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Does Vitamin D Supplementation have a Positive and Important Response in the Immune System on Covid-19 Pandemic? A Short Critical Analysis

Eliza Miranda Ramos[1, 3], Francisco José Mendes dos Reis[1], Igor Domingos de Souza[2], Sandra Luzinete Félix de Freitas[2], Matheus Dullius de Lima[4], Antônio Carlos de Abreu[5] Hugo Vieira Ramos[6], Emerson Luiz Lima Araújo[7], Valter Aragão do Nascimento, Phd[1]

Resume

In recent years, new viruses have emerged and caused pandemics in several countries, making it a global health problem through respiratory infection. This study aims to demonstrate through an analysis of evidence, that vitamin D supplementation in cases of hypovitaminosis D in risk groups induces an increase changes in the immune system due to worsening and, thus, the body becomes conducive to development viral diseases like COVID-19. Therefore, methodological techniques were used in meta-analysis and systematic reviews parallel to the FINER strategy in the selection of the included studies to be used in the construction of this critical analysis. In this study, 05 articles were selected for inclusion in this critical analysis. Vitamin D plays an immune protective role in the body, decreasing the risk of complications in COVID-19. The decrease in immune cells and cytokines can be used as a biomarker in the process of worsening COVID-19.

Keywords: Vitamin D, cytokines, immune system, COVID-19.

Introduction

In the last hundred years there have been three pandemics in the world in which it has been possible to identify three different antigenic subtypes of influenza viruses [22], such as influenