# D-Dimer Assays

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## Feature

### Synonyms

XDP, Fragment D-dimer, Fibrin degradation fragment.

### Test Description

The D-dimer assay is specific for fibrin derivatives. In this assay, the presence of cross-linked D-dimer domain is diagnostic for lysis of a fibrin clot, and confirm that thrombin was formed and Factor XIII was activated with reactive fibrinolysis. Since fibrinogen derivatives do not contain the cross-linked D-dimer domain, they are not recognized by the D-dimer assay, even when present in high concentration. In other words, **fibrin derivatives in plasma containing D-Dimer (XDP) are specific markers for fibrinolysis, as opposed to fibrinogenolysis**. D-dimers are detected by immunoassays using monoclonal antibodies specific for the cross-linked D-dimer domain in fibrinogen. Commercially available assays include latex agglutination, immunoturbidimetry, and ELISA.

### Patient Preparation

No specific patient preparation is required for the measurement of D-dimers.

### Specimen

Citrated, platelet-poor plasma is used for the D-dimer assay.

### Specimen Collection and Preparation

Citrated, platelet-poor plasma is prepared from venous blood collected by venipuncture or from an indwelling catheter. The blood is collected into 3.2%) trisodium citrate at a ratio of 9:1. The blue-top tube automatically fills to the correct volume; spurious results may occur if this ratio is not maintained. The citrate concentration must be adjusted in patients with a HCT >55%. Plasma should be separated from the cells as soon as possible after the specimen is obtained. D-dimers are stable for 8 hours in citrated plasma maintained at room temperature, for seven days if stored at 2-8°C, and up to two months at -20°C.

### Test Methodology

D-dimers are detected by immunoassays using monoclonal antibodies specific for the cross-linked D-dimer domain in fibrinogen. Present commercially available assays are based on particle agglutination, immunoturbidimetry, and ELISA.

ELISA assays are the reference standard for D-dimer quantitation. These assays utilize microtiter wells coated with an antibody with a high affinity for D-dimer. Incubation with plasma results in the binding of any D-dimer present. A labeled antibody is then added and the amount of bound labeled substance is determined by a colorimetric reaction. In spite of their high sensitivity and specificity, conventional ELISA assays are expensive, labor intensive, and time consuming to perform. Therefore, they have not been practical in most clinical situations, where rapidly available results are needed.

Latex agglutination (LA) assays use latex microparticles coated with monoclonal antibodies specific for D-dimer. Incubation with plasma results in the formation of macroscopic agglutinates. The sensitivity of the assay is usually adjusted to 1 μg/ml during the manufacture of the latex particles. Although conventional latex agglutination as-
## Test Methodology

Immunoturbidometric assays are automated microparticle assays in which a beam of monochromatic light is passed through a suspension of latex microparticles coated by covalent bonding with monoclonal antibodies specific for D-dimer. The wavelength of the light (540 nm) is greater than the diameter of the latex microparticles and so the solution of latex microparticles only slightly absorbs the light. When the plasma is added to the suspension, any D-dimer present in the sample causes the latex microparticles to agglutinate, becoming aggregates with diameters greater than the wavelength of the light. This increases the absorbance of the light, which is measured photometrically, and proportional to the amount of D-dimer present in the test sample. These assays are cost effective, relatively rapid to perform, and have a sensitivity comparable to conventional ELISA.

A commercially available whole blood assay for D-dimer uses a bispecific antibody specific for D-dimer and a red blood cell antigen. A drop of whole blood is incubated with the monoclonal antibody solution, causing visible agglutination of the red cells if D-dimers are present. Many reports have indicated a high sensitivity for the assay, and it is widely used in clinical settings.

