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Vitamin D Supplementation May Prevent the Severity of Sars-Cov-2 Infection: A Prospective Study among Moroccan Health Professionals

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Abstract

Background: Vitamin D deficiency can increase susceptibility to viral infections such as Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2). The current study has two aims; first, measuring 25-hydroxyvitamin D (25 (OH) D) concentration in a group of Moroccan health professionals, in order to determine the prevalence of hypo-vitaminosis D and to supplement those at risk. Second, conducting a 5-month flow-up; In order to detect individuals contracting SARS-CoV-2 infection, whether or not they manifest severe respiratory symptoms, and therefore to evaluate the impact of Vitamin D supplementation on their immune system.

Methods: This is a prospective, observational study, which had been occurred at Children's hospital of UHC Ibn Sina of Rabat. Measurement of 25-hydroxyvitamin D was determined by ARCHITECT 25-OH VITAMIN D at the biochemistry laboratory of Ibn Sina Hospital in Rabat. After 25 (OH) D measurements, a supplementation of cholecalciferol 100,000 IU VITD 3 was administered according to its status for each participant.

Results: Sixty-five participants were enrolled in this study; 85% were females. The average value of 25-hydroxyvitamin D in the general population was 17 ± 7 ng/ml, with extreme values of 7 and 34 ng/ml. Ninety-two percent of the studied population presented hypo-vitaminosis D. Thirteen participants (20%) were infected with SARS-CoV-2. Although, no cases required hospitalization or respiratory support.

Conclusion: It appears necessary to supplement individuals at risk of contracting respiratory viral infections, particularly health professionals who are on the front line against COVID-19 pandemic.

Keywords: Vitamin-D • Hypovitaminosis-D • SARS-CoV-2 • COVID-19 • Supplementation • Health professionals

Introduction

Vitamin D (VITD) is a fat soluble pro-hormone, synthesized in the dermis, it is essential for overall health, especially bone health. Moreover, VITD plays many functions; as anti-infectious agent, anti-inflammatory agent, anti-tumour and cardiovascular protector [1]. Human body gets VITD from two natural sources; a fungi-based source (Vitamin D2 or ergocalciferol) and an animal-based source (vitamin D3 or cholecalciferol) [2].

Apart from oral supplementation, it is difficult to reach an optimal serum 25-hydroxyvitamin D (25(OH) D) concentration, which must be greater than or equal to 30 ng/mL to maintain good bone health [3]. In the Middle East and North Africa (MENA), hypovitaminosis D is estimated at 96% [4]. Our country, Morocco, belongs to regions where VITD levels are the lowest; consequently, hypovitaminosis D is very common, estimated at more than 90% among women [5,6] and 85% among men [7]. VITD status decreases as age increases. Its level is not always associated with ageing. In fact; several risk factors are involved. Particularly, the limited sun exposure, sunscreen use, darker skin tones, and the high body mass index (BMI). Hence, a systematic supplementation of VITD is extremely necessary [8-11].

The VITD is known for its role and effects on the immune system. It regulates the immune response, against any type of bacterial or viral infection, by eliminating cytokine inflammatory response [12-14]. Therefore, hypovitaminosis D can enhance susceptibility to viral respiratory infections that cause many complications. For instance, the acute respiratory distress that is one of the symptoms of COVID-19, caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), triggering the global pandemic of COVID-19 that has imposed catastrophic effects worldwide [15].

Given the above on the protective role of VITD against developing an acute respiratory tract infection caused by COVID-19, it is interesting to provide evidence-based arguments for VITD to be included in a preventive strategy against SARS-CoV-2 infection. Accordingly, we hypothesize the necessity to supply front line Moroccan health professionals with VITD supplements. To check this hypothesis, the present study was conducted to measure the status of VITD in a cohort of Moroccan health professionals in the University Hospital Center (UHC) of Rabat; those with hypo-vitaminosis

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D were given VITD supplements. Then, a 5-month follow-up was conducted, to identify individuals contracting SARS-CoV-2 infection, and to evaluate the impact of VITD supplementation on their immune system against severe respiratory symptoms.

Methodology

Study design

This is a prospective, observational study that took place from July 1st, 2020 to January 31st 2021. Participant recruitment was conducted at Children's Hospital. Serum 25 (OH) D concentrations was measured at the biochemistry laboratory of Ibn Sina Hospital of Rabat.

Data collection and analysis

We have voluntarily and indiscriminately included a group of health professionals, including physicians, nurses, paramedics and support workers, of both genders that have never been infected with SARS-CoV-2.

