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Impairment in selenocysteine synthesis as a candidate mechanism of inducible coagulopathy in COVID-19 patients

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ABSTRACT

Coagulopathy has recently been recognized as a recurring complication of COVID-19, most typically associated with critical illness. There are epidemiological, mechanistic and transcriptomic evidence that link Selenium with SARS-CoV-2’s intracellular latency. Taking into consideration the vital role of selenoproteins in maintaining an adequate immune response, endothelial homeostasis and a non-prothrombotic platelet activation status, we propose that impairment in selenocysteine synthesis, via perturbations in the aforementioned physiological functions, potentially constitutes a mechanism of coagulopathy in COVID-19 patients other than those developed in critical illness.

Background

COVID-19 patients exhibit frequently blood coagulation disturbances, including venous, arterial and catheter-related thrombosis. The hematologic laboratory profile of COVID-19 patient consists of derangements in cell counts, inflammatory markers and coagulation cascade. Finally, anticoagulants have been proven beneficial in the context of SARS-CoV-2 infection. Thus, SARS-CoV-2 infection should be regarded as a risk factor for coagulation abnormalities and the thorough understanding of its pathogenesis should involve a thorough examination of coagulation derangements.

Several hypotheses on COVID-19 associated coagulopathy have been proposed. SARS-CoV-2 infection fosters the excessive production of inflammatory mediators (such as cytokines IL-2R, IL-6, IL-10 [1] and TNF-α and biomarkers procalcitonin, ferritin and C-reactive protein [2]), configuring a pro-inflammatory milieu. Dysregulated immune response, through hyperinflammation, cytokine storm syndrome and secondary hemophagocytic lymphohistiocytosis, has been postulated as a vital component of COVID-19 coagulopathy [3].

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Delangement of endothelial function, via indirect infection-mediated endothelial dysfunction, as well as direct viral invasion and injury are well described aspects of SARS-CoV-2 infection pathogenesis [4]. Endothelial dysfunction may promote coagulation abnormalities by various means, including endothelial activation and thrombin generation, attenuated fibrinolysis [5] and thromboinflammation mediated primarily by activated platelets [6].

No study to date has examined the putative role of Se and Selenoproteome perturbations as triggers for coagulopathy in the setting of COVID-19, regardless of severity.

Hypothesis

The hypothesis examined herein is that SARS-CoV-2 induced perturbations in cellular Se homeostasis contribute to the manifestation of COVID-19 coagulopathy.

Evaluation of the hypothesis

Selenium and COVID-19

There are limited observational studies on the clinical and biochemical correlates of COVID-19 and Se levels. A recent epidemiological study from China outlined an association between background regional Se status and COVID-19 outcomes, with lower levels associated with more severe disease [2].

Observational studies have demonstrated that prevalence of...
Selenium deficiency in COVID-19 patients is noteworthy, manifesting in accordance with disease severity [7]. Serum Se status in survivors is significantly higher and displays a progressively recovering pattern contrary to non-survivors [7].

SARS-CoV-2, selenium and coagulation: the proposed mechanism

Combining the aforementioned data, with bioinformatics analysis of SARS-CoV-2 virus [8], it is reasonable to speculate that Se deficiency and the consequent impairment in stress-related selenoprotein synthesis [9], plays a part in COVID-19 pathogenesis.

Firstly, it is well established that Se is useful for the competency of the cellular component of both innate and adaptive immunity [10]. The immunostimulant and lymphoproliferative effect of Se has been documented in various studies. Dietary Se supplementation has been associated with evident augmentation of circulating cytotoxic lymphocytes in healthy adults [11], in the elderly [12], as well as after flu and poliovirus vaccination [13,14]. Viral challenge via poliovirus vaccination in Se supplemented subjects resulted in a robust Th1 response, manifested by the cytokines produced, and enhanced viral clearance as a functional outcome of viral handling with Se supplementation [14]. Possible mechanistic explanations of the lymphoproliferative effect of Se are, on the one hand, Se-mediated control of many cell-cycle regulatory genes towards cell proliferation [15], on the other, the inability of T-cell proliferation, due to ROS-mediated attenuated T-cell receptor signaling [16], via IL-2 receptor [17]. In view of the aforementioned correlation between SARS-CoV-2 infection and Se deficiency, the above evidence is of paramount importance, specifically bearing in mind that lymphopenia (in both CD4+ T cells and CD8+ T cells) in COVID-19 patients is a prominent laboratory finding with major prognostic implications [18].

Decreased NK cell-mediated cytotoxicity in HIV-1 infected adults with a low Se status [19], as well as enhanced NK cell activity in case of dietary Se supplementation [20] have been reported. Thus, competent NK cell function, an essential component of innate immune system’s response against viral infections, is heavily dependent on adequate Se levels.

