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VITAMIN D AND COVID-19: IT IS TIME TO ACT

Abstract: Vitamin D (VitD) deficiency is considered a global problem and might be associated with higher risk to get COVID-19 illness. In the light of COVID-19 pandemic, VitD might be a promising agent for fighting the SARS-CoV-2, since VitD is involved in various pathophysiological mechanisms that occur during COVID-19 infection. High-dose VitD supplementation, particularly for risk groups, could be recommended to achieve and maintain optimal (range 40-60 ng/ml) serum 25-hydroxy vitamin D levels (marker of VitD status) both for COVID-19 prevention and treatment.

Keywords: vitamin D; 25-hydroxy vitamin D; calcitriol; COVID-19; SARS-CoV-2; supplementation

1. Methods

The relationship between vitamin D (VitD) and COVID-19 still has many controversies and uncertainties – both for the scientific community and the clinicians, despite the fact that the number of papers on this theme is constantly growing. There is a need to summarize the key aspects known up till now as well as to give the main implications for clinical practice, in particular, regarding assessing VitD status in patients and VitD supplementation principles during the COVID-19 pandemic. This review is mainly based on a literature search that was performed using the PubMed, Google Scholar and Research.net databases. The both keywords “COVID-19” and “vitamin D” were used for the search. The

last search was done in August 10, 2020. Only the papers in English were selected for a further analysis. In addition, some papers referenced in the primary articles were also analyzed.

2. The COVID-19

Originated in China at the end of 2019, a new disease caused by a novel coronavirus named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) continues to spread rapidly around the world and still is a huge challenge for many countries. This disease was named a Coronavirus disease 2019 (COVID-19), and in 11th of March, 2020 the WHO declared the coronavirus outbreak a pandemic [1].

While there are still some uncertainties regarding the origin of the virus, the clinical presentations of COVID-19 disease are well described. The incubation period lasts from 2 to 14 days. Fever, cough and shortness of breath are the main symptoms and occur in many patients suffering from symptomatic COVID-19. However, many other symptoms can also occur: general weakness, sputum production, as well as sore throat, rhinorrhea, nasal congestion, chest pain, gastrointestinal symptoms (nausea, vomiting, diarrhea), muscle aches, bone pain, joint pain, headache, confusion; sudden anosmia (loss of smell), ageusia (loss of taste), stroke or chilblains were also reported [1-3]. Most infected people develop mild to moderate illness and recover without hospitalization; however, some cases present with a severe COVID-19 forms that might require oxygen therapy or mechanical ventilation. Some patients develop lymphocytopenia and thrombocytopenia, and those findings in blood are considered risk factors for developing severe forms of COVID-19 [1]. Severe pneumonia, acute respiratory distress syndrome (ARDS), septic shock and multiorgan failure are the main causes of death, and higher mortality rates were found to be associated with older age, smoking, hypertension, obesity, diabetes, cardiovascular diseases, cancer, and multimorbidity [1, 4, 5]. Noteworthy, in many cases the COVID-19 can occur as asymptomatic and those infected persons naively can widely spread the virus. Moreover, SARS-CoV-2 is highly contagious (more than the influenza virus) and that also contributes to the fast spread of this disease [1-3].

Undoubtedly, COVID-19 pandemic is a significant burden on global health systems as well as a major issue for global economics. Unfortunately, at the time of writing, no specific prevention (vaccine) against

SARS-CoV-2 exists. And no specific widely-accepted treatment is available for COVID-19 patients, despite the fact that some drugs, e.g., the anti-viral remdesivir, have shown promising results in some countries. Therefore, mainly nonspecific measures are on the use in many countries for control of the disease spread, e.g. regular hand washing with soap, frequent disinfection of hands and surfaces, wearing a face mask and covering a cough with an elbow, introducing social distancing measures, "stay at home" guidelines, traveling restrictions and closing state borders, expansive testing, and contact tracing [3]. There is a need to find additional agents that could be effective and acceptable for fighting the COVID-19 pandemic, especially keeping in mind the possible "second wave" of COVID-19 expected to be in the next autumn or winter. From the beginning of 2020, there is an accumulating evidence that VitD is a potential candidate for that purpose.

3. Vitamin D

For humans, the main source of VitD is its synthesis in the skin under the influence of solar ultraviolet radiation. After two hydroxylation steps, VitD is transformed into an active form 1,25-dihydroxyvitamin D, or calcitriol. The first step takes place in the liver and produces 25-hydroxyvitamin D (25OH-D). The second hydroxylation is performed by renal proximal tubular epithelial cells as well as by some extra-renal tissues and cells, like endothelium and macrophages. The major circulating form of VitD is 25OH-D and it is currently accepted as the best marker of VitD status. Calcitriol produces its effects via the VitD receptors that are found almost on all cell types of the human organism, and thus is capable to suppress or to stimulate the expression of numerous genes [6].

VitD appears to be essential not only for "healthy bones" but also for many other organs and tissues [7]. However, low VitD status seems to be a global problem: it was estimated that about 1 billon humans could have VitD deficiency or insufficiency [8]. A high prevalence of low VitD was found in many European countries as well, particularly in the Eastern and Central Europe [9-11]. Much better VitD statuses were found to be in such countries like Norway and Sweden [12], the latter findings might be explained by high consumption of oily fish, cod liver oil, fortified food and/or higher rates of VitD

supplementation [13]. There is increasing evidence that VitD deficiency may have been underestimated/ignored in low latitudes, even in tropical countries [14]. More recent data showed that, in European countries, in particular Southern, Eastern and Western Europe prevalence of VitD deficiency (if defined as serum 25OH-D levels <20 ng/ml) could be 30-60%, and up to 80% – in the Middle East [13]. Many factors can contribute to high prevalence of low VitD, e.g., modern sedentary life style (less and less time outside in the sunlight), obesity, air pollution (particularly, in large cities) that reduces the amount of solar UV radiation reaching the humans, dietary habits (decreased consumption of diary and sea fish), avoidance of sunlight even during leisure time, use of sunscreen (fear of skin cancer), cultural habits (e.g., clothing style) in some populations, as well as low rates of VitD supplementation and absence of food fortification with VitD programs in many countries [15-17]. All these reasons are also important as risk factors for VitD deficiency for those living in "sunny" Southern European countries like Italy and Spain, where avoidance of heat (and the sunlight, too) is also a common practice. Besides that, one must consider a growing number of elderly people in those countries that are at extremely high risk to develop VitD deficiency. It is well known that older persons (aged >60 years) may tend to have low VitD due to many reasons: lessened mobility (due to chronic diseases), increased adiposity, reduced rates of synthesis of VitD in the skin (mainly, due to reduced amounts of 7-dehydrocholesterol – the precursor of vitamin D3 – in the skin), reduced appetite, poorer nutrition, and reduced vitamin D absorption in the gut. In addition, pharmaceutical drug use typically increases with age, and some medications (e.g., certain antiepileptics, antifungals, antihypertensives, antineoplastics, antibiotics, and anti-inflammatory agents) are known to impair VitD metabolism and to decrease serum 25OH-D levels [4, 18, 19].

