Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COVID-19 in Metabolism

Commentary: Myths and facts on vitamin D amidst the COVID-19 pandemic

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"*It is not the Answer that Enlightens but the Question.*"
[Eugene Ionescu]

COVID-SARS-2 pandemic has struck and spread at light speed, reaching 6 continents within 3 months, transforming our societies globally [1]. In <6 months, numbers rose exponentially to 5,159,674 cases and 335,4186 fatalities (6.5%); a third roughly are in the US (May 22, 2020) [2]. Disease severity and mortality rates are higher in the elderly, African Americans, patients with diabetes mellitus, chronic lung and cardiovascular diseases [3,4], all groups with low vitamin D levels. Should we supplement patients with vitamin D? We examine the biological plausibility and evidence for a role of vitamin D in COVID-19 patients, and provide a framework for guidance on supplementation, based on a rigorous and systematic approach. We interrogated the Systematic Reviews database Epistemonikos, and four medical databases including Cochrane.

The beneficial role of the sunshine vitamin on musculoskeletal health is undisputed. Vitamin D insufficiency, a serum 25-Hydroxy vitamin D [25(OH)D] between 20 and 50 nmol/L (8–20 ng/mL), causes calcium malabsorption, secondary hyperparathyroidism, accelerated bone loss, osteoporosis and fractures in adults [5]. Deficiency, a serum 25 (OH)D < 20 nmol/L, decreases the serum calcium-phosphate product, and leads to rickets in children and osteomalacia in adults [5]. Both can be prevented with daily supplements of 400–800 IU of vitamin D, provided calcium intake is adequate. In elderly or institutionalized subjects, vitamin D at doses of 800–2000 IU/day, co-administered with calcium, reduces the risk of hip fractures by 15–30%, and of other non-vertebral fractures by 20% [5–7]. These doses are within ranges recommended by major organizations pre-COVID times.

Ecological studies suggest that high latitudes (>+30°N), and winter season, risk factors for low vitamin D, are associated with higher mortality rates in COVID-19 infections [8,9]. Several exceptions exist and are likely explained by other contributing factors such as population age, density and ethnicity, lifestyle factors, and social distancing measures [10]. Obesity is a risk factor to all non-communicable diseases, and an increasing number of reports identify obesity as a risk factor for COVID-19 related morbidity and mortality [11,12]. However, although BMI is a known predictor of vitamin D status [13–15], hypovitaminosis D in this population may be explained by poor lifestyle habits, vitamin D sequestration in adipose tissue, and altered metabolism [16]. Retrospective case-control studies reveal inverse associations between serum 25 (OH)D level and the risk of COVID-19 infection or severity. They all suffer from major limitations [17–20]. Two are non-peer-reviewed papers [17,20]. In the case of UK Biobank studies samples were collected in 2006–2010 [17,18], while studies from Switzerland and Belgium did not characterize controls, nor adjusted for other predictors [19,20]. Clear support for causality between serum 25(OH)D levels and COVID-19 therefore remains elusive.

Hypovitaminosis D increases the risk for viral respiratory infections [21]. The most feared complications, in a report of over 46,000 COVID-19 patients, were bilateral pneumonias (76%), acute respiratory distress syndrome (ARDS) with ICU admissions (29%), and multi-organ failure (8.5%) [22]. They reflect an immune and inflammatory response, involving both T-cells and B-cells, to the acute phase of the viral infection [23]. SARS-CoV-2 infects respiratory epithelial cells through the ACE2 receptor, triggers pyroptosis, the release of pro-inflammatory cytokines such as IL6, and chemokines. These attract monocytes, macrophages, and T cells, the latter producing IFN-γ further contributing to inflammation. In an immune-compromised host, this progresses to the cytokine storm, which coupled with the production of non-neutralizing antibodies by B cells, leads to further organ damage [23]. Vitamin D modulates innate and adaptive immunity, through the Vitamin D Receptor (VDR) and CYP27B1, the enzyme converting it to the active metabolite calcitriol, both of which are expressed in immune cells [23–25]. The effect of vitamin D on immunity and viral respiratory diseases has been tested. Vitamin D metabolites do not consistently influence replication or clearance of respiratory viruses, nor antibody titers to vaccination, but they decrease the expression of cytokines induced by the viral infection, including IL6, TNF-α and IFN-β [26–28]. Other anti-inflammatory effects of vitamin D include modulation of macrophage chemotactic protein1, interleukin 8, type 1 interferon, TNF-α and lowering of oxygen reactive species [26,29]. The efficacy of vitamin D trials in patients with influenza infections is not well established [25,27,28]. Prevention trials, mostly conducted in the pediatric age group, are negative [28,30–37]. However, two systematic reviews of controlled trials showed promising results. The first investigating the effectiveness of vitamin D in the

