hirota

Eu li este Termo de consentimento e discuti as minhas dúvidas com a Dra. Andréa Harumi Hirota ou seu(ua) representante a respeito dos procedimentos do Estudo. Eu tive a oportunidade de fazer perguntas, que foram respondidas satisfatoriamente.

Eu fui completamente informado sobre o Estudo acima descrito e sobre os seus potenciais riscos e benefícios, e consinto com a realização dos procedimentos necessários a realização do referido Estudo.

Data: ____/_____/_____ _____

Participante

Data: ____/_____/_____ _____

Investigador

Data: ____/_____/_____ _____

Testemunha

Anexo 2: Aprovação pelo comitê de ética médica.

UNIFESP

HOSPITAL DO RIM E HIPERTENSÃO
Fundação Oswaldo Ramos
Órgão Suplementar da UNIFESP-EPM

Utilidade Pública Federal, Decreto nº 99395 de 28/03/88
Utilidade Pública Estadual, Lei nº 8226 de 11/11/88
Utilidade Pública Municipal, Decreto nº 23099 de 10/04/87
Certificado de Entidade de Fins Filantrópicos - CNAS: Resolução nº 131 de 15/12/95

São Paulo, 31 de maio de 2004.

Ilmo. Sr.
Prof. Dr. Marcelo Costa Batista
Disciplina de Nefrologia – UNIFESP - EPM

Ref.: Protocolo No. 161 intitulado "Polimorfismo de genes de citocinas: impacto nas subfrações de lipoproteínas em hipertensos estratificados de acordo com os componentes da síndrome metabólica."

Prezado Doutor,

O Comitê de Ética em Pesquisa do Hospital do Rim e Hipertensão - Fundação Oswaldo Ramos aprovou em 26 de maio de 2004 o Protocolo supra citado juntamente com o Termo de Consentimento Livre e Esclarecido.

Atenciosamente,

Prof. Dr. Osvaldo Kohlmann Junior
Presidente do Comitê de Ética em Pesquisa
Hospital do Rim e Hipertensão
Fundação Oswaldo Ramos

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