4. COVID-19 & Vitamin D: data from studies

Already in February, 2020 it was proposed that VitD deficiency might increase COVID-19 risk, since low VitD was shown to be prevalent in many people (including otherwise "healthy" ones), mostly at the end of winter season, particularly, in people who are housebound, or institutionalized; and COVID-19 was firstly identified in winter 2019 and mostly affected middle-aged to elderly people [20].

It was also suggested that geographical location might influence the risk of mortality from COVID-19, since mortality was relatively low for many countries below 35 degrees latitude [21]. Not surprisingly, higher sunlight intensity should increase VitD production in the skin and, consequently, improve VitD status and potentially the health. However, high mortality rates were reported from "sunny" Italy, Spain and France, i. e., from countries where severe VitD deficiency is also prevalent. Therefore, the location (the latitude) of the country or the city seems to be not the main factor determining VitD status as well as COVID-19 mortality rates [21]. Indeed, multiple confounders, age in particular, may interfere any potential relationship between VitD and COVID-19, since age of population is an important determinant of severe COVID-19 outcomes [22, 23].

It was also hypothesized in March, 2020 that low VitD could be the link between age, comorbidities and increased susceptibility to complications and mortality due to COVID-19 infection in some regions, e.g., northern Italy [24]. Indeed, the COVID-19 virus is found to be more dangerous for the elderly, especially for those who have comorbidities, in particular, arterial hypertension, obesity, diabetes, cardiovascular or cerebrovascular diseases, as well as for ethnic minority populations with darker skin, since those patients have higher risk of severe COVID-19 and also higher mortality rates [1, 14, 17, 25]. Interestingly, those mentioned COVID-19 risk groups could also be considered as risk groups for VitD deficiency [17, 19, 26]. Epidemiological studies of the past showed inverse relationships between VitD status and certain clinical events: lower 25OH-D levels are associated with higher risk to develop ARDS, heart failure and sepsis; the latter conditions are also known to increase risk for severe COVID-19 and death from COVID-19 [4, 27]. In addition, higher mortality rates in men could be explained, at least in part, by the fact that elderly men have higher prevalence of VitD deficiency; however, the role of different levels of sex hormones and other factors also seem to be important [28].

In Switzerland, a cohort study that analyzed patients who underwent a nasopharyngeal swab PCR analysis for SARS-CoV-2 found that COVID-19 positive cases had significantly lower median 25OH-D levels than COVID-19 negative ones [29]. In contrast, analysis of UK biobank data [30] found no association between 25OH-D and COVID-19 infection (presence, regardless of severity) after adjusting for potential confounders; despite 25OH-D concentration being lower in black and minority ethnic participants,

no evidence that it might play a role in their higher risk of COVID-19 infection was found. But, as correctly stressed by the latter study authors, they used baseline measurements including 25OH-D levels and health status that have been obtained a decade ago (between 2006 and 2010), and "It would be preferable to have measurements immediately preceding development of COVID-19" [30].

Some authors propose that VitD status could also strongly account for variability in COVID-19 severity [31]. This suggestion might be supported by the data from European countries: there exists a negative correlation between levels of mean 25OH-D and number of cases of COVID-19 for 1 million (1 M) of population in each country, as well as a negative correlation between levels of mean 25OH-D and the number of deaths caused by COVID-19/1 M [23]. Similar findings regarding mean 25OH-D levels and COVID-19 mortality rates were found by others in the study on data from 12 European countries [17]. However, a retrospective study on data from 20 European countries found a significant negative correlation for levels of mean vitamin D with COVID-19 cases, but not with death rates per 1 M of population [32]. But in a recent meta-analysis with a total of 1,368 COVID-19 positive patients, low VitD levels (i.e., deficiency) were significantly associated with poorer patient outcomes (e.g., development of ARDS, intensive care unit admission or death) and prognosis [33].

Of note, VitD could also give some protection from other infectious diseases. As stated in many reviews, studies showed that adequate VitD status is associated with lower risk of seasonal influenza and acute upper respiratory tract infections, Dengue fever, rotavirus infection, viral hepatitis B, as well as infections caused by some other coronavirus species; some interventional studies (however, not all) found that VitD supplementation could also reduce the risk of some aforementioned infectious diseases [4, 19, 27, 34-36].

Taken together, all these facts undoubtedly suggest relationships between low VitD and COVID-19. Some authors even suggested that patients having VitD deficiency should be considered as high risk group for getting severe illness from COVID-19 [37]. In addition, more and more humans have a risk to get less sun exposure due to "stay at home" mitigation strategies [3, 17], consequently, many of us could be named as members of risk group for VitD deficiency, and, paradoxically, can obtain a higher risk to get ill with

COVID-19 or other infections. Definitely, further observational studies are needed; some guidelines for research in this COVID-19 and VitD field were also recently suggested [31, 37].

5. Physiopathology

VitD, via its active form, calcitriol, has pluripotent activity on the human organism. Some of them, in the light of COVID-19, need to be discussed.

5.1. Maintenance of tissue integrity

VitD helps to maintain firm intercellular junctions, e.g., tight junctions, gap junctions, and adherent junctions. It is known that some viruses can disturb junction integrity, increasing infection by the virus and other microorganisms [4]. Strong physical barriers through effective cell junctions is the body's first line of defense against pathogens [19]. In addition, the maintenance of tight junctions is necessary to prevent the infiltration of immune cells in lungs and other respiratory tissues [38]; therefore, this might be important for prevention of developing severe pneumonia and ARDS in COVID-19.

