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# Vitamin D and Coronavirus Disease (COVID-19); Is Deficiency and Maintenance Supplementation Therapy Necessary?

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***ABSTRACT***

Vitamin D is a fat soluble vitamin with a well-known general metabolism and actions in bone structure and immune system regulation. Vitamin D exhibits direct antimicrobial activities against a spectrum of microbes, including Gram-positive and Gram-negative bacteria, enveloped and non-enveloped viruses, as well as fungi. An observational study showed that concentrations of 38 ng/ml or more were associated with a significant more than twofold reduction in the risk of developing acute respiratory syndrome (17% vs. 45%). Some clinical trials on vitamin D showed a decrease in incidence and severity of the Coronavirus Disease 2019 (COVID-19). To achieve the optimum vitamin D3 levels, approximately half of the population should take at least 2000–5000 iu/d of vitamin D3. Various loading doses were proposed for achieving a 25(OH)D concentration of 30 ng/ml. A study reported that to achieve the concentration of 40–60 ng/ml a weekly or fort nightly dose totaling 100,000–200,000 iu over 8 weeks (1800 or 3600 iu/d) as loading should be prescribed. Approximately about half the people, using 5000 iu/d of vitamin D3 or 30,000–35,000 iu/wk would increase 25(OH)D concentration to 40 ng/ml and 6235–7248 iu/d can ensure that 97.5% of the people have concentrations > 20 ng/ml. Well-designed human clinical studies over the dosage and combination of micronutrients such as vitamin C and D and Zinc in different populations are required to substantiate the benefits of micronutrient supplementation against infection.

***Keywords:*** Vitamin D, Supplementation, COVID-19

## Introduction

Vitamin D is a fat soluble vitamin with a well-known general metabolism and actions in bone structure and immune system regulation (Grant *et al.*, 2020a). Vitamin D3 or oral vitamin D is converted to 25(OH)D in the liver and 1,25(OH)2D (calcitriol) in the kidneys. Vitamin D helps maintain tight junctions while viruses destroy the junction integrity and reduce the replication of rotavirus both in vitro and in vivo (Grant and Garland, 2003).

Vitamin D enhances cellular innate immunity partly through the induction of antimicrobial

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peptides, including human cathelicidin, LL-37 and 1,25(OH)2D (Liu *et al.*, 2006), defenses and modulate citokine storm of pro-inflammatory Th1 cytokines, such as tumor necrosis factorα and interferon γ (Huang *et al.*, 2020, Sharifi *et al.*, 2019).

Vitamin D exhibits direct antimicrobial activities against a spectrum of microbes, including Gram-positive and Gram-negative bacteria, enveloped and non-enveloped viruses, as well as fungi (Grant and Garland, 2002, Grant *et al.*, 2020a).

Serum 25(OH)D concentrations tend to decrease with age (Grant *et al.*, 2020a), which may play an important role in COVID-19 case-fatality rates (CFRs).

Vitamin D supplementation also enhances the expression of genes related to antioxidation (glutathione reductase and glutamate–cysteine ligase modifier subunit) with antimicrobial activities (Colunga Biancatelli *et al.*, 2020) that has been proposed to prevent and treat COVID-19 (Grant *et al.*, 2020a). Seasonal influenza infections can cause mortality due to respiratory involvement generally peak in winter (Grant *et al.*, 2020a), which are partly caused by seasonal solar UVB doses that affect vitamin D concentrations. In addition, some weather conditions of low temperature and relative humidity can allow the influenza virus to survive longer outside the body than in warmer conditions.

## *Clinical findings and epidemiologic studies on vitamin D and COVID-19*

The first step in developing a hypothesis is to consider the epidemiological and clinical findings regarding the disease of interest and to investigate the relationship of these results with 25(OH)D concentrations. An observational study showed that concentrations of 38 ng/ml or higher were associated with a significant ($P < 0.0001$) more than two-fold reduction in the risk of developing acute respiratory syndrome (17% vs. 45%) (Huang *et al.*, 2020).

The recent epidemiological and clinical studies indicate that COVID-19 infection is associated with the increased secretion of pro-inflammatory cytokines, C-reactive protein (Huang *et al.*, 2020), increased risk of pneumonia (Wang *et al.*, 2020), sepsis, acute respiratory distress syndrome, and heart failure (Zhou *et al.*, 2020). Case fatality rates in China ranged from 6% to 10% for those with cardiovascular diseases, chronic respiratory tract diseases, diabetes, and hypertension (Wang *et al.*, 2020).

We know that Corona viruses destroy the lung epithelial cells and facilitate pneumonia by increasing the secretion of Th1-type cytokines such as interferon γ, as part of the innate immune response and the cytokine storm. However, COVID-19 infection also initiates increased secretion of the Th2 cytokines (e.g., interleukins 4 and 10) that suppress inflammation (Sabetta *et al.*, 2010).

## *Clinical trials in vitamin D on prevention and treatment COVID-19*

Some clinical trials on vitamin D showed decreased incidence and severity of COVID-19. A high-dose (250,000 or 500,000 iu) of vitamin D3 trial was used in COVID-19 patients under ventilation in intensive care unit in Georgia with the mean baseline 25(OH)D concentration of 20–22 ng/ml. The findings showed that hospital stay reduced from 36 ± 19 days in the control group to 25 ± 14 days in the 250,000-iu group (25(OH)D, 45 ± 20 ng/ml) and 18 ± 11 days in the 500,000-iu group (25(OH)D, 55 ± 14 ng/ml), $P = 0.03$ (Han *et al.*, 2016). Moreover, the data support the role of higher 25(OH)D concentrations in reducing the infection incidence and death from acute respiratory tract syndrome, including those from influenza ((Cianferotti *et al.*, 2017)). Thus, vitamin D3 supplementation should be started or increased several months before winter to raise 25(OH)D concentrations to the range necessary to prevent acute respiratory tract syndrome.

