Asian Journal of Biomedical and Pharmaceutical Sciences *ISSN 2249-622X*

Potential mechanisms for vitamin D protective effect for COVID-19 morbidity and mortality.

Petre Cristian Ilie[1*], Simina Stefanescu[2], Lee Smith[3]

[1]Research and Innovation Department, The Queen Elizabeth Hospital Foundation Trust, King's Lynn, UK

[2]The University of East Anglia, Norfolk, UK

[3]The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge, UK

Abstract

Ilie et al. have described a correlation between the mean levels of vitamin D with the number of cases of COVID-19 and the mortality per million caused by this disease in several European countries. Other studies have subsequently reported similar findings. The present short commentary aims to discuss the potential mechanisms behind the potential vitamin D protective role for COVID-19.

Keywords: COVID-19, SARS-Cov2, Vitamin D, 1,25-dihydroxycholecalciferol, Calcitriol.

Accepted on June 15, 2020

The Mechanism

In a previous paper, we described a correlation between mean levels of vitamin D and the number of cases of COVID-19 and the mortality per million caused by this disease in several European countries [1]. Other studies have subsequently reported similar findings. The present short commentary aims to discuss the potential mechanisms behind the vitamin D protective role for COVID-19.

The main role of vitamin D is in calcium and bone homeostasis. Besides this well-known activity, 1,25-dihydroxycholecalciferol, the active form of vitamin D, also has a role in regulating the renin-angiotensin system which is important in sepsis, during which it gets activated. 1,25-dihydroxycholecalciferol suppresses endothelial cell-dependent vasodilation and this can have a protective effect on the blood pressure [2]. In the pathogeny of COVID-19, ACE2 has an important role, as the receptor for the virus. To enter the cell, SARS-CoV2 interacts and traps inside the infected cells multiple ACE2 receptors which leads to a reduction in the ACE2 levels. Vitamin D can increase the levels of ACE2, and previous studies have shown that in the lung, ACE2 protects against acute lung injury in several animal models of acute respiratory distress syndrome [3]. Furthermore, the ACE2 receptors are also present in the arterial and venous endothelial cells and arterial smooth muscle cells [4]. This can explain the severe manifestations at the vascular level especially in some children [5]. Another important supportive role for vitamin D that can improve the outcome is an anticoagulant effect [2]. Coagulation was one of the important complications associated with COVID-19 and the anticoagulant effect of vitamin D may offer some protection. Although data concerning the relationship between vitamin D and thrombosis are scarce, there is some evidence of low 25(OH)D levels associated with venous thromboembolism. In COVID-19 pathogeny, macrophage plays an important role in protection as well as potential augmentation of the normal processes that may lead to increased response and cytokine storm. Vitamin D can modulate the role of macrophage as well as the cytokine generation [2].

Another important role in improving the outcome of patients with COVID-19 is by reducing the levels of prostaglandins by repressing the expression of cyclooxygenase-2 and upregulation the expression of 15-hydroxyprostaglandin dehydrogenase, an enzyme important for prostaglandin catabolism [6,7]. Unregulated inflammation can lead to a cytokine storm. Through the NF-κB-mediated pathway, 1,25-dihydroxycholecalciferol also inhibits the expression of IL-6 and IL-8, as well as regulated on activation, normal T cell expressed, and secreted (RANTES) [8-12]. In cases of severe compared with uncomplicated SARS-CoV infected patients, higher levels of serum proinflammatory cytokines (IFN-γ, IL-1, IL-6, IL-12, and TGFβ) and chemokines (CCL2, CXCL10, CXCL9, and IL-8) were detected, including IL-6 and IL-8 [13].

The role of vitamin D in reducing inflammation was described in studies where Toll Like Receptors' expression downregulation and a corresponding decrease of pro-inflammatory cytokine production was observed after vitamin D supplementation. The same changes were described ex vivo, after the exposition of peripheral blood mononuclear cells to vitamin D. These findings have potentially significant implications for the treatment of a variety of conditions, where achieving optimal vitamin D levels may help reduce inflammation [14,15].