5.2. Stimulates synthesis of human cathelicidin and defensins

In conjunction with toll-like receptors, those substances have an antimicrobial activity, e.g., killing bacterial cells and reducing viral replication [4, 19]. For instance, cathelicidin has direct antiviral activity against enveloped viruses such as hepatitis B virus, influenza, respiratory syncytial virus, and possibly the SARS-CoV-2 as well [14]. A cationic peptide LL-37, derived from cleavage of the cathelicidin peptide, binds to target microbes, creating a pore in vulnerable bacteria or destroying the envelope of envelope viruses such as those of the Corona virus family [39]. LL-37 is the only identified member of the cathelicidin family in humans that is expressed by respiratory epithelial cells [40]. It was demonstrated that during viral infection, calcitriol can be produced in the alveolar epithelial cells, and expression of

cathelicidin gene increases [41]. Human beta-defensin 2 can serve as a chemoattractant for other inflammatory cells involved in the defense system against pathogens [19].

5.3. Modulates specific immunity and inflammation, and can slow down the "cytokine storm"

VitD suppresses responses mediated by the T helper cell type 1 (Th1), by primarily repressing production of inflammatory cytokines IL-2 and interferon gamma (INFγ); also, promotes cytokine production by the T helper type 2 (Th2) cells, which helps enhance the indirect suppression of Th1 cells by complementing this with actions mediated by a multitude of cell types; and also promotes induction of the T regulatory cells, thereby inhibiting inflammatory processes [4]. Cytokine storm (CS) can be triggered by infectious diseases, rheumatic diseases, and tumor immunotherapy, and it generally presents as systemic inflammation and multiple organ failure [5]. It is well known that CS is one of the main mechanisms that can severely damage the lungs and other organs in patients suffering from severe COVID-19. CS is characterized by uncontrolled release of various pro-inflammatory cytokines and chemokines, e.g., interleukin (IL)-1 beta, IL-6, IL-1RA, TNF (tumor necrosis factor)-alpha, IL-17, monocytes chemoattractant protein-1, and many others, followed by increased serum ferritin levels, decreased natural killer (NK) cell count and alleviated NK function. All this results in damage of healthy cells, vascular leakage, severe exfoliation of alveolar epithelial cells, alveolar septal widening and damage, edema and inflammatory cell infiltration, ultimately leading to lung dysfunction and hypoxia, as well as to hypercoagulability, thrombosis, and multiple organ damage [2, 3, 38]. VitD is thought to be beneficial for prevention and/or treatment of CS, via the ability to decrease synthesis and secretion of various pro-inflammatory cytokines and to increase synthesis of some anti-inflammatory cytokines [4, 5, 13, 19, 38].

Of note, regulation of inflammation is of particular importance in older adults, in the obese and those with chronic conditions as they have constant low-grade chronic (systemic) inflammation and may already be pre-set for a higher inflammatory response if exposed to COVID-19. In other words, those aforementioned ones, in comparison to younger and otherwise healthier persons, are less capable to

"shut-down" their inflammatory and immune response at the right moment, when that response becomes more dangerous than protective. A heightened immune response in people who are VitD deficient may therefore increase the potential for CS and consequent ARDS [17, 42, 43].

5.4. Stimulates antioxidative processes

It is well known that reactive oxygen species (ROS) production is augmented in various inflammatory diseases, and increased release of ROS may also contribute to the damage of many organs and tissues. Therefore, via decreasing the intensiveness of inflammation, as mentioned above, VitD might also help to fight the oxidative stress. In addition, it was shown that VitD might act directly on the production of ROS, e.g., in mitochondria and endoplasmic reticulum [44, 45]. VitD also increases the gene expression of antioxidative enzymes, e.g., glutathione reductase and glutamate–cysteine ligase modifier subunit, and this was shown to help maintain higher levels of vitamin C, which is antioxidant and has antimicrobial activity as well, and is suggested as a potential agent for fighting COVID-19 [4].

5.5. Modulates renin-angiotensin system activity and increases angiotensin converting enzyme 2 receptor expression

Renin-angiotensin system (RAS), also known as renin-angiotensin-aldosterone system, is an important regulator of many actions in human organism, e.g., the vascular tone, diuresis, and blood pressure. However, during some diseases, the overactivity of RAS results in increase of angiotensin II production and may lead to undesirable effects, like prolonged vasoconstriction, arterial hypertension, augmented production of pro-inflammatory cytokines, thrombosis, fibrosis (e.g., in lungs), insulin resistance, and liver dysfunction [38, 46]. Some SARS-CoV-2-related COVID-19 symptoms and pathological processes like pulmonary hypertension, coagulopathy, diarrhea, anosmia, ageusia, dermatitis, autoimmune inflammation of the central nervous system, and damages to various organs such as the lung, heart, kidney, and testicle, are likely linked to an over-reaction of RAS in SARS-CoV-2-infected persons [28, 46]. VitD could reduce

the synthesis of renin in the kidneys, and VitD hypovitaminosis may contribute to increase of RAS activity [38, 46]. As shown in animal models, VitD may be beneficial in treating ARDS – it decreases lung permeability via modulating RAS activity (see the references in [47]).

VitD can also increase angiotensin converting enzyme 2 receptor (ACE2) expression in the lung tissue and this could ameliorate lung damage in case of some infections [23]. ACE2 is a transmembrane enzyme that catalyzes conversion of angiotensin II into angiotensin 1-9 (Ang 1-9), which is converted by ACE into the angiotensin vasodilator peptide 1-7 (Ang 1-7) that acts via the Mas receptor; Ang 1-7 has also hypotensive and diuretic effects [5]. SARS-CoV-2 uses ACE2 of target cells (e.g., type II pneumocytes) for fixation and penetration into these cells: spike glycoprotein of the virus binds to ACE2, and therefore, ACE2 was named a functional receptor of SARS-CoV-2 [1, 14]. The binding of COVID-19 spike protein to ACE2 has been shown to downregulate ACE2 and to promote ACE activity, forming more angiotensin II; and, in turn, to decrease Ang 1-7 production. This mechanism may be involved in the pathogenesis of pulmonary hypertension and insufficiency caused by SARS-CoV-2 infection [28, 48]. It might appear that increase of ACE2 expression (e.g., caused by VitD) could increase COVID-19 infection risk, although there are also some data that VitD could decrease ACE2 expression [3, 19]. Interestingly, angiotensin converting enzyme inhibitors and angiotensin II type I receptor blockers can also increase the expression of ACE2, but there is no evidence that such effect is indeed harmful (e.g., increasing mortality from COVID-19) [5]. Many authorities conclude that VitD, via decreasing RAS activity and (probably) increasing the expression of ACE2, overall has beneficial effects in case of COVID-19 infection [28, 38, 48-50].

5.6. Modulates the coagulation system

In severe COVID-19 cases, there is a high risk of coagulopathies, in particular, risk of thrombosis, including microvascular thrombosis in the lungs [51]. VitD hypovitaminosis is tightly associated with increased risk of thrombosis [52, 53]. It was demonstrated that VitD or its analogs could decrease the expression of tissue factor, as well as pro-thrombotic plasminogen activator inhibitor-1 and

thrombospondin-1, and upregulate the expression of thrombomodulin [54, 55]. Therefore, it seems possible that restoring normal VitD status could help in reducing risk of thrombosis.

5.7. Other effects

During COVID-19 disease, impaired functions of type-II pneumocytes decrease the surfactant levels and increase surface tension. VitD can stimulate surfactant synthesis in alveolar type-II cells, therefore, reduce surface tension [37] and improve lung function. VitD also helps in regeneration of endothelial lining and therefore may attenuate alveolar damage in case of ARDS [1]. Importantly, VitD can downregulate the development of pulmonary fibrosis, which has been widely described as a common complication of ARDS [56].

In conclusion, there are many different pathways where VitD is involved, most of them being very promising and supporting the beneficial role of VitD. However, the processes described above were discussed separately just for simplicity. Indeed, they are very complex and interconnected, and sometimes it might be very difficult to prove that certain mechanism is dependent mostly on VitD itself rather than on the other agents used for treatment or prevention of such infections like COVID-19.

6. Improving vitamin D status: variability in recommendations

To be honest, one must point out that, up till now, there is no clear strong evidence that VitD or its analogues could significantly impact the COVID-19 incidence, severity or mortality. But some clinical trials (e.g., NCT04334005) aiming to investigate those associations have already started, and that gives some hope that the exact VitD role in preventing COVID-19 and treating the patients will be elucidated. However, the COVID-19 is relatively a "new" medical problem and this can also explain the lack of evidence from large-scale RCTs regarding VitD role in prevention or treatment.

Nevertheless, VitD supplementation should be considered an adjuvant therapy for COVID-19 patients and also the whole population supplementation might be recommended. Improvement in circulating 25OH-D levels opens possibilities for slowing disease progression or even improving survival of patients, and keeping in mind the good tolerability and safety of even high doses of vitamin D (for almost all patients), this approach complies *primum non nocere* principle [37, 47]. Indeed, it was postulated that, in general, the risk of overdosing VitD tends to be next to zero, unless very large doses without physician supervision are being used for an extended period of time or mega-doses like 1 million IU daily are taken for a few days [19, 57]. It was also speculated that VitD could be a cheaper alternative for expensive drugs suggested for treatment of COVID-19 patients, e.g., tocilizumab [31], or might have potency to be used together with drugs approved for COVID-19 treatment, e.g., remdesivir [58]. It is reasonable to advocate VitD supplementation more widely during COVID-19 pandemic, since supplementing VitD in people who are already ill might be too late to be effective – in particular, in those patients who are presented to hospital in the hyperinflammatory stage of the disease [59, 60].

There is much controversy regarding overall "normal" or "optimal" serum 25OH-D levels [61, 62]. However, many scientists and clinicians prefer to use the cut-off value 30 ng/ml (75 nmol/l) as a lower bound of adequate VitD status, as it was suggested by the Endocrine Society [63], and some also suggested, in the light of COVID-19 pandemic, to achieve and maintain 30 ng/ml levels at least in the elderly [29] or in citizens of countries having high prevalence of VitD deficiency, particularly, in those patients with COVID-19 who are at high risk of intensive care unit admission [40]. In contrast, others suggested 40–60 ng/ml as an optimal range for human health, since such levels might reduce the risk of some infections (influenza, other coronaviral etc.), as well as the risk of certain types of cancer (e.g., colorectal), diabetes, rheumatic diseases, and pregnancy complications [4, 37, 57, 64]. Indeed, levels 40-60 ng/ml seem to be acceptable, since they are much lower than the "toxic" 25OH-D levels considered to be at ≥ 100 ng/ml [26] or at ≥ 150 ng/ml [40]. In addition, one could speculate that many patients won't benefit from 30–<40 ng/ml 25OH-D levels if they are "low-responders" to the VitD [64, 65]. Overall, it is clear that for majority of patients the minimal target is to achieve and to maintain at least 30 ng/ml 25OH-D levels, but it is desirable to achieve and maintain 40-60 ng/ml.

Who should be measured for serum 25OH-D levels? Some authorities proposed that all inpatient and outpatient populations with COVID-19 should be tested [37], while others suggested that serum 25OH-D levels had to be measured in every patient before starting the general COVID-19 treatment [20] and all hospitalized patients upon arrival should be tested for VitD status [66]. In regard to all population, it was suggested to test the groups of people who were likely to have low 25OH-D concentrations and could benefit from higher concentrations, such as pregnant women, the obese, people with chronic diseases, and the elderly [4, 67]. Testing of all hospital inpatients seems reasonable, at least from practical point of view, since many other blood tests are performed for these patients during their stay at hospital. However, testing of outpatients for 25OH-D levels seems to be problematic in some way: the COVID-19 patients (usually having mild COVID-19 illness or no symptoms) should keep strict rules of self-isolation, and the COVID-19-negative persons, during the COVID-19 pandemic, should avoid visiting any clinic or laboratory, unless it is extremely needed, particularly if they belong to the COVID-19 risk group (e.g., persons aged >60 years, or patients with certain chronic illnesses).

What dose of VitD should be recommended? In general, some experts still suggest taking small VitD doses, e.g. the Association of UK dietitians recommended recently 400 IU per day [68], and researches from TILDA study recommended minimal daily dose of 400 IU in general, and 600-800 IU daily dose for those who are housebound (due to illness or quarantine for an extended period), and 800-1,000 IU daily dose for persons older than 70 years [69]. While the other advised taking 800 IU to 2,000 IU daily for all hospital inpatients, nursing home residents and elderly, as well as for other vulnerable groups (e.g., those with obesity or overweight, those with diabetes, immunocompromised peoples, vegetarians, smokers, dark skinned, or healthcare workers) [34]. Recent review stated that 2,000 IU per day is enough to maintain strong immunity against respiratory infections [70]. USA experts suggested 800-4,000 IU daily dose, since there is no clear evidence that higher than 4,000 IU VitD doses are effective for COVID-19 prevention or treatment [71]. In line with this, daily or weekly, daily equivalent doses of 1,000-4,000 IU were proposed recently [72], and others also recommended not to exceed 4,000 IU daily dose, keeping in mind also VitD from other sources than supplements (i.e., the skin and fortified food) [73]. However, is it very questionable whether daily doses up to 2,000 IU would be really sufficient for achieving the desirable 25OH-D levels of

40-60 ng/ml, particularly in low VitD risk groups, since, in fact, those doses should be considered only as prophylactic for non-risk group patients (in regard to VitD deficiency) in order to achieve and maintain 25OH-D levels at ≥ 30 ng/ml [26].

