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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].

Derangement 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

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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]. Taking into consideration that neutrophilia is an infrequent finding, albeit of particular prognostic significance in COVID-19 patients [4,29], the role of Se in modulating the hyperinflammation may be of utmost significance.

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 pathophysiologic 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 peroxidases, 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.

References

[1] Chen G, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020. https://doi.org/10.1172/JCI137244.
[2] Terpos E, et al. Hematological findings and complications of COVID-19. Am J Hematol 2020. https://doi.org/10.1002/ajh.25829.
[3] Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020. https://doi.org/10.1182/blood.2020006000.
[4] Gupta A, et al. Extrapulmonary manifestations of COVID-19. Nat Med 2020. https://doi.org/10.1038/s41591-020-0968-3.
[5] Pons S, Fodil S, Azoulay E, Zafrani L. The vascular endothelium: the cornerstone of organ dysfunction in severe SARS-CoV-2 infection. Crit Care 2020. https://doi.org/10.1186/s13054-020-03062-7.
[6] Nicolai L, et al. Imunothrombotic dysregulation in COVID-19 pneumonia is associated with respiratory failure and coagulopathy. Circulation 2020. https://doi.org/10.1161/circulationaha.120.048488.
[7] Moghaddam A, et al. Selenium deficiency is associated with mortality risk from COVID-19. Nutrients 2020. https://doi.org/10.3390/nu12072098.
[8] Seale LA, Torres DJ, Berry MJ, Pitts MW. A role for selenium-dependent GPX1 in SARS-CoV-2 virulence. Am J Clin Nutr 2020. https://doi.org/10.1093/ajcn/nqaa177.
[9] Labunskyy VM, Hatfield DL, Gladyshev VN. Selenoproteins: molecular pathways and physiological roles. Physiol Rev 2014. https://doi.org/10.1152/physrev.00039.2013.
[10] Rayman MP. Selenium and human health. Lancet 2012. https://doi.org/10.1016/S0140-6736(11)61452-9.
[11] Hawkes WC, Kelley DS, Taylor PC. The effects of dietary selenium on the immune system in healthy men. Biol Trace Elem Res 2001. https://doi.org/10.1385/BTER:81:3:189.
[12] Peretz A, et al. Lymphocyte response is enhanced by supplementation of elderly subjects with selenium-enriched yeast. Am J Clin Nutr 1991. https://doi.org/10.1093/ajcn/53.5.1323.
[13] Ivory K, et al. Selenium supplementation has beneficial and detrimental effects on immunity to influenza vaccine in older adults. Clin Nutr 2017. https://doi.org/10.1016/j.clnu.2015.12.003.
[14] Broome CS, et al. An increase in selenium intake improves immune function and poliovirus handling in adults with marginal selenium status. Am J Clin Nutr 2004.
[15] Huawei Z. Selenium as an essential micronutrient: roles in cell cycle and apoptosis. Molecules 2009. https://doi.org/10.3390/molecules14031.
[16] Carlson BA, et al. Role of selenium-containing proteins in T-cell and macrophage function. Proc Nutr Soc 2010. https://doi.org/10.1017/S002966511000176X.
[17] Roy M, Kiremidjian-Schumacher L, Wishe HI, Cohen MW, Stotzky G. Supplementation with selenium and human immune cell functions – I. Effect on lymphocyte proliferation and interleukin 2 receptor expression. Biol Trace Elem Res 0 1994. https://doi.org/10.1007/BF02917221.
[18] Zhang X, et al. Viral and host factors related to the clinical outcome of COVID-19. Nature 2020. https://doi.org/10.1038/s41586-020-2355-0.
[19] Mantero-Atienza E, et al. Selenium status of HIV-1 infected individuals. JPEN J Parenter Enteral Nutr 1991. https://doi.org/10.1177/0148607191015006693.
[20] Kiremidjian-Schumacher L, Roy M, Wishe HI, Cohen MW, Stotzky G. Supplementation with selenium and human immune cell functions: II. Effect on cytotoxic lymphocytes and natural killer cells. Biol Trace Elem Res 1994. https://doi.org/10.1007/BF02917222.
[21] Beck MA, et al. Selenium deficiency increases the pathology of an influenza virus infection. FASEB J 2001. https://doi.org/10.1096/fj.00-0721fje.
[22] Hoffmann PR, Berry MJ. The influence of selenium on immune responses. Mol Nutr Food Res 2008. https://doi.org/10.1002/mnfr.200700330.
[23] Jaspers I, et al. Selenium deficiency alters epithelial cell morphology and responses to influenza. Free Radical Biol Med 2007. https://doi.org/10.1016/j.freeradbiomed.2007.03.017.
[24] Zhou F, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020. https://doi.org/10.1016/S0140-6736(20)30566-3.
[25] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020. https://doi.org/10.1007/s00134-020-05991-x.
[26] Cummings MJ, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet 2020. https://doi.org/10.1016/S0140-6736(20)31189-2.
[27] Alehagen U, Alexander J, Aaseth J, Larsson A. Decrease in inflammatory biomarker concentration by intervention with selenium and coenzyme Q10: a subanalysis of osteopontin, osteoprotergerin, TNFr1, TNFr2 and TWEAK. J Inflamm 2019. https://doi.org/10.1186/s12950-019-0210-6.
