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Pregledni rad

D-Dimer – A laboratory point of view

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Abstract D-dimer (D-D) is a marker of fibrin deposition and secondary fibrinolysis and, as such, an indirect marker of thrombotic activity. D-D testing is efficient in the exclusion of venous thromboembolism (VTE), but it also has some implications in the prediction of recurrent VTE, in the prediction and prognosis of arterial thrombotic events, diagnosis of disseminated intravascular coagulation, as well as the potential exclusion of aortic aneurism. In spite of excellent characteristics for the exclusion of VTE, D-D is high (false positive) even in the absence of thrombosis in different clinical conditions. Therefore the use of D-D in the elderly, pregnancy, malignancy, after surgery, etc has to be careful with the potential adjustment of the reference range. On the other hand, D-D assays standardization and absence of international calibrator standard are still a critical issue from the laboratory perspective and therefore clinicians need to be aware of the different performance characteristics of the available D-D assays. Finally the turnaround time for laboratory testing, which may significantly improve efficacy in emergency departments, has become very important. Thus the introduction of a rapid, easy to perform point of care (POC) D-D assay would be desirable and would help physicians to make safe and timely therapeutic decisions. This brief review discusses all those issues of potential importance for cardiologists.

Key words D-dimer, venous thromboembolism, recurrence, aortic aneurism.

The key event in hemostasis is the formation of fibrin. Through a series of steps in which plasma zymogens of serine proteases are transformed into active enzymes, the coagulation system leads to the formation of the thrombin enzyme that catalyzes the transformation of fibrinogen into fibrin. Fibrin, the final product of coagulation, is the main substrate for the fibrinolytic system, the role of which is to locate fibrin clots at the site of an injury and dissolve them[1].

During fibrin formation, fibrinogen is converted into fibrin by the enzymatic (thrombin) cleavage of the fibrinopeptides A and B. This is followed by factor XIIIa induced aggregation of the resulting fibrin monomers producing "cross-linked fibrin". Plasmin proteolysis of "cross-linked fibrin" generates DD and E fragments as terminal products. Proteolysis of fibrinogen or "non cross-linked fibrin" produces fibrin(ogen) degradation products (FDP) but does not result in the release of D-dimers. Therefore although D-dimer (D-D) is generated during fibrinolysis, it is an indicator of *in-vitro* fibrin formation rather than a pure fibrinolysis marker[2]. It circulates in the blood several days after intravascular thrombus formation (the half life is approximately 8 hours[3]) and is associated with conditions such as: deep venous thrombosis (DVT), pulmonary embolism (PE), disseminated intravascular coagulation, malignancy, postoperative states, trauma and preeclampsia[4]. The measurement of D-D has become possible after the development of monoclonal antibodies which distinguish it from fibrinogen degradation products[5].

The role of D-dimer in different clinical conditions

Venous thromboembolism

The most important role of D-D is in the diagnostic approach to venous thromboembolism (VTE). VTE is a common cause of morbidity and mortality in the Western world with the annual incidence of about 1/1000[6]. Since, in terms of golden standards, radiological methods (e.g. venography) are not widely available and are both costly and invasive, the use of alternative diagnostic approaches, including D-D, has been widely evaluated. The negative predictive value of D-D is high and normal D-D may be used to rule out VTE.[7] However the increase of D-D does not enable the diagnosis of VTE since it is not specific and could rise in different clinical conditions (e.g. ageing, trauma, pregnancy, malignancy.[2] In hospitalized patients D-D testing has less utility due to the high frequency of false-positive results[8-9], while most of the data validating the use of D-D in VTE come from the ambulatory setting.[10]

D-D levels significantly increase with age possibly due to a higher incidence of co-morbidity[11]. Although the incidence of VTE increases with age, the usefulness of D-D decreases, allowing exclusion in only 5% of patients 80 years old (compared to more than 50% in patients aged 40 years or less)[12]. Therefore it has been suggested that the D-D cut-off value should be higher in the elderly[13] but it seemed that such an approach may increase the num-

