

View Point

Recommendations for High Vitamin D Supplementation to help Fight the COVID-19 Pandemic and its Inclusion in National COVID-19 Management Guidelines

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B A C K G R O U N D

Vitamin D is a fat-soluble vitamin, formed in the skin under the action of UVB light and is known as sunshine vitamin with immunomodulatory as well as classical endocrine actions in calcium control. It has a role in both innate and adaptive immune responses. Intracellular synthesis of 1,25(OH)D in immunocytes promotes the production of cathelicidin and human b-defensin-2 which areantimicrobial peptides produced by neutrophils, macrophages, and epithelial cells that facilitate the killing of the pathogenic encapsulated viruses.¹ Vitamin D also plays a role in inhibiting pro-inflammatory cytokines and activating anti-inflammatory cytokines. It provides antiviral immunity by promoting autophagy. Epidemiological studies have shown an association between low vitamin D levels and a variety of respiratory tract infections, both bacterial and viral. Global data correlates severe vitamin D deficiency with COVID-19 due to similar pathological processes being involved.^{2,3} Almost certainly a major factor in determining disease severity in those infected by COVID-19 is the blood level of 25(OH)D3 (the reservoir form).

Vitamin D in the human body is mainly synthesised in the skin on exposure to sunlight. Dietary sources like fish, fortified food, and supplements are highly variable exogenous sources but usually fail to source the required levels of vitamin D. Vitamin D levels are assessed by measuring circulating blood levels of the storage form produced by the liver, 25-hydroxyvitamin D [25(OH)D]. The optimal range of serum 25(OH)D level is 40-60 ng/ml. Diagnostic cut-offs for deficiency are < 20 ng/ml for depletion, 20-30 ng/ml for insufficiency, and > 30 ng/ml for sufficiency,⁴ but even higher levels are desirable especially for

acute infections like COVID-19, and levels up to 100 ng/ml are perfectly safe.

Problem Statement

India is grappling with the massive second wave of COVID-19 with the total positive cases nearing 2.9 crores. The death rate has been 1.22% with more than 70% of the reported deaths in individuals with associated comorbidities.⁵ India began the administration of COVID-19 vaccines on 16 January 2021 with a promise of conducting a large vaccination programme. However, it will take time to produce and procure vaccines particularly for the younger population (who in any case are at a much lower risk of the disease).⁶ In any case, the vaccines themselves do not address defective intrinsic immunity caused by vitamin D deficiency. In view of the threat of future waves of COVID-19 or similar infections, simple additional alternatives are required.

This leaves two major factors upon which the Government and population need to focus to prevent any future devastating surge of COVID-19 cases and deaths viz., measures of personal protection and immune enhancement.⁷ For immune enhancement, vitamin D presents a simple, safe, and inexpensive defence, but vitamin D deficiency is quite rampant all over the country, increasing susceptibility to severe COVID-19 infection and consequent mortality. Reasons for this include cloud cover, atmospheric pollution, dark skin colour, sun avoidance, occlusive clothing and use of sunscreens. Numerous studies, both community- and hospital-based, throughout India, have reported vitamin D deficiency ranging from 40-99% with most citing a prevalence of 80-90% irrespective of age, sex, and geography.⁸ It is also important to maintain a diet adequate in vitamin A (700 to 900 mcg for an adult), as this acts with vitamin D.

Role of Vitamin D Deficiency in COVID-19

A meta-analysis done in Europe indicated that countries with a high prevalence of vitamin D deficiency had much higher mortality than those in the equatorial region or where people had adequate levels of serum vitamin D.⁹ Kaufman et al. in the US, in a retrospective observational study, matched the results of SARS-CoV-2 testing with 25(OH)D results and showed an association between lower SARS-CoV-2 positivity rates and higher circulating 25(OH)D levels, which remained significant in a multivariable logistic model adjusting for all included demographic factors (adjusted odds ratio [OR], 0.984 per ng/mL increment; $P < 0.001$).¹⁰ Another observational study in India reported an inverse correlation between serum vitamin D level and SARS-CoV-2 infection rate.¹¹

A controlled trial conducted in a COVID-19 ward in Spain showed a reduced mortality risk with an OR 0.21 [95% CI

0.10; 0.43] when calcifediol, 25(OH)D, the activated form of vitamin D was given on admission.¹² Jayawardena et al. reported positive correlations for the prevalence of vitamin D deficiency with COVID-19 infections ($r = 0.55$; $p = 0.01$; $R^2 = 0.31$) and mortalities ($r = 0.50$; $p = 0.01$; $R^2 = 0.25$) in Asian countries.¹³ A randomised control trial in India likewise concluded that individuals with adequate vitamin D levels turned SARS-CoV-2 RNA negative far earlier than the individuals who had vitamin D deficiency.¹⁴ Rather in a recent study in India, it has been seen that high doses of vitamin D are required in COVID-19 patients in India for better chances of survival.^{14,21}

From our personal experiences and observations in various categories of COVID patients in New Delhi, we have found quite promising results with calcifediol in ICU patients and vitamin D injections (100,000 units IM or orally) in those less sick. We have data of 95 participants which include 42 females and 53 males. Out of them, 20 were severe cases of COVID-19 whom we have given calcifediol capsule 50000 IU stat and to others 3 lakh IU single dose (Figure 1). All patients recovered without any adverse outcome.



