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VITAMIN D AND COVID 19: A WAY FORWARD

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ABSTRACT

The severity of coronavirus 2019 infection (COVID-19) is determined by the presence of pneumonia, severe acute respiratory distress syndrome (SARS-CoV-2), myocarditis, microvascular thrombosis and/or cytokine storms, all of which involve underlying inflammation. A principal defence against uncontrolled inflammation, and against viral infection in general, is provided by T regulatory lymphocytes (Tregs). Treg levels have been reported to be low in many COVID-19 patients and can be increased by vitamin D supplementation. Low vitamin D levels have been associated with an increase in inflammatory cytokines and a significantly increased risk of pneumonia and viral upper respiratory tract infections. Vitamin D deficiency is associated with an increase in thrombotic episodes, which are frequently observed in COVID-19. Vitamin D deficiency has been found to occur more frequently in patients with obesity and diabetes. These conditions are reported to carry a higher mortality in COVID-19. If vitamin D does in fact reduce the severity of COVID-19 in regard to pneumonia/ARDS, inflammation, inflammatory cytokines and thrombosis, it is our opinion that supplements would offer a relatively easy option to decrease the impact of the pandemic.

KEYTERMS: Vitamin D, COVID 19, Immunity.

BACKGROUND

In COVID-19 patients the severity of the illness is frequently determined by the presence of pneumonia/acute respiratory distress syndrome (ARDS), myocarditis, microvascular thrombosis and/or cytokine storm, all of which involve underlying inflammation. While the COVID-19-specific CD8 T cells and the specific antibodies produced by B cells are critical for eliminating the virus, uncontrolled non-specific inflammation and cytokine release can cause catastrophic injury to the lungs and other vital organs. Consequently, decreasing this early non-specific inflammation during COVID-19 may provide time for the development of specific acquired immunity against COVID-19.

Mechanism

A principal defence against uncontrolled inflammation, and against viral infection in general, is provided by T regulatory lymphocytes (Tregs). Treg levels have been reported to be low in one group of COVID-19 patients, and 'markedly lower in severe cases'.[1] In a study of older nursing home patients, high Treg blood levels were found to be associated with a reduced level of respiratory viral disease.[2] These observations suggest that if Treg levels can be increased, this might be of benefit in diminishing the severity of viral disease and perhaps of COVID-19.

Treg levels can be increased by vitamin D supplementation.[3,4] The importance of vitamin D in cases of respiratory infection is illustrated by the fact that low vitamin D levels are common in populations worldwide and low levels have been associated with a significantly increased risk of pneumonia[5] and viral upper respiratory tract infections.[6] Vitamin D deficiency (serum 25-hydroxyvitamin D (25(OH)D) <50 nmol/L) is present in 30–60% of the populations of western, southern and eastern Europe and in up to 80% of populations in middle-eastern countries.[7] In addition, even more severe deficiency (serum levels <30 nmol/L) is reported in over 10% of Europeans.

Low levels of vitamin D are also associated with an increase in inflammatory cytokines.

A study of healthy women in the USA found a significant inverse relationship between the serum levels of 25(OH)D and TNF-alpha.[8] In another report, the levels of IL6 were found to be increased in those who were vitamin D deficient. In a wide variety of animal studies and *in vitro* cell models, vitamin D3 has been demonstrated to down regulate the production of inflammatory cytokines, such as TNF-alpha and IL6, while increasing inhibitory cytokines.[9] These studies raise the possibility that adequate levels of vitamin D may reduce the incidence of cytokine storm, which can occur in COVID-19.

Thrombotic complications are common in COVID-19 patients.[10] Of those with severe disease, over half have been found to have elevated D-dimer levels. Interestingly, vitamin D is also involved in the regulation of thrombotic pathways, and vitamin D deficiency is associated with an increase in thrombotic episodes.[11] Vitamin D deficiency has also been found to occur more frequently in patients with obesity and diabetes. These conditions are reported to carry a higher mortality in COVID-19. An increased risk of death with COVID-19 is also observed in black, Asian and minority ethnic (BAME) groups. As melanin reduces the production of vitamin D associated with exposure to the ultraviolet radiation in sunlight, this may help to explain the observed frequent occurrence of vitamin D deficiency in BAME groups.

One recurring question regarding COVID-19 is whether, once a patient has had the infection, they are unlikely to be re-infected at a later date. The answer to that question is still unknown and depends to some extent on the production, longevity and efficacy of the specific antibodies. However, in the case of influenza A virus (IAV), exposure to the virus results in the production of memory regulatory T cells (mTregs), which persist in the host.[12] In mice exposed to influenza A infection, the infusion of mTregs into their tail vein significantly reduces weight loss and lung pathology (particularly the inflammatory infiltrate), relative to the infusion of Tregs that have not previously been exposed to the virus. This study illustrates the potential efficacy of Tregs in combatting viral infection. Given that women have higher levels of Treg cells than men,[13] the observation might provide one reason why women have a lower mortality when infected by COVID-19.

Should we supplement with vitamin D?

Based on these findings, we ask three questions. Do patients hospitalised with severe COVID-19 illness have lower vitamin D and Treg levels than COVID-19 positive patients whose illness is milder and who remain quarantined at home? Does vitamin D supplementation increase Tregs in these patients? Does vitamin D supplementation in the general population (particularly those who are vitamin D deficient) reduce hospitalisation (or days in hospital) when COVID-19 occurs? If vitamin D has beneficial effects against COVID-19, it would follow that the severity of the disease should lessen in the Northern hemisphere as exposure to increasing sunlight on the skin in springtime increases endogenous production of vitamin D through the photolysis of 7-dehydrocholesterol. Our opinion is that if vitamin D does in fact reduce the severity of COVID-19 with regard to pneumonia/ARDS, inflammation, inflammatory cytokines, and thrombosis, then supplements would offer a relatively easy option to decrease the impact of the pandemic.

It is important to recognize that there is a potential for vitamin D toxicity. Consequently, more than the usual daily supplement should only be taken under medical supervision. The efficacy of vitamin D supplements in the prevention of acute respiratory tract infections has best been demonstrated with the chronic intake of low doses, rather than the bolus administration of large doses.[14] This is well illustrated by the failure of a single, large enteral dose to improve the outcomes of vitamin D-deficient patients admitted to the intensive care unit (ICU) with pneumonia, sepsis, shock, or respiratory failure, relative to ICU patients given a placebo.[15]

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