Therefore, suggestions to take 2,000-5,000 IU or even higher doses in case of VitD deficiency seem more reasonable [4, 19, 64]. Interestingly, it was demonstrated that a daily oral supplement of 4,000 IU of VitD during 10 days represented an adequate dose to enhance dengue virus control and reduce the cytokine response, *in vitro*, suggesting that VitD can, in fact, restrict the viral assault [74].

Grant *et al.* [4] suggested, as alternative, for people at risk of influenza and/or COVID-19 consider taking 10,000 IU/day of vitamin D3 for a few weeks to rapidly raise 25OH-D levels up to 40-60 ng/ml, and after that 5,000 IU/day to maintain those levels ("Grant's schema"). However, they warned, when such high doses of vitamin D are being taken, calcium supplementation should not be high to reduce risk of hypercalcemia [4]; in addition, they recommended supplementation with magnesium (daily dose in the range 250–500 mg/d), since magnesium acts as a cofactor in many enzymes involved in VitD metabolism. Others suggested using Vit D loading doses of 200,000–300,000 IU in 50,000 IU capsules to reduce the risk and severity of COVID-19 [57].

For COVID-19 patients, in order to achieve 25OH-D levels above 40 ng/ml, Ebadi *et al*. [37] suggested 50,000 IU VitD twice a week in the first week (100,000 IU total), and to continue with the dose of 50,000 IU taken once a week for the second and third weeks. Then, following doses of 50,000 IU are recommended along with monitoring 25OH-D levels ("Ebadi's schema").

7. Vitamin D dosing: creating practice guidelines

In developing practical guidelines for VitD supplementation in adults during the COVID-19 pandemic, several main aspects should be considered:

7.1. Daily VitD dose up to 10,000 IU is considered generally safe for almost all patients [4]. Only few patients are "vitamin D hypersensitive", since they have or are at higher risk to develop hypercalcemia even from small supplemental VitD doses, e.g., in case of primary hyperparathyroidism or granulomatous

diseases such as sarcoidosis or active tuberculosis [26, 63, 75], or in rare cases when catabolism of VitD metabolites is impaired due to mutation of specific genes (e.g. CYP24A1) [76].

7.2. If recent 25OH-D measurement is not available, all those without prior supplementation could be considered as potential VitD deficient cases that might require high VitD doses to reach sufficient 25OH-D levels. Some patients, e.g., obese persons, the elderly, or patients having malabsorption syndrome (further in the text named VitD risk groups) might require much higher VitD doses [26, 59, 63].

7.3. If recent 25OH-D measurement is not available, those already taking supplements should increase their doses 1.5-2-fold, since the older target for their 25OH-D level supposed to be at least 30 ng/ml, and not at least 40 ng/ml as it is suggested currently. If the recommended doses from previous guidelines [26, 63] are multiplied by 2, they will be closer to or within the recommended range of 5,000-10,000 IU/d as discussed above.

7.4. If patient is on supplementation and the VitD supplement is well tolerated, consider using the same supplement.

7.5. Regarding dosing regime, taking supplements daily or once a week seems to be a better choice than taking mega-doses once in 1-3 months [4, 19, 35].

7.6. If currently 25OH-D measurement is not available and the large dose (either daily or weekly) is still prescribed, analysis of 25OH-D levels (preferably, serum calcium levels, too) should be performed in no longer than 1-1,5 months, for 2 reasons: a) to evaluate the efficacy of supplementation (very important in case malabsorption is suspected), and b) to detect VitD intoxication early enough [26, 32, 63, 77].

In summary, basing on those assumptions, brief simplified recommendations may be drafted:

1. All inpatients suffering from COVID-19 should be tested for 25OH-D levels at the admission day. If 25OH-D levels are below 40 ng/ml, VitD dosing according “Grant’s schema” or “Ebadi’s schema” should be started as soon as possible.

2. Outpatients with COVID-19 and those without COVID-19:

- if baseline 25OH-D levels are unknown (measurement is not possible at the moment):
  - for those already on supplementation, increase the doses 2-fold (however, daily doses should be within range 4,000-10,000 IU) for 1-1,5 month; then check 25OH-D levels;

- for those without prior supplementation, suggest VitD dose 4,000 IU/day (for those of VitD risk groups – consider 6,000-8,000 IU/day), or alternatively, 50,000 IU once a week; check 25OH-D levels in a 1-1,5 month.

- if current 25OH-D levels were measured, strategy depends on the results:
  - levels less than 40 ng/ml: if on supplementation, increase doses 2-fold (daily doses should be within range 4,000-10,000 IU) for 1-1,5 month, then check 25OH-D levels; if without prior supplementation - suggest VitD dose 4,000 IU/day (for those of VitD risk groups – consider 6,000-8,000 IU/day), or alternatively, 50,000 IU once a week; check 25OH-D levels in a 1-1,5 month.
  - levels 40-60 ng/ml: follow the current supplement dosing.
  - levels >60-100 ng/ml: suspend VitD supplementation for 1 or 2 months, then check 25OH-D levels.
  - levels >100 ng/ml: stop VitD supplementation, access calcemia and calciuria, administer treatment in case of hypercalcemia etc. as described elsewhere [26].

8. Conclusions

Vitamin D is almost undoubtedly linked to many viral infections, including COVID-19, although the mechanisms of those associations are still a large field for further research. The widely accepted vitamin D dosing guidelines are still under development, and large-scaled double-blind randomized trials are extremely warranted. However, the huge amount of data collected up to date presume that larger vitamin D doses can be safe and potentially beneficial for majority of patients in regard to COVID-19 infection. Overall, during COVID-19 pandemics, there is nothing to lose from the implementation of vitamin D supplementation in populations where vitamin D deficiency is prevalent, and potentially much to gain [60].

