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MINI REVIEW ARTICLE

COVID-19 and vitamin D supplementation: Is there any evidence based to reduce the risk?

Amina Chentouf *

Faculty of Medical Sciences, Oran1 University, Algeria

Abstract

Several studies and meta-analysis suggest that vitamin D deficiency constitutes a risk factor for acute respiratory infections while supplementation may reduce this risk. Given the current context of the COVID-19 pandemic, the role of vitamin D supplementation in the prevention and improvement of the prognosis of affected patients has been suggested by some studies and refuted by others. Through this article, we report the mechanisms of action and properties of vitamin D, and we discuss the different hypotheses of the involvement of vitamin D in respiratory infections, especially COVID-19 in the light of the most recent published data.

Keywords: COVID-19, SARS-CoV-2, Vitamin D deficiency, Vitamin D supplementation, 1.25-dihydroxyvitamin D.

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1 Introduction

In recent years, vitamin D has been the subject of considerable attention, which has enabled major advances in the knowledge of its metabolism and its mechanisms of action. Indeed, over the past decade, the understanding of the role of essential micronutrients in the genesis of several diseases has changed dramatically. Data around vitamin D has increased significantly in recent years. Vitamin D deficiency is frequent, relatively misdiagnosed, and affects all age groups. It is estimated that a billion people around the world would be affected, and 50% to 80% of the elderly would have such deficiency [1]. Moreover, vitamin D deficiency is frequent in the North African population, particularly in Algeria where it is associated with an increased risk of type 1 diabetes [2]. This constitutes a major public health issue because it could have significant repercussions on health [3].

2 Origin of vitamin D

Unlike other vitamins being exclusively provided by food, vitamin D has a dual origin: exogenous, furnished by daily food intake, and endogenous [4] occurring in the epidermis, following exposure to sunlight ultraviolet B (UVB) radiation. Vitamin D is made from 7-dehydrocholesterol, an intermediate in the synthesis of cholesterol, present in cell membranes of the dermis and epidermis. The energy supplied by UVB rays contributes to its conversion into pre-vitamin D3, rapidly converted by heat into vitamin D3 and then released into blood circulation. The vitamin D synthesis is therefore closely linked to sun exposure.

It has long been known that the endogenous synthesis of vitamin D is influenced by seasonal variations, timing of exposure and latitude [5]. Indeed, winter is associated with very reduced neo-synthesis. In addition, beyond the 35th degree of north latitude, the synthesis capacity is considered to be absent between November and February. Other anthropomorphic parameters such as age, skin pigmentation, obesity or overweight tend to reduce its synthesis [6].

Several factors, linked to the modern way of life, also promote insufficiency. This is in particular the case of sedentary lifestyle leading to less exposure to the sun, as well as the increase in the use of sunscreens [5]. Air pollution by blocking part of UVB radiation also contributes to the reduction of vitamin D synthesis. Furthermore, socio-cultural aspects such as wearing covering clothing also limit endogenous synthesis.

Vitamin D is stored in different tissues including adipose tissue and muscle [7], but this reserve does not ensure a sufficient intake of vitamin D during winter.

We are therefore currently in a delicate situation: the rate of vitamin D provided by food is low and the neosynthesis previously covering a considerable part of vitamin D needs is considerably reduced due to modern lifestyle and very limited vitamin D storage capacity, that largely explains the high prevalence of vitamin D deficiency [8].

3 Vitamin D metabolism

Vitamin D from food being absorbed in the proximal part of the small intestine via cholesterol transporters, is then transported by chylomicrons to the liver [9]. Neosynthesized vitamin D is predominantly linked to Vitamin D Binding Protein (VDBP) [10]. When vitamin D metabolites are linked to VDBP, they are less accessible than circulating free forms, thereby prolonging their plasma half-life and stabilizing their concentrations [11].

As discussed above, vitamin D is stored primarily in fat and muscle cells as both vitamin D and 25 (OH) D. This storage, especially in adipose tissue, could be the cause of deficiencies by volumetric dilution, particularly in obese people [12].

In liver, vitamin D is captured and hydroxylated into 25-hydroxyvitamin D (25 (OH) D) whose half-life is relatively long

* **Corresponding author**: Amina Chentouf. Faculty of Medical Sciences, Oran1 University. Email: chentouf.amina@univ-oran1.dz

(3 to 4 weeks). This latter circulates in the blood, bound to the VDBP, then it is endocytosed in the proximal renal tubule cells prior being re-excreted into the bloodstream, or hydroxylated in 1.25-dihydroxyvitamin D (1,25 (OH) 2D) or calcitriol, considered the main active form of vitamin D [13]. The half-life of 1.25 (OH) 2D is too short (approximately 4 hours) and its concentration a thousand times lower than that of 25 (OH) D as shown on Figure 1.

