D-Dimer and Its Relationship to Fibrinogen/Fibrin Degradation Products (FDPs) in Disorders Associated With Activation of Coagulation or Fibrinolytic Systems

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Levels of D-dimer and fibrinogen/fibrin degradation products (FDPs) are significantly elevated in patients with deep venous thrombosis, pulmonary embolism, disseminated intravascular coagulation, or other complications. The diagnosis of these disorders can be difficult, time-consuming, and expensive. Assays for the detection of FDPs and D-dimer are used in many laboratories to investigate these disorders. The aim of this study was to compare plasma D-dimer levels obtained by the immuno-turbidimetric method (Liatest D-Dimer; Diagnostica Stago, Asnières, France) with plasma FDPs were measured by latex agglutination to investigate the relationship between these parameters. These immunoassays were tested in 144 blood samples from patients with suspected disorders

associated with activation of coagulation or fibrinolytic systems. D-dimer and FDPs assays were performed in plasma samples by the use of Liatest D-dimer and plasma FDPs (Diagnostica Stago), respectively. Patients were divided into four groups according to plasma D-dimer levels. In group 1, 47.4% had negative FDPs and 52.6% had positive FDPs. In group 2, 15.4% had negative FDPs and 84.6% had positive FDPs. In group 3, 10.3% had negative FDPs and 89.7% had positive FDPs. All of the patients in group 4 had positive FDPs. It was shown that plasma D-dimer levels measured by Liatest D-dimer have a relation to FDP levels measured by latex agglutination. *J. Clin. Lab. Anal.* 17:77–79, 2003. © 2003 Wiley-Liss, Inc.

Key words: hemostasis; D-dimer; fibrinogen/fibrin degradation products; fibrinolysis; immunoassays

INTRODUCTION

Hemostasis requires an interesting balance between coagulation and fibrinolysis. During thrombus formation, plasmin degrades cross-linked fibrin polymers, resulting in the formation of a number of soluble cross-linked fibrin degradation products of various molecular weights. The smallest and most well characterized of these products is D-dimer (1,2).

Although low levels of D-dimer and fibrinogen/fibrin degradation products (FDPs) can be detected in the circulation of healthy individuals, concentrations are significantly elevated in patients with deep venous thrombosis (2–5), pulmonary embolism (6–10), disseminated intravascular coagulation (5), or other complications. The diagnosis of venous thromboembolism, whether as deep vein thrombosis or pulmonary embolism, can be difficult, time-consuming, and expensive.

There is increasing interest in the use of D-dimer tests to improve the diagnostic procedure by reducing the need for expensive and invasive testing (11). Assays for the detection FDPs and D-dimer are used in many laboratories for the investigation of disorders associated with activation of the coagulation and/or fibrinolytic systems. It is now accepted that D-dimer, which is formed only by plasmin-mediated proteolysis of cross-linked fibrin, is the most specific marker for thrombosis and physiological fibrinolysis (1).

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Many of the tests currently used to determine D-dimer levels involve enzyme-linked immunosorbent assay (ELISA) or latex agglutination technologies. The aim of this study was to compare plasma D-dimer levels obtained by the immuno-turbidimetric method (Liatest D-Dimer) with plasma FDPs levels measured by latex agglutination to investigate the relationship between these parameters.

MATERIALS AND METHODS

In this study 144 blood samples from patients with suspected disorders associated with activation of the coagulation or fibrinolytic systems were tested using D-dimer and FDPs immunoassays. Patients were classified into four groups according to plasma D-dimer levels. This protocol was approved by the Ethics Committee of Santa Casa Hospital.

Blood samples were collected by venous puncture and put into tubes containing a 0.109 mol/L concentration of trisodium citrate (9:1, vol:vol). Platelet-poor plasma was obtained by centrifuging the samples for 10 min at 2,500 g. D-dimer and FDPs assays were performed on each sample.

The Liatest D-dimer (Diagnostica Stago, Asnières, France) is a quantitative and automated immunoassay. A microlatex suspension was coated covalently with two complementary monoclonal antibodies specific for fibrin degradation products. The assay was performed by mixing 50 μ L of undiluted plasma with 100 μ L of reaction buffer, and the test was initiated with 150 μ L of latex suspension. The test is fully automated. The change in absorbance, measured at 540 nm on STA Compact analyzer (Diagnostica Stago), was automatically recorded for 140 sec and represented a direct relationship to D-dimer concentration in the specimen. Results were expressed in ng/mL of fibrinogen equivalent units.