Participants were interviewed using a survey checking the following parameters:

- Epidemiological data and general characteristics
- Health state
- Eating habits
- Biological analysis: VITD, Calcium, Phosphorus

Measurement of serum 25 (OH) D levels

Blood samples were taken from all participants in July 2020, from 8:30 a.m. to 9:30 a.m. by venepuncture, collected in dry tubes and quickly transported in a bad of ice to the biochemistry laboratory to measure 25 (OH) D, calcium and phosphorus concentrations.

Serum 25 (OH) D was measured by ARCHITECT 25-OH VITAMIN D. It is a microparticulate Chemiluminescence Immunoassay (CMIA), which provides a quantitative determination of 25 (OH) D in human serum.

Variable description

Body Mass Index (BMI): For each participant, weight and height were measured to determine BMI using the following formula: BMI=Weight/Size (kg/m^2).

BMI (kg/m^2) thresholds have been defined according to the WHO definition:

- Obesity: BMI ≥ 30
- Overweight: 30>BMI ≥ 25
- Normal: 25>BMI ≥ 18.5
- Underweight: BMI ≤ 18.5

Vitamin D values: After measurement of 25 (OH) D, participants were divided into 3 categories depending on their deficiency, insufficiency or normality. The thresholds were defined as follows:

- Optimal level: 25 (OH) D ≥ 30 ng/ml
- Insufficient level: 10 ≤ 25 (OH) D<30 ng/ml
- Moderate insufficient level 20 ≤ 25 (OH) D<30 ng/ml
- High insufficient level 10 ≤ 25 (OH) D<20 ng/ml
- Deficient level: 25 (OH) D<10 ng/ml

Vitamin D supplementation

After 25 (OH) D measurements, a supplementation of cholecalciferol 100,000 IU VITD 3 was administered according to its status for each participant:

Optimal level: 1 preventive intake of 100,000 IU;

Moderate insufficient level: 3 intakes of 100,000 IU spaced 15 days apart;

High insufficient level: 4 intakes of 100,000 IU spaced 15 days apart;

Deficient level: 5 intakes of 100,000 IU spaced 15 days apart.

Participant follow-up

During the follow-up period (that was extended from September 1st, 2020 to January 31st, 2021), and after supplementing those suffering from hypovitaminosis, all participants benefited from COVID-19 molecular screening testing. The molecular tests were carried out at virology laboratory of Rabat CHU. The qRT-PCR test results were obtained from the department's database. Clinical characteristics of individuals infected with SARS-CoV-2 were collected after their work resumption from sickness leave.

Statistical analysis

The data were statistically analyzed using the Statistical Package for the Social Sciences (SPSS 19.0) (License of the University Mohammed V-Rabat). First a descriptive analysis was done, the qualitative variables were expressed as effective and percentages and the quantitative variables were expressed as mean and Standard Deviation (SD). Then the data were analyzed using the Student t-test to compare the means and the Fisher exact test to compare the percentages. A value of $p<0.05$ was considered statistically significant.

Ethical consideration

The study protocol was approved by the Ethics Committee of the biomedical research of the Faculty of Medicine and Pharmacy in Rabat, Morocco (N°: 17/20). All participants were well-informed about the study aims and received a summary of the protocol. Informed written consent was obtained from all participants.

Results

Characteristics of the population

Sixty-five participants were enrolled, with a female predominance; 86% were females and 14% were males with a sex ratio of 0.16. Participants' mean age was 33 ± 11 years with extremes of 21 and 61 years. The predominant age range was between 20 and 30 years. All participants reside in urban areas and the vast majority benefited from privileged academic education. Participants' characteristics have been summarized in Table 1.

Table 1. Characteristics of the population studied (N=65).

	N (%)
Gender	
Male	9 (14)
Female	56 (86)
Age	
Mean ± SD (Years)	33 ± 11
20-30	38 (58)
31-40	15(23)
41-50	4(6)
≥ 51	8(12)
Academic level	
Primary school	1(2)
Middle school	6(9)
High school	6(9)
College degree	52(80)
BMI in all participants	
Mean ± SD (Extremes) (Kg/m^2)	25 ± 5 (16-41)

Obesity	13(20)
Overweight	14(22)
Normal	34(52)
Underweight	4(6)
BMI in males	
Mean ± SD (Extremes) (Kg/m^2)	25 ± 4(17-30)
Overweight	4(44)
Normal	5(56)
BMI in females	
Mean ± SD (Extremes) (Kg/m^2)	25 ± 5(16-41)
Obesity	13(23)
Overweight	10(18)
Normal	29(52)
Underweight	4(7)
SD: Standard Deviation	

