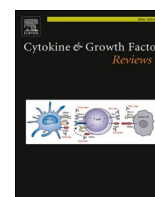




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# Antiphospholipid antibodies and risk of post-COVID-19 vaccination thrombophilia: The straw that breaks the camel's back?

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## ABSTRACT

Antiphospholipid antibodies (aPLs), present in 1–5 % of healthy individuals, are associated with the risk of antiphospholipid syndrome (APS), which is the most common form of acquired thrombophilia. APLs may appear following infections or vaccinations and have been reported in patients with CORonaVirus Disease-2019 (COVID-19). However, their association with COVID-19 vaccination is unclear. Notably, a few cases of thrombocytopenia and thrombotic events resembling APS have been reported to develop in recipients of either adenoviral vector- or mRNA-based COVID-19 vaccines.

The aim of this review is therefore to speculate on the plausible role of aPLs in the pathogenesis of these rare adverse events.

Adenoviral vector-based vaccines can bind platelets and induce their destruction in the reticuloendothelial organs. Liposomal mRNA-based vaccines may instead favour activation of coagulation factors and confer a pro-thrombotic phenotype to endothelial cells and platelets. Furthermore, both formulations may trigger a type I interferon response associated with the generation of aPLs. In turn, aPLs may lead to aberrant activation of the immune response with participation of innate immune cells, cytokines and the complement cascade. NETosis, monocyte recruitment and cytokine release may further support endothelial dysfunction and promote platelet aggregation. These considerations suggest that aPLs may represent a risk factor for thrombotic events following COVID-19 vaccination, and deserve further investigations.

## 1. Introduction

The year 2021 started with the hope of definitely defeating the CoronaVirus Disease 2019 (COVID-19) pandemic with introduction of a global vaccination plan. COVID-19 is an infectious disease driven by an enveloped single stranded (ss) RNA virus, called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The outbreak initiated in Wuhan in the Fall of 2019 has rapidly spread across the globe [1]. The disease is characterized by high morbidity and mortality rates, but its course is extremely unpredictable and ranges from asymptomatic individuals to cases with life-threatening complications, like disseminated intravascular coagulopathy (DIC) or acute respiratory distress syndrome (ARDS) [2]. The elderly, being male and chronic comorbidities are considered risk factors for worse prognosis [3]. The tendency towards a hyper-coagulable status represents one of the most emblematic aspects of COVID-19, and negatively influences the prognosis of the disease [4].

Although antiphospholipid antibodies (aPLs) have been detected in the serum of COVID-19 patients, their role in driving thrombosis is uncertain [5–8]. APLs are notoriously associated with the antiphospholipid syndrome (APS), an immune-mediated thrombophilia with predisposition to recurrent episodes of arterial and venous thrombosis, foetal loss, as well as other obstetric complications [9]. APS has a multifactorial pathogenesis and infections are recognized to be among the environmental triggers of the disease [10]. Molecular mimicry may induce generation of cross-reacting antibodies directed against microbial and self-epitopes, including protein-phospholipid complexes. Furthermore, in asymptomatic and untreated patients having pre-existent aPLs, infections may trigger pro-inflammatory cascades able to promote development of a full-blown APS. It is possible that the same scenario can take place following parenteral inoculation of vaccines, including those formulated against SARS-CoV-2. Several months after the introduction of mass COVID-19 vaccination campaign, concerns were raised as to the

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