Vitamin K and SARS-CoV-2

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Prevalent coagulopathy and thromboembolism are observed in severe COVID-19 patients with 40% of COVID-19 mortality being associated with cardiovascular complications. Abnormal coagulation parameters are related to poor prognosis in COVID-19 patients. Victims also displayed presence of extensive thrombosis in infected lungs. Vitamin K is well-known to play an essential role in the coagulation system. Latest study revealed an existing correlation between vitamin K deficiency and COVID-19 severity, highlighting a role of vitamin K, probably via coagulation modulation.

Keywords: COVID-19 ; SARS-CoV-2 ; thromboembolism ; vascular disease ; vitamin K

1. Introduction

Since its emergence in December 2019 in Wuhan, China, the novel coronavirus known as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and responsible for the disease Coronavirus disease 19 (COVID-19), has infected over 100,000,000 people and killed over 2,000,000 worldwide according to the World Health Organization [1]. Interestingly, despite intense research, the critical mechanisms underlying the patient morbidity and mortality remain largely obscure. One of the predominant theories favors the concept of a “cytokine storm” in which the immune response is exacerbated through the induction of an excessive pro-inflammatory cytokine response driving lung injury [2]. It was reported that presence of a high viral load causes massive destruction of lung tissues, in turn leading to hyperinflammation causing acute respiratory distress syndrome (ARDS) [3]. In addition to respiratory symptoms, a growing body of evidence also shows that the virus can specifically infects endothelial cells affecting thus the normal process of coagulation [4]. Severe COVID-19 patients were found to possess coagulopathy characterized by abnormal coagulation parameters [4][5] widespread presence of blood clots [6] as well as arterial and venous thromboembolism [7][8]. Furthermore, preliminary data from several studies seem to indicate that anticoagulant therapy is associated with lower mortality in COVID-19 patients [9]. Vitamin K is an essential component preventing blood clotting and a major player of the coagulation system of which a link between vitamin K deficiency and the worst COVID-19 outcomes was recently revealed [10].

2. Respiratory Illness Associated with COVID-19

It is well established that SARS-CoV-2 virus affects primarily the respiratory system with infection being both asymptomatic and symptomatic. Mechanistically, SARS-CoV-2 infection involves the binding to its functional receptor the Angiotensin converting enzyme 2 (ACE2) [11][12]. ACE2 is known to be highly expressed on lung epithelial cells as well as on endothelial cells [13]. As far as we know, clinical presentations of mild COVID-19 infection are wide-ranging and not much distinct from upper respiratory tract infections caused by various respiratory viruses such as influenza A virus (IAV) [14][15]. Fever, cough, myalgia and headache are commonly reported symptoms in COVID-19 patients.

COVID-19 respiratory symptoms are heterogeneous and may sometimes lead to serious complications. Similar to other severe respiratory diseases, severe forms of COVID-19 induce pneumonia, acute lung injury (ALI), ARDS and sepsis leading to multiple organ failure and death [16]. Studies have shown that the respiratory symptoms can worsen with development of ARDS occurring as fast as 9 days post onset [14]. Damage to the lungs characterized by a pulmonary ground glass opacification was observed by computed tomography (CT) scan in even asymptomatic cases indicating that the plethora of complications arising from COVID-19 is still far from being fully understood [17].

Cytokine storm is considered to be one of the major causes of ARDS and multiple-organ failure [18] and plays a crucial role in the process of disease aggravation [19]. The cytokine storm is the result of an exacerbated immune response resulting in the excessive production of pro-inflammatory cytokines. Whilst it is revealed that SARS-CoV-2 infection could alter both the innate and adaptive immunity [20][21], respiratory epithelial cells and myeloid cells are thought to play an important role in orchestrating innate immunity in the airway [22]. Infiltration of a large number of inflammatory immune

cells is observed in the lungs from severe COVID-19 patients [23] with majority being macrophages and neutrophils [24]. Such increase in infiltration and accumulation of immune cells (macrophages, neutrophils) enhance the probability of rupture of atherosclerotic plaques potentially leading to cardiovascular complications.

Lung infiltration of macrophages has been reported in COVID-19 infection [25]. Pro-inflammatory cytokines such as IL-6 [26], IL-1 [27] and TNF [28] are thought to be produced by macrophages, reported to be hyper-induced during SARS-CoV-2 infection and are found to be positively correlated with disease severity relating to cytokine storms [29][30].

Neutrophils are the most abundant leukocytes in circulating blood which are responsible for the formation of the neutrophil extracellular trap (NET) [31]. Neutrophil elastase is a component of NET and is capable of the degradation of elastin within the pulmonary extracellular matrix which leads to the loss of elastic recoil of the lung and thus impairs normal lung function [32]. Interestingly, markers specific for NET formation are found to be elevated in COVID-19 patients and are up-regulated to a larger extent in patients who required mechanical ventilation when compared to patients with mild symptoms [33]. Moreover, elastin fragments are chemotactic to macrophages which are major drivers of the ongoing inflammation [32]. Furthermore, the macrophages secrete MMP proteins 8 and 9 which degrade COL1A1 resulting in formation of collagen-derived peptide Pro-Gly-Pro that can act as chemoattractant for neutrophils [32]. On the other hand, repairment of the ECM is driven by transforming growth factor (TGF)-β among other mediators [32]. Stored TGF-β in neutrophils could be activated by local elastase and contributes to the induction of pulmonary fibrosis through the differentiation of fibroblasts to myofibroblasts [34]. Therefore, by limiting viral infection through the generation of reactive oxygen species, by trapping the pathogen in the NET, and at the same time inducing pulmonary immunopathology and pulmonary fibrosis, neutrophils can act as double-edged sword in lung injuries.

