D-dimers: a most misunderstood test

Abstract

The role of D-dimers in the management of venous thromboembolism is well established and testing for D-dimers has become common in most acute settings. Although it has been validated for the purpose of excluding venous thromboembolism, the test is increasingly ordered to 'diagnose' venous thromboembolism. Furthermore, in the COVID-19 pandemic, heavy reliance has been put on this test with the inclusion of D-dimers to guide treatment pathways. This review summarises the appropriateness of D-dimer tests in these different clinical settings.

Key words: Anticoagulation; COVID-19; D-dimer; Fibrinogen; Thromboembolism

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Introduction

D-dimer measurement has become one of the most common blood tests ordered in an acute medical setting. It is an extremely valuable test to exclude venous thromboembolism in patients who have a low clinical probability for this diagnosis (Adam et al, 2009). It may also be helpful in patients who develop the complication of disseminated intravascular coagulation and in the diagnostic algorithm for an aortic aneurysm (Weitz et al, 2017). It has been thrust into the limelight during the COVID-19 pandemic where it is (purported) to predict venous thromboembolism and also mortality (Lippi and Favaloro, 2020). Despite this varied usefulness, this laboratory test is often inappropriately requested as a marker of clot formation, despite it never being intended for this purpose.

What is D-dimer?

To understand more about the test, it is important to understand how D-dimer is created in the body (Figure 1). During the coagulation process, thrombin, generated from prothrombin with the action of various clotting factors, acts on fibrinogen (which consists of two D domains and one E domain) to form fibrin monomers, where the D domains come together (Thachil et al, 2017). The fibrin monomers then polymerise into an insoluble network which gives the tensile strength to a clot. To ensure the clot is limited to the site of vessel injury and does not completely occlude the blood vessel, fibrinolytic proteins break down the cross-linked fibrin (Adam et al, 2009; Thachil et al, 2017). This process creates various fragments including D-dimers. So, D-dimers are the product of the proteolytic breakdown of cross-linked fibrin created by the action of thrombin. The commonly used D-dimer tests are monoclonal antibodies specific for these D domains (Dempfle, 2005).

What makes D-dimer levels increase?

As already discussed, the presence of D-dimers signifies clot breakdown. The coagulation system is always on the look-out for vessel injury to facilitate the rapid sealing of wounds, and limit loss of blood. As such, D-dimer levels can be elevated in any condition where there may be tissue injury (minor and major trauma, surgeries and interventional procedures) (Lippi et al, 2008). It may also be noted that the normal D-dimer result is never zero, but a numerical value that varies between laboratories based on the methodology used (for example <500 ng/ml) (Longstaff et al, 2016). This minimal amount of D-dimer is created by the fibrinolytic system as a result of constant breakdown of thrombi formed anywhere in the body to maintain uninterrupted blood flow.

However, the formation of clots is not limited to inside blood vessels. A fibrin mesh can form a scaffold that the various inflammatory proteins can use as a foundation to

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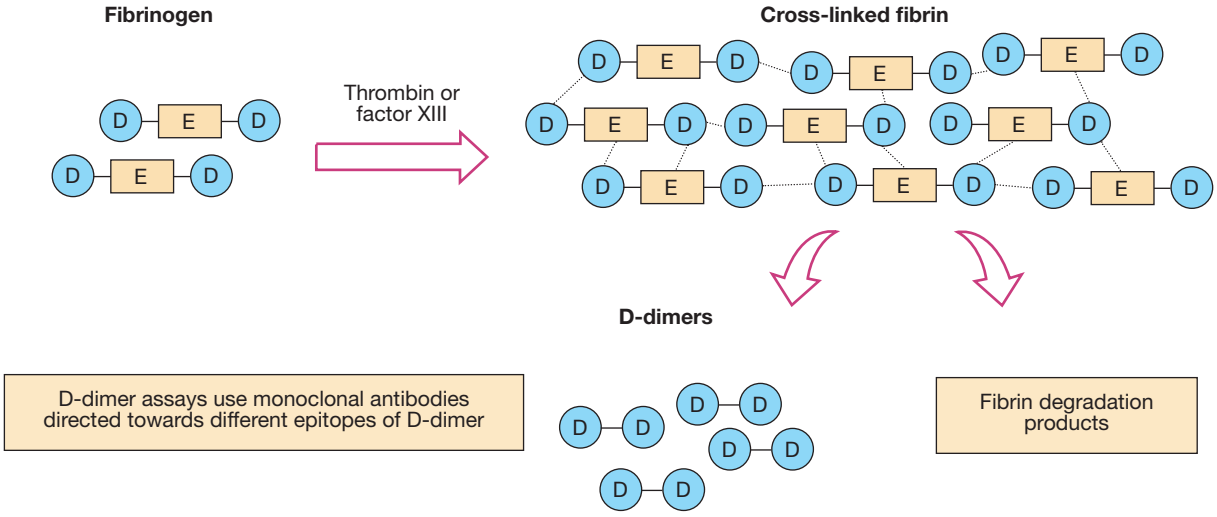