The plasma FDPs assay (Diagnostica Stago) is a semiquantitative assay for the detection of FDPs. In the presence of corresponding antigens, the latex particles coated with monoclonal anti-FDPs antibodies agglutinate to form macroscopic clumps. Following the manufacturer's protocol, each patient's plasma was tested at two dilutions: 1:2 and 1:8. The assay was performed by mixing 20 μ L of the patient's 1:2 diluted plasma with 20 μ L of latex suspension and 20 μ L of the patient's 1:8 diluted plasma with 20 μ L of latex suspension at different positions of the test card. The assay was performed in 3 min, and results were expressed in μ g/mL (<5 μ g/mL, 5–20 μ g/mL, and $\geq$ 20 μ g/mL). In this study, the FDPs results were classified as positive when their levels were $\geq$ 5 μ g/mL, and negative when they were <5 μ g/mL.

D-dimer levels in the groups were compared with FDPs using chi-square tests with adjusted residuals. The relationship between the specificity and sensitivity of the D-dimer and FDPs assays were compared by use of a receiver operating characteristics (ROC) curve.

RESULTS

Plasma D-dimer levels in the groups ranged from 410 to 1,980 ng/mL (see Table 1).

Of the 57 patients in group 1, 27 (47.4%) had negative FDPs and 30 (52.6%) had positive FDPs. In group 2 (n = 26), four patients (15.4%) had negative FDPs and 22 (84.6%) had positive FDPs. In group 3 (n = 29), three patients (10.3%) had negative FDPs and 26 (89.7%) had positive FDPs. In group 4 (n = 32), when plasma D-dimer levels were >1,600 ng/mL, all patients had positive FDPs, as shown in Table 2 and Fig. 1. ROC analysis demonstrated that plasma D-dimer levels >1,420 ng/mL were directly associated to positive FDPs (FDPs levels $\geq$ 5 μ g/mL).

DISCUSSION

This study demonstrated a relationship between plasma D-dimer and FDPs levels in the patients studied. It was verified that when D-dimer levels increased in the groups, FDPs detection increased also. However, when small alterations in plasma D-dimer levels occurred in patients with disorders associated with activation of the coagulation or fibrinolytic systems, the FDPs were generally negative. Although FDPs are consistently elevated in hemostatic disorders, and have become well established in the armamentarium of many coagulation

TABLE 1. D-dimer levels in the patient groups

	D-dimer (ng/mL)
Group 1	590 $\pm$ 120
Group 2	920 $\pm$ 90
Group 3	1380 $\pm$ 100
Group 4	1780 $\pm$ 110

Results expressed in mean $\pm$ SD.

TABLE 2. FDPs results in the patient groups

	Negative FDPs	Positive FDPs
Group 1 (n = 57)	27 ^a	30
Group 2 (n = 26)	4	22
Group 3 (n = 29)	3	26
Group 4 (n = 32)	0	32 ^a

Results expressed in number of patients with negative or positive FDPs.

^aP < 0.05.

Fig. 1. Relationships between plasma D-dimer levels and FDPs in four patient groups.

laboratories, a lack of specificity in the assay has been one of the most important objections to their use (6). The poor performance of latex FDPs assays may be attributable, in part, to two factors: the assay is semiquantitative, and the interpretation of agglutination patterns varies among investigators.

Plasma D-dimer levels obtained by the immunoturbidimetric method (Liatest D-Dimer) are important parameters for pulmonary embolism exclusion diagnosis (9) and other hemostatic disorders. The measurement of D-dimer levels by Liatest D-dimer has more advantages than the measurement of plasma FDPs by latex agglutination. More importantly, there is a strong agreement between results from the Liatest D-dimer technique and the standard ELISA method (8).

In conclusion, plasma D-dimer levels measured by Liatest D-dimer have a relation to FDPs levels measured by latex agglutination, and D-dimer levels $\geq 1,420$ ng/mL are directly associated with positive FDPs. The measurement of D-dimer in plasma has a definite role in the diagnosis of patients with disorders associated with activation of coagulation or fibrinolytic systems, including pulmonary embolism, deep venous thrombosis, disseminated intravascular coagulation, and other complications.

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