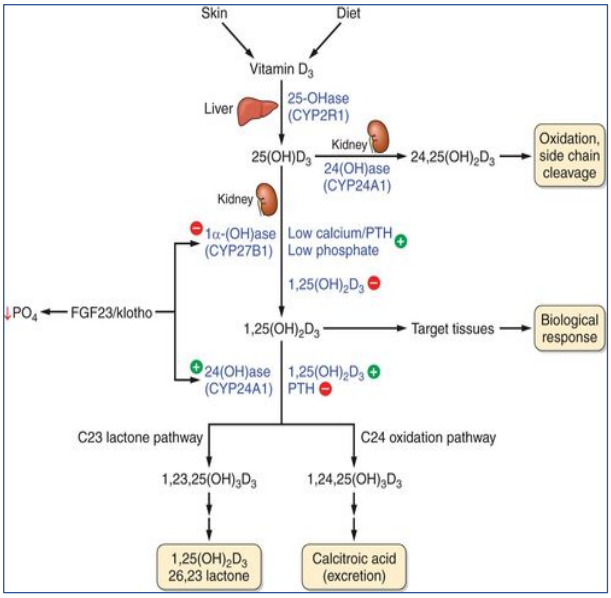

Figure 1: Metabolic pathway for vitamin D [4]

4 Mechanisms of action

The actions of the active metabolite 1.25 (OH) 2D require binding to a specific receptor, the Vitamin D Receptor (VDR), as well as translocation of the occupied VDR to the cell nucleus[14]. In the nucleus, the VDR-1.25 (OH) 2D couple binds to specific DNA sequences of promoter regions and controls the genes expression involved in bone metabolism, but also in the proliferation and differentiation of numerous cell types.

The main recognized actions of 1.25 (OH) D are intestinal and bone. In the small intestine cell, the action to promote the active absorption of calcium is carried out through a receptor coupled to retinoic acid VDR to increase the expression of the epithelial calcium channel TRPV6. In bones, the action is manifested by an increase in the expression of Receptor Activator of nuclear factor -κB ligand (RANKL), which will interact with its RANK receptor on the pre-osteoclast to induce mature osteoclastic activity with release of calcium and phosphorus [15].

5 Extra osseous properties of vitamin D

Vitamin D possesses other properties (anti-inflammatory, anti-cancer, cardiovascular protector and anti-infective) [16-18]. Indeed, vitamin D receptors (VDR) are present in most tissues (immune system, cardiovascular system, lung, kidney, pancreas, intestine, brain, bones, and muscles). This explains the extra-osseous effects of vitamin D on the function of the tissue or organ where they were detected. In addition, it has been shown that the expression of more than 900 genes, some of which are involved in autoimmune diseases [19], cancers [20] and arterial hypertension, is modulated by the effects of the 1-25-(OH) 2D complex/VDR. In addition, the demonstration of 1-alpha hydroxylase in certain extrarenal cells, thus allowing local synthesis of 1-25 (OH) 2D[21], also supports the growing interest in the extraosseous effects of vitamin D. It is therefore not surprising that several associations have been shown between a vitamin D deficiency and a large number of pathologies (cardiovascular diseases [22], hypertension[23], diabetes [24], cancers [25], inflammatory or dysimmune diseases [26-30] and infections [31,32].

6 Vitamin D: immune-regulatory effects and respiratory infections

Besides its classic effects, vitamin D presents other lesser-known effects and a wide range of activities. Indeed, recent studies have shown the beneficial role of vitamin D in inflammatory response associated with metabolic syndrome [33] and autoimmune diseases such as Behçet disease [34]. In this context, the immunoregulatory function of vitamin D is argued by downregulation of pro-inflammatory cytokine and Nitric oxide synthase 2 expression. Otherwise, the association between vitamin D and acute respiratory infections was studied by several researchers [35,36]. In the literature, convincing data link vitamin D deficiency with susceptibility to both acute and chronic infections [18,32]. Vitamin D is believed to be involved in the risk of infection for its effects on innate and adaptive immunity [37,38].

Indeed, the actions of vitamin D on macrophage defense against viral pathogens have shown a predominant impact on cytokine response rather than on viral killing. Vitamin D stimulates macrophage maturation and prevents macrophages from releasing high amounts of inflammatory cytokines and chemokines [39]. When exposed to an infectious agent, monocytes and macrophages overexpress the Toll-like receptor "Toll-like receptor", VDR and 1-alpha-hydroxylase. Activation of VDR induces both a decrease in pro-inflammatory cytokines (tumor necrosis factor-alpha, interleukin-1, interferon-alpha) and an increase in anti-inflammatory cytokines (especially interleukin-10). Locally produced 1-25- (OH) 2D activates macrophages by driving the autophagy mechanism and the process of synthesizing antimicrobial peptides, especially cathelicidin [40], which is involved in the body's first line defense against a pathogen [41]. Antimicrobial peptides are considered natural antibiotics that will help destroy the infectious agent in bacterial infections and reduce the risk of influenza infections [32] and possibly the virus causing the disease COVID-19.

7 Vitamin D and COVID-19

The relationship between vitamin D deficiency and COVID-19 infection is a very controversial topic. Indeed, in a recent study on 1.326 COVID-19 patients, Raisi-Estabragh *et al.* have rejected the hypothesis of a correlation between the risk of severe COVID-19 forms and vitamin D deficiency [42]. Furthermore, another study showed that vitamin D supplementation reduced

Th2 responses during Aspergillus infection in patients with cystic fibrosis [43]. However, it is admitted that pulmonary aspergillosis is an opportunistic infection in patients with severe forms of COVID-19 [44]. The authors suggest that vitamin D supplementation could expose COVID-19 patients to the risk of secondary Aspergillosis.