Another interesting observation is that of prolonged QTc duration and QTc dispersion in patients with type 2 diabetes, especially those with 25-OHD deficiency [16]. As we know patients affected by COVID-19 are at an increased risk of developing prolonged QTc interval especially if treated with Hydroxychloroquine and or Azithromycin [17].

Conclusion

Starting from known effects of vitamin D in the body, we have described pathways that we consider relevant for the protective effects of vitamin D in patients with COVID-19.

References

1. Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clin Exp Res. 2020; 1 - 4.
2. Targher G, Pichiri I, Lippi G. Vitamin D, thrombosis, and hemostasis: More than skin deep. Semin. Thromb. Hemost. 2012; 38: 114–24
3. KeijiKuba, Yumiko Imai, Josef M Penninger. Angiotensin-converting enzyme 2 in lung diseases. Curr Opin Pharmacol. 2006: 6: 271-76.
4. Hamming I, Timens W, Bulthuis ML, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004; 203: 631 - 37.
5. Bertoncelli D, Guidarini M, Della Greca A, et al. COVID19: potential cardiovascular issues in pediatric patients. Acta Biomed. 2020; 91:177 - 83.
6. Krishnan AV, Feldman D. Molecular pathways mediating the anti-inflammatory effects of calcitriol: Implications for prostate cancer chemoprevention and treatment. EndocrRelat Cancer. 2010; 17: R19–R38.
7. Chenevard R. Selective COX-2 inhibition improves endothelial function in coronary artery disease. Circulation. 2003; 107:405–409.
8. Equils O, Naiki Y, Shapiro AM, et al. 1,25-Dihydroxyvitamin D inhibits lipopolysaccharide-induced immune activation in human endothelial cells. Clin Exp Immunol. 2006; 143: 58–64.
9. Martinesi M, Bruni S, Stio M, et al. 1,25-Dihydroxyvitamin D3 inhibits tumor necrosis factor-alpha-induced adhesion molecule expression in endothelial cells. Cell Biol Int. 2006; 30: 365–75.
10. Collins T, Read MA, Neish AS, et al. Transcriptional regulation of endothelial cell adhesion molecules: NF-κ B and cytokine-inducible enhancers. FASEB J Off Publ Fed Am SocExp Biol. 1995; 9: 899–09.
11. Talmor Y, Bernheim J, Klein O, et al. Calcitriol blunts pro-atherosclerotic parameters through NF-κB and p38 in vitro. Eur J ClinInvestig. 2008; 38: 548–54.
12. Stach K, Kälsch AI, Nguyen XD, et al. 1α,25-Dihydroxyvitamin D3 Attenuates Platelet Activation and the Expression of VCAM-1 and MT1-MMP in Human Endothelial Cells. Cardiol. 2011; 118: 107–15.
13. Chien JY, Hsueh PR, Cheng WC, et al. Temporal changes in cytokine/chemokine profiles and pulmonary involvement in severe acute respiratory syndrome. Respirol. 2006; 11:715-722.
14. Alvarez Rodriguez L, Lopez Hoyos M, Garcia Unzueta M, et al. Age and low levels of circulating vitamin D are associated with impaired innate immune function. J Leukoc Biol. 2012; 91: 829–38.
15. Ojaimi S, Skinner NA, Strauss BJ, et al. Vitamin D deficiency impacts on expression of toll-like receptor-2 and cytokine profile: A pilot study. J Transl Med. 2013;11: 176.
16. Yetkin DO, Kucukkaya B, Turhan M, et al. The effect of 25-hydroxyvitamin D levels on QT interval duration and dispersion in type 2 diabetic patients. Croat Med J. 2015; 56:525 - 30.
17. Chorin E, Wadhwani L, Magnani S, et al. QT interval prolongation and torsade de pointes in patients with COVID-19 treated with Hydroxychloroquine/ Azithromycin. Heart Rhythm. 2020; 20: 1547-5271.

*Correspondence to

Petre CristianIlie

Research and Innovation Department

The Queen Elizabeth Hospital Foundation Trust

King's Lynn, UK

E-mail: dr.cristianilie@gmail.com