[28] Avery JC, Hoffmann PR. Selenium, selenoproteins, and immunity. Nutrients 2018. https://doi.org/10.3390/nu10091203.
[29] Wu C, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020. https://doi.org/10.1001/jamainternmed.2020.0994.
[30] Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol 2020. https://doi.org/10.1038/s41577-020-0311-8.
[31] Iba T, et al. The unique characteristics of COVID-19 coagulopathy. Crit Care 2020. https://doi.org/10.1186/s13054-020-03077-0.
[32] Varga Z, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020. https://doi.org/10.1016/S0140-6736(20)30937-5.
[33] Kasinathan G, Sathar J. Haematological manifestations, mechanisms of thrombosis and anti-coagulation in COVID-19 disease: a review. Ann Med Surg 2020;56:173–7.
[34] Hottz ED, et al. Platelet activation and platelet-monocyte aggregates formation trigger tissue factor expression in severe COVID-19 patients. Blood 2020. https://doi.org/10.1182/blood.2020007252.
[35] Wright FL, et al. Fibrinolysis shutdown correlation with thromboembolic events in severe COVID-19 infection. J Am Coll Surg 2020. https://doi.org/10.1016/j.jamcollsurg.2020.05.007.
[36] Suzuki Y, Yasui H, Brzoska T, Mogami H, Urano T. Surface-retained tPA is essential for effective fibrinolysis on vascular endothelial cells. Blood 2011. https://doi.org/10.1182/blood-2011-05-353912.
[37] Escher R, Breakey N, Lämmle B. Severe COVID-19 infection associated with endothelial activation. Thromb Res 2020. https://doi.org/10.1016/j.thromres.2020.04.014.
[38] Conway EM, Pryzdial ELG. Is the COVID-19 thrombotic catastrophe complement-connected? J Thromb Haemost 2020. https://doi.org/10.1111/jth.15050.
[39] Zuo Y, et al. Neutrophil extracellular traps in COVID-19. JCI Insight 2020. https://doi.org/10.1172/jci.insight.138999.
[40] Lopes Junior E, Leite HP, Konstantyner T. Selenium and selenoproteins: from endothelial cytoprotection to clinical outcomes. Transl Res 2019. https://doi.org/10.1016/j.trsl.2019.01.004.
[41] McCarty MF. Oxidants downstream from superoxide inhibit nitric oxide production by vascular endothelium – a key role for selenium-dependent enzymes in vascular health. Med Hypotheses 1999. https://doi.org/10.1054/mehy.1997.0762.
[42] Violi F, Pignatelli P. Platelet oxidative stress and thrombosis. Thromb Res 2012. https://doi.org/10.1016/j.thromres.2011.12.002.
[43] Ricetti MM, et al. Selenium enhances glutathione peroxidase activity and prostacyclin release in cultured human endothelial cells: concurrent effects on mRNA levels. Biol Trace Elem Res 1994. https://doi.org/10.1007/BF02790072.
[44] Chan YH, et al. Adverse systemic arterial function in patients with selenium deficiency. J Nutr Health Aging 2012. https://doi.org/10.1007/s12603-011-0086-5.
[45] Ricetti MM, et al. Effects of sodium selenite on in vitro interactions between platelets and endothelial cells. Int J Clin Lab Res 1999. https://doi.org/10.1007/s005990050068.
[46] Manne BK, et al. Platelet gene expression and function in COVID-19 patients. Blood 2020. https://doi.org/10.1182/blood.2020007214.
[47] Braunwald E, et al. The problem of persistent platelet activation in acute coronary syndromes and following percutaneous coronary intervention. Clin Cardiol 2008. https://doi.org/10.1002/clc.20363.
[48] Järemo P, Eriksson M, Lindahl TL, Nilsson S, Milovanovic M. Platelets and acute cerebral infarction. Platelets 2013. https://doi.org/10.3109/09537104.2012.712168.
[49] Ranucci M, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J Thromb Haemost 2020. https://doi.org/10.1111/jth.14854.
[50] Komosa A, et al. Platelets redox balance assessment: current evidence and methodological considerations. Vasc Pharmacol 2017. https://doi.org/10.1016/j.vph.2017.06.002.
[51] Shamova EV, et al. Redox regulation of morphology, cell stiVness, and lectin-induced aggregation of human platelets. Eur Biophys J 2011. https://doi.org/10.1007/s00249-010-0639-2.
[52] Perona G, Schiavon R, Guidi GC, Veneri D, Minuz P. Selenium dependent glutathione peroxidase: a physiological regulatory system for platelet function. Thromb Haemost 1990. https://doi.org/10.1055/s-0038-1647308.
[53] Meydani M. Modulation of the platelet thromboxane A2 and aortic prostacyclin synthesis by dietary selenium and vitamin E. Biol Trace Elem Res 1992. https://doi.org/10.1007/BF02783995.
[54] Zbikowska HM, Wachowicz B, Krajewski T. Comparative effects of selenite and selenite on the glutathione-related enzymes activity in pig blood platelets. Biol Trace Elem Res 1997. https://doi.org/10.1007/BF02785294.
[55] Guidi G, Schiavon R, Biasioli G, Perona G. The enzyme glutathione peroxidase in arachidonic acid metabolism of human platelets. J. Lab. Clin. Med. 1984.
[56] Smeda M, Chlopicki S. Endothelial barrier integrity in COVID-19-dependent hyperinflammation: does the protective facet of platelet function matter? Cardiovasc Res 2020. https://doi.org/10.1093/cvr/cvaa190.