Furthermore, several studies support the hypothesis of susceptibility to COVID-19 in individuals with vitamin D deficiency [45,46]. Indeed, a recent review suggests that vitamin D deficiency could be a risk factor for the occurrence and severity of infection with COVID-19 disease [45]. The authors report two arguments supporting the role of vitamin D in reducing the risk of COVID-19. On the one hand, the COVID-19 pandemic occurred in winter in the northern hemisphere, at a time when 25- (OH) D3 concentrations are lowest. On the other hand, morbidity is low in the southern hemisphere, which was then in the late summer period [45-47]. In addition, two observations are associated with a lower 25- (OH) D3 concentration: first, the vitamin D deficiency contributes to acute respiratory infections and, then, the lethality rate due to COVID-19 increases with age and with associated comorbidities, especially chronic diseases[45,48].

In a recent study involving 20 European countries, negative correlations between the average levels of vitamin D and mortality by COVID-19 were observed. Vitamin D levels were very low in the elderly population, being the most vulnerable to COVID-19 infection [49]. Another study showed that patients with COVID-19 and vitamin D deficiency had a poorer prognosis than those with high vitamin D levels [50].

Several observational studies and clinical trials have indicated that sun exposure or vitamin D supplementation reduces the risk of influenza and may do so for COVID-19 as well [51,52].

Moreover, supplementation to achieve concentrations of at least 40-50ng / mL (100-125 nmol / L) may help reduce hospital infections [53,54].

Ebadi *et al.* [55] suggested using 50,000 IU of vitamin D twice a week to boost the immune system. The intake can be repeated after a week to quickly replenish the body's stores of vitamin D, which could reduce the risk and severity of COVID-19. In terms of safety, monthly supplementation with 100,000 IU of vitamin D3 does not significantly increase the risk of kidney stones or hypercalcemia [56].

Vitamin D supplementation may therefore reduce the risk of the onset and severity of infection with COVID-19 disease. Management of the COVID-19 pandemic therefore encourages ensuring that the population at risk does not suffer from vitamin D deficiency. Assessment of vitamin D status and maintenance of optimal serum levels should be considered for anyone at risk of COVID-19 such as old people as well as patients with diabetes, asthma and obesity. Grant *et al.* recommended that all people at risk of COVID-19, and in particular hospital staff, should receive treatment with 10.000 IU of vitamin D per day for a few weeks to rapidly increase serum vitamin D levels, followed by 5.000 IU per day [45]. The purpose of supplementation should be to increase serum 25- (OH) D3 levels above 40 to 60 ng/mL [45].

To date, no specific treatment for COVID-19 has been identified. The need to act quickly justifies the reuse of existing drugs, some of which may offer hope to help control the COVID-19 pandemic. The hypothesis that vitamin D is a timely adjuvant therapy should be considered. The recommendation of broad supplementation, inexpensive, well tolerated and without harmful effects even with high doses, aimed at reducing the occurrence and/or severity of COVID-19 thus deserves, in our opinion, to be seriously considered [57]. It would also be reasonable to consider vitamin D supplementation in people at risk of deficiency due to their home confinement. Thus, supplementation or exposure to the sun "at window", a balanced diet and physical exercise would be beneficial for overall health, physical and mental, during this COVID-19 pandemic.

The role of vitamin D in protecting individuals at risk or in the management of SARS-CoV-2 infection has yielded potentially encouraging results. Vitamin D is believed to be involved in the risk of acute viral respiratory infections for its effects on innate and adaptive immunity as indicated above. However, more studies are required to elucidate the possible main mechanisms of action of vitamin D in fighting these viral infections. In addition, there is still a lack of consistent research allowing objectifying a cause and effect relationship, to be able to give indications on the supplementation necessary to reduce the risk of acute respiratory viral infections such as COVID-19. The preventive effect of vitamin D also remains to be defined by placebo-controlled intervention studies on major events and deaths from COVID-19 causes.

8 Conclusions

Vitamin D is involved in "integral health" and should be considered as one of the essential factors that support the fight against certain diseases. Several data support the role of vitamin D, which acts as a protector against acute respiratory infections. However, additional studies are essential to elucidate the main mechanisms of action of vitamin D in the fight against SARS-CoV-2 infections and to point out a significant preventive impact, by randomized intervention studies, on morbidity and mortality in COVID-19.

Assessing vitamin D status and maintaining optimal serum levels should be considered for anyone at risk for COVID-19. Daily or weekly vitamin D supplementation may reduce the risk of developing a SARS-CoV-2 infection. The use of vitamin D in the drug approach to decrease the risk of COVID-19 deserves to be considered pending the results of randomized clinical trials launched in Spain (NCT04334005), Argentina (NCT04411446), France (NCT04344041) and Iran (IRCT20200324046850N1).

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ORCID:
Amina CHENTOUF: https://orcid.org/0000-0002-6004-019X

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