Could Sulodexide be Helpful in COVID-19?

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Abstract
Vascular disorder is prominent in COVID-19, mainly characterized by endothelial damage, severe inflammation and thrombotic trend. We reviewed the data suggesting that sulodexide, a glycosaminoglycan with endothelial protective, vascular anti-inflammatory, and antithromotic activities, could be helpful in this disease.

Introduction
The Coronavirus SARS Cov-2 is a highly contagious virus causing a pandemic with several millions of infected people in the whole world. The disease caused by this virus, called COVID-19, has wide clinical spectrum, ranging from asymptomatic, mild or severe symptoms and death, with a high fatality-rate, mainly in the elderly [1]. The main clinical manifestations are respiratory, although extrapulmonary involvement as thrombotic complications, myocardial dysfunction, gastrointestinal symptoms, hepatocellular and kidney injury, as well as dermatologic rash are recognized [2].

Mortality of COVID-19 is still high despite all therapeutic measures. Few treatments have shown to improve severely ill patients in intensive care unit as corticosteroids, thromboprophylaxis with low-molecular-weight heparin, and remdesivir [1,3]. However, up to October 2020 no effective treatment has been approved, including therapy for ambulatory subjects not so severely ill, where the goal is to prevent disease worsening and hospitalization. Here, we are supporting data that sulodexide could be considered as an important therapeutic option for COVID-19.

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Endothelial injury including glyocalyx damage

Viral infection of endothelial cells causes an endothelial injury that may be severe. This endothelialitis has been observed in postmortem reports [7,8]. High plasma levels of markers of endothelial cell activation and platelet activation as von Willebrand Factor (vWF) antigen, soluble thrombomodulin and soluble P selectin were found in COVID-19 patients and were associated with critical illness and death. SCAD40L a marker of T cell activation, as well as Plasminogen Activator Inhibitor-1 (PAI-1), vWF activity and factor VIII activity plasma levels were higher in intensive care patients. D-Dimer and thrombin-antithrombin complexes were also higher in chronic diseases with endothelial dysfunction as diabetes and hypertension that might predispose to a further viral endothelial damage leading to platelet and leukocyte activation as well as abnormal anticoagulant and fibrinolytic mechanism [10].

Also, exploring sublingual microvessels with intravital microscopy by sidestream dark field imaging in patients with COVID-19, a marked reduction of the density of small capillaries and severe glyocalyx damage were observed especially in those patients with mechanical ventilation. In these subjects severity of COVID-19 was correlated with several markers of endothelial dysfunction, strikingly von Willebrand factor-activating protease, and Vascular Endothelial Growth Factor-A (VEGF-A) [11].

Hypercoagulability and thrombosis

Activation of coagulation, starting from endothelial damage, is related to the severity of the disease. Higher levels of D-dimer and fibrin degradation products, longer prothrombin time and activated thromboplastin time in non-surviving than in surviving patients with severe COVID-19 pneumonia have been shown in Wuhan, China. Furthermore, severe cases have been complicated by disseminated intravascular coagulation, 74% of the non-survivors met criteria of disseminated intravascular coagulation compared with 6% of survivors [12]. Global viscoelastic hemostatic assay (thromboelastography) parameters and blood parameters of hemostasis were consistent with a state of hypercoagulability [13]. Incidence of Venous Thromboembolism (VTE) was 25% [20/81] in patients with severe coronavirus pneumonia. Higher levels of D-dimer were predictive of VTE [14]. Superficial thrombophlebitis can also occur in patients with COVID-19 [15], and in purpuric lesions of the skin thrombogenic vasculopathy with C5-9 and C4d accumulation (evidence of complement activation) has been found [16]. The role of inflammation in deep venous thrombosis has been recently addressed [17].

Significant inflammation is present at the beginning in COVID-19 with elevated levels of IL-6, C reactive protein, high ESR, and high fibrinogen levels. Some patients appear to have a more pronounced inflammatory response to infection with SARS-CoV-2, such as seen with Systemic Inflammatory Response Syndrome (SIRS) or cytokine storm, which may explain more dramatic changes in coagulation tests results, including significantly elevated D-dimer. Activation of host defense systems results in subsequent activation of coagulation and thrombin generation through humoral and cellular amplification pathways, a term called thromboinflammation. In sepsis, coagulation is activated by the inflammatory response through several procoagulant pathways. Cytokines elevation also result in activated vascular endothelial injury with resultant prothrombotic properties [18].

The mechanisms that activate coagulation in SARS-CoV-2 infection appear to be linked to endothelial damage and inflammatory responses rather than specific properties of the virus.

The three main pathophysiological features of COVID-19 appear to be severe microvascular and endothelial disturbances (including glyocalyx), hypercoagulability and severe inflammation.

Sulodexide

Sulodexide is a glycosaminoglycan composed of two distinct fractions: 80% of fast moving heparin and 20% of dermatan sulfate. Sulodexide has polypharmacological actions including endothelial protection, anti-thrombotic, profibrinolytic, and anti-inflammatory. Its therapeutic use is in vascular diseases, mainly in chronic venous disease, in prevention of recurrent venous thromboembolism, and in diabetic nephropathy [19-23].