Figure 1. Patient receiving Calcifediol Orally

Recommendations

We, therefore, agree with the findings of numerous studies that vitamin D supplementation can prevent COVID-19 incidence, symptoms, and severity, and can reduce the risk of spread of COVID-19. In contrast to vaccines and other drugs, vitamin D3 is a natural body product of proven safety. Recognition of vitamin D deficiency as a public health problem and implementation of population-based interventional strategies by governing bodies is the most pressing need of the hour.

1. The Endocrine Society of India recommends 400 international units (IU) of vitamin D a day for infants,

600-1000 IU for children, 1000 IU for adolescents and pregnant women after 12 weeks gestation, and 1000-2000 IU for adults vitamin D supplementation for Indian people to combat the country's high prevalence of vitamin D deficiency.¹⁵ However, we believe that this level of supplementation will only suffice for the prevention of rickets, and its adult equivalent, osteomalacia; in order to optimise defensive immunity, a much higher dose is necessary.¹⁶

2. For adults: 3000 IU each day for a 60 kg adult, and 6000 IU each day for a 120 kg obese adult. Alternatively, approximately 7 times as much can safely be taken once a week.
3. For pregnant and lactating women: There is strong evidence that pre-eclampsia is linked to vitamin D deficiency.¹⁷ Vitamin D supplementation during pregnancy improves maternal and infant 25(OH)D concentrations and may play a role in maternal insulin resistance and foetal growth.¹⁸ Infant growth can be improved by vitamin D supplementation in pregnancy which also reduces the risk of SGA, without increasing the risk of congenital abnormality or foetal/ neonatal mortality. It is estimated that a dose of 2000 IU/d may help in mitigating the risk of foetal/ neonatal mortality.¹⁹ Therefore, vitamin D deficiency must be actively avoided throughout pregnancy, necessitating supplementation of 2,000 to 4,000 units of vitamin D daily which has been shown to be completely safe. Achieving optimal blood levels helps to minimise complications of pregnancy and also to mount an effective primary immune response in the event of COVID-19 disease.²⁰ This is in contrast to the WHO recommendation of a mere 200 units daily which is clearly far too low, and this supplementation should also be continued during breastfeeding as it further helps to maintain adequate levels in the breastfed infant.
4. For newborn and young children: Although the main consideration in this age group is to prevent rickets, maintaining levels sufficient for activation of immune system is of paramount importance. Vitamin D is excreted in mother's milk, provided maternal intake is adequate. To be safe, the newborn should thereafter be given 400 units daily, scaling up to 1000 units daily at age one year and 2000 units from age 5 years onwards. These doses can conveniently be given all at once, once a week, or even once monthly. 100 units of vitamin D per kilogram body weight per day being a good guide.

It must be recognised that although vitamin D in its natural state is excellent in the prevention of the damaging effects of COVID-19, people who are seriously ill requiring admission to hospital must be treated with vitamin D in its activated form of calcifediol, 25(OH)D. The reason is that the activation

of vitamin D in the liver is a slow process. It might take two weeks before the deficiency is corrected to achieve an ideal blood level of 25(OH)D. This is too slow to be of help to the critically ill, and this has been demonstrated in Brazil.²² However, if calcifediol itself is given, it reaches an ideal level within two hours, and this is the reason for its dramatic benefit.²³

Table 1. Recommendations of Vitamin D for Various Groups of Population

Age Group	Recommendations
For newborn and young children	400 IU/day scalable to 1000 IU
For children of age more than 5 years	1000 - 3000 IU/day
For adults	3000 IU/day for an individual of 60kg 6000 IU/day for an individual of 120kg
For pregnant and lactating women	2000 - 4000 IU/day
For COVID-19 positive patient	1 amp of 600000 IU IM stat
Adjunctive Pulse D therapy can be added safely to the existing treatment protocols of COVID-19 for improved outcomes	Therapeutic improvement in vitamin D to 80 - 100 ng/ml

The presence of a global COVID-19 pandemic affecting the immune system warrants a prompt response. Large scale supplementation of vitamin D is a feasible and effective solution as it is cheap, readily available, has an easy mode of administration and can be made widely available through out-patient clinics, PHC etc. Therefore, the authors recommended that inclusion of vitamin D in national and state-level treatment guidelines would be a highly beneficial and cost-effective strategy.

Conflict of Interest: None

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