ORIGINAL MANUSCRIPT

Hemostatic Risk Marker Associated with Cardiovascular Events in Metabolic Syndrome

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Abstract

Background: Cardiovascular disease (CVD) is the leading cause of death in developing countries. Individuals with metabolic syndrome (MS) are at increased risk for CVD. The traditional risk factors, altogether, do not explain all cardiovascular events. The von Willebrand factor (vWF), involved in platelet aggregation and thrombosis, has been investigated in this context.
Objective: To investigate the relationship between the vWF and CVD in patients with MS, with and without previous cardiovascular events.
Methods: The study included 77 outpatients, ≥18 years, with MS, according to the criteria established by NCEP-ATP III. The plasma level of vWF was measured and the mean values were compared between the groups with prior CVD (n=30) and without documented CVD (n=47).
Results: In the study population, 66.0% were female, 78.0% were white, mean age 63.7±8.9, mean weight 82.9±14.9 kg, and body mass index 32.2±4.8 kg/m^2. The average plasma level of vWF was similar in patients with and without previous CVD, with values of 154.5±52.1 and 155.47±41.4, respectively. There was an association between diabetes mellitus (DM) and established CVD, which remained significant after adjusting for other variables included in the multivariate model.
Conclusions: There was no difference in the mean plasma level of vWF among patients with MS, with and without documented CVD. The presence of DM, however, was independently associated with CVD in this population.

Keywords: Cardiovascular diseases; Metabolic syndrome X; Diabetes mellitus

Introduction

CVD is a major cause of death in Brazil[1] and accounts for 35.0% of deaths in the United States[2].

The relationship between abdominal obesity and CVD has been established in population-based studies, both in women[3] and in men[4]. The volume of intra-abdominal adiposity and the presence of a high waist circumference are associated with increased resistance to insulin[5-7].

Individuals with this profile have higher levels of triglycerides and reduced plasma concentrations of LDL-cholesterol, increasing the total cholesterol/HDL ratio, a known predictor of risk for heart diseases[8]. Together, these changes meet the criteria established by NCEP-ATP III[9] for the diagnosis of metabolic syndrome (MS), independently implicated with increased risk for cardiovascular events[10].

The established risk factors for developing CVD, some of which are present in MS (hypertension, dyslipidemia, diabetes mellitus), in addition to smoking, are present in many, but not in all individuals who develop CVD[11-13]. Hemostatic and inflammatory markers such as the von Willebrand factor (VWF) may contribute to endothelial

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ABBREVIATIONS AND ACRONYMS

- *AH – arterial hypertension*
- *AMI – acute myocardial infarction*
- *BMI – body mass index*
- *CAD – coronary artery disease*
- *CVD – cardiovascular disease*
- *DM – diabetes mellitus*
- *MS – metabolic syndrome*
- *vWF – von Willebrand factor*

dysfunction due to its role in thrombosis[14] and is potentially involved in atherosclerosis[15]. The vWF is a major glycoprotein produced specifically by the vascular endothelium cells. It operates in hemostasis and thrombosis as an important cofactor in platelet adhesion and aggregation, and acts as a protein that carries the VIII factor of coagulation[14].

Population-based studies including individuals without established atherosclerotic disease have associated high levels of vWF with increased risk of CVD[16-18]. However, this association was not confirmed in epidemiological studies that followed patients with pre-existing vascular disease[19-21] and has shown controversial results in the outpatient setting and case studies and control group studies[22].

This study aimed to investigate the association between the hemostatic von Willebrand factor, known risk factors for CVD and the presence of CVD established in individuals with MS followed on an outpatient basis in a tertiary institution.

Methods

This is an observational study conducted from January 2012 to July 2014, which sought to analyze the risk factors and hemostatic markers of a population of 77 (51 women and 26 men) individuals consecutively assisted in the cardiometabolic risk outpatient care unit of Hospital São Lucas da PUCRS (HSL-PUCRS).

This study was approved by the Research Ethics Committee of Pontifícia Universidade Católica do Rio Grande do Sul under no. 06/03546. All patients signed an Informed Consent Form.

The following inclusion criteria apply: men and women aged ≥18 years, with MS, with and without previous CVD. Exclusion criteria were: patients with morbid obesity (BMI ≥40 kg/m^2) and those who did not signed the informed consent form.

