stefano mancin[1] and Francesca Vecchio[1]

[1]Affiliation not available

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Abstract

In recent months, since the Sars-Cov-2 pandemic has hit the entire world landscape, one of the most heated debates involving researchers has concerned the potential role that vitamin D could play in relation to infection by COVID-19.

In particular, numerous scientific studies have shown that the deficiency of this vitamin is present in a large part of the sick subjects, in a Spanish study[1] this association was reported in about 80% of the sample considered, furthermore other studies[2,3,4] attribute to this hormone a potentially protective role by stimulating type I interferon and enhancing innate immunity.

This review of the literature investigating, through a bibliographic search in the Pubmed - Medline database, aims to evaluate the possible association between vitamin D and Sars-Cov-2 infection in terms of outcomes such as: association between levels of vitamin D and infection, disease severity, mortality, analyzing a total of 274 studies, of which 8 reviews were finally evaluated, which allowed, through a review of the literature, to demonstrate a positive association of vitamin D in the prevention and treatment of infection from Sars-Cov-2 and in other pathologies such as flu, pneumonia and chronic diseases such as diabetes, obesity and arterial hypertension, or conditions favorable to complications during Covid-19 infection.

[1]Nurse specialist in Clinical nutrition and wound care, Dialysis clinic IRCCS Humanitas Research Hospital Rozzano (MI) **Stefano.mancin@humanitas.it**

[2]Nurse, multi-specialist department IRCCS Humanitas Research Hospital Rozzano(MI)

Keyword:

Vitamin D, Sars-Cov-2 Covid-19, infection, immune system, obesity elderly patient ACE2

INTRODUCTION

Vitamin D is a fat-soluble vitamin and a hormone that plays a central role in maintaining calcium / phosphorus balance and bone homeostasis in close interaction with the parathyroid hormone, it acts on classic target tissues, such as: bones, kidneys, intestine and parathyroid glands. However, the endocrine system, by regulating several genes (about 3% of the human genome) is able to exert pleiotropic effects on extra-skeletal tissues, such as the immune system, cardiovascular system, pancreatic endocrine cells, muscles and adipose tissue. Several studies have demonstrated the preventive role of vitamin D. through integration in the treatment of various autoimmune diseases, activation of the immune system, improvement of metabolism, muscle function and adipose tissue[5].

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Vitamin D physiology and metabolism

The nutritional intake deriving from animal and vegetable foods guarantees a daily ration able to cover about 20% of the daily requirement of vitamin D[6], in the form of vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol), the remaining portion is produced endogenously thanks to solar irradiation which converts 7-dehydrocholesterol into previtamin D3 and subsequently into vitamin D3, thanks to body temperature.

Vitamin D3 then binds to an alpha-globulin known as vitamin D binding protein (DBP) and is transported to the liver, where it undergoes hydroxylation at position 25 and is released as 25-hydroxyvitamin D 3 [25 (OH) vitamin D 3]. Additional hydroxylation is required for the activation of vitamin D, in C1a, in the kidney. Hydroxylation on C25 is catalyzed by several enzymes, the most important of which is CYP2R1, also known as vitamin D 25-hydroxylase[7] and in the proximal renal tubule by the enzyme CYP27B1, an activity also identified in keratinocytes, macrophages and other tissues[5].

Once vitamin D is activated, in the form of 1,25 (OH) 2 D, it is able to interact with the nuclear receptor VDR[8] (vitamin D receptor), inducing modifications and activating classical effects, i.e. the control of bone metabolism through a direct action on the kidney, intestine, parathyroid hormone, calcitonin and IGF1, moreover it also exerts non-classical effects called pleiotropic effects since it is expressed by different tissues including: vascular endothelium, smooth muscle and cardiomyocytes, playing an important role regulator in the physiology of the immune system, skeletal muscle, adipose tissue, meta-bolism, skin, cardiovascular, reproductive and neurocognitive functions, together with the modulation of cell proliferation.[9,10]

Vitamin D and the immune system

All immune cells express the VDR receptor, in particular APC cells (antigen presenting cells), which are capable of producing 1,25 (OH) 2D3 through the same enzyme expressed in the kidney, but only as a result of an immune stimulus, such as IFN-alpha.

Vitamin D exerts its action on the innate immune system as well as on the acquired immune system, albeit with

opposite effects.

