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Vitamin D Clinical Pharmacology: Relevance to COVID-19 Pathogenesis

Paige-Ashley Campbell, B.S., Mimi Wu Young, M.D., Raphael C. Lee, M.S.(BmE), M.D., Sc.D.

Author affiliations: Paige-Ashley Campbell, Pritzker School of Medicine, University of Chicago, Chicago, IL; Mimi Wu Young, Department of Surgery, University of Chicago, Chicago, IL; Raphael C. Lee, Departments of Surgery, Medicine, and Organismal Biology, University of Chicago, Chicago, IL

At this point in Chicago's COVID-19 epidemic, approximately 48.7% of the COVID-19 fatalities are African American and 26.2% are Latinx, despite less than 31% of the city's population being either African American or Latin American. The novel SARS-CoV-2 virus causes the highly lethal COVID-19 infection, especially in minority populations. Explanations for the ethnic differences in disease incidence have mostly focused on the consequences of socio-economic status, nutrition, as well as healthcare access disparities, which are important and correctable causes. However, another ethnically variable factor is the amount of Vitamin D3 (VD3) production by the skin in response to UVB absorption in the epidermis.[2,3]

People of color have higher melanin content in their skin and a fundamental role of melanin is regulation of sunlight catalyzed VD3 production.[2] It is well established that at higher latitudes, the average population serum levels of VD3 are lower in people with higher melanin content in their skin.[3] A study by Matsouka et al.[3] documented substantial ethnic differences in sunlight catalyzed VD3 production between black and white Americans after a fixed amount (27 mJ/cm^2) of UVB exposure. More sunlight was required in black patients to achieve normal serum levels of VD3. Indeed, melanin content in the skin was found to be a paramount regulating factor of sunlight catalyzed VD3 production.

The possible link between VD3 deficiency and SARS-CoV-2 vulnerability has recently received international attention by the public news media as well as multiple medical journals.[4,5] Is it possible that VD3 is a risk determining factor for COVID-19 associated inflammatory syndrome? The purpose of this communication is to illustrate plausible molecular pathways in which VD3 regulates cellular biological processes involved in both SARS-CoV-2 replication and cell survival.

The SARS-CoV-2 virus contains proteins in its capsid that are partially hydrophobic. When it enters susceptible eukaryotic cells, the viral proteins trigger a cellular stress response known as the Unfolded Protein Response (UPR) that is more commonly observed when native cellular proteins are not folded properly.[6,7] Proteins expose hydrophobic peptide sequences that are normally shielded from the intracellular water when they are denatured or not properly folded. When hydrophobic protein segments are exposed in the protein-dense cytoplasm, cellular metabolic processes are impeded. This triggers the well-known metabolic stress response that occurs after cell injury or common disease states, which acts to remove unfolded proteins and preserve cell viability.[8]

The UPR activates the NF-κB pathway,[9] which enhances the expression of many inflammatory gene promoters involved in the systemic inflammatory response associated with COVID-19. The initial step is phosphorylation of the inhibitory molecule, IκBα.[10,11] The ubiquitously expressed master immune response transcription factor, NF-κB, is fundamental to eukaryotic cell defense and activates hundreds of genes that encode for the inflammatory response (Figure 1). NF-κB activation promotes viral RNA replication and systemic inflammation.[12] This process results in more hydrophobic proteins within the cellular organelles, leading to more lethal endoplasmic reticulum and mitochondrial cell death sequence activation.[13,14] This signaling dynamic is a common strategy of respiratory viruses[6] and is similar to the manner in which other highly fatal coronaviruses, such as MERS and SARS-CoV (ie SARS), are known to take control of the NF-κB pathway.[15] It is postulated that this results from multiple catalytic interactions that occur between the viral nucleocapsid proteins and NF-κB mediated immunomodulation (Figure 1).[16,17]

VD3 is an inhibitor of NF-kB activation and is known to inhibit the production of the proinflammatory cytokine TNFα, interleukins, and other key activators of the cellular