MS was established according to NCEP-ATP III[9]: waist circumference (men >102 cm, women >88 cm); systolic blood pressure (SBP) > 130 mmHg or diastolic blood pressure (DBP) > 85 mmHg; triglycerides > 150 mg/dL, fasting glucose >110 mg/dL, HDL-cholesterol (men < 40 mg/dL, women < 50 mg/dL). Those patients that presented at least one of these criteria were characterized as MS patients.

The following risk factors were analyzed: current smoking or exposure to smoking for at least for 10 years, dyslipidemia, arterial hypertension (AH), DM and family history of coronary artery disease (CAD). The following anthropometric variables were considered: weight, height, BMI and waist circumference; in addition to sex and age of the participants.

Abdominal circumference was measured in the standing position, after expiration, with the tape positioned between the costal margin and the iliac crest. Height and weight were assessed by a precision scale and the BMI was calculated by the formula [weight (kg)/height (m^2)].

Blood pressure was measured in the sitting position after 5 minutes of rest. The average of two measurements performed in the beginning and in the end of the visit was considered for analysis.

Blood was collected from all patients, after a 12-hour fasting, for blood glucose, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and vWF analysis.

The hemostatic factor studied was determined by the turbidimetric immunoassay method, ACL TOP500 CTS equipment (Instrumentation Laboratory, Bedford, MA, USA)[23].

The variables studied were analyzed and compared between the two groups with MS: without prior CVD and with established CVD: acute myocardial infarction (AMI) and cerebrovascular accident (CVA), confirmed by diagnostic methods (electrocardiogram, myocardial scintigraphy, cardiac catheterization, echocardiography, skull computed tomography and magnetic resonance imaging). The group without prior CVD included individuals with no history of AMI and stroke.

For the statistical treatment of the data, the program SPSS version 17.0 was used. Data were expressed as means and standard deviations for continuous variables and frequencies for categorical variables. The analytical statistics was performed using the chi-square test and

continuous variables using the Student's t test. The differences between variables presenting a $p < 0.05$ were considered significant.

Results

Study population composed of 77 patients (51 women and 26 men), 78.0% white, mean age 63.7±8.9 years, mean weight 82.9±14.9 kg, BMI 32.2±4.8 kg/m^2. DM present in 52.0% and AH in 95.0% of participants; 7.0% were smokers (Table 1).

It was observed that the mean serum value of hemostatic von Willebrand factor did not differ (p=0.931) between the two groups analyzed: with established CVD and no history of CVD (Table 2).

The frequencies of the other variables studied in the two groups are shown in Table 2.

The presence of DM ($p < 0.0001$) and male sex (p=0.048) were associated with higher prevalence of CVD. The variables: age (p=0.574), weight (p=0.916), BMI (p=0.678), ethnicity (p=0.258), AH (p=0.161) and current exposure to smoking (p=0.652) showed similar distribution among individuals with and without prior CVD.

Table 1
Characteristics of the population studied

Characteristics	Population (n=77)
Sex n (%)	
Men	26 (34.0)
Women	51 (66.0)
Ethnicity n (%)	
White	67 (78.0)
Non-white	10 (12.0)
Diabetes mellitus n (%)	
Yes	40 (52.0)
No	37 (48.0)
Arterial hypertension n (%)	
Yes	73 (95.0)
No	4 (5.0)
Smoking n (%)	
Yes	5 (7.0)
No	72 (93.0)
Age (years) average±SD	63.7±8.9
Weight (kg) average±SD	82.9±14.9
Body mass index (kg/m^2) mean±SD	32.2±4.8
von Willebrand Factor mean±SD	155.1±45.5

SD — standard deviation

Table 2
Variables studied and their association with CVD

		Cardiovascular disease		p value
		Yes	No	
Sex n (%)	Men	14 (46.0)	12 (25.0)	0.048
	Women	16 (53.0)	35 (75.0)	
Ethnicity n (%)	White	19 (95.0)	35 (85.0)	0.258
	Non-white	1 (5.0)	6 (15.0)	
Diabetes mellitus n (%)	Yes	24 (80.0)	16 (34.0)	<0.001
	No	6 (20.0)	31 (66.0)	
Arterial hypertension n (%)	Yes	27 (90.0)	46 (98.0)	0.161
	No	3 (10.0)	1 (2.0)	
Smoking n (%)	Yes	2 (7.0)	3 (6.0)	0.652
	No	28 (93.0)	44 (94.0)	
Age (years) average±SD		64.4±9.7	63.3±8.4	0.574
Weight (kg) average±SD		82.6±16.1	83.0±14.3	0.916
Body mass index (kg/m^2) average±SD		31.9±5.2	32.3±4.7	0.678
von Willebrand factor mean±SD		154.5±52.1	155.47±41.4	0.931

SD — standard deviation

Discussion

MS is a disorder that includes several factors that predispose to the development of CVD[24]. The high and increasing morbidity and mortality from CVD, regardless of age, in Brazil[25], reinforces the importance of studying MS in the context of metabolic and cardiovascular diseases[26].