As for innate immunity, vitamin D and its metabolites stimulate the differentiation of macrophages and a diet deficient in vitamin D3 shows an impairment of IL-6, TNF and IL-1 by compromising antimicrobial activity[11], vice versa infectious stimuli that mediate the expression of the Tool Like Receptor on the surface of the macrophages stimulates the expression of the VDR receptor.

Interestingly, a study in Mycobacterium tuberculosis[5]showed that African American individuals, known to have increased susceptibility to tuberculosis, have low levels of 25 (OH) D3, a finding that supports the presence of a potential link between TLR and vitamin D by regulating innate immunity.

This suggests that the different susceptibilities to microbial infections among various human populations could be based on interracial differences in ability to produce vitamin D.

Conversely, at the level of acquired immunity, 1.25 (OH) 2D3 inhibits the surface expression of class II MHC and co-signaling molecules on antigen-presenting cells, decreasing the activity of Th1 and Th17 cells, and up-regulates regulatory T cells (T-regs) by inhibiting cytokine production12.

It is also interesting to note how Sars-Cov-2 uses ACE2 as an entry site expressed in the cells of the respiratory system, creating a down regulation of this enzyme and an increase in angiotensin 2^{13} levels, which would favor the development of inflammation, worsening of respiratory function up to pulmonary edema.

Vitamin D also stimulates the production of antimicrobial peptides on the respiratory epithelium and in particular is able to reduce the cascade activation promoted by angiotensin 2, promoting the expression of the ACE2 enzyme and limiting the consequent inflammatory response.

(Figure 1).

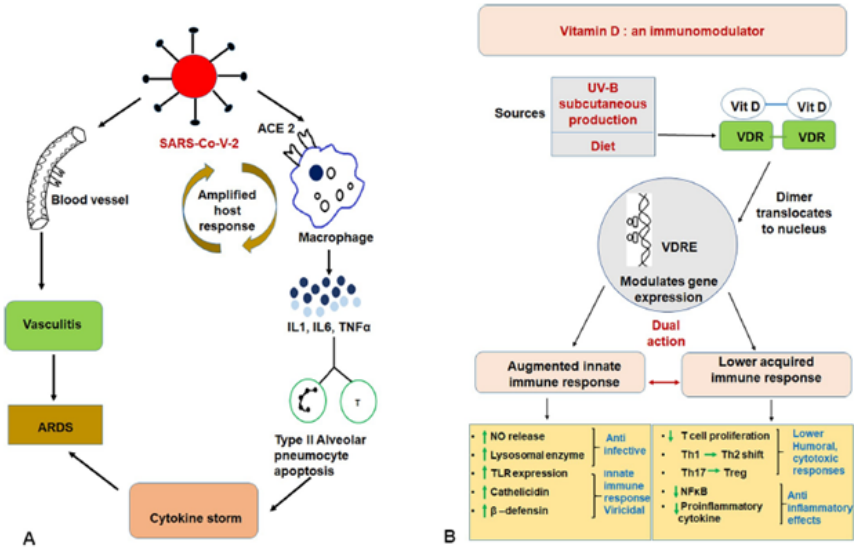

Fig 1. Fig 1A depicts the basic pathophysiology of COVID-19 and the development of ARDS. Fig 1B shows vitamin D's dual action on immune response and inflammation. Vitamin D is capable of modulating the expression of various genes which results in augmented innate immune response and lower acquired immune response. ACE 2, angiotensin-converting enzyme 2; ARDS, acute respiratory distress syndrome; COVID-19, Coronavirus Disease 2019; IL, interleukin; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TH1, T helper type 1; TH2, T helper type 2; TH17, T helper type 17; TLR, toll-like receptor; TNFα, tumor necrosis factor alpha; TREG, regulatory T cell; UVB, ultraviolet B rays; VDR, vitamin D receptor; VDRE, vitamin D receptor element.

Figure 1 Source: Mradul Mohan, et Al. 2020 doi: https://doi.org/10.1371/journal.ppat.1008874.g001

Vitamin D and adipose tissue

The international literature has shown through several clinical studies[14,15], that obese individuals are subject to greater susceptibility to more severe effects during Sars-Cov-2 infection, probably partly due to the presence of greater comorbidities and impaired activation. of the immune system and cascade activation of a phenomenon called "cytokine storm" as indicated in the ISS Covid-19 48/2020[16] report.