The average BMI was 25 ± 5 kg/m^2 (minimum=16 kg/m^2, maximum=41 kg/m^2), 25 ± 5 kg/m^2 for women and 25 ± 4 kg/m^2 for men. 18% of participants have taken VITD supplementation in the last six months. Moreover, 68% of the participants do not have any chronic diseases, two of whom had Anemia, while, 32% of them presented chronic diseases (21 cases); in particular, hypertension (3 cases) and asthma (3 cases), The other chronic illnesses recorded were: diabetes, psoriasis, Hashimoto's thyroiditis, allergy, functional colopathy, chronic lupus, pituitary adenoma, celiac disease, thyroid gland disorders, epilepsy, mitral insufficiency, acute rheumatic fever, obstetrical paralysis of the brachial plexus, chronic pharyngitis, eczema, hypotension, osteoarthritis, thrombocytopenia, immunosuppression.

Vitamin D status

The mean serum 25(OH) D in the whole study population was of 17 ± 7 ng/ml. Serum 25(OH) D values ranged between 7 and 34 ng/ml. Its mean value in patients with hypovitaminosis D was 16 ± 6 ng/ml, versus 32 ± 1 ng/ml in patients with normal VITD levels. It was of 22 ± 8 ng/ml in males and 16 ± 7 ng/ml in females.

There was a statistically significant difference between the mean dose of VITD between the two genders (p=0.01).

There was a statistically significant difference between the mean dose of VITD between the two genders (p=0.01) with a significantly higher mean of 25(OH) D concentration in men compared to women (22 ± 8 ng/ml vs. 16 ± 7 ng/ml). Participants that usually expose their forearms and/or legs to the sun had a significantly higher mean 25(OH) D concentration than those who do not (18 ± 7 ng/ml vs. 14 ± 6 ng/ml; p=0.04). Similarly, those who have been taking VITD supplementation in the last six months had a significantly higher mean 25(OH) D concentration than those who did not (24 ± 6 ng/ml vs. 15 ± 6 ng/ml; p<0.001) (Table 2).

Table 2. Average concentration of 25 (OH) D in the whole study population (N=65).

	N (%)	Mean ± SD	p-Value
Total number of participants		17 ± 7	
Deficient level	12(18)	9 ± 1	
Insufficient level	48(74)	18 ± 5	
High insufficient level	33(69)	16 ± 3	
Moderate insufficient level	15(31)	25 ± 2	
Optimal level	5(8)	32 ± 1	
Gender			
Male	9(14)	22 ± 8	0.01
Female	56(86)	16 ± 7	
Sun exposure			
Yes	52(80)	18 ± 7	0.13
No	13(20)	14 ± 6	
Exposure of forearms and/or legs to the sun			
Yes	40(62)	18 ± 7	0.04
No	25(38)	15 ± 7	
Vitamin D supplementation in the last six months			
Yes	12(18)	24 ± 6	<0.001
No	53(82)	15 ± 6	
SD: Standard Deviation			

The data were analyzed using the Student t-test to compare the means.

Of the 65 subjects, 60 (92%) had strictly hypovitaminosis D (<30 ng/ml), while 18% of them were VITD deficient (<10 ng/ml), of whom 12 were women (22%). Therefore 74% of deficiency cases (25(OH) D: 10 ≤ 25 (OH) D<30 ng/ml) were recorded, of which 69% had high insufficiency and 31% had moderate insufficiency represented by 7 men and 41 women (Figure 1).

The difference between the different VITD status according to age groups was statistically significant (p=0.03). There were no statistically significant differences between the different VITD status according to gender (p=0.07) and BMI (p=0.6) (Table 3).

Table 3. Vitamin D status according to age, gender and BMI (N=65).

	Deficiency	Insufficiency	Optimal level	P Value
Gender				
Males	0(0)	7(78)	2(22)	0.07
Females	12(22)	41(73)	3(5)	
Age groups (Years)				
20-30	5(13)	29(76)	4(11)	0.03
31-40	2(13)	13(87)	0(0)	
41-50	0(0)	3(75)	1(25)	
≥ 51	5(62.5)	3(37.5)	0(0)	
BMI (Kg/m^2)				
Obesity				0.6
Overweight				
Normal				
Underweight				

Note: The data were analyzed using the Fisher exact test to compare the percentages.

Calcemia and phosphoremia

Calcemia and phosphoremia were measured in all participants. They all had normal values, except one person who was hypercalcemic.

