

# The Fritsma Factor

YOUR INTERACTIVE HEMOSTASIS RESOURCE



## Isolated Chronically Elevated D-dimer

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### Introduction

Hello, I apologize for providing a generalized answer to your question about your chronically elevated D-dimer value. Once you've read this, please feel free to contact me for clarification, for further information or questions. *I am a medical laboratory scientist, so I confine my comments to the physiological, technical and clinical applications of the D-dimer assay.* I refer you to your physician for medical and treatment decisions, as your physician knows your full medical history. You may reach me at [george@fritsmafactor.com](mailto:george@fritsmafactor.com).

### D-dimer Assay

D-dimer is one of the family of blood-borne protein particles called fibrin degradation products [FDPs] that are produced during clot breakdown, called *fibrinolysis*. When the plasma enzyme plasmin digests a fibrin clot the FDPs X, Y, D, and E, and D-dimer, are measured using an immunoassay [antibody] technique. Of all the FDPs, the D-dimer test is the most reliable assay as D-dimer fragments are produced from linked D fragments that are the normal end point of blood clot formation, called coagulation.<sup>1</sup>

### D-dimer Assay Purposes

The most important purpose for the D-dimer assay is to rule out deep venous thrombosis [DVT, clots in large leg veins] or pulmonary emboli [PE, clots in the lungs].<sup>2</sup> When a patient goes to a physician suspecting a DVT or PE, the physician asks about the symptoms and applies a patient history-based clinical scoring system such as the "Wells Score" to establish the "pre-test probability" of a DVT or PE.<sup>3</sup> When the pre-test probability is low or moderate, the physician orders a D-dimer assay. If the D-dimer is normal or negative, the physician looks for other causes for the patient's symptoms. The D-dimer is reliable when ruling out a DVT or PE when the Wells score is low or moderate. If the pre-test probability is high, the physician orders imaging studies to locate and measure the clot. However, if the pre-test probability is low but the D-dimer assay result is elevated, the doctor goes on to order imaging studies to rule out a clot.<sup>4</sup>

A second D-dimer purpose is to assess the severity of the often-fatal condition called disseminated intravascular coagulation [DIC], a major derangement of clotting.<sup>5</sup> The D-dimer is part of a profile of laboratory assays used to diagnose DIC, and is often markedly elevated, indicating uncontrolled clotting and fibrinolysis.<sup>6</sup>

Some physicians choose to employ the D-dimer when preparing to discontinue antithrombotic therapy [blood thinners] such as warfarin [trademark Coumadin], Xarelto, or Eliquis. If after a period of therapy, the D-dimer is elevated, the physician may decide to continue treatment for an additional interval, often six months. There is some evidence that a continued elevated D-dimer following blood thinner therapy predicts an elevated risk of a secondary adverse thrombotic event.<sup>7</sup>

In 2020, medical lab scientists learned that the D-dimer predicts progression from mild to severe COVID-19 infection.<sup>8</sup> When COVID is first suspected, the test is ordered as a baseline, then reordered during the infection to help the doctor plan the COVID therapy. If it rises, an anticoagulant, usually heparin, is prescribed to control clotting. If the D-dimer results decline over time, the patient is probably recovering.

## D-dimer Sensitivity and Specificity

D-dimer assays are designed to be sensitive, thus a negative D-dimer is firm evidence for the lack of a clotting disorder, but an elevated D-dimer has relatively little intrinsic significance as a stand-alone assay.<sup>9</sup> The D-dimer assay is described as “promiscuous,” implying that it is elevated in the presence of any common form of chronic or acute inflammation. *The elevated D-dimer alone doesn't indicate thrombosis risk* [thrombophilia, hypercoagulability]. The D-dimer may be elevated in association with a chronic autoimmune condition such as hypothyroidism, rheumatoid arthritis, lupus erythematosus, or diabetes mellitus. D-dimer elevation also accompanies an upper respiratory infection, a systemic infection, recovery from an injury, recovery from surgery, sarcoidosis, hypo- or hyperthyroidism, chronic heart disease, or even lifestyle circumstances such as chronic smoking, obesity, psychosocial stress, and exposure to heat, cold, or physical exertion. While an elevated D-dimer may signal a chronic inflammatory condition, it does not indicate a need for antithrombotic therapy, nor should a patient be exposed to the risks of blood thinners based on D-dimer results alone. *Conversely, chronic inflammation itself is associated with a raised risk of DVT, PE, strokes, heart attacks, dementia, and cancer, motivating us to live a healthy lifestyle.*<sup>10</sup>