It is relevant that in obese subjects the levels of vitamin D are reduced, in particular this is due to the abundant presence of adipose tissue and, being the latter a fat-soluble vitamin, it would be diluted in the storage fats and its release would be reduced. Furthermore, vitamin D deficiency is correlated with almost all aspects of the metabolic syndrome, such as obesity, insulin resistance, hypertension, dyslipidemia, type 2^{17} diabetes mellitus.

Finally, leptin and resistin, two elevated hormones in obese subjects are negatively correlated with vitamin D levels, while adiponectin is positively correlated[18].

Vitamin D and age

In elderly people, 7-Dehydrocholesterol levels tend to decrease since in these subjects these deposits are reduced despite adequate sun exposure[19], in part this phenomenon is due to a reduction in skin thickness which can induce a decrease in vitamin D production up to 4 times less than a young subject.

Furthermore, in this population sample, the oral intake of vitamin D sources through the diet is reduced, often correlated with forms of malnutrition that can reach values of more than 50% prevalence in long-term care facilities[20].

METHODOLOGY

The analysis of the literature for the elaboration of the systematic review was carried out in the Pubmed and Medline databases using review criteria based on the PRISMA statement guidelines drawn up by the Ottawa Hospital Research Institute with the last update in 2015.

Keywords used were:

Vitamin D - Sars-Cov-2 - Covid-19 - infection - immune system - obesity - elderly patient –ACE2

Objective of the study

Evaluation of the possible association between vitamin D and Sars-Cov-2 infection in terms of outcomes such as the association between vitamin D levels and: incidence of infection, disease severity, mortality.

Bibliographic research

The present bibliographic search, considered the data available on the Pubmed-Medline search engine, producing 274 initial results, 57 articles were selected after an analysis of the abstracts, selecting them after reading the full-text 8.

Inclusion criteria used were:

- Recent articles published during the period November '19 - November '20,
- Articles available in full text
- Studies conducted as clinical trials and randomized control trials
- Review and systematic review

Since from the analysis of the selected literature several clinical trials were already included in the systematic reviews analyzed[21,22,23,24,25], , in consideration of the PRISMA statement guidelines used as a tool for evaluating the studies, we reached the conclusion by selecting 8 reviews .

(figure 2)

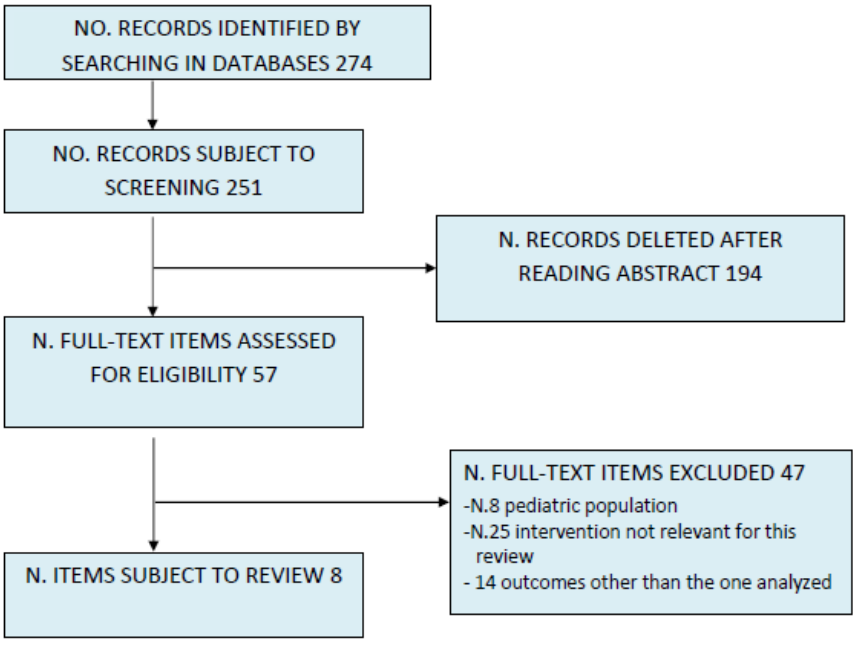

Figure 2. Systematic review flow chart (PRISMA guidelines)

RESULTS

All the reviews taken into consideration were evaluated according to the PRISMA statement review methodology, highlighting that vitamin D plays a primary role in the modulation of the human immune system, counteracting the uncontrolled inflammatory cascade generated by the activation of the renin-angiotensin-system. aldosterone through down regulation of the ACE2 enzyme caused by Sars-Cov-214,27 viral infection.