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References

1. Kakodkar P, Kaka N, and Baig MN. A Comprehensive Literature Review on the Clinical Presentation, and Management of the Pandemic Coronavirus Disease 2019 (COVID-19). *Cureus,* 2020; **12**(4): e7560. DOI: 10.7759/cureus.7560

2. Misra DP, Agarwal V, Gasparyan AY, and Zimba O. Rheumatologists' perspective on coronavirus disease 19 (COVID-19) and potential therapeutic targets. *Clin Rheumatol,* 2020; **39**(7): 2055-62. DOI: 10.1007/s10067-020-05073-9

3. Zabetakis I, Lordan R, Norton C, and Tsoupras A. COVID-19: The Inflammation Link and the Role of Nutrition in Potential Mitigation. *Nutrients,* 2020; **12**(5): 1466. DOI: 10.3390/nu12051466

4. Grant WB, Lahore H, McDonnell SL, *et al.* Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. *Nutrients,* 2020; **12**(4): 988. DOI: 10.3390/nu12040988

5. de Lucena TMC, da Silva Santos AF, de Lima BR, de Albuquerque Borborema ME, and de Azevedo Silva J. Mechanism of inflammatory response in associated comorbidities in COVID-19. *Diabetes Metab Syndr,* 2020; **14**(4): 597-600. DOI: 10.1016/j.dsx.2020.05.025

6. Carlberg C. The physiology of vitamin D-far more than calcium and bone. *Front Physiol,* 2014; **5**: 335. DOI: 10.3389/fphys.2014.00335

7. Holick MF. Vitamin D: extraskeletal health. *Endocrinol Metab Clin North Am,* 2010; **39**(2): 381-400. DOI: 10.1016/j.ecl.2010.02.016

8. Muller DN, Kleinewietfeld M, and Kvakan H. Vitamin D review. *J Renin Angiotensin Aldosterone Syst,* 2011; **12**(2): 125-8. DOI: 10.1177/1470320311410924

9. van Schoor NM and Lips P. Worldwide vitamin D status. *Best Pract Res Clin Endocrinol Metab,* 2011; **25**(4): 671-80. DOI: 10.1016/j.beem.2011.06.007

10. Lips P. Vitamin D status and nutrition in Europe and Asia. *J Steroid Biochem Mol Biol,* 2007; **103**(3-5): 620-5. DOI: 10.1016/j.jsbmb.2006.12.076

11. Pludowski P, Grant WB, Bhattoa HP*, et al.* Vitamin d status in central europe. *Int J Endocrinol,* 2014; **2014**: 589587. DOI: 10.1155/2014/589587

12. Wahl DA, Cooper C, Ebeling PR*, et al.* A global representation of vitamin D status in healthy populations. *Arch Osteoporos,* 2012; **7**(1): 155-72. DOI: 10.1007/s11657-012-0093-0

13. Lips P, Cashman KD, Lamberg-Allardt C*, et al.* Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society. *Eur J Endocrinol,* 2019; **180**(4): P23-P54. DOI: 10.1530/EJE-18-0736

14. Kara M, Ekiz T, Ricci V*, et al.* 'Scientific Strabismus' or two related pandemics: coronavirus disease and vitamin D deficiency. *Br J Nutr,* 2020; **124**(7): 736-41. DOI: 10.1017/S0007114520001749

15. Gueli N, Verrusio W, Linguanti A*, et al.* Vitamin D: drug of the future. A new therapeutic approach. *Arch Gerontol Geriatr,* 2012; **54**(1): 222-7. DOI: 10.1016/j.archger.2011.03.001

16. Mazahery H and von Hurst PR. Factors Affecting 25-Hydroxyvitamin D Concentration in Response to Vitamin D Supplementation. *Nutrients,* 2015; **7**(7): 5111-42. DOI: 10.3390/nu7075111

17. Laird E, Rhodes J, and Kenny RA. Vitamin D and Inflammation: Potential Implications for Severity of Covid-19. *Ir Med J,* 2020; **113**(5): 81.

18. Grober U and Kisters K. Influence of drugs on vitamin D and calcium metabolism. *Dermatoendocrinol,* 2012; **4**(2): 158-66. DOI: 10.4161/derm.20731

19. Hribar CA, Cobbold PH, and Church FC. Potential Role of Vitamin D in the Elderly to Resist COVID-19 and to Slow Progression of Parkinson's Disease. *Brain Sci,* 2020; **10**(5). DOI: 10.3390/brainsci10050284

20. Zhang L and Liu Y. Potential interventions for novel coronavirus in China: A systematic review. *J Med Virol,* 2020; **92**(5): 479-90. DOI: 10.1002/jmv.25707

21. Marik PE, Kory P, and Varon J. Does vitamin D status impact mortality from SARS-CoV-2 infection? *Med Drug Discov,* 2020; **6**: 100041. DOI: 10.1016/j.medidd.2020.100041

22. Garg M, Al-Ani A, Mitchell H, Hendy P, and Christensen B. Editorial: low population mortality from COVID-19 in countries south of latitude 35 degrees North-supports vitamin D as a factor determining severity. Authors' reply. *Aliment Pharmacol Ther,* 2020; **51**(12): 1438-39. DOI: 10.1111/apt.15796

23. Ilie PC, Stefanescu S, and Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. *Aging Clin Exp Res,* 2020; **32**(7): 1195-98. DOI: 10.1007/s40520-020-01570-8

24. Giustina A and Formenti A. Re: Preventing a covid-19 pandemic Can high prevalence of severe hypovitaminosis D play a role in the high impact of Covid infection in Italy? *BMJ,* 2020: 368.

