D-Dimer plasma levels in patients with coronary artery disease

Níveis plasmáticos de Dímero D em pacientes com doença arterial coronariana

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We have previously reported that prothrombin fragment 1+2 levels were not associated to the presence or severity of coronary artery disease (CAD) and do not provide further information on subjects with CAD diagnosed by angiography. Thus, in the present study another marker of hypercoagulability was evaluated in the same subjects. This study aimed at determining D-Dimer plasma levels in a group of subjects undergoing coronary angiography to establish a likely relation between this parameter and the severity of CAD. D-Dimer plasma levels were determined in 17 subjects with no coronary atheromatosis (controls), 12 subjects with mild/moderate atheromatosis and 28 subjects with severe atheromatosis. No significant differences were observed among the three groups. Data analysis enables an inference on a tendency towards an increase in fibrinolytic activity in patients with atheromatosis, reflected by the increase in D-Dimer concentrations in the severe atheromatosis group in subjects with CAD diagnosed by coronary angiography.


Palavras-chave: D-Dimer; coronary artery disease; coronary angiography.

Introduction

Several decades of clinical and laboratory research have pointed out the association between hemostatic system constituents and CAD investigating the possible predictive value of these constituents in the progression of the disease. Both coagulation and fibrinolytic systems play an important role in the clinically silent evolution and progression of atheroma and in events that follow the rupture of the plaque resulting in clinical symptoms. Thrombus formation in a disrupted atherosclerotic plaque triggers most of the cardiovascular ischemic events. As the thrombus is dissolved by the fibrinolytic system, researchers hypothesized that a decrease in fibrinolytic activity could be a risk factor for ischemic events. When the conversion of fibrinogen in fibrin takes place, the mechanism that keeps the hemostatic balance is activated, with the conversion of plasminogen to plasmin, for fast removal of fibrin, preventing thrombotic complications.

D-Dimer fragments are produced when plasmin, an enzyme that activates fibrinolytic system, degrades fibrin to remove it from blood vessels, ducts and organic fluids.
Materials and Methods

The protocol of this study had approval from ethical and formal points of view by both Research Ethics Committees of Socor Hospital and Federal University of Minas Gerais. The subjects selected to take part in this research were informed about the aims of the study and those who agreed signed informed consent forms. A clinical form reporting important data was filled in for all cases. Fifty-seven subjects, with ages ranging from 40 to 65 years, who had been submitted to coronary angiography in the Department of Hemodynamics of Socor Hospital, Belo Horizonte, Brazil, were selected. Seventeen subjects (controls) did not present atheromatosis in the coronary arteries, 12 subjects presented mild/moderate atheromatosis and 28 subjects, severe atheromatosis (Table 1). Subjects with previous histories (up to 3 months) of acute coronary syndrome; oral anticoagulants, hypolipemiant drugs or estrogen use; carriers of intercurrent diseases, such as coagulation disorders, kidney, liver and autoimmune diseases, diabetes mellitus and cancer were excluded from the study.

Coronary angiography was performed by the Judkins' technique; films were examined by three experienced cardiologists and decisions made according to defined criteria considering stenosis of one or more arteries: up to 30% stenosis it was classified as mild atheromatosis; from 30 to 70% stenosis as moderate atheromatosis and above 70% stenosis as severe atheromatosis.

Venous blood samples were obtained after 12 hours of fasting and collected in tubes containing 3.2w/v sodium citrate as anticoagulant. Blood samples were centrifuged at 2500 rpm for 10 minutes to obtain plasma.