Figure 1. Cross-linked fibrin is created from fibrinogen by the action of thrombin and then factor XIII. The cross-linked fibrin is broken down into D-dimers and fibrin degradation products by fibrinolytic enzymes. Monoclonal antibodies that recognise D-dimer domains in the blood are commercially available as D-dimer assays.

perform their pro-inflammatory function (Wagers et al, 2004). This is typical of situations where inflammatory proteins leak into the extravascular space, ie inflammatory disorders. In these clinical situations, the coagulation proteins 'escape' the blood vessel and form a clot in the extravascular space (Thachil et al, 2021). These clots are broken down in a similar fashion to those formed as a result of endothelial injury at the sites of vessel damage and thus create 'extravascular D-dimers' (Thachil et al, 2021). These D-dimers are then absorbed into the blood and are readily detectable by blood tests. This explains the elevated D-dimer levels seen in patients with inflammatory conditions where no clots are identifiable by the imaging techniques used to detect venous thromboembolism. In a similar way to inflammatory states, extravascular fibrinolysis in the cancer stromal spaces has been suggested as a reason for increased D-dimer levels in patients with malignancies (Thachil et al, 2021).

Why do inappropriate D-dimer requests happen?

Requests for D-dimer measurement have become routine despite the appropriateness of this being questionable in many scenarios. Acute physicians and haematologists are commonly approached to deal with a positive D-dimer result despite no evidence of thrombosis in a patient. A key reason for this erroneous requesting is the widespread belief that a positive D-dimer signifies a high likelihood of venous thromboembolism, although the test was never meant for this purpose. On the contrary, D-dimers are most helpful in excluding venous thromboembolism in those with low clinical probability for this condition (Di Nisio et al, 2007). This is clearly included in several guidelines for the diagnosis of venous thromboembolism including the National Institute of Health and Care Excellence guidance (Lim et al, 2018; National Institute of Health and Care Excellence, 2020). It is paramount that, in a patient with a high probability of venous thromboembolism based on a clinical prediction model like the Well's score, a D-dimer assay is not requested unless there is a delay in appropriate imaging. D-dimer tests should never be considered a substitute for a good clinical assessment in these settings. On the other hand, for those patients who have a low clinical probability for venous thromboembolism, a negative D-dimer result (values within normal range) would give added confidence in excluding a thrombus.

D-dimer epidemic during the COVID-19 pandemic

In the biggest pandemic for over a century, D-dimers have become one of the most examined laboratory tests (a search on PubMed using keywords D-dimer and COVID-19 identified

1496 articles in March 2021). In the first months of the pandemic, several investigators were considering differing doses of anticoagulation based on the D-dimer values; prophylactic anticoagulation for those with modestly elevated D-dimer values and higher doses including therapeutic anticoagulation for those who have markedly elevated D-dimer levels (discussed in a debate by Gomez et al, 2021). This practice probably stemmed from the belief that high levels of D-dimers equate to high rates of venous thromboembolism, although such a concept was never established pre-COVID-19 and has not been demonstrated conclusively during the pandemic either. In support of this lack of efficacy in predicting venous thromboembolism, guidelines now recommend against the use of D-dimers for anticoagulant intensification (Moores et al, 2020; Cuker et al, 2021). So, if increased D-dimer levels are not indicating clot burden in patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, why are they so elevated? COVID-19 is associated with an intense inflammatory response to the virus, usually manifesting as acute lung injury in severe cases (Grasselli et al, 2020). As described above, the intense inflammation that accompanies this infection stimulates extravascular fibrinolysis and thus production of large amounts of D-dimers (Thachil et al, 2021). It is therefore not surprising that D-dimer levels correlate with mortality in these patients since they are a marker of intense inflammation which is causing organ damage, especially acute lung injury (Yao et al, 2020; Zhang et al, 2020).