This study sought to identify, in a sample of outpatients with MS, the relationship of traditional risk factors and the hemostatic marker vWF with the occurrence of cardiovascular events.

The high rate of patients with hypertension (95.0%) and diabetes (48.0%) found in this study reflects the same picture of developed countries[27] and other scenarios in Brazil[24]. In a study of patients with similar characteristics to the universe studied here, in a cross-sectional analysis of a cohort of patients with atherosclerotic disease, a high prevalence of MS (46.0%) and its components was identified, in which participants with documented AMI had hypertension and DM rate of 61.0% and 34.0%, respectively[28].

This study found no difference in the serum level of vWF among individuals with MS with and without established CVD. This result is consistent with a recent case study and a control group study[28] that showed significantly higher levels of vWF in patients with acute coronary syndrome (ACS) compared with healthy individuals; however, in the group of individuals with stable CAD, the hemostatic factor levels were similar[22]. The vWF was studied as a prognostic marker for CVD in initially healthy individuals in the ARIC study[16], where the association initially found (RR=1.3) disappeared after adjustment for traditional risk factors, especially DM. A stronger association between vWF and CVD (RR=2.0), comparing the highest quartile with the lowest quartile was found in two Swedish cohorts. However, this association also lost significance after controlling for other factors coexisting in the multivariate model[17]. Another case and control group study with a prospective cohort of men and middle-aged women without CVD found an independent association between high levels of vWF and incident cardiovascular events[18].

However, in the PRIME[29] study (Prospective Epidemiological Study of Myocardial Infarction) of case and control groups, the risk of MI was three times higher in individuals with plasma levels of vWF in the highest quartile compared to the lowest one. This difference persisted after adjustment for inflammatory markers and traditional cardiovascular risk factors. The same association, however, was not found in participants diagnosed with stable angina, a similar context to that of the present study, in which patients were studied on an outpatient basis without coronary instability.

The paradigm study Framingham Heart Study[30] was the first large study that aimed to identify the factors that contribute to the development of cardiovascular diseases, following, for a long time, a large number of participants who had not yet developed evident symptoms of cardiovascular diseases. Its findings led to the identification of the major risk factors for CVD. In one of its sub-studies, the impact on the development of CVD was compared between nondiabetic and diabetic patients. The incidence of CVD in diabetic men was two times higher than in non-diabetic men. Among diabetic women, the incidence of cardiovascular disease was three times higher than in those who are not diabetic[31].

This study[30] and other epidemiological studies cited, in which the presence of DM was the variable responsible for the loss of independence in the association between high levels of vWF and CVD, put plasma glucose abnormalities in the center of the atherosclerotic process and its destabilizations. This statement is additionally supported in the Framingham Offspring Study[32], in which high levels of vWF were associated with cardiovascular diseases only in individuals with DM or insulin resistance. This observation may explain the link between vWF and CVD and suggests that this hemostatic factor be considered a cardiovascular risk variable especially in patients with DM or other forms of dysglycemia.

The expansion of knowledge about the real role of hemostatic markers such as vWF, especially in individuals with DM, must occupy increasing space in research related to the development of cardiovascular diseases in order to impact the context of primary and secondary prevention.

This study has limitations inherent in all cross-sectional studies in which exposures and outcomes are evaluated in a single moment, making it impossible to establish a clear causal relationship between the variables studied.

Additional studies are needed to try to identify a more consistent association between levels of vWF, DM and

CVD, both in the outpatient setting and in the emergency and cardiovascular intensive care unit settings, where patients with ACS are managed. Based on evidence in the literature, there seems to be a stronger relationship between the hemostatic factors such as vWF, since they cause endothelial dysfunction and interfere with thrombosis and platelet aggregation, the mechanisms involved in the occurrence of cardiovascular events.

Conclusion

There was no difference in the mean plasma level of vWF in a universe of outpatients with MS, with and without established CVD. The presence of DM, however, is independently associated with CVD in this population.

Potential Conflicts of Interest

No relevant potential conflicts of interest.

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Academic Association

This study is not associated with any graduate programs.

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