Sulodexide protects glyocalyx and endothelial cells: Sulodexide endothelial protection includes glyocalyx and endothelial cells. Glyocalyx is a thin layer constituted by proteoglycans, glycosaminoglycans and glycoproteins that covers the endothelial cells. Glyocalyx is a thin layer constituted by proteoglycans, glycosaminoglycans and glycoproteins that covers the endothelium of all the vessel walls. It has several important physiological functions [24,25] and if perturbed may worsen endothelial dysfunction [26]. Endothelial glyocalyx is injured in acute respiratory distress syndrome induced in mice by endotoxemia. Protection against endothelial injury by accelerating glyocalyx synthesis, attenuates glyocalyx damage, decreases IL-6 levels and improves survival rate in animal models [27]. Sulodexide inhibits glyocalyx permeability disturbances and oxidative stress in experimental ischemia-reperfusion injury [28]. In cultured endothelial cells sulodexide restores glyocalyx barrier [29]. In a balloon-injury of carotid artery model in rats, intraarterial injections of sulodexide could reconstruct endothelial glyocalyx, increased endothelial nitric oxide synthase levels, attenuated endothelial hyperplasia and inhibited platelet aggregation, decreased expression of CD31 and Intercellular Adhesion Molecule-1 (ICAM-1), normalized osteopontin and Vascular Cell Adhesion Molecule-1 (VCAM-1), and prevented CD68 inflammatory infiltration of vascular wall [30]. It has been demonstrated in diabetic subjects with reduced dimensions of endothelial glyocalyx that sulodexide given by oral route restores the glyocalyx thickness [31].

In cultured endothelial cells exposed to high glucose concentration sulodexide suppresses inflammation phenotype decreasing Reactive Oxygen Species (ROS), Monocyte Chemoattracting Protein-1 (MCP-1) and interleukin-6 (IL-6) and also
increases the speed of wound repair of the cells layer [32]. A similar study with experimental human endothelial aged cells showed that sulodexide reduces senescence-related changes [33]. Sulodexide improves endothelial dysfunction in streptozotocin-induced diabetes in rats, while in cultured human umbilical vein endothelial cells, sulodexide counteracts inflammation and endothelial dysfunction induced by serum of patients with advanced chronic venous disease, or by metabolic stress (methylglyoxal) or irradiation. In these studies, cytoprotective effects of sulodexide resulted in a reduction of ROS production, a diminished synthesis and release of pro-inflammatory cytokines as IL-1, IL-6, IL-18, tumor necrosis factor-α (TNF-α), MCP-1, ICAM-1, and DNA damage [34-36]. Sulodexide also prevents apoptosis of endothelial cells exposed to oxygen-glucose deprivation. This protective effect seems to be mediated by reduced oxidative stress [37].

**Sulodexide as anti-thrombotic:** Sulodexide shows anti-thrombotic effects on platelet aggregation, plasma coagulation and fibrinolysis. It inhibits platelet aggregation in response to cathepsin G, thrombin and tissue factor. Counteracts plasma coagulation factors Xa and IIa, thus showing an anti-thrombin effect similar in vitro to enoxaparin [38-40]. Thrombolytic activity has been initially shown adding sulodexide to thrombi formed 6 hours before [41]. Sulodexide administered by oral route decreases Plasminogen Activator Inhibitor-1 (PAI-1) and enhances Tissue Plasminogen Activator (tPA) [42,43]. Antithrombotic activity of sulodexide given by oral route has been confirmed in clinical studies that have shown its efficacy for the prevention of recurrent venous thromboembolic episodes [44,45].

**Sulodexide shows anti-inflammatory effects:** Anti-inflammatory effects of sulodexide have been demonstrated in several studies in vitro, in animal models and in human beings. Sulodexide acts on regulatory inflammatory response decreasing mediators of inflammation as interleukins (IL) IL-6, IL-8, IL-1β, IL-2, IL-10, IL-13, interferon β, Macrophage Inflammatory Protein-1β (MIP-1β), Transforming Growth Factor-β1 (TGF-β1), Vascular Endothelial Growth Factor (VEGF), Monocyte Chemoattractant Protein-1 (MCP-1), Tumor Necrosis Factor-α (TNF-α), granulocyte colony stimulating factor and granulocyte-monocyte colony stimulating factor. Sulodexide decreases oxidative stress by reducing Reactive Oxygen Species (ROS) and enhancing Super Oxide Dismutase (SOD), and diminishing metalloproteinase-9 which can cause tissue damage [46-48].

**Sulodexide is safe:** Remarkably, sulodexide lacks severe adverse effects. Long term treatment (two years) did not show more bleeding cases than placebo. Furthermore, in meta-analysis showed less cardiovascular and total mortality than comparators: Direct oral anticoagulants, vitamin K antagonists, aspirin and placebo [49,50].

**Conclusion**

Endothelial damage, inflammation and thrombotic trend are important pathophysiologic features in COVID-19. Among therapeutic resources to address thromboinflammation in COVID-19 [51], sulodexide should be considered an important agent in patients with mild or severe COVID-19, because it acts against the major components of COVID-19 pathophysiology (Figure 1). Clinical investigation is warranted.

**References**

11. Frati, Lecuona and Bautista are employees of Alfasigma Laboratories Mexico. Flores has been speaker for Alfasigma Laboratories and Servier Laboratories.