25. Carter SJ, Baranauskas MN, and Fly AD. Considerations for Obesity, Vitamin D, and Physical Activity Amid the COVID-19 Pandemic. *Obesity (Silver Spring),* 2020; **28**(7): 1176-77. DOI: 10.1002/oby.22838

26. Rusinska A, Pludowski P, Walczak M*, et al.* Vitamin D Supplementation Guidelines for General Population and Groups at Risk of Vitamin D Deficiency in Poland-Recommendations of the Polish Society of Pediatric Endocrinology and Diabetes and the Expert Panel With Participation of

National Specialist Consultants and Representatives of Scientific Societies-2018 Update. *Front Endocrinol (Lausanne),* 2018; **9**: 246. DOI: 10.3389/fendo.2018.00246

27. Molloy EJ and Murphy N. Vitamin D, Covid-19 and Children. *Ir Med J,* 2020; **113**(4): 64.

28. La Vignera S, Cannarella R, Condorelli RA*, et al.* Sex-Specific SARS-CoV-2 Mortality: Among Hormone-Modulated ACE2 Expression, Risk of Venous Thromboembolism and Hypovitaminosis D. *Int J Mol Sci,* 2020; **21**(8). DOI: 10.3390/ijms21082948

29. D'Avolio A, Avataneo V, Manca A*, et al.* 25-Hydroxyvitamin D Concentrations Are Lower in Patients with Positive PCR for SARS-CoV-2. *Nutrients,* 2020; **12**(5). DOI: 10.3390/nu12051359

30. Hastie CE, Mackay DF, Ho F*, et al.* Vitamin D concentrations and COVID-19 infection in UK Biobank. *Diabetes Metab Syndr,* 2020; **14**(4): 561-65. DOI: 10.1016/j.dsx.2020.04.050

31. Silberstein M. Vitamin D: A simpler alternative to tocilizumab for trial in COVID-19? *Med Hypotheses,* 2020; **140**: 109767. DOI: 10.1016/j.mehy.2020.109767

32. Ali N. Role of vitamin D in preventing of COVID-19 infection, progression and severity. *J Infect Public Health,* 2020. DOI: 10.1016/j.jiph.2020.06.021

33. Munshi R, Hussein MH, Toraih EA*, et al.* Vitamin D insufficiency as a potential culprit in critical COVID-19 patients. *J Med Virol,* 2020. DOI: 10.1002/jmv.26360

34. McCartney DM and Byrne DG. Optimisation of Vitamin D Status for Enhanced Immuno-protection Against Covid-19. *Ir Med J,* 2020; **113**(4): 58.

35. Martineau AR, Jolliffe DA, Hooper RL*, et al.* Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ,* 2017; **356**: i6583. DOI: 10.1136/bmj.i6583

36. Ginde AA, Mansbach JM, and Camargo CA, Jr. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. *Arch Intern Med,* 2009; **169**(4): 384-90. DOI: 10.1001/archinternmed.2008.560

37. Ebadi M and Montano-Loza AJ. Perspective: improving vitamin D status in the management of COVID-19. *Eur J Clin Nutr,* 2020; **74**(6): 856-59. DOI: 10.1038/s41430-020-0661-0

38. Martin Gimenez VM, Inserra F, Tajer CD*, et al.* Lungs as target of COVID-19 infection: Protective common molecular mechanisms of vitamin D and melatonin as a new potential synergistic treatment. *Life Sci,* 2020; **254**: 117808. DOI: 10.1016/j.lfs.2020.117808

39. Crane-Godreau MA, Clem KJ, Payne P, and Fiering S. Vitamin D Deficiency and Air Pollution Exacerbate COVID-19 Through Suppression of Antiviral Peptide LL37. *Front Public Health,* 2020; **8**: 232. DOI: 10.3389/fpubh.2020.00232

40. Hadizadeh F. Supplementation with vitamin D in the COVID-19 pandemic? *Nutr Rev,* 2020. DOI: 10.1093/nutrit/nuaa081

41. Aygun H. Vitamin D can prevent COVID-19 infection-induced multiple organ damage. *Naunyn Schmiedebergs Arch Pharmacol,* 2020; **393**(7): 1157-60. DOI: 10.1007/s00210-020-01911-4

42. Iddir M, Brito A, Dingeo G*, et al.* Strengthening the Immune System and Reducing Inflammation and Oxidative Stress through Diet and Nutrition: Considerations during the COVID-19 Crisis. *Nutrients,* 2020; **12**(6). DOI: 10.3390/nu12061562

43. Meftahi GH, Jangravi Z, Sahraei H, and Bahari Z. The possible pathophysiology mechanism of cytokine storm in elderly adults with COVID-19 infection: the contribution of "inflame-aging". *Inflamm Res,* 2020; **69**(9): 825-39. DOI: 10.1007/s00011-020-01372-8

44. Berthelot JM, Drouet L, and Liote F. Kawasaki-like diseases and thrombotic coagulopathy in COVID-19: delayed over-activation of the STING pathway? *Emerg Microbes Infect,* 2020; **9**(1): 1514-22. DOI: 10.1080/22221751.2020.1785336

45. Sanz R, Mazzei L, Santino N, Ingrasia M, and Manucha W. Vitamin D-mitochondria cross-talk could modulate the signaling pathway involved in hypertension development: a translational integrative overview. *Clin Investig Arterioscler,* 2020; **32**(4): 144-55. DOI: 10.1016/j.arteri.2020.02.002

46. Annweiler C, Cao Z, Wu Y*, et al.* Counter-regulatory 'Renin-Angiotensin' System-based Candidate Drugs to Treat COVID-19 Diseases in SARS-CoV-2-infected patients. *Infect Disord Drug Targets,* 2020. DOI: 10.2174/1871526520666200518073329

47. Jakovac H. COVID-19 and vitamin D-Is there a link and an opportunity for intervention? *Am J Physiol Endocrinol Metab,* 2020; **318**(5): E589. DOI: 10.1152/ajpendo.00138.2020

48. Cao Z, Wu Y, Faucon E, and Sabatier JM. SARS-CoV-2 & Covid-19: Key-Roles of the 'Renin-Angiotensin' System / Vitamin D Impacting Drug and Vaccine Developments. *Infect Disord Drug Targets,* 2020; **20**(3): 348-49. DOI: 10.2174/1871526520999200505174704

49. Mansur JL. Letter: low population mortality from COVID-19 in countries south of latitude 35 degrees North supports vitamin D as a factor determining severity. *Aliment Pharmacol Ther,* 2020; **52**(2): 411-12. DOI: 10.1111/apt.15820

50. Kumar D, Gupta P, and Banerjee D. Letter: does vitamin D have a potential role against COVID-19? *Aliment Pharmacol Ther,* 2020; **52**(2): 409-11. DOI: 10.1111/apt.15801

51. Bilezikian JP, Bikle D, Hewison M*, et al.* MECHANISMS IN ENDOCRINOLOGY: Vitamin D and COVID-19. *Eur J Endocrinol,* 2020. DOI: 10.1530/EJE-20-0665