## D-dimer Reporting Units

Regrettably, there is no harmonization among D-dimer results generated from various laboratories based on various test distributors' kits.<sup>11</sup> Some report in D-dimer units [DDUs] where the normal limit is ~240 ng/mL also expressed as 0.24 mg/L or 0.24 ug/mL. Others report fibrinogen equivalent units [FEUs] where the normal limit is ~500 ng/mL or 0.5 mg/L or 0.5 ug/mL. Some labs fail to specify FEUs or DDUs in their reports. Each manufacturer's kit is based on a unique monoclonal antibody with varying measurement characteristics. Furthermore, normal limits are age-adjusted. If someone is over 50, we multiply age by 10 ng/mL FEUs. For example, the limit for age 60 = 600 ng/mL FEUs, age 70 = 700 ng/mL FEUs, and age 80 = 800 ng/mL.

Using FEUs in ng/mL, a person with any inflammation may have results of ~1500 ng/mL FEUs, whereas a person with DIC or advanced COVID infection may have results of ~8,000 ng/mL FEUs or greater. The values range widely. A D-dimer result in the normal interval, less than 240 ng/mL DDUs or less than 500 ng/mL FEUs is evidence there is no DVT or PE.

## Isolated Chronically Elevated D-dimer

In 2020, largely in response to the COVID-19 pandemic, labs around the world have seen an increase in D-dimer orders.<sup>12</sup> Perhaps as a result, Fritsma Factor has received communication from several unrelated people from around the world who report chronically elevated D-dimer results without evidence of a thrombotic disorder. Most had gotten their first D-dimer test in response to an indication such as chest pain, shortness of breath, which may lead to suspicion of Covid-19 infection; or the indications of a DVT that include pain, swelling, redness, and a sense of heat in the affected leg. Subsequent D-dimer results, however, did not return to baseline even after the symptoms resolved or no clot was present at the outset. Naturally, all those who inquire worry and wonder what to do next.

*The most likely answer is inflammation.* One person mentioned ulcerative colitis, another, thalassemia, which is an inherited form of anemia, another reported hypothyroidism, another told of a recent minor surgery, another had a mild kidney disorder. Many of our correspondents worried about cancer, however none of our inquirers has had a cancer diagnosis though several had CT and MRI scans performed to rule out tumors. *Often a separate assay for inflammation such as C-reactive protein, or ferritin may confirm inflammation.*

*The second possibility is an artifact.* There is a relatively common antibody called human anti-mouse antibody [HAMA] that forms in response to certain modern meds that are synthesized in mouse cell cultures. HAMA cross-reacts with some D-dimer assay reagents and causes an elevated result that is unrelated to the individual's condition. Rheumatoid arthritis is an inflammatory disorder. It is usually accompanied by a protein called *rheumatoid factor [RF]* that also interferes with the D-dimer result. Many manufacturers add blocking reagents to their D-dimer kits that prevent interference from HAMA and RF. One clue to an artifact is when a person's D-dimer levels are elevated when tested in one laboratory but normal when tested by another. Also, when the D-dimer is elevated but all other inflammation test results are normal, an artifact may be the culprit. In one case, a small child had markedly elevated D-dimer results from one lab and normal results from another. It appeared that the blood collection event at the first lab had been traumatic, causing damaged tissue to mimic D-dimer in the assay.

I [Geo] consulted with several US experts plus one in Italy and another in Australia, all of whom focused on inflammation as the cause of isolated elevated D-dimer. One in vitro diagnostics company scientist said that most of the companies now add blockers to their reagents to reduce artifact interference. Two respected researchers documented people with no identifiable inflammatory disorder but with chronically elevated D-dimers. One lab colleague of an expert had recorded elevated D-dimer results on themselves for 25 years with no other indications and no adverse events. This is anecdotal information and there are no scientific publications offering data that document isolated elevated D-dimers.

We hope this information is helpful. Feel free to contact Fritsma Factor at [george@fritsmafactor.com](mailto:george@fritsmafactor.com).

## References

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