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ber of false-negatives becoming unsafe.[14] However in one recent meta-analysis it has been shown that the use of the age-adjusted D-dimer cut-off value (age×10 μg/L in patients aged >50 years) increased the specificity of D-dimer in all age categories and was more than doubled in patients aged more than 80 years. It was associated with a small insignificant decrease in sensitivity, which remained above 97% in all patients.[15]

Both the high prevalence of VTE and elevated baseline level may influence the utility of D-D in patients with cancer. In spite of the data that D-D had a lower negative predictive value in those patients[16], a similar level of ability to exclude VTE between patients with and without cancer was observed in other studies[17, 18].

D-D is higher in pregnant women and increases progressively during pregnancy[19] which may compromise its utility. However it seems that D-D has acceptable sensitivity for exclusion of VTE but is not cost-effective due to poor specificity[20].

D-dimer levels appear to return to normal values within 3 months of starting treatment for acute VTE and generally remain within normal range after anticoagulant therapy is withdrawn in the majority of patients[21]. Therefore, D-D testing should be useful in patients with suspected recurrence[22] while D-D measurement after cessation of anticoagulation had a high negative predictive value for recurrent VTE[23]. It has been postulated that high D-D is associated with an increased risk of recurrent VTE while patients presenting D-D above cut-off after cessation of oral anticoagulation may benefit from extended prophylaxis[24]. Finally it seems that D-D is positively associated with the development of post thrombotic syndrome (PTS)[25].

Aortic dissection

Another application of D-D is in the diagnosis or exclusion of aortic dissection. In a recently published meta-analysis it was suggested that plasma D-D <500 ng/ml is a useful screening tool to identify patients who do not have aortic dissection[26]. D-D may be useful in the differential diagnosis of aortic dissection since patients with acute chest pain due to an acute coronary syndrome generally display D-D levels within or close to normal range, whereas D-dimer levels are massively elevated in patients with acute aortic dissection[27, 28]. Therefore it has been proposed that, as a general rule, patients with acute chest pain and massively elevated D-dimer levels should not receive anticoagulant and antiplatelet agents before aortic dissection has been excluded[29].

Arterial thrombosis

It has been shown in different studies that D-D may be predictive for the first coronary event, but the real importance for individual patients is still not clear[24]. It has also been suggested that D-D may be a clinically useful risk marker in atrial fibrillation (AF)[30]. In stroke patients, in spite of common increase, D-D is neither sensitive nor specific enough to be utilized in the diagnostics[31].

Disseminated intravascular coagulation

The main diagnostic application for D-D in critical care is the diagnosis and monitoring of disseminated intravascular coagulation (DIC)[29]. DIC is a life-threatening syndrome associated with different underlying conditions (e.g. sepsis, malignancy, trauma). D-D may be used as a fibrin-related marker of the DIC score which is a tool to establish a DIC diagnosis [32]. Normal D-D may rule out DIC, but elevated levels may or may not reflect its presence [33]. D-D has been included into the scoring systems given by the International Society on Thrombosis and Haemostasis Scientific Subcommittee [34].

D-dimer laboratory assays

Enzyme-linked immunosorbent assays (ELISA) were initially developed for D-dimer detection in research purposes. They are extremely sensitive (98%) with the negative predictive value of >95% [35]. However ELISA assays are complicated, time consuming and labour intensive and could be performed in most laboratories only during daily working hours. Furthermore most of them are not designed for single sample testing, and until recently, were not easily automated for clinical use [36]. Several technological advances in assay format and instrumentation made ELISA-based assays more convenient for routine use. Vidas ELISA is the most widely used among those assays. It has excellent sensitivity and is capable of detecting elevated D-dimer antigen associated with a variety of clinical disorders[37].