In addition, an adequate Se status contributes to immune modulation. As far as animal studies are concerned, Se deficient mice infected with influenza virus exhibited higher number of total cells in the lungs, increased percentage of lung macrophage infiltration and enhanced expression of certain proinflammatory cytokines [21]. Furthermore, transgenic mice characterized by decreased overall selenoprotein levels, expressed pro-inflammatory cytokines in heightened levels in lung tissue in comparison with controls [22]. Moreover, influenza-infected differentiated human bronchial epithelial cells displayed increased IL-6 levels in Se-deficient circumstances [23]. Notably, increased IL-6 levels in COVID-19 patients have been associated with adverse prognosis [24–26]. Selenoproteins, mainly glutathione peroxidases, Selenoprotein K and selenoprotein P, have been associated, in human studies, with the regulation of inflammation [27] and immune responses [28], thus preventing excessive and uncoordinated immune system operation. Furthermore, lower granulocyte counts have been observed in Se supplemented patients, and the authors speculated that it may be explained by adequate immune regulation of the nonspecific immune response triggered secondary to a specific immune response [11].

In conclusion, it is reasonable to speculate that Se deficiency renders the potentially defective cellular immunity ineffective in eliminating successfully the virus, thus, along with the poorly regulated immune response, leading to the development of the firmly established hyperinflammation in COVID-19 patients [1,2,4].

Dysregulated immune response, via establishment of a pro-inflammatory feedback loop, presumably exerts damage to the lung parenchyma [30] and triggers a peculiar hemophagocytic lymphohistiocytosis [31], which has been extensively demonstrated in severe COVID 19 patients. Endothelial injury, mediated by direct SARS-CoV-2 infection of endothelial cells [32] (in which selenium-dependent GPX1 may play a crucial part by enhancing SARS-CoV-2 virulence [8]) and the generalized excessive pro-inflammatory state, has been robustly implicated in COVID-19 coagulopathy [33], via multiple mechanisms including platelet activation [34], fibrinolysis shutdown [35,36], massive von Willebrand factor release [37], increased thrombin production [4], disproportionate complement activation leading to thrombogenesis [38] and Neutrophil Extracellular Traps (NETs) formation [39]. Therefore, impairment in selenocysteine synthesis may contribute to COVID-19 coagulopathy via the dysregulated immune response pathway.

Additionally, preclinical data have demonstrated that Se deficiency, via impaired antioxidant enzymes synthesis, contributes directly to endothelial dysfunction, due to attenuated selenoprotein-mediated endothelial cytoprotection [40], decrease in endothelium-dependent NO synthesis [41] leading to enhanced platelet activation [42] and prostacyclin release [43]. Adverse systemic arterial function, assessed by PWV as a surrogate of arterial stiffness, has been associated with Se deficiency [44]. Thus, it is clear that Se deficiency contributes to endothelial activation and dysfunction, promoting a pro-inflammatory and pro-thrombotic milieu [4] and modulating platelet-endothelial interaction [45].

Furthermore, certain alternations in platelets’ transcriptome in COVID 19 patients in comparison with healthy donors [46] may, allegedly and partially, be explained by impairment in selenocysteine synthesis. In COVID-19 patients, gene expression studies have shown mitochondrial dysfunction, significant increase in markers of platelet activation (i.e. P-selectin and PDGF [34], marked elevation in platelet-white blood cell aggregates (notably platelet-monocytes aggregates expressing tissue factor and triggering the coagulation cascade [34]) and a platelet hyperreactive state, mediated partially by MAPK pathway signaling and thromboxane generation [34,46]. Platelet hyperreactivity is a significant pathophysiological constituent in the pathogenesis of vascular occlusive events, such as Acute Coronary Syndrome (ACS) and stroke and plays a part in adverse prognosis [47,48]. In addition, COVID 19 patients exhibit increased platelet contribution to clots, thus highlighting the importance of platelet activation in COVID 19-associated thrombus formation [49].

Previous studies have shown that oxidative stress is a consistent pathway of platelet activation [42]. A major determinant of intracellular concentration of Reactive Oxygen Species (ROS) is glutathione-peroxidase, a Se-dependent enzyme, which is, therefore, correlated with platelet redox balance and platelet activation [50,51]. As a consequence, Se-dependent synthesis of platelets’ glutathione peroxides, major determinants of redox balance, has been implicated in platelet activation, aggregation [52], subsequent interplay with the endothelium [45] and Se supplementation modulated platelet activation via the glutathione-redox status pathway [53,54]. Finally, experiments have revealed that glutathione peroxidase controls thromboxane production, by affecting peroxide formation [55]. A recent hypothesis is that In view of the effect of Se on platelet glutathione peroxidase activity and platelet redox status, the thromboxane metabolic pathway [55] and, consequently, platelet activation [54,53], it is reasonable to propose that impairment in selenocysteine synthesis may be implicated in some of these alterations in platelets’ functions [56].

Thus, considering the multifaceted role of platelets in safeguarding the endothelial homeostasis, preventing endothelial-mediated hyperinflammation and preserving endothelial integrity, it is reasonable to speculate that impairment in selenocysteine synthesis in COVID-19 patients may be the missing link in the vicious circle of endothelial dysfunction, platelet activation and COVID-19 coagulopathy.
Author contributions
All authors contributed equally to the manuscript.

Declaration of Competing Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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