3. Coagulopathy and COVID-19

A growing body of evidence suggests coagulopathy as a potential complication of COVID-19 resulting in higher risk of developing venous and arterial thromboembolism [7]. Indeed, patients with severe COVID-19 present with abnormal coagulation parameters which are associated with poor disease prognosis [35]. Likewise, COVID-19 patients present with higher than normal levels of fibrinogen [35], resulting from a high level of IL-6 in the serum. IL-6 is known to stimulate the production of fibrinogen by hepatocytes [36]. In addition, plasma levels of the procoagulation protein, von Willebrand factor is also increased in COVID-19 patients [5]. Levels of D-dimer and fibrin degradation product, which can reflect the occurrence of thrombosis and is associated with a diagnosis of disseminated intravascular coagulation (DIC), are found to be significantly enhanced in severe COVID-19 cases [35]. Although, the prevalence of DIC in COVID-19 is still in debate [4][35], pulmonary microthrombi formation is clearly observed in COVID-19 [37][38].

Pulmonary embolism, strokes and heart attacks can be a direct consequence of thrombosis. Indeed, pulmonary embolism is observed in 50% of COVID-19 patients admitted to ICU [39]. Adequate oxygenation and ventilation are recommended for COVID-19 patients with ARDS [40]; however, the development of pulmonary embolism may limit their usefulness by obstructing the circulation of oxygenated blood. Altogether, tackling thrombotic complications observed in COVID-19 patients need urgent investigation.

Autopsies of COVID-19 victims reveal a widespread presence of blood clots in infected lungs suggesting the involvement of pulmonary vascular endothelial cells in lung inflammation and coagulation [41]. Studies demonstrate that SARS-CoV-2 can infect endothelial cells, cells which represent one third of the total cells in lungs [42] and hence can contribute directly to thrombosis via endothelial cell lysis. Damage to the endothelial wall exposes the subendothelial collagen that is involved in platelet adhesion, activation and ultimately coagulation [43]. Secretion of factors involved in coagulation by the endothelial cells is also altered [44].

The idea of using anticoagulant therapy in COVID-19 patients to lower the mortality is well established [9]. In fact, the coagulation process is a balance between procoagulation and anticoagulation factors that require a strict control. Dysregulation towards either ends could lead to thrombophilia or coagulopathy. Protein C and protein S are among the key players in this process [45]. Interestingly, a low protein C activity is found in severe and aged COVID-19 patients favoring a hypercoagulability state [46].

Taken together, SARS-CoV-2 should not be regarded as an ordinary respiratory virus solely, but a virus which may possess a much broader tropism and could induce systemic symptoms and complications. Understanding the different disease mechanisms caused by infection will be vital in drug discovery for COVID-19 treatment.

4. Vitamin K

Vitamin K was first discovered by Henrik Dam in the early 1930s. This lipid soluble factor was first isolated for its “antihemorrhagic” properties [47][48][49]. Because of its requirement for hemostasis, Dam designated this factor as “Koagulations vitamin”, hence vitamin K. A second isoform, named K2, was isolated few years later by Edward Doisy from putrefied fish meals [50]. The importance of the discovery of vitamin K was highlighted when the prophylactic treatment of newborns who presented with vitamin K deficiency was shown to decrease significantly the neonatal mortality and thus was awarded a Nobel prize in Physiology or Medicine in 1943 [51]. The existence of vitamin K has been known for over 80 years mainly due to its involvement in coagulation. Subsequent discovery of different isoforms has suggested other potential functions of vitamin K beyond coagulation. Nowadays, vitamin K remains a fundamental bioactive compound used as supplement in optimizing body function.

5. Using Vitamin K to Improve COVID-19 Outcomes

Very little is known concerning the potential benefits of using vitamin K to improve COVID-19 outcomes, however it is clearly established that patients with severe COVID-19, present with prevalent signs of coagulopathy and thromboembolism. Impaired coagulation function has been demonstrated in COVID-19 patients. Findings from several recent studies have further suggested that anticoagulant therapy is beneficial and can lower the mortality in COVID-19 patients. Furthermore, patients with pre-conditions such as diabetes, hypertension and cardiovascular disease which are known to be associated with vitamin K deficiency are prompt to develop a more severe COVID-19 disease. This is particularly evident in patients suffering from chronic kidney disease (CKD), a population characterized by enhanced number of severe COVID-19 cases. These patients suffer from subclinical vitamin K deficiency resulting from its high demand for the activation of VKDPs to inhibit calcification . As a result, CKD patients are shown to present with high levels of non-phosphorylated non-carboxylated MGP, increasing the risk of vascular calcification and development of cardiovascular disease. Vitamin K supplementation of CKD patients was shown to reach target tissues including the vessel wall as well as improve the consequences resulting from vitamin K deficiency. Furthermore, the progression of cardiovascular calcification in healthy adults was significantly reduced when supplemented with daily phylloquinone (0.5 mg) . The CKD population serves as a valuable indicator when addressing potential consequences of poor vitamin K status, a status that represents an aggravating risk factor in COVID-19. Indeed, recently a direct association between low levels of vitamin K and severe cases of COVID-19 was reported. Altogether, this evidence points to the existence of a possible link between vitamin K and COVID-19 as well as highlight the potential benefits of using vitamin K as a supplement.

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