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prevention or treatment of infectious diseases reported that the strongest evidence was in reducing the risk of acute respiratory illness and influenza [38]. More recently, an individual patient meta-analysis of 25 trials, of over 11,000 participants, showed vitamin D supplementation to reduce the risk of acute respiratory infections, including viral, by 12% in all participants. This effect was noted with daily or weekly doses (by 19%), but not bolus doses, and was most pronounced in patients with serum 25(OH)D levels below 50 nmol/L (20 ng/mL) [39]. The evidence from trials in critically ill patients is also mixed. Vitamin D had no significant effects on mortality, ventilation, or length to stay in one meta-analysis [40], while it was associated with a 30% reduction in mortality compared to placebo, in another [41]. Finally, the most recent randomized trial of 1360 ICU patients reported that early administration of 540,000 IU of vitamin D3 did not improve 90-day mortality [42]. Differences in inclusion criteria, diseases treated, baseline 25(OH)D levels, and regimens used (doses, regimens, and formulations), in trials included in these 2 meta-analyses may explain opposing results.

We screened the Cochrane database, the 2019 Novel Coronavirus Research Compendium (NCRC) on pharmaceutical interventions [43], WHO primary trial registries [44], and ClinicalTrials.Gov [45], for vitamin D supplementation trials in COVID-19 individuals. None is completed yet. Eight identified trials aim at prevention or treatment and span 1–12 weeks. Two ongoing prevention trials evaluate the effect of vitamin D supplementation, alone (1600 IU on day 1 and 800 IU on days 2–5) or in combination with Zinc and Plaquenil (vitamin D dose not provided), on COVID-19 infection risk in health care providers, high risk, or institutionalized individuals. A third compares vitamin D3 1000 IU/day given for 2 months, to placebo, on both infection and complication rates. Three controlled trials explore the effect of vitamin D supplementation in COVID-19 positive patients on mortality, as a primary outcome, hospital complications, time to recovery and inflammatory markers, as secondary outcomes. The vitamin D arms consist of vitamin D (25,000 IU, single oral dose), the active vitamin D (Calcifediol 266 μg, 2 capsules day 1 and 1 capsule on days 3, 7, 14, 21, 28), or 2 vitamin D doses (400,000 IU or 50,000 IU in a single oral dose) compared to each other. One trial compares a vitamin D analogue (Ergocalciferol 1.25 μg daily) to vitamin D3 1000 IU daily, for 3 weeks, on symptoms recovery. One study investigates the efficacy of vitamin D 50,000 IU weekly for 2 weeks, with or without aspirin, in reducing the risk of hospitalization for COVID-19 patients.

What are optimal doses of the sunshine vitamin in COVID-19 times? Vitamin D3 supplementation, daily or weekly, at daily equivalent doses of 1000–4000 IU, is advisable. The wide range targets a desirable 25 (OH) > 75 nmol/L (30 ng/mL). Both accommodate the anticipated higher needs across the lifespan incurred by lockdown measures, immobilization, and hospitalization. They also allow flexibility in tailoring doses to individual needs, factoring in considerations such as prevention or treatment, baseline risks, COVID-19 status and health care settings. Importantly, our approach is anchored in abundant safety data across the life course [6], not exceeding the upper tolerable level [46]. It is based on clear evidence for efficacy in fracture risk reduction and possibly falls in institutionalized individuals [7], an important consideration in frail COVID-19 patients. It is also well aligned with recommendations from the Center for Evidence Based Medicine [47]. Alternative guidance has been proposed. Preventive doses of vitamin D3 of 10,000 IU/day for 4 weeks followed by 5000 IU/day to reach a target 25(OH)D level of 100–150 nmol/L [24], and treatment doses >6000 IU/day in deficient individuals to reach a similar level and reduce disease progression [48], are suggested. The former is based on a publication on the role of vitamin D in influenza and pneumonia, and a target level associated with a reduction in viral respiratory infections in one observational study [24]. The latter is based on indirect evidence derived from a single study in tuberculosis patients [48]. However, loading doses do not seem to have added beneficial effect on acute respiratory infections [39], may adversely affect fall and fracture outcomes [49,50], and possibly other COVID-19 respiratory outcomes. Major gaps are to be filled before making solid recommendations. The role of vitamin D supplementation in COVID-19 patients, to enhance disease resistance or as adjuvant therapy, awaits results of well-designed experimental studies. Independent associations between low vitamin D and COVID-19 morbidity and mortality need to be established first. This can be achieved with observational studies with low selection bias, adjusted analyses, and 25(OH)D level measurements using gold standard assays. Initiation time, dosing regimens and vitamin D preparations can only be determined through randomized controlled trials. Considering the relatively small number of subjects in current trials, additional multicenter trials would be needed. Investigators should ideally consider protocols of current studies to define dosing regimens and primary outcomes. This would enable individual patient meta-analyses and shed much needed light to strengthen the evidence on the role of vitamin D in these dark COVID-19 times.

Declaration of competing interest

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