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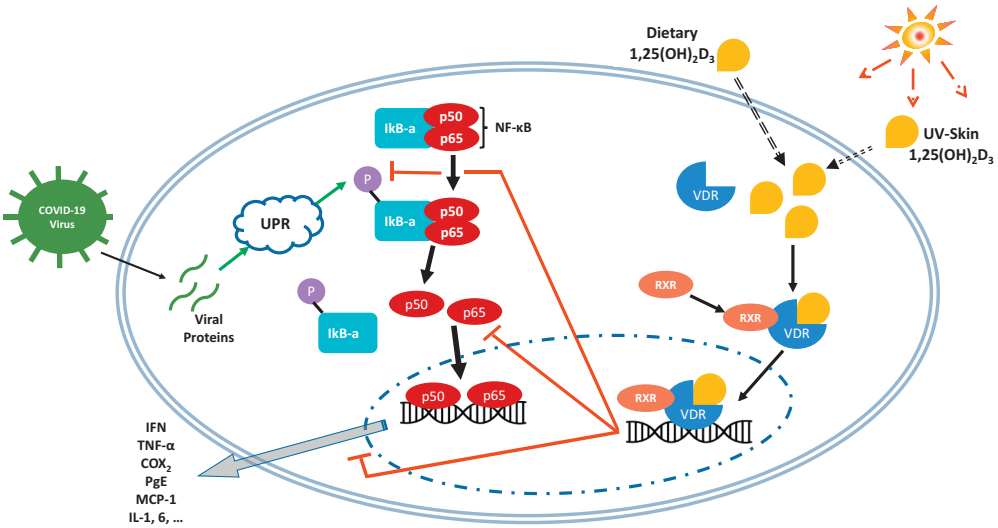
Figure 1. Potential VD3 interactions with COVID-19 Inflammatory Signaling: SARS-CoV-2 viral hydrophobic proteins cause an unfolded protein response (UPR) in organelles, leading to activation of the NF-κB pathway through phosphorylation mediated detachment of IκBα. NF-κB gene promoters translocate into the nucleus and upregulate expression of many inflammatory cytokines (partial list, bottom left). The VD3 + VDR (vitamin D receptor) + retinoid X receptor (RXR) complex activate genes that inhibit NF-κB activation. The RXR receptor is a steroid family nuclear receptor. Based on its pharmacology, VD3 should down-regulate COVID inflammation.



immune defense as illustrated in Figure 1.[18] Furthermore, VD3 promotes shifting of mammalian cellular immunity towards an anti-inflammatory phentype.[19] Several clinical investigation reports indicate that VD3 deficiency is associated with a greater risk of having an upper respiratory infection as well as increased severity once infected.[20–22] This association is stronger when there are clinical manifestations of chronic VD3 deficiency, such as asthma and COPD.[22] The therapeutic benefit of VD3 on respiratory viral infections appears to be most pronounced with VD3 deficient individuals.[23] In the case of respiratory syncytial virus, VD3 increases synthesis of the NF-κB inhibitor, IκBα, in airway epithelium, resulting in decreased expression of pro-inflammatory genes. This response was found to be specific to VD3, because when the vitamin D receptor (VDR) was silenced using siRNA, no decreased expression of pro-inflammatory genes was then observed.[24] Additionally, single nucleotide polymorphisms in the VDR are known to be associated with more severe outcomes of respiratory syncytial virus.[25]

Regarding the ongoing COVID-19 pandemic, epidemiological reports indicate that African Americans and Latin Americans manifest both increased incidence of the COVID-19 disease and related mortality.[1–3] Given the central role of NF-κB signaling in COVID-19 pathogenesis and the inhibitory effect of VD3 on NF-κB mediated inflammatory pathways, it is very plausible that VD3 deficiency is linked to the clinical severity of COVID-19. In fact, a recent large clinical study that included over four thousand COVID-19 positive patients, found that vitamin D deficiency was associated with almost double the risk of contracting COVID-19 disease.[26] This report also concluded that testing positive for COVID-19 was associated with (1) increasing age and (2) being both non-white race and likely vitamin D deficent.[26]

The proper dose of VD3 to convey partial protection from the SARS-CoV-2 viral infection outcomes is unknown and is undergoing investigation. Important considerations regarding dose are that circulating serumVD3 levels are tightly controlled by the skin, liver, and kidney.[27] The serum level of VD3 is a lagging indicator of total body VD3 status as the tissue backup stores are depleted before serum VD3 levels drop below normal.[28] Further research regarding the appropriate loading dose for VD3 deficient patients in the acute setting to improve COVID-19 outcomes is underway.[29,30] However there is a general understanding that restoring tissue levels to normal takes more time and prolonged application.[31,32]

In summary, although there are substantial structural and healthcare inequities that contribute to increased COVID-19 disease incidence and mortality in the African American and Latin American populations in the United States, VD3 deficiency is likely a significant factor as well. From what is known about its physiology, it is no surprise that VD3 modulates severity of the COVID-19 infection. Stay-at-home orders could further reduce VD3 tissue levels if not prevented by oral VD3 supplementation. Given the fact that VD3 deficiency is neither difficult nor

expensive to prevent, it should not be a significant factor impacting outcomes associated with COVID-19 infection if appropriately addressed.

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