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COMMENTARY

Association of alpha-1-antitrypsin deficiency with vitamin D status: who is most at risk of getting severe COVID-19?

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Abstract

Introduction Coronavirus disease 2019 (COVID-19), a new disease that we do not know yet how to treat, is rapidly evolving and has forced us to stay indoors. Surprisingly, a broad range of symptoms has been reported since COVID-19 emergence. Individual variations in susceptibility to SARS-CoV-2 can be due to non-genetic and genetic factors. Alpha-1-antitrypsin deficiency (AATD) is an inherited condition that is associated with an increased risk of liver and lung diseases which may increase susceptibility to COVID-19 infection. At the same time, there could be a possibility of developing non-hereditary AATD.

Discussion In addition to some evidence showing the role of vitamin D deficiency in COVID-19 pathology, it has been recognized that there is a biological link between AAT and vitamin D. Therefore, here we offer a new perspective that lower vitamin D levels in COVID-19 patients can cause acquired AATD that provide a condition with more disease severity and a higher risk of death. As a consequence, COVID-19 individuals with vitamin D deficiency may have a higher risk of morbidity and mortality.

Conclusion Therefore, early vitamin D and AAT assessments and optimal interventions could be helpful to prevent severe COVID-19 outcomes.

Keywords Coronavirus disease 2019(COVID-19) · Alpha-1-antitrypsin deficiency · Vitamin D

Abbreviations

COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
AATD	Alpha-1-antitrypsin deficiency
AAT	Alpha-1-antitrypsin
TMPRSS2	Transmembrane serine protease 2
ADAM17	A disintegrin and metalloproteinase-17
ACE2	Angiotensin-converting enzyme 2
RAS	Renin–angiotensin–aldosterone system
1, 25(OH)2D3	*1,25-Dihydroxy-vitamin D3*
IL-10	Interleukin 10
ARDS	Acute respiratory distress syndrome
25(OH)VD	25-Hydroxy-vitamin D
COPD	Chronic obstructive pulmonary disease

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Introduction

In December 2019, coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared in China and led to a rapidly progressing pandemic. Following that, communications were declined and people were quarantined in their homes. Strangely and sadly enough, responses and reactions to COVID-19 appear to be widely different, ranging from asymptomatic or mild to severe conditions and death, among different people and regions. Non-genetic factors, including age, comorbid conditions such as cancer and cardiovascular disorders, and environmental risk factors like air pollution, may confer differential susceptibility to SARS-CoV-2 infection. Similarly, host genetic factors can influence the severity of the disease. Therefore, understanding the non-genetic/

genetic effects on host immune function may help identify why some COVID-19 cases display severe disease, while others experience mild to no symptoms? [1–3].

The effect of alpha-1-antitrypsin deficiency on covid-19 infection

Among genetic factors, one candidate gene might be *SERPINA1* which encodes the alpha-1-antitrypsin (AAT) protein. AAT is an acute-phase protein that is mainly produced by liver cells and subsequently secreted into the plasma but is also secreted to a lesser extent by monocytes, macrophages, pulmonary alveolar cells, and intestinal epithelium [4]. In addition to its anti-proteinase function and inhibition of neutrophil proteinases including neutrophil elastase, cathepsin G, and proteinase 3; AAT has several known non-proteinase effects including anti-inflammatory and immunomodulatory characteristics and antimicrobial/antiviral properties [5, 6]. Hereditary AATD is characterized by decreased serum level or abnormal AAT functions and is also associated with an increased risk of liver and lung diseases [7] which may increase susceptibility to COVID-19 infection. Considering the information provided, the article by Shapira et al. reported that frequencies of AATD alleles were positively correlated with the COVID-19 fatality rate [8]. Moreover, since the Lombardia region in Italy with 37.8% of COVID-19 casualties, also had 47% of all AATD cases, Vianello and Braccioni suggested that AATD may explain the high mortality rate of COVID-19 [7]. Notably, these findings could be due to the fact that TMPRSS2 (transmembrane serine protease 2) which promotes COVID-19 cell entry, cannot be suppressed by AAT in AATD patients. Besides, AAT improves inflammatory conditions by reducing ADAM17 (a disintegrin and metalloproteinase-17) activity which is responsible for the breakdown of ACE2 (angiotensin-converting enzyme 2) and the imbalance of the renin–angiotensin–aldosterone system (RAS) [7, 9].

Remarkably, Ray et al. demonstrated that while any underlying genetic reason for the observed AATD had been ruled out in their tropical pulmonary eosinophilia subjects, acquired AATD existed as a result of the chronic inflammation and oxidative stress. Ray et al., also, had ruled out the possibility of any intestinal AAT loss in their worm-infested pulmonary eosinophilia subjects [10]. Accordingly, it could be possible to assume non-hereditary AATD development in COVID-19 patients. Thus, in the following section, this article will dive into a way that how AATD acquisition can be developed by COVID-19 patients?

The link between vitamin D status and alpha-1-antitrypsin levels

AATD and vitamin D deficiency are tightly linked to inflammation and autoimmunity [11, 12]. Both AAT and vitamin D have strong immune-modulating roles in the airways environment [13]. A study by Dimeloe et al. reported that vitamin D active form (1,25(OH)2D3) causes CD4 + T cells to secrete AAT, and AAT, via direct interaction with complement C3a, promotes IL-10 (interleukin 10) secretion; meaning that AAT is essential for 1,25(OH)2D3 to induce IL-10. Dimeloe et al., also, stated that 1,25(OH)2D3 failed to enhance IL-10 transcription in CD4 + T cells from hereditary AATD individuals (PiZZ) compared to the healthy subjects [13]. This implies that 1,25(OH)2D3 is a key upstream regulator in this anti-inflammatory axis in CD4 + T cells.

At the same time, Lindley et al.'s study on type 2 diabetic patients showed that low circulating levels of AAT were positively associated with lower 25(OH)VD levels, suggesting that 25(OH)VD deficiency may predispose type 2 diabetic patients to AATD which may cause a higher incidence of COPD (chronic obstructive pulmonary disease) in diabetes [14]. Moreover, Crane-Godreau et al.'s study on mice exposed to cigarette smoke reported that vitamin D deficiency causes a significantly lower AAT expression in the lungs and emphysema [15].

In the meantime, vitamin D and COVID-19, both, have the same target which is RAS and the immune system. Luckily, vitamin D regulates the RAS and avoids bradykinin accumulation, and has a strong protective effect against acute lung injury and acute respiratory distress syndrome (ARDS). Conversely, COVID-19 kills through bradykinin storm, along with the cytokine storm. It is a well-known fact that vitamin D decreases remarkably in severely ill patients with COVID-19 [16–18]. Several studies have reported the possible link between vitamin D concentrations and COVID-19 severity and fatality [19–22]. However, not much is known about the potential role of vitamin D in preventing and treating COVID-19 infection. Yet, here we suggested that vitamin D deficient COVID-19 individuals may acquire AATD, and that is what makes the illness more severe once the patients are infected.

Conclusion

In conclusion, lower vitamin D levels in COVID-19 patients may cause acquired AATD that provides a condition with more disease severity and a higher risk of death. Further investigations are required to demonstrate

the association between AAT levels and vitamin D status. Notably, vitamin D and AAT assessments would be essential to detect deficient persons and optimal interventions could be helpful to prevent severe COVID-19 outcomes.

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Declarations

Conflict of interest The authors have no conflict of interest to declare that are relevant to the content of this article.

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