SARS-CoV-2 infection

From September 1st, 2020 to January 31st, 2021, thirteen participants (20%) were infected with SARS-CoV-2. Although, no cases required hospitalization or respiratory support. The outcome of all cases was favorable. The finding showed that clinical symptoms were mild without pneumonia manifestation. Headache, fatigue, loss of smell and/or taste and myalgia were the most common symptoms (Figure 1 and Table 4).

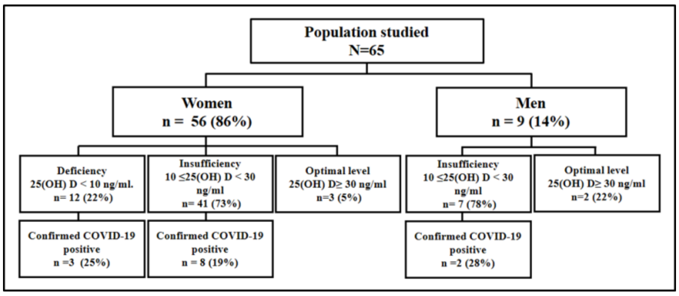

Figure 1. Flow chart of the population studied regarding gender, 25(OH) D levels and COVID-19 infection.

Table 4. Symptoms of COVID-19 (N=13).

	N (%)
Headache	5(38)
Fatigue	5(38)
Loss of smell and/or taste	5(38)
Myalgia	5(38)
Fever	4(31)
Cough	4(31)
Chills	2(15)
Rhinorrhea	2(15)
Difficulty breathing	2(15)
Nausea	1(8)
Pharyngitis	1(8)

Discussion

The high prevalence of hypo-vitaminosis D was reported in several studies [8,16]. This vitamin deficiency affects all age groups and it is therefore a public health problem [17].

There is no consensus on what VITD insufficiency and deficiency are; neither there are available determined references values, which have given rise to many discussions in recent years. Unlike most biological parameters, reference values for VITD are not established by taking the extreme values of a reference population including apparently healthy individuals. Indeed, depending on the factors influencing VITD synthesis, the concentrations of 25 (OH) D can change greatly. It is therefore recommended to determine 25 (OH) D concentrations below of which, bones health is affected (which is related with Para Thyroid Hormone (PTH) elevation), as well as the concentrations for which beneficial effects have been demonstrated in intervention studies. This method, "health-based reference values", is based on an analysis of data from the literature. Organizations such as the IOF (International Osteoporosis Foundation), the GRIO (Osteoporosis Research and Information Group) and the US Endocine Society distinguish three levels of VITD measurement: deficiency, insufficiency and optimal level [18-21]. These organizations agree on a minimum recommended concentration of 30 ng/ml. Regarding the deficiency, the US endocrine society considers the threshold to be 20 ng/ml, unlike the others for whom the deficiency threshold is 10 ng/ml. The insufficiency/deficiency barrier is set at 10 ng/ml mainly based on the Para Thyroid Hormone (PTH) measurement [21, 22]. Indeed, above 10 ng/ml, Chapuy et al. have demonstrated that PTH remains at a stable level, (approximately 36 pg/ml) [23]. However, below 10 ng/ml, PTH concentrations increase, with a risk of bone mineralization [24].

In our study, despite sun exposure and consumption of vitamin D-rich foods, hypovitaminosis D was still too high among the participants. In fact, only 8% of them had optimal VITD levels. These results are consistent with the study conducted by Allali et al. in Rabat city in a group of women in whom hypovitaminosis D was 91% and the mean value of 25 (OH) D was 18.1 ± 7.9 ng/ml [25]. Comparing to our study, this value was 16.2 ± 6.7 ng/ml in the group of women. According to a Tunisian study conducted in 2016 and 2017, the average VITD level in healthy women was 7.88 ± 6.08 ng/ml [26].

In France, Deplanque et al. revealed that 92.3% of healthy subjects present a VITD level strictly below 30 ng/ml [27]. The systematic review, published by Hilger et al. in 2014, reported a large variability in the mean and median value of 25(OH) D worldwide, even between different studies within the same country or regions [16].

The main active form of VITD is calcitriol (1.25 (OH) 2D3), the last metabolite whose synthesis begins at the cutaneous level under the effect of UVB, then hydroxylated in the liver and finally dihydroxylated in the kidneys [28]. VITD is stored in the human body in the form of 25 (OH) D, which is also the circulating form that enables the assessment of vitamin status and which will be transported to the various tissues in need *via* the blood [3,29].

Since VITD is known for its multiple health benefits, its deficiency can lead to serious health problems affecting many tissues and organs [17, 30]; including the accumulation of osteoid, which results in rickets in children and bone fissures caused by osteomalacia in adults. It also has pleiotropic effects on muscles and immune system [31,32]. In addition, VITD has many protective roles against various conditions. However, the extra-bone effects of VITD are explained by the presence of vitamin D-specific receptors in most human tissues [17].

