

Vitamin D supplementation in diabetic retinopathy in the era of COVID-19

The outbreak of COVID-19 has generated public health crisis at a global level. The SARS-CoV-2 coronavirus is an enveloped RNA virus. Infection provokes a remarkable range of responses from complete lack of symptoms through to cytokine storm and life-threatening acute respiratory distress syndrome. Mortality from COVID-19 is higher amongst people who are older, male, and obese. All these factors are related with increased prevalence of vitamin D deficiency. Male sex is associated with reduced impact of vitamin D on the immune response.^[1]

Diabetes mellitus is known to be associated with increased risk of infections. Poor glycemic control impairs numerous aspects of the immune response to viral infection and also to the secondary bacterial infection in the lungs. Diabetes does not seem to increase the risk of occurrence of COVID-19, although diabetes is more frequent in patients with severe COVID-19.^[2]

Vitamin D plays a fundamental role in calcium and mineral metabolism. It is needed for the maintenance of normal blood levels of calcium and phosphate that are required for normal mineralization of bone, muscle contraction, nerve conduction, and general cellular function. Vitamin D is also recognized to influence a wide range of fundamental biological functions such as cell differentiation and immunomodulation associating it to variety of clinical disorders such as diabetes, hypertension, autoimmune disorders, and malignancy.^[3] The 25-hydroxyvitamin D (25OHD) is the major circulating metabolite and 1,25-dihydroxy-vitamin D₃ (calcitriol) is the biologically active form. Serum 25OHD is the most reliable indicator of the vitamin D status of an individual. Serum 25OHD levels less than 20 ng/mL is considered as “deficiency” and levels greater than 30 ng/mL is considered as “normal”.

Significant evidence supports a link between vitamin D deficiency and COVID-19 severity. Experimentally, vitamin D causes an upsurge in the ratio of angiotensin-converting enzyme 2 (ACE2) to ACE. This increases angiotensin II hydrolysis and reduces subsequent inflammatory cytokine response to pathogens and lung injury.^[1] A significant negative correlation has been observed between mean vitamin D levels and COVID-19 cases per one million population in European countries. However, the correlation of vitamin D with COVID-19 deaths of these countries was not significant.^[4]

Vitamin D plays an important role in normal insulin secretion in response to glucose.^[5-7] Vitamin D is believed to help improve the body's sensitivity to insulin and thus reduce the risk of insulin resistance, which is often a precursor to type 2 diabetes mellitus. Evidences suggest that, through its effects on the immune system, vitamin D may play a role in the pathogenesis of diabetic retinopathy (DR). Inflammatory cytokines, such as TNF- α , TNF- β , IL-6, and plasminogen activator inhibitor-1 are up regulated in type 2 diabetes mellitus. Vitamin D decreases the production of several pro-inflammatory cytokines, such as IL-2, IL-6, IL-8, IL-12, and TNF- α .^[5] Vitamin D also exerts an anti-inflammatory effect by

reducing the proliferation of helper T-cells, cytotoxic T-cells, and natural killer cells.^[5] Vitamin D deficiency is also associated with vascular endothelial dysfunction in middle-aged and elderly adults. This dysfunction is linked to increased vascular endothelial cell expression of the pro-inflammatory transcription factor and nuclear factor κ B.^[8]

Vitamin D may also contribute to DR via angiogenesis mechanisms. Active metabolite of vitamin D, calcitriol, is a potent inhibitor of retinal neovascularization *in vivo*.^[9] Calcitriol also inhibits retinal endothelial cell capillary morphogenesis *in vitro*.^[9] Moreover, calcitriol downregulates hypoxia-inducible factor-1 (HIF-1) transcriptional activity and HIF-1 target genes, such as vascular endothelial growth factor (VEGF).^[10]

Complications in DR, such as macular edema and neovascularization, are driven by VEGF production.^[11-13] Vitamin D could exert its positive effect via calcitriol mediated VEGF reduction. In my earlier study, deficiency of vitamin D was found to accelerate the severity of retinopathy. Serum vitamin D levels of ≤ 18.6 ng/mL were found to serve as sensitive and specific biomolecular biomarker for proliferative disease, among patients of DR.^[14]

People who are at higher risk of vitamin D deficiency during this global pandemic should consider taking vitamin D supplements to maintain the circulating 25OHD in the optimal levels (75–125 nmol/L). Vitamin D supplementation should be strongly advised for people likely to be deficient.^[1] RDA of 600-800 IU is recommended to maintain adequate levels of vitamin D.^[15] In our country, Indian Council of Medical Research (ICMR) recommends a daily supplement of 400 IU/day of vitamin D for Indians under situations of minimal exposure to sunlight.^[16]

In India, Vitamin D deficiency is widespread. Clinically diagnosed cases symbolize only the tip of the iceberg. Vitamin D deficiency needs to be taken into consideration with due attention and strong action.^[17]

Diabetes is one of the utmost significant comorbidities related to the severity of COVID-19. There is satisfactory indication of a common pathophysiologic and mechanistic link between diabetes and COVID-19 which is more evident in the presence of vitamin D levels below 10 ng/ml.^[18] In the COVID-19 era, lockdown added to the already existing vitamin D deficiency in the vulnerable group of patients with diabetes mellitus. Levels of 25OHD have been found to be lower in COVID-19 cases who have been hospitalized. Also, such patients had a higher prevalence of deficiency of Vitamin D.^[19] In these unprecedented COVID-19 times, patients of DR should be advised vitamin D supplementation after monitoring serum vitamin D levels.

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