



Nutrition in acute and chronic diseases

Perspective: improving vitamin D status in the management of COVID-19

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Introduction

A novel coronavirus disease 2019 (COVID-19) outbreak is a global dramatic pandemic that is immeasurably impacting our communities. Considering massive health and economic burden of the COVID-19 pandemic, any means by which to improve the condition of patients to accelerate recovery and to reduce the risk of deterioration and death would be considered of significant clinical and economical importance.

In patients with COVID-19, SARS-CoV-2 virus binds to angiotensin converting enzyme 2 (ACE2) receptors in the respiratory tracts of infected patients to enter host cells [1]. At early stages of the disease, protective immune response is responsible for eliminating virus and, therefore, strategies to improve immune responses are of importance. As disease progresses, lung inflammation and fibrosis occur due to the release of pro-inflammatory cytokines, namely interleukin (IL)-1B and IL-18 by activated macrophages and type 1 T helper (Th1) immune cells [2]. Older patients and those that are immunocompromised are at the higher substantial risk [3]. Unfortunately, current knowledge gap on human immune response to SARS-CoV-2 is a critical barrier for treating the disease; however, potential immunomodulators may help alleviate severity and improve outcomes.

Vitamin D is a secosteroid that has a wide spectrum of immunomodulatory, antiinflammatory antifibrotic, and anti-oxidant actions. Expression of inflammatory cytokine [e.g., IL-1 α , IL-1 β , tumor necrosis factor- α] was inhibited by vitamin D and its insufficiency was associated with over-expression of Th1 cytokines [4]. We have recently found that severe vitamin D deficiency (<25 nmol/L) is associated

with disease progression and increased mortality in patients with autoimmune liver diseases [5]. This attribute has generated interest in vitamin D as a pathogenic factor that can be measured, monitored, and manipulated [6].

Vitamin D deficiency in COVID-19 high risk patients

Patients with common variable immunodeficiency and bronchiectasis [7] as well as older adults [8] who are detected with mild to severe vitamin D deficiency, constitute high risk groups for getting severe illness from COVID-19. In addition, vitamin D has an important role in cardiovascular diseases and diabetes mellitus [9]. Vitamin D deficiency is also common in obesity [10] and smokers [11]. In Chicago, more than half of COVID-19 cases and around 70% of COVID-19 deaths were observed in African-American individuals [12] who are at the greater risk for vitamin D deficiency [13].

Among environmental factors, seasonal variation in sun exposure, geographic latitudes, air pollution, and darker skin influence in vitro vitamin D formation by sunlight [14]. Recent investigation of an association between temperature and latitude in the cities affected with COVID-19 indicated similarity in temperature and latitude among those highly affected areas [15]. This is an important notion that must be considered as vitamin D concentrations tended to be lower in high-latitude countries [16]. High prevalence of vitamin D deficiency and insufficiency was reported previously for those affected areas (Table 1); however, it should be acknowledged that divergent included populations may limit the generalizability of the study to other populations. Moreover, prevalence of vitamin D deficiency differs among various geographical regions of each country, which limit our ability to simplify the results.

Vitamin D and respiratory tract infections

Epidemiological studies have reported that vitamin D deficiency is associated with viral respiratory tract infections

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Table 1 Overview of vitamin D deficiency in regions highly affected by COVID-19.

| Country | Population of study | 25(OH) D status | Prevalence |
|----------------------|--|---|--|
| China [30] | 364 Chinese men aged 60–75 | Deficiency: <50 nmol/L Insufficiency: 50–75 nmol/L | 72% 22% |
| Iran [31] | Meta-analysis of 48 studies including 1911 men and 3683 women (excluding pregnant women, children, and patients) | Deficiency: <50 nmol/L | Pooled prevalence 55.21% in men 64.71 in women |
| Italy and Spain [32] | 420 patients ≥65 years old admitted to rehabilitation centers | Deficiency: <50 nmol/L Insufficiency: 50–75 nmol/L | 94.3% 81.2% |
| United States [33] | 26010 adults in the National Health and Nutrition Examination Survey 2001–2010 | Deficiency: <50 nmol/L Insufficiency: 50–75 nmol/L | 28.9% 41.4% |
| France [34] | 297 subjects studied in January and February 2015 | Deficiency: <50 nmol/L | 75.1% |
| United Kingdom [35] | 278 patients with chronic obstructive pulmonary disease, aged 41–92 years in London | Deficiency: <50 nmol/L | 61.5% |

and acute lung injury [17]. Vitamin D agonist, calcitriol, exhibited protective effects against acute lung injury by modulating the expression of members of the renin–angiotensin system such as ACE2 in lung tissue [18], supporting the role of vitamin D deficiency as a pathogenic factor in COVID-19.

Vitamin D receptors (VDRs) are extensively distributed in respiratory epithelial cells and immune cells (B cell, T cell, macrophages, and monocytes). 25-hydroxyvitamin D (25OHD), the major circulating form of vitamin D can be converted to the active form (1,25-dihydroxyvitamin D) in the bronchial epithelium and immune cells [19]. The enzyme, 1 α -Hydroxylase (CYP27B1), required for vitamin D activation, is induced by diverse stimuli, including cytokines and toll-like receptor ligands in the respiratory tract. However, adequate serum levels of 25(OH)D is required to increase levels of 1,25-dihydroxyvitamin D and consequently improve the immune response to respiratory virus infections [20].