The broad and complex role of VITD in the regulation of the immune system has been supported by several studies; it appears that it modulates innate and adaptive immunity; the VDR (VITD receptor) and 1 α-hydroxylase are expressed on lymphocytes (T and B), on macrophages and on antigen presenting cells, after fixation of 25 (OH) D, these cells will convert it into its active metabolite which will act on the surrounding immune system [33-35].

Mounting evidence indicates that VITD is strongly linked to pathogens elimination. In fact, the toll-like receptor 2/1 and 25OHD3 combination stimulate cathelicidin expression; an antimicrobial protein implicated in cytokine recruitment and macrophage differentiation [36].

Moreover, VITD can increase the production of regulatory T cells through the adaptive immune response. Randomized controlled trials in healthy adults have consistently shown that a significant reduction in respiratory tract infections has been confirmed in people taking daily VITD supplementation compared with controls [37]. A meta-analysis of nine studies by Laplana et al. settled that VITD can inhibit enveloped viruses [38]. Furthermore, inadequate VITD levels in the elderly are associated with weakened innate immune activity [39]. A recent study conducted by Wei et al. found that 70.3% of elderly people in China have been defined as VITD deficient [40].

In response to the global outbreak of COVID-19 pandemic, several studies were conducted to reveal approaches that can reduce the severity of respiratory symptoms while waiting for the vaccine to become widely available. According to Ilie et al. it was demonstrated that the highest rates of infection and mortality from COVID-19 were found in populations with low VITD levels [41]. Despite the increased exposure to sunlight of some countries, such as Spain and Italy, VITD deficiency is still observed. Consequently, mortality due to COVID-19 was very pronounced. Whereas in Norway and Sweden, where VITD supplementation and food fortification are more common, mortality and infection rates were lower [41,42]. Hence, several studies as the previous have been supporting the protective role of VITD against COVID-19 [12, 43-45].

In the current study, after VITD supplementation, we monitored all participants to determine who would contract COVID-19. Among the thirteen (20%) COVID-19 positive cases, 11 (85%) were females, of whom 3 cases had VITD deficiency and 8 had VITD insufficiency. The other two infected males were insufficient for VITD. None of them had developed acute complications, neither had needed hospitalization. This might be explained by the protective role of VITD against COVID-19 that has been reported by several worldwide studies.

Knowing that hypo-vitaminosis D increases the risk of contracting COVID-19 to 54%, Kaufman et al. reported the important impact of VITD on reducing the possibility of contracting SARS-CoV-2 infection as well as its severe respiratory symptoms [46]. A similar finding was reported in several studies regarding the protective role of VITD against SARS-CoV-2 infection. Castillo et al. reported that calcifediol can significantly reduce the admission of COVID-19 patients to Intensive Care Units (ICU) [47]. In the same sense Vassiliou et al. showed that COVID-19 non-survivor's cases had lower 25 (OH) D levels at ICU admission comparing to survivors. This finding shows that there is a potential link of low levels of 25 (OH) D with poor prognosis among patients with COVID-19 pneumonia [48]. In the Indian population, two studies were realized in order to analyze the impact of VITD level on COVID-19 severity. They revealed a significant association of the lower levels of 25 (OH) D with SARS-CoV-2 related deaths and the susceptibility to infection [49,50]. In a further turkish study, Karahan and Katkat, concluded that the mean serum 25 (OH)D level was significantly lower in patients with severe-critical COVID-19 comparing to moderate COVID-19 (10.1 ± 6.2 vs. 26.3 ± 8.4 ng/mL, p<0.001) [51]. Whereas, according to Ling et al., high-dose of cholecalciferol supplementation, apart from baseline serum 25 (OH) D levels, appears to be associated with a reduced risk of mortality due to COVID-19. The study also suggests that serum 25 (OH) D levels were not associated with COVID-19 mortality [52].

Conclusion

Hypo-vitaminosis D remains one of the most prevalent public health concerns worldwide. Based on the results obtained in the current study and given the protective role of VITD against COVID-19, the high prevalence of hypo-vitaminosis D should be managed in order to improve public health status and consequently decrease the mortality rate. Thus, it is essential to support the immune system of people at risk, especially COVID-19 front line health workers, by prescribing VITD supplementation. It is as important to develop a public health policy to reduce the hypo-vitaminosis D consequences in the Moroccan population.

Conflict of Interest

The author has no conflict of interest to declare.

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