52. Tian Y and Rong L. Letter: Covid-19, and vitamin D. Authors' reply. *Aliment Pharmacol Ther,* 2020; **51**(10): 995-96. DOI: 10.1111/apt.15764

53. Mohammad S, Mishra A, and Ashraf MZ. Emerging Role of Vitamin D and its Associated Molecules in Pathways Related to Pathogenesis of Thrombosis. *Biomolecules,* 2019; **9**(11). DOI: 10.3390/biom9110649

54. Quesada-Gomez JM, Entrenas-Castillo M, and Bouillon R. Vitamin D receptor stimulation to reduce acute respiratory distress syndrome (ARDS) in patients with coronavirus SARS-CoV-2 infections: Revised Ms SBMB 2020_166. *J Steroid Biochem Mol Biol,* 2020; **202**: 105719. DOI: 10.1016/j.jsbmb.2020.105719

55. Verdoia M and De Luca G. Potential role of hypovitaminosis D and Vitamin D supplementation during COVID-19 pandemic. *QJM,* 2020. DOI: 10.1093/qjmed/hcaa234

56. Panfili FM, Roversi M, D'Argenio P*, et al.* Possible role of vitamin D in Covid-19 infection in pediatric population. *J Endocrinol Invest,* 2020. DOI: 10.1007/s40618-020-01327-0

57. Wimalawansa SJ. Global epidemic of coronavirus—COVID-19: what can we do to minimize risks. *Eur. J. Biomed. Pharm. Sci.,* 2020; **7**(3): 432–38.

58. Arya A and Dwivedi VD. Synergistic effect of vitamin D and remdesivir can fight COVID-19. *J Biomol Struct Dyn,* 2020: 1-2. DOI: 10.1080/07391102.2020.1773929

59. Rhodes JM, Subramanian S, Laird E, Griffin G, and Kenny RA. Perspective: Vitamin D deficiency and COVID-19 severity - plausibly linked by latitude, ethnicity, impacts on cytokines, ACE2 and thrombosis. *J Intern Med,* 2020. DOI: 10.1111/joim.13149

60. Martineau AR and Forouhi NG. Vitamin D for COVID-19: a case to answer? *Lancet Diabetes Endocrinol,* 2020; **8**(9): 735-36. DOI: 10.1016/S2213-8587(20)30268-0

61. Ross AC, Manson JE, Abrams SA*, et al.* The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab,* 2011; **96**(1): 53-8. DOI: 10.1210/jc.2010-2704

62. Pludowski P, Holick MF, Grant WB*, et al.* Vitamin D supplementation guidelines. *J Steroid Biochem Mol Biol,* 2018; **175**: 125-35. DOI: 10.1016/j.jsbmb.2017.01.021

63. Holick MF, Binkley NC, Bischoff-Ferrari HA*, et al.* Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab,* 2011; **96**(7): 1911-30. DOI: 10.1210/jc.2011-0385

64. Charoenngam N and Holick MF. Immunologic Effects of Vitamin D on Human Health and Disease. *Nutrients,* 2020; **12**(7): 2097. DOI: 10.3390/nu12072097

65. Carlberg C and Haq A. The concept of the personal vitamin D response index. *J Steroid Biochem Mol Biol,* 2018; **175**: 12-17. DOI: 10.1016/j.jsbmb.2016.12.011

66. Caccialanza R, Laviano A, Lobascio F*, et al.* Early nutritional supplementation in non-critically ill patients hospitalized for the 2019 novel coronavirus disease (COVID-19): Rationale and feasibility of a shared pragmatic protocol. *Nutrition,* 2020; **74**: 110835. DOI: 10.1016/j.nut.2020.110835

67. Grant WB, Al Anouti F, and Moukayed M. Targeted 25-hydroxyvitamin D concentration measurements and vitamin D3 supplementation can have important patient and public health benefits. *Eur J Clin Nutr,* 2020; **74**(3): 366-76. DOI: 10.1038/s41430-020-0564-0

68. The association of UK Dietitians. *COVID-19 / Coronavirus - Advice for the General Public*. 2020. Available from: https://www.bda.uk.com/resource/covid-19-corona-virus-advice-for-the-general-public.html. Accessed: May 23, 2020

69. Laird E and Kenny RA. *Vitamin D deficiency in Ireland – implications for COVID-19. Results from The Irish Longitudinal Study on Ageing (TILDA)*. 2020. Available from: https://tilda.tcd.ie/publications/reports/pdf/Report_Covid19VitaminD.pdf. Accessed: May 23, 2020

70. Calder PC, Carr AC, Gombart AF, and Eggersdorfer M. Optimal Nutritional Status for a Well-Functioning Immune System Is an Important Factor to Protect against Viral Infections. *Nutrients,* 2020; **12**(4). DOI: 10.3390/nu12041181

71. Adams KK, Baker WL, and Sobieraj DM. Myth Busters: Dietary Supplements and COVID-19. *Ann Pharmacother,* 2020; **54**(8): 820-26. DOI: 10.1177/1060028020928052

72. Chakhtoura M, Napoli N, and El Hajj Fuleihan G. Commentary: Myths and facts on vitamin D amidst the COVID-19 pandemic. *Metabolism,* 2020; **109**: 154276. DOI: 10.1016/j.metabol.2020.154276

73. Lanham-New SA, Webb AR, Cashman KD*, et al.* Vitamin D and SARS-CoV-2 virus/COVID-19 disease. *BMJ Nutrition, Prevention & Health,* 2020; **3**(1): 106-10. DOI: 10.1136/bmjnph-2020-000089

74. Arboleda JF and Urcuqui-Inchima S. Vitamin D Supplementation: A Potential Approach for Coronavirus/COVID-19 Therapeutics? *Front Immunol,* 2020; **11**: 1523. DOI: 10.3389/fimmu.2020.01523

75. Grant WB and Boucher BJ. Requirements for Vitamin D across the life span. *Biol Res Nurs,* 2011; **13**(2): 120-33. DOI: 10.1177/1099800410391243

76. Schlingmann KP, Kaufmann M, Weber S*, et al.* Mutations in CYP24A1 and idiopathic infantile hypercalcemia. *N Engl J Med,* 2011; **365**(5): 410-21. DOI: 10.1056/NEJMoa1103864

77. Collins A. Practice implications for preventing population vulnerability related to vitamin D status. *J Am Assoc Nurse Pract,* 2013; **25**(3): 109-18. DOI: 10.1111/1745-7599.12005