Type-II pneumocytes are the primary target of coronaviruses and ACE2 receptors are highly expressed on these cells. Impaired function of type-II pneumocytes decrease the surfactant level and increase surface tension in COVID-19 [21]. Metabolites of 1,25-dihydroxyvitamin D have been reported to stimulate surfactant synthesis in alveolar type-II cells [22]. In vitro culture of human fetal and adult alveolar type-II cells with 1,25-dihydroxyvitamin D increased VDR and the expression of surfactant-associated protein B, a lipid-associated protein of the pulmonary surfactant [23], indicating the potential of vitamin D to reduce surface tension in COVID-19.

In line with our objective to improve vitamin D status and its associated outcomes in patients with COVID-19, studies have shown treatment with high dose of 250,000–500,000 IU vitamin D to be safe in mechanically ventilated, critically ill patients and was associated with decreased hospital length of stay, improved ability of the blood to carry oxygen and increased hemoglobin levels [24, 25]. The risk of acute viral respiratory tract infections

was twofold less if the vitamin D serum levels were ≥95 nmol/L (hazard ratio 0.51; 95% CI, 0.25–0.84; $p < 0.0001$) and the percentage of sick days was five times less (0.80% vs. 3.9%, $p = 0.02$) compared with the patients with levels <95 nmol/L [26].

Suggested plan of action

To our knowledge, no study to date has measured vitamin D levels and performed high-dose vitamin D treatment in patients with COVID-19. High prevalence of vitamin D deficiency in elderly, smokers, patients with chronic diseases, and excess uptake by adipose tissue in obesity make investigations of its role as a therapeutic agent in COVID-19 conceivable. Accordingly, it should be necessary to measure serum 25(OH)D levels in all inpatient and outpatient populations with COVID-19 and in different stages of the disease to identify the importance of maintaining or promptly increasing circulating levels of 25(OH)D into the optimal range of 40–60 ng/ml (100–150 nmol/L) [27]. In this regard, relationship between baseline vitamin D status and disease severity, laboratory biochemical tests of white blood cell count, C-reactive protein, lymphocyte count, lactate dehydrogenase, IL-6, platelet count, albumin, and serum ferritin, required hospitalization and intensive care unit admission should be determined. This will help us to identify the ability of low vitamin D levels to risk stratify patients and allow for care to be provided to those who are at increased risk of progression.

We acknowledge that the primary stage in treating vitamin D deficiency is to measure a baseline 25(OH)D serum levels and then consider the supplementation dose based on the target level and how rapidly that level must be reached. However, based on previous studies in patients with reparatory disease [28] and in order to quickly and safely increase serum 25(OH)D levels, we recommend patients with low circulating levels (below 50 nmol/L) should be offered vitamin D supplementation of 50,000 IU twice a week at the diagnosis (100,000 IU total). Overall, doses

above 6000 IU/d are needed to achieve serum 25(OH)D concentrations above 100 nmol/L and intakes of vitamin D up to 15,000 IU/d were found to be safe [29]. Association between patients' initial response to vitamin D supplementation with disease progression, recovery, and various clinical outcomes need to be investigated. Following 100,000 IU start dose, we propose patients to continue with the dose of 50,000 IU taken once a week for the second and third weeks. Following doses of 50,000 IU is suggested to achieve optimal levels of 25(OH)D in patients with poor baseline vitamin D status. Supplemented patients should be monitored to ensure their circulating vitamin levels are normalized and sustained for the duration of the COVID-19 pandemic. This suggested plan presents important challenges to identify how disease features and progression, hospital admission and length of stay, duration of mechanical ventilation, hospital mortality, and respiratory failure differ between the early responder and nonresponder groups.

Conclusion

Due to the lack of data, symptomatic management is used for COVID-19 infection including oxygen therapy and mechanical ventilation for those with severe infection. Considering the range of beneficial effects ascribed to vitamin D, its safety and ease of administration, as well as direct effects of vitamin D on immune cell proliferation and activity, pulmonary ACE2 expression and reducing surface tension, evaluation of vitamin D supplementation as an adjuvant therapeutic intervention could be of substantial clinical and economic significance. Empiric intervention with vitamin D is a clinical decision that can be justified by low serum levels and the risk of impaired immune system. Importantly, improvement in circulating 25(OH)D levels opens possibilities for slowing disease progression or even improving survival of patients.

In summary, given the high prevalence of vitamin D deficiency and in order to rapidly, safely, and significantly raise serum concentrations, high-dose vitamin D intervention with potential benefit in decreasing risk of COVID-19 severity and mortality is suggested, which is a safe and noninvasive treatment. Patients would take large doses of vitamin D for a week, followed by several thousand IU/d vitamin D for a period of 2 weeks. This will provide a quick and sustainable restoration of serum vitamin D levels, thus, potentially triggering an improvement in clinical status and prognosis. However, prospective clinical studies are required to address this speculation and overcome the obstacles in our current understanding of vitamin D role as an adjuvant therapy in patients with COVID-19.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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