The automated quantitative turbidimetric assays based on latex agglutination were developed next and their sensitivity level is similar to that of ELISAs[38, 39]. However those assays are still performed on large laboratory analysers in central and/or hospital based laboratories.

Different D-D assays are commercially available and they are not identical because the antigen is present on a different size degradation products, the monoclonal antibodies recognize different epitopes, and the assay format, calibration and instrumentation are different [36]. To make life even more complicated two different types of units have been in use for D-D: the fibrinogen equivalent unit (FEU) and the D-dimer unit[40], while presentation has been in ng/mL, μg/ml or μg/L[41]. Therefore clinicians need to be aware of the performance characteristics of the particular D-D (including units) used in their institution. Cut-off values for different clinical conditions also need to be established.

Point of care (POC) D-dimer testing

Since VTE is a potentially life-threatening condition, primary care physicians usually refer all such patients to institutions where specialized diagnostic services for objective testing are available and where VTE could be safely and adequately ruled out. However, numerous studies have revealed that 80–90% of these referred patients do not have VTE[7, 42]. Therefore, it would be ideal to safely exclude VTE on the level of primary care in a large proportion of these patients, avoiding referral, and consequently decreasing costs[43].

On the other hand emergency department overcrowding and prolonged patient stay are an increasing problem in most hospitals in the Western world. Rapid testing of D-dimer may have a similar impact on time reduction in the emergency department as cardiac markers, and it can reduce unnecessary hospital admissions[44].

A number of POC D-D assays have been introduced recently and they are described by manufacturers as highly sensitive for VTE. We, at the Clinical Chemistry Laboratory at Karolinska University Hospital, have validated some of those assays recently[45]. Our evaluation as well as data observed by others indicate that Pathfast D-dimer, Cardiac D-dimer and Stratus CS D-dimer may safely and adequately rule out VTE in out-patients[45-53].

The main potential problem with POC assays is inadequate quality control since assays are most commonly performed by personnel without laboratory training and knowledge of quality control procedures, while assays commonly use whole blood and such samples for quality control are not available. Clinicians need to be aware of those issues[54, 55].

Conclusions

D-D is a clinically useful marker of coagulation activation and *in vivo* fibrin formation and may serve to exclude VTE (but also recurrent VTE, VTE in pregnant women and cancer patients). D-D role in the prediction of VTE recurrence and post thrombotic syndrome seems to be beneficial, but needs definitive confirmation. The predictive value and use of D-dimer in other diseases (e.g. arterial thrombosis or atrial fibrilation) needs further validation. However it seems that D-D may be used in the diagnostic approach of the DIC and (or at least for the exclusion) of aortic dissection. D-D assays are based on the use of monoclonal antibodies and the widely used automated quantitative turbidimetric assays based on latex agglutination have excellent sensitivity. However, permanent requests for improvement operations and decreasing cost both in primary care and emergency departments lead to the need for near patient D-D testing. It seems that several POC D-dimer assays have the analytical profile (primary sensitivity and negative predictive value) comparable to those obtained using standard laboratory assays. Nevertheless, clinicians need to be aware of the different performance characteristics of the available D-dimer assays, in order to make safe and timely therapeutic decisions.

Key messages to take home:

- D-dimer is a unique marker of fibrin degradation.
- D-dimer is increased in different clinical conditions and therefore its positive predictive value is low.
- Sensitivity and negative predictive value of standard ELISA and automated quantitative turbidimetric assays are excellent and therefore negative D-dimer may be used for ruling out VTE (even in specific clinical conditions).
- D-dimer may have a role in the prediction of recurrent VTE and PTS, and in the diagnosis (exclusion) of aortic dissection.
- D-dimer is an important marker for the diagnosis of DIC.
- POC D-dimer assays have a profile comparable to laboratory methods and can be used for near patient testing, improving turnaround time and decreasing costs.
- Clinicians need to be aware of the performance characteristics and cut-off values of the particular D-dimmer assay used in their institution.

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