## Normal Values and Critical Limits

The reporting standard for D-dimers varies with the test methodology and reagent manufacturer. Latex and whole blood agglutination results are usually reported as a D-dimer range (ng/mL). ELISA and immunoturbidimetric assays are usually reported in fibrinogen equivalent units (FEU). One FEU is the quantity of fibrinogen that was initially present before it was broken down. The actual quantity of D-dimer is approximately half of an FEU (when 1.0 of fibrinogen μg/mL is broken down, 0.5 μg/mL of D-Dimer remain).

## Interferences

Rheumatoid factor may cause a false positive D-dimer assay. Lipemia may interfere with immunoturbidimetric and ELISA assays.

## Clinical Utilization

XDPs are cross-linked fibrin degradation products which arise directly from fibrin. Thus, the measurement of XDPs, unlike total FDPs, is a specific measure of fibrinolysis. Elevated D dimers are seen in DIC, pulmonary embolism, arterial and venous thrombosis, septicemia, cirrhosis, carcinoma, sickle cell crisis, and following operative procedures. Both FDPs and XDPs are present during late pregnancy and for approximately 48 hours post-surgery. During fibrinolytic therapy the FDP test is positive, while the D-dimer test is negative in the absence of thrombolysis.

Disseminated intravascular coagulation (DIC, consumption coagulopathy) is one of the most common and clinically important acquired disorders of hemostasis. In DIC, intravascular activation of the coagulation system results in the widespread deposition of fibrin microthrombi in the microcirculation, the consumption of platelets and clotting factors, and activation of the fibrinolytic system. At the same time that thrombin converts fibrinogen to fibrin, it also activated Factor XIII to form a plasma transglutaminase, Factor XIIIa, which stabilizes fibrin by cross-linking the gamma chains of fibrinogen in the region of the D-domain. Plasmin digests fibrin and fibrinogen to produce fibrin(ogen) degradation (FDP) (or split, FSP) products (X,Y,D, and E), which are removed from the circulation by the reticuloendothelial system.
DIC is not a specific disease, but a sequela of many pathologic conditions, including acute intravascular hemolysis, hemolytic transfusion reactions, shock, hyperthermia, extensive tissue damage, malignancies, obstetric complications, hyperthermia, snake bites, etc. Prompt diagnosis and therapy of DIC is essential, since the associated hemorrhage, small vessel thrombosis, and occasional large vessel thrombosis can lead to the impairment of blood flow, ischemia, end-organ damage, and death. The clinical signs and symptoms in DIC are variable and non-specific, and include fever, hypotension, acidosis, proteinuria, hypoxia, petechiae and purpura, subcutaneous hematomas, bleeding (surgical wound, traumatic wound, venipuncture), and arterial line oozing.

There is no laboratory assay pathognomonic of DIC. However, peripheral smear examination is among the most helpful. In fulminent cases, this shows a characteristic combination of schistocytes (red blood cell fragments), mild polychromatophilia, leukocytosis with a left shift, thrombocytopenia, and large young platelets. However, the diagnosis of DIC cannot be excluded by an absence of schistocytes, since these occur in only 50% of patients. In addition to peripheral smear review, the prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet count, and serum fibrin/fibrinogen degradation products are the best screening tests for DIC. The D-dimer assay is more specific, and can be used to confirm the diagnosis.

The D-dimer has received much attention in recent years as a critical part of the evaluation of emergency care patients with suspected pulmonary embolism (PE) or deep venous thrombosis (DVT). Generally, numerous studies have shown that the more advanced ELISA and immunoturbidometric assays have a sensitivity of 90% or greater for PE or DVT in this setting, and a negative predictive value of 90% or greater for the exclusion of disease. However, there is presently much debate about how the results should be correlated with other findings, particularly radiographic studies.

The analysis of plasma D-dimers has been reported to be of diagnostic value in patients with suspected complications of pregnancy such as pre-eclampsia and the HELLP syndrome, to monitor anticoagulant and thrombolytic therapy, and to correlate with disease severity in rheumatoid arthritis. CSF D-dimers have been reported positive in patients with subarachnoid hemorrhage, but not in normal patients or those with traumatic lumbar puncture.

References


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