D-dimer measurement has also been rapidly assimilated into the World Health Organization diagnostic criteria for paediatric multisystem inflammatory disorder with COVID-19 (World Health Organization, 2020), and is recommended as one of the initial investigations in a new presentation. The raised D-dimer level may again be secondary to significant extravascular fibrinolysis. While knowledge is rapidly expanding in this area, without a lack of robust evidence, caution should be applied to interpreting D-dimer levels in this setting. There is a paucity of evidence demonstrating that serial D-dimer measurements provide useful and clinically significant data for management or outcomes.

D-dimer levels as a guide to the duration of therapy

Three D-dimer based prediction scores – The DASH Prediction Score, the Vienna Prediction Model and the HERDOO2 model – have been proposed to guide duration of anticoagulation in patients with unprovoked venous thromboembolism. As an example, the DASH score uses age, gender, hormone use (at onset of venous thromboembolism) and crucially D-dimer level, 1 month after cessation of anticoagulation (Tosetto et al, 2012). It is suggested that a score of 1 or fewer makes a patient 'low risk' and cessation of anticoagulation can be contemplated. Common consensus suggests that a venous thromboembolism recurrence rate of less than 5% per annum is an acceptable level at which cessation of anticoagulation can be considered (Kearon et al, 2010). However, some data suggest that the annual incidence in this 'low risk' group exceeds 5% (Tosetto et al, 2017; MacDonald et al, 2019). Therefore, it is reasonable to conclude that venous thromboembolism recurrence using D-dimer measurement, and subsequent cessation of anticoagulation, should be used with caution, as incidence even in the low risk groups may be unacceptably high.

Might there be benefits from non-specific D-dimer testing?

In the new test-oriented clinical world, D-dimer tests are often requested even before a clinical assessment is made, especially in patients with cardiorespiratory symptoms. This is supposed to make things 'easier' for the patient by avoiding repeat phlebotomy, but this needs reexamination. Since the practice of non-specific requests for D-dimer tests has already become widespread, might there be a silver lining among the dark clouds? In a patient who does have pulmonary embolism as their diagnosis, D-dimer levels correlate with disease severity (Keller et al, 2018). In a study of approximately 160 patients, elevated D-dimer levels correlated with thrombus burden and were predictive for right ventricular dysfunction in normotensive patients (Keller et al, 2018). Another study looked at the predictive value of D-dimer levels for disease severity and survival and found a correlation for higher D-dimer levels with clinical (pulse rate, blood pressure and oxygen saturations

Key points

- D-dimer is a clinically useful measurement, but is often inappropriately sent to investigate 'clot formation'.
- D-dimer levels can increase as a result of intravascular clot fibrinolysis, but also extravascular fibrinolysis.
- Despite D-dimers being a commonly requested test in patients with COVID-19, guidelines now suggest against using this as a measurement to intensify anticoagulation.
- D-dimer levels correlate with clinical severity markers of pulmonary embolism, suggesting there may be some additional benefits to D-dimer testing.

and the need for thrombolysis) and imaging (right-to-left ventricle diameter ratios ≥1), but not with long-term mortality (possibly because of aggressive treatment) (Geissenberger et al, 2019). In patients who do not have venous thromboembolism, a markedly elevated D-dimer level has been suggested to be specific for an underlying malignancy even if a venous thromboembolism had been diagnosed in an otherwise clinically stable patient (Schutte et al, 2016). In this Dutch retrospective cohort study of adult patients with markedly elevated D-dimer levels (>5000 µg/litre), cancer was diagnosed in almost a third of patients if a primary diagnosis of venous thromboembolism was excluded, and the patients had not undergone surgery and did not have trauma or sepsis.

Conclusions

D-dimer tests should only be requested in patients who have a low clinical probability for venous thromboembolism and not in those who have a high likelihood of venous thromboembolism. Elevated levels of this laboratory marker in patients with COVID-19 may be the result of intense inflammation triggered by the virus, in addition to clot breakdown which occurs from the high incidence of venous thromboembolism. D-dimer quantification may be beneficial in patients with pulmonary embolism as a marker of disease severity while its serial testing may prove helpful in monitoring critically ill patients who may run the risk of acute lung injury. Markedly elevated D-dimer levels may suggest the possibility of underlying cancer in those with or without venous thromboembolism. Nicolo Machiavelli once stated: 'All courses of action are risky, so prudence is not in avoiding danger (it's impossible), but calculating risk and acting decisively'. Perhaps this is the mantra we should adopt when deliberating over the utility of the D-dimer measurement.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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