All authors indicated that deficient vitamin D levels (range [?]30 ng / ml) are associated with a higher risk of Covid-19 infection and more severe clinical outcomes, in particular one study[28]showed that this problem is particularly frequent with a prevalence in 50% of the population of over 40 countries which has levels below 50% with peaks of 70% in nations such as India, vice versa having serum levels between 40 and 60 ng / ml proves to be a more protective factor against the infection and its outcomes.

Furthermore, several authors underline the association between low levels of vitamin D and pulmonary pathologies[26], chronic pathologies associated with metabolic syndrome[4], vascular damage[27], thrombotic episodes[28] confirming that this deficiency associated with these conditions involves a serious risk for the development of SARS infection. Cov-2[29]. The research does not reveal a homogeneity of treatment since the therapeutic dosages indicated by the authors or administered in the various clinical trials have dosages of cholecalciferol that can vary from a daily dosage of 1800 ui up to 100,000 ui per week.

Furthermore, there is no well-defined time schedule of administration, since precise treatment intervals are not expressed in several reviews, in contrast to others which in turn express dose and time of administration with punctuality (summarized in table 1)

Author	Nation	PRISM Checklist item	N ° selected articles	Type of study	Treapeutic supplementation	Blood range vit.D therapeutic
Grant WB et Al.[3]	USA	9	157	Review	1800-3600 ui / day	40-60 ng / ml.
Ali N. et Al[26]	Bangladesh	15	75	Review	ND	75-125mg / ml
Mitchell F.[4]	Canada	11	17	Review	100,000 ui / week for 2 weeks, then 50,000 ui for 1 week.	40-60 ng / ml
Mohan M et Al.[28]	India	7	35	Review	ND	≥20ng / ml
Mansur JL et Al.[29]	Argentina	10	75	Review	10,000ui / day For 1 month and then 5000 IU for maintenance	40-60 ng / ml
Malek et Al.[14]	Iran	9	77	Review	ND	≥30ng / ml
Zhang J et Al.[27]	USA	9	38	Review	ND	≥30ng / ml
Meftahi GH.[30]	USA	8	7	Review	10,000 IU / day	40-60 ng / ml

Table 1: comparison between the various studies analyzed

CONCLUSIONS

Adequate levels of vitamin D have been shown to have a protective effect against Sars-Cov-2 infection by reducing the inflammatory response generated by the activation of the renin-angiotensin- aldosterone system, promoting the production of antimicrobial peptides at the level of the mucosa of the respiratory system and by improving the modulation of regulatory T lymphocytes[30].

Several studies and reviews[3,4,2627,30], analyzed according to the PRISMA statement methodology[31] have shown an association between low levels of vitamin D and other diseases such as: flu, pneumonia, vascular diseases, thrombosis and chronic diseases including diabetes, hypertension and obesity[4.27], that is, unfavorable conditions during Covid-19 infection.

Unfortunately, vitamin D deficiency appears to be a frequent condition, in over 40 countries, levels of vitamin D deficiency were detected in 50% of the population analyzed[28], demonstrating that vitamin D supplementation plays a relevant role in the treatment of this pathology[29] .

It is also necessary to consider as limitations of this review, the lack of randomized controlled studies and large-scale cohorts, which could provide more precise data in order to be able to implement the administration of vitamin D with an adequate treatment scheme shared internationally both in terms of dosage and intervals of administration, which are still based on empirical schemes to reach adequate levels, which represent estimated values in a range between 40 and 60ng / ml.

In this regard, all these factors may represent possible sources of bias or confounding due to both the selection of the non-homogeneous patient sample and the difference in dosages and administration times.

The news of a European country (UK) has recently been published[32] which has promoted the free administration of vitamin D starting from December '20 to all elderly people hospitalized in long-term care facilities (over 2 million people) considered fragile. and at high risk of contracting Covid-19 infection in a severe way and, consequently with the advent of clinical trials or cohort studies on population samples such as the latter and with more data available, they could have in a near future superior quality scientific evidence to support today's data.

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Conflict of Interest : the author declares that there is no collateral interest.

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