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COVID-19, hypercoagulation and what it could mean for patients with psychotic disorders

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It has been very recently shown COVID-19 is associated with a clinically significant coagulopathy. Several studies have indicated that elevated markers of fibrin degradation (D-dimers) in hospitalised patients are associated with poorer prognosis (death or ICU admission).^{1,2} Coagulation test screening is suggested and routine thromboprophylaxis measures (including use of low molecular weight heparin) are recommended, but full anticoagulation is not yet advised in the management of such patients unless otherwise clinically indicated.² We wish to draw attention to a potentially enhanced risk of thromboembolic complications in patients with psychotic disorders.

Coagulation and COVID-19

Virchow's triad describes three types of factors that contribute to development of thrombosis: stasis (abnormalities in blood flow); endothelial injury (abnormalities of the blood vessel wall; and a hypercoagulable state (abnormalities of the blood constituents). COVID-19 patients are likely to be less mobile in the context of their infection, especially in severe cases, increasing the risk of stasis. The SARS-CoV-2 virus is understood to become incorporated within host cells via binding to the angiotensin-converting enzyme 2 (ACE2) receptor. This receptor is expressed widely in endothelial cells, enabling the virus to contribute to endothelial injury. A hypercoagulable state may be induced as a result of the intense release of pro-inflammatory cytokines. These are key mediators of the immune response which can also activate the complement system, a key component of the innate immune system among the body's arsenal of early responses to infection. The complement system interacts closely with and can cause activation of the coagulation pathway.³ Activation of coagulation in COVID-19 is in keeping with observations of increased incidence of venous thromboembolism in critically ill patients.⁴

Coagulation and psychotic disorders

Patients with psychotic disorders such as schizophrenia may have an approximately 2- to 3-fold increased risk of deep vein thrombosis or pulmonary embolism compared to controls.⁵ Several factors may underlie this association (see Figure). Obesity, atherosclerosis and cardiovascular disease are

common physical co-morbidities in people with schizophrenia which are associated with abnormalities of blood flow and thromboembolic risk. There is evidence that schizophrenia may be associated with endothelial dysfunction, as evidenced by elevated levels of plasma endothelial markers such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1).⁶ These normally aid leukocyte adhesion to endothelium as part of the immune response, but if left unchecked may lead to endothelial damage as occurs in the development of atherosclerosis. There is well-described evidence for chronic, low-grade immune activation and inflammation in schizophrenia which may drive, or occur in association with, endothelial injury. There is growing evidence that psychosis phenotypes are associated with abnormalities in blood constituents indicative of a hypercoagulable state.^{7,8} Our proteomic studies we have implicated complement activation and hypercoagulation prior to the onset of subclinical psychotic experiences and psychotic disorder in the general population.^{9,10} These findings suggest that aberrations of the complement and coagulation systems are present early in the course of psychosis and may be part of the underlying associated pathophysiology. However, the influence of factors such as exposure to medication, chronic lifestyle factors or physical co-morbidity may increase with chronicity of the disorder. Antipsychotic therapy, for example, may be associated with an increased risk of thromboembolism¹¹ although it is unclear whether this is as a direct result of their therapeutic pharmacological actions or secondary to other effects such as sedation or weight gain.

Implications

Patients with psychosis may be at increased thromboembolic risk in part due to lifestyle, medication and environmental factors, but the association may also be driven by biological dysregulation associated with the underlying disorder, acting in concert with these other factors. Given the accumulating evidence for coagulopathy associated with COVID-19, patients with psychosis who acquire COVID-19 may be at enhanced risk for thromboembolic complications. While this potential link is informed by the risk factors and evidence for hypercoagulation associated with both conditions, in the absence of sufficient data it remains speculative. There is an urgent need for research to formally evaluate the risk of thromboembolic complications in patients with psychosis who develop

infection with COVID-19 to guide clinical management decisions in this at-risk population. Clinicians in psychiatry, general medicine and intensive care should evaluate these factors with special consideration of the potential for increased risk of thromboembolic complications. Screening for coagulation abnormalities should be implemented in line with current (and rapidly developing) guidance.

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CONFLICTS OF INTEREST

DM, MC and DRC report a patent pending (UK Patent Application No. 1919155.0, “Biomarkers to predict psychosis”). The authors otherwise report no conflicts of interest in relation to this work.

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FIGURE

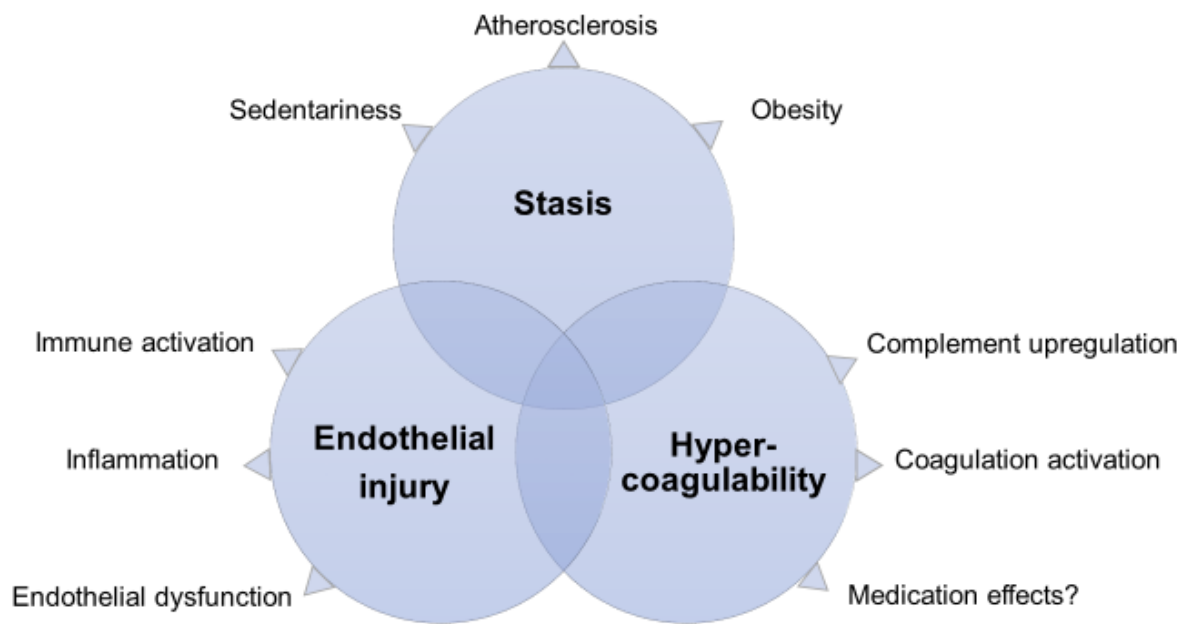


Figure. Examples of factors that may underlie the association between psychotic disorders and thromboembolic risk according to Virchow's triad.