Robust and Well-Designed Studies are Needed to Clarify Whether COVID-19 Vaccines can Interfere with Coagulation

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Received: 15 December 2021; **Accepted:** 17 December 2021

To the editor,

Since the beginning of the COVID-19 vaccinations, doubts have arisen about the risk of inducing a thrombotic profile in some subjects via the administration of the vaccine, just as it occurs in COVID-19 patients. The mechanisms by which these vaccines could interfere with coagulation are not yet completely understood. It has been documented that SARS-COV-2 infection can provoke increased blood clotting (Lundstrom *et al*., 2021). Critically ill COVID-19 patients presented elevated D-dimer levels about 60% of the times (Iba *et al*., 2020). D-dimer is a biomarker of fibrin formation and degradation, and its increase is an absolute confirmation of abnormal blood clotting taking place somewhere in the body (Weitz *et al*., 2017). A significant elevation of D-dimer was also reported in all patients with vaccine-induced (immune) thrombocytopenia (VITT)- as this is included among the tests for suspected COVID-19 VITT (Favaloro, 2021).

Doubts have been raised that also mRNA vaccines could determine increased blood clotting, because a significant elevation of D-dimer was found in a high percentage (about 60%) of subjects who were vaccinated for COVID-19 with any type of vaccine, as was also reported to the site for reporting adverse drug events of Italian Medicines Agency (AIFA). In addition, a recent article has reported that coagulation profiles changed significantly after vaccination, in the short-term (7 days) after the first inoculation, coagulation profiles were leaning toward shorter Prothrombin Time (PT), whereas the long term (28 and 42 days) effect was toward activated partial thromboplastin time and PT prolongation. By day 90, the profiles returned back to those before vaccination (Liu *et al*., 2021). Considering the above, we believe that D-dimer should be considered in any coagulation study regarding COVID-19 vaccines (Shutte *et al*., 2016).

In addition to the autoimmune mechanisms induced by adenovirus vaccines, it has been hypothesized that the spike protein itself could directly damage the endothelial cells and can bind to platelet ACE2 receptor enhancing platelets aggregation and thrombosis (Zhang *et al*., 2020). While there is no scientific evidence available supporting the fact that the spike proteins synthetized after COVID vaccinations could be toxic and damaging our organs, there is no scientific evidence on this topic by pharmaceutical companies producing vaccines, to eliminate any doubt either. On April 5th, 2021, the Association of American Physicians and Surgeons released an important statement: "blood clotting needs to be watched with all COVID vaccines" (Association of American Physicians and Surgeons, 2021).

In conclusion, as discussed above, this important topic should be clarified as soon as possible to remove all doubt on the issue. We believe that robust and well-designed studies are needed to completely exclude that COVID-19 vaccines may interfere with clotting, particularly in some predisposed subjects, these are lacking at present.

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