

D-Dimer Testing in Clinical Practice

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Abstract

D-Dimer (DD) is the smallest fibrinolysis-specific degradation product found in the circulation. Its dosage is well known in the diagnosis of venous thromboembolism and deep vein thrombosis but also in other clinical settings as disseminated intravascular coagulation. In the daily management, it has been suggested its predictive negative value in the diagnosis of deep vein thrombosis and its prognostic value for pulmonary embolism but also other clinical information may be found in clinical practice.

Introduction

D-Dimer (DD) is the smallest fibrinolysis-specific degradation product found in the circulation [1]. DD testing is involved in all clinical conditions in which there is hyperfibrinolysis alone or hyperfibrinolysis associated to hypercoagulation, with or without associated vascular thrombosis. For this reason, DD testing is present in several flow-charts to diagnose thrombotic disorders in particular venous thromboembolism (VTE), deep vein thrombosis (DVT), pulmonary embolism (PE), disseminated intravascular coagulation (DIC) [2,3].

However, several problems are related to the clinical interpretation of DD testing because the high sensitivity of clotting test that induces its slight increase also in clinical conditions not associated to vascular thrombosis [4] and for this reason its positivity needs a confirm by objective test to perform a diagnosis of thrombosis [2,3].

In this short review, we include clinical diagnostic options in which is useful to consider DD but also other roles of DD testing from a diagnostic and prognostic point of view.

Positive and Negative DD in VTE

VTE includes several diseases associated with venous vascular thrombosis diagnosed with objective methods (e.g. vascular ultrasound or CT scan or MR scan). Because it's relevant morbidity and mortality the diagnostic flow chart of VTE is always matter of discussion [5], and its difficult approach may be related to the fact that VTE may occur with confounding signs and symptoms referred by patients in nearly 10-20% of cases. For this reason in the clinical approach to VTE, in particular, proximal DVT it is important to take in mind thrombotic risk factors (e.g. familial history for VTE, previous VTE, hormonal treatment, recent surgery, recent prolonged hypo mobility, molecular inherited and/or acquired thrombophilia, and cancer with its related therapies) [6]. Furthermore, clinical scores are available to suspect DVT or PE in order to go on with a specific test to confirm VTE, the most common know suspicion score is the wells score but other scores have been also tested for this objective [7].

Yet in the VTE flow chart after clinical suspicion based on the presence of clinical signs, associated to the presence of thrombotic risk factors for VTE and positive preclinical score, confirmation tests are required form laboratory and imaging.

DD is the most sensible and used test to confirm hypercoagulation. Its positivity is present in more than 90% of cases of VTE but not all used DD testing are similar [8]. Several methods, in fact, are associated to higher sensitivity compared to low specificity and for this reason, after several years of experiences, the scientific community suggest to use DD tests that have a correct ratio between sensitivity\specificity [8]. Actually one of the most used DD tests in clinical practice is the immunolateral test for the determination of d-dimer.

Yet, related to this high sensitivity without a parallel specificity, the scientific community suggests considering DD also for its predictive negative value to disconfirm VTE diagnosis [5-8] in order to re-address clinical suspicion to other diseases and other diagnostic tools.

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Positive DD and DIC

Because DD is the smallest fibrinolysis-specific degradation product found in the blood circulation, its role may be found in other pathologies associated with hyper fibrinolysis as DIC [3]. During a DIC DD is one of several markers of hyper fibrinolysis because associated with the increased clotting activity and fibrinogen-related consumption. Increased DD in DIC is one of the first laboratory signs that may appear, before than decrease of plasmatic fibrinogen and of platelet count that appears in following phases of the disease [9]. Furthermore in last stages of DIC DD levels remain elevated and are associated also to prolonged prothrombin time that is the last step before bleeding complications associated to DIC [9].

Usually, DD levels are persistently elevated also during major bleedings associated with DIC.

Other Clinical Conditions Associated with Increased DD without Vascular thrombosis

Otherwise, we could find high DD levels in many pathological conditions different from VTE: disseminated intravascular coagulation, acute aortic dissection, acute myocardial infarction and so on [9-11].

During an acute thrombotic disease other than VTE or DIC, the hyper activation of clotting system that leads to vascular occlusion (i.e. a thrombosis) may induce an increase of DD because of fibrinogen consumption and because of the hyper activation of the fibrinolytic system too [3].

For this reason, we may find a slight increase of DD also in acute coronary syndromes or acute aortic dissection [10,11].

Yet an asymptomatic hypercoagulable state may be present and detected in blood samples also in other diseases as cancer and its therapeutic approach [12], as in systemic infection as sepsis [13], so DD may be found increased also in this clinical conditions. Several types of cancer may have an increased clotting activity associated with hyper activation of fibrinolysis too, so showing increased levels of DD [12]. For this reason, DD was suggested also as an asymptomatic biomarker of occult malignancy but large studies did not confirm this additional diagnostic role of this test.

On the other hand systemic infection and in particular sepsis due to Gram-negative bacteria showed hyper activation of clotting system through several ways [14] and for this reason increased levels of DD and/or thrombosis of small vessels as in first phases of DIC are frequently associated to this clinical setting.

Yet, also in physiological condition as pregnancy,, an increased activity of blood coagulation due to multiple conditions as the reduction of protein C, protein S and antithrombin and a hyper activation of fibrinolytic way may induce increased levels of DD without thrombosis [15]. In this clinical condition, in fact, a diagnosis of VTE during pregnancy may be difficult without a confirmation with an objective test as vascular ultrasound.

Furthermore, increased levels of DD may be found also in asymptomatic healthy subjects carriers of inherited or acquired thrombophilia [4].

From a clinical point of view, all the above conditions confirm that a positive DD test needs a confirm with an objective method to perform a diagnosis of VTE or other thrombotic diseases, so underling one more time that the major clinical role of DD test is due to its predictive negative value [2].

Prognostic role of DD

Reported data are sufficient to testify that high DD is not sufficient to formulate a diagnosis of VTE or DVT or PE and because of its frequent positivity also in absence of an objective thrombosis, it has been suggested to parallel its value to aging although this score in suspected VTE is not accepted by all expert.

Yet, based on the fact that high DD may be a challenge to perform diagnosis of life-threatening disease as PE or DIC it has been postulated a potential role of DD as a prognostic factor for death in these clinical setting [16-18].

Several authors, in fact, reported that values of DD major than 4 mcg\dl have been associated with an increased rate of death after a PE diagnosis within 15-30-90 days [16,17].

On the other hand,, also increased the value of DD with or without a decrease in fibrinogen levels after a DIC diagnosis seem to be associated with an increased rate of death in this clinical setting [18].

Yet, none studies confirmed that a reduction of DD during treatment of a VTE of a DIC is associated to a better prognosis, so monitoring of DD levels after diagnosis of VTE or DIC is not suggested in clinical practice.

Take home messages

D-Dimer testing may have several advantages to the daily clinical management.

A negative d-dimer value is always useful to exclude an acute VTE. A strong increase of D-Dimer after that a VTE diagnosis has been confirmed may have a prognostic about overall mortality or mortality for PE at 15-30-90 days after VTE diagnosis.

In the daily management of DIC, D-Dimer testing may support a bad prognosis if also other markers show similar trends.

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