Plasma D-Dimer levels were determined using the VI-DAS D-Dimer New Kit (BioMérieux® - France) in a MiniVidas (BioMérieux®) device according to the manufacturer's instructions. Its analytical principle is an enzyme linked fluorescent assay (ELFA). In principle, the test samples were transferred into wells containing an alkaline-phosphatase labeled anti-D-D monoclonal antibody. The sample/conjugate mixture was cycled in and out of the solid phase receptacle (SPR) several times to increase the reaction speed. Unbound components were eliminated during washing phases. The addition of the substrate (4-methyl-umbelliferyl phosphate) and its subsequent hydrolysis by conjugate enzyme produces a fluorescent product (4-methyl-umbelliferone), which is measured at 450nm. The values were then automatically calculated by the instrument in relation to two calibration curves performed using two calibrators provided by the manufacturer, corresponding to the two detection steps. All of the assay steps were performed automatically by the instrument. The lower limit of detection for the assay was 45 ng/mL. The intra and inter assay coefficients of variations for 488 ng/mL D-Dimer were 2.9% and 6.8%, respectively (BioMérieux, Marcy-l’Etoile, France).

Data were analyzed by Sigma Stat version 1.0 software system using one-way analysis of variance (ANOVA) after log-transformation of the data, which did not present normal distribution. Pearson's correlation coefficient was used to measure the linear association between D-Dimer and Plasma F1+2 levels. Differences were considered statistically significant when p-value < 0.05.

Results

The results for the biomarker assay are shown as mean and standard deviations, and median and interquartile ranges in Table 1. Statistically significant differences were not found among the three groups. However, the plasma D-Dimer levels showed a positive and significant association with Plasma F1+2 levels. Differences were considered statistically significant when p-value < 0.05.

Discussion

Several authors have showed the association between high D-Dimer levels with the presence of CAD and their results support the concept of the contribution of intravascular fibrin in atherothrombogenesis. However, few studies assessed the association between severity of CAD and D-Dimer plasma levels. Koenig et al. were unable to find any association between D-Dimer concentration and severity and extent of CAD, considering percentage of stenosis and number of coronary arteries affected. Similar results were obtained in this study, since data showed that there were no significant differences for D-Dimer plasma levels among the groups studied (Table 1). The presence of one very high value (3867.4 ng/mL, Figure 1) in the mild/moderate atheromatosis group contributed to
and severity of CAD in the subjects studied, since the results do not enable an inference of a gradual rise in D-Dimer levels consistent with thrombin generation in the studied population.

Data analysis enables an inference on a tendency towards an increase in fibrinolytic activity in patients with atheromatosis, reflected by the increase in D-Dimer concentrations in the severe atheromatosis group in subjects with CAD diagnosed by coronary angiography, and suggests a greater fibrin deposition with consequent action of the fibrinolytic system.

Resumo

Em estudo prévio, os níveis plasmáticos do fragmento 1+2 da protrombina não foram associados com a presença ou com a gravidade da doença arterial coronariana (DAC), não trazendo benefício adicional pelo menos em indivíduos com diagnóstico de DAC estabelecido por angiografia. Desta forma, neste estudo outro marcador de hipercoagulabilidade foi avaliado nos mesmos pacientes. O presente estudo teve como objetivo determinar os níveis plasmáticos do dímero D de um grupo de indivíduos submetidos à angiografia coronariana, buscando estabelecer a possível correlação entre este parâmetro e a gravidade da DAC. Os níveis plasmáticos do dímero D foram determinados em amostras de sangue de 17 indivíduos com ausência de ateromatose nas coronárias (controles), 12 indivíduos apresentando ateromatose leve/moderada e 28 indivíduos apresentando ateromatose grave. Não foram encontradas diferenças estatisticamente significativas entre as médias dos três grupos para o parâmetro avaliado. Uma análise dos dados permite inferir sobre uma tendência ao aumento da atividade fibrinolítica nos pacientes com ateromatose, refletida pela elevação da concentração de dímero D no grupo ateromatose grave em indivíduos com diagnóstico de DAC estabelecido por angiografia coronariana. Rev. bras. hematol. hemoter. 2006; 28(4):280-283.

Palavras-chave: Dímero D; doença arterial coronariana; angiografia coronariana.
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References

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