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Sulodexide: A Benefit for Cardiovascular Sequelae of Long COVID Patients?

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Dear Editor,

The elaborate and precise review of *Harry N. Magnani* didactically demonstrates the complex pathophysiological aspects of coronavirus disease 2019 (COVID-19) emphasizing the roles of vascular endothelial dysfunction and coagulation cascade as key features of disease progression.[1] Moreover, this article brings up that glycosaminoglycane (GAG) antithrombotics likely interfere with inflammatory and coagulation activity in an effective fashion.[1] Thereafter this postulate has become advocated as the application of sulodexide (Vessel Due F; ALFASIGMA, Italy) (SDX), an unexpensive and orally administrable GAG antithrombotic drug reduced the necessity for both hospital admission and oxygen supplementation in the early phase of SARS-Cov-2 infection under a randomized placebo-controlled out-patient trial.[2] Interestingly, these patients also showed lower serum levels of C-reactive protein (CRP) and D-dimer as markers of inflammation and prothrombotic state. Of note, instead of regularly recommended and prescribed 250 RLU twice-daily dose, the clinical trial applied the higher, 500 RLU twice-daily dosing regimen in which an antithrombotic effect was safely achieved in a clinical setting.

Conversely, there is still a relatively little but emerging information "long hauler" sufferers who have recovered from the acute presentation and have a negative polymerase chain reaction (PCR) SARS-CoV-2 test yet still continue to have COVID-19 symptoms for weeks or even months later, or those who present cardiovascular complications weeks or months later.

Recent findings proclaim that endothelial cells (ECs) play pivotal role in SARS-CoV-2 infection, not only as target organs but also as effectors, with several pathways possibly involved, all more widely analysed in the acute phase. However, the exact mechanism of post-COVID-19 cardiovascular events has not been fully clarified. It has been found that elevation in D-dimers is a common feature of COVID-19 patients during convalescence. Higher D-dimer levels mostly persisted despite normalization of inflammatory mediators and other coagulation parameters.[3] Recent data firstly demonstrated that prolonged EC activation can last up to 10 weeks subsequent to acute SARS-CoV-2 infection being more common in older, comorbid persons and in-patients. EC biomarkers comprising VWF:Ag, VWF propeptide (VWFpp), Factor VIII (FVIII:C) as well as plasma soluble thrombomodulin (TM) levels were measured to be significantly higher in convalescent patiens compared to non-hospitalized asmptomatic SARS-CoV-2 positive controls.[4] Interestingly, this persistent endotheliopathy is independent of ongoing acute phase reaction and is related to augmented thrombin generation potential. Shedding of TM from EC has been postulated to likely take part in the abruption of endothelial quiescence.[4] Furthermore, the disintegration of the vascular lumen with the destruction of the glycocalyx layer and concomitantly elevated serum levels of endothelial glycocalyx compounds (eg syndecan-1) provide a higher probability of microvascular thrombosis and dysregulated leukocyte adhesion.[5]

In this regard the reconstruction of the endothelial glycocalyx layer seems to be of paramount importance from the

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aspect of thrombosis prophylaxis and the alleviation of inflammation,[1] although in convalescent patients, the restoration of the endothelium integrity should focus on rehabilitating a general homeostasis rather than only on modulating a thrombo-inflammatory response.

Low-molecular-weight heparins (LMWHs) and even unfractionated heparin are widely used in the hospital setting for their anticoagulation properties and proven benefit in reducing mortality in critically ill patients.[1] They also have non-anticoagulant effects that may be of further benefit to COVID-19 patients but data of their use in COVID-19 long haulers is limited and presumably less preferred due to the need for parenteral administration.[2] SDX is a blend of 80% fast-moving heparin and 20% dermatan sulfate, also available in oral capsules; its *in vitro* anti-thrombotic effects share similarities with those of LMWHs and its most pivotal effects are the restoration of the glycocalyx barrier and the attenuation of glycocalyx permeability disturbances.[1,2] Further beneficial properties are fully listed by the commented article.[1] Unlike LMWHs SDX is available in oral capsules and not deleterious in renal insufficiency and less likely related to heparin-induced thrombocytopenia (HIT), drug-induced hypersensitivity and drug interactions.[1,2] A recent Bayesian meta-analysis found that SDX was the most favorable agent compared with direct oral anticoagulants (DOACs), vitamin K antagonists and aspirin at reducing the risk of major and clinical relevant non-major bleeding and also for preventing mortality from deep vein thrombosis (DVT), pulmonary embolism (PE) or stroke. SDX and DOACs appeared to be nearly equally effective approaches for reducing PE risk however SDX was notably weaker in DVT prophylaxis.[6]

This premise may give impetus to an application of SDX in post-COVID-19 conditions to normalize endothelial function and simultaneously prevent cardiovascular complications as aftermaths of SARS-CoV-2 infection. Prompt controlled and powered clinical trials are proposed to determine whether prolonged EC activation with intensified coagulation has a role in stratifying patients for post-COVID thromboprophylaxis and vascular protection and also to test the efficacy of SDX among convalescent patients which seems to be in harmony with the core message of the fundamental article.[1]

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