



EDITORIAL

Thrombotic risk associated with COVID-19 and diabetes; Is PAI-1 the link?

Riesgo trombótico asociado a COVID-19 y diabetes: ¿es PAI-1 el nexo?

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It became apparent in the initial periods of the SARS-CoV-2 pandemic (COVID-19) that the disease was associated with severe coagulopathy, which favoured the development of thrombotic complications, leading to high morbidity and mortality in hospitalised patients.^{1,2} These complications included venous thromboembolism, myocardial infarction, stroke, and other microvascular complications, mainly at the level of the pulmonary microcirculation, resulting in the development of respiratory distress syndrome and other systemic manifestations, and which could trigger multi-organ failure. These complications were the result of a hypercoagulable state with intravascular fibrin generation and were present in up to 30%–80% of patients admitted to intensive care units and associated with high mortality rates.^{2,3} The hypercoagulable state was exacerbated by an impaired fibrinolytic system, the body's defence system responsible for fibrin degradation.

Fibrinolysis is initiated by the conversion of the proenzyme plasminogen into the active enzyme plasmin by the action of plasminogen activators (t-PA and u-PA). Plasmin is responsible for the proteolytic degradation of fibrin,

resulting in the generation of degradation products, D-dimer being the most relevant in patients with COVID-19, as extraordinarily high levels are observed after infection.⁴ This system is tightly regulated by the action of plasminogen activator inhibitors, such as PAI-1, and plasmin, to prevent excessive fibrinolysis that would promote bleeding, while an excess of PAI-1 would contribute to a hypofibrinolytic state that promotes thrombosis.

SARS-CoV-2 has been reported to induce PAI-1 expression by endothelial cells and may be the link between cardiovascular risk factors (smoking, diabetes, etc.) and the clinical manifestations of COVID-19 infection.⁵ Previous studies have shown PAI-1-mediated fibrinolytic resistance and a significant increase in PAI-1 inhibitor in patients with COVID-19, up to 4 times higher than that observed in controls, which would lead to decreased fibrinolysis.^{5–7} Some studies have shown that up to 80% of patients with COVID-19 and thrombosis meet the criteria for fibrinolytic shutdown, and its association with the presence of thrombosis in the microcirculation in the lung and other organs (kidney, brain, etc., etc.).^{8–10} Finally, the persistence of a hypofibrinolytic state is associated with an unfavourable prognosis, as it is associated with the severity of the infection.^{11,12} Consequently, the haemostatic coagulation/fibrinolysis balance is altered in these patients, with activation of coagulation and decreased fibrinolysis, resulting in a hypercoagulable state that promotes thrombosis.

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It is known that type 2 diabetes mellitus (DM) and associated hyperglycaemia carries a high risk of thromboembolic complications.¹³ It is also known that patients with DM have platelet hyperactivity and haemostatic disturbances and other comorbidities (obesity, dyslipidaemia, fatty liver, etc.), which contribute to a hypercoagulable state. However, it is not known whether the presence of hyperglycaemia and/or type 2 DM would aggravate this state should these patients suffer COVID-19 infection. Previous studies have described a close relationship between PAI-1 and diabetes, which could favour the development of thrombotic complications and may be a link in patients with COVID-19.¹⁴

In this issue of *Clínica e Investigación en Arteriosclerosis*, Basurto et al. analyse the association between PAI-1 and DM/hyperglycaemia in a large population of 181 patients hospitalised for COVID-19, of whom 38% had a previous history of DM and 51% had pre-existing hyperglycaemia and/or DM.¹⁵ They observed a significant increase in PAI-1 in this group of patients in relation to non-hyperglycaemic hospitalised patients. They also demonstrated a correlation between inhibitor and glucose levels and an association of PAI-1, hyperglycaemia, and/or DM with COVID-19 severity. This suggests that hyperglycaemia may contribute to the hypercoagulable state. This is the largest series to examine this association, as a previous study involving 30 patients with COVID-19 and DM had also observed a significant increase in PAI-1.¹⁶ The most relevant finding of the study by Basurto et al. stems not only from the association between glucose levels and PAI-1, but also from the potential prognostic significance of this fibrinolytic biomarker in patients with DM, due to its relationship with the severity of COVID-19 infection. The authors acknowledge some inherent limitations of the study, as the determination of only one of the fibrinolytic components, PAI-1, does not provide information on the overall fibrinolytic activity.

In summary, when patients with hyperglycaemia and/or DM are infected by COVID-19, their thrombotic risk is significantly increased, and PAI-1 plays a key role in the hypercoagulable state associated with coagulopathy. This is of interest because of the possibility of inhibiting PAI-1 as a new antithrombotic strategy in these patients.¹⁷

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Conflict of interests

The author has no conflict of interest to declare.

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