Studies reviewed various optimum vitamin D3 concentrations such as 25(OH)D concentrations of 20–30 ng/ml or 38 ng/ml as the appropriate concentrations. The optimal range appears to be in




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the range of 40–60 ng/ml or 100–150 nmol/l) (Sabetta *et al.*, 2010).

### *What is the optimum vitamin D dosage for loading dose and maintenance?*

To achieve the optimum vitamin D3 levels, approximately half the population should take at least 2000–5000 iu/d of vitamin D3 (Heaney *et al.*, 2003). Various loading doses were proposed for achieving a 25(OH)D concentration of 30 ng/ml. One study showed that a weekly or fort nightly dose totaling 100,000–200,000 iu over 8 weeks (1800 or 3600 iu/d) (van Groningen *et al.*, 2010) as loading. However, to achieve the concentration of 40–60 ng/ml higher loading doses should be prescribed. A trial among Canadian breast cancer patients with bone metastases treated by bisphosphonates but without comorbid conditions showed that 10,000 iu/d of vitamin D3 over a four-month period had no adverse effects (Amir *et al.*, 2010). Thus, from the literature, one may suggest that taking 10,000 iu/d for a month is effective in rapidly increasing the circulating levels of 25(OH)D into the preferred range of 40–60 ng/ml.

To maintain optimal level of vitamin D3 after that first month, the dose can be decreased to 5000 iu/d (Shirvani *et al.*, 2019). But we must consider that according to the risk of hypercalcemia in high doses of vitamin D prescription, calcium supplementation should not be high. A recent review proposed using vitamin D loading doses of 200,000–300,000 iu in 50,000-iu capsules to reduce the risk and severity of COVID-19 (Gasmi *et al.*, 2020).

Many countries proposed that the optimal goals of 20 ng/ml (50 nmol/l) are adequate. According to the statement by European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases, “attainment of serum 25(OH)D levels well above the threshold desired for bone health cannot be recommended based on current evidence, since safety has yet to be confirmed (Cianferotti *et al.*, 2017). However, this statement, published in 2017, is no longer correct since a number of vitamin D supplementation studies reported that long-term vitamin D supplementation had health benefits without adverse health effects, e.g., 2000 iu/d for cancer risk reduction and 4000 iu/d for reduced progression from pre diabetes to diabetes (Pittas *et al.*, 2019).

### *Recommendations in COVID-19 pandemic status*

A recent review on vitamin D primary goals in vitamin D deficiency treatment reported that “a 25(OH)D level of > 50 nmol/l or 20 ng/ml is the primary treatment goal, although some data suggest a benefit for a higher threshold (Grant and Garland, 2002). As another article noted “although 20 ng/ml seems adequate to reduce the risk of skeletal problems and acute respiratory syndromes, concentrations above 30 ng/ml have been associated with reduced risk of cancer, type 2 diabetes mellitus, as well as adverse pregnancy and birth outcomes (Grant *et al.*, 2020b). However, based on several studies that provided some recommendations for breast and colorectal cancer prevention (Garland *et al.*, 2009), the desirable concentration should be at least 40–60 ng/ml.

In 2011, the Endocrine Society recommended supplementation of 1000–4000 iu/d of vitamin D and a serum 25(OH)D concentration of 30 ng/ml or higher in this area (Holick *et al.*, 2011). These guidelines addressed all chronic disease patients. The United State Institute of Medicine showed no adverse effects of vitamin D supplementation in daily doses of < 10,000 iu/d (Ross *et al.*, 2011).

Measuring serum 25(OH)D concentration is useful to determine the baseline and achieved 25(OH)D concentrations goals specially in some sub groups that need higher doses to achieve optimal goals, such as pregnant women, the obese, people with chronic diseases, and the elderly (Grant *et al.*, 2020b).

In addition, some factors increase 25(OH)D concentration during vitamin D supplementation, including genetics, digestive system health, weight, and the baseline 25(OH)D concentration.

The 25(OH)D concentration increased to 40 ng/ml and 6235–7248 iu/d in about half of the people who used 5000 iu/d of vitamin D3 or 30,000–35,000 iu/wk, ensuring that 97.5% of the




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people had concentrations > 20 ng/ml (Veugelers *et al.*, 2015) that did not exceed the 10,000 iu/d threshold. However, vitamin D fortification of the basic foods such as dairy and flour products (Grant and Boucher, 2019) can raise the serum 25(OH)D concentrations up to a few ng/ml (Camargo *et al.*, 2012, Martineau *et al.*, 2017). To reach more benefits, daily or weekly vitamin D supplementation is recommended (Martineau *et al.*, 2017) based on the annual measurement of serum 25(OH)D concentration for those with health risks evaluations (Grant *et al.*, 2020b).

Magnesium supplementation in the range of 250–500 mg/d is also recommended during vitamin D supplement therapy. Magnesium, as a cofactor in the enzymatic reactions of the liver and kidneys, activates vitamin D and regulates calcium and phosphate homeostasis to influence the growth and maintenance of the bones (Uwitonze and Razzaque, 2018).

A recent review concluded that despite contradictions, available evidences show that supplementation with multiple micronutrients plays immune-supporting roles that modulate the immune function and reduce the risk of infection. In this vein, micronutrients such as vitamins C and D and zinc have the strongest evidence for immune support are (Gombart *et al.*, 2020).

The hypothesis that vitamin D supplementation can reduce the risk of influenza, COVID-19 risk, and mortality should be studied in trials to propose safety, efficacy, the optimal doses, and serum 25(OH)D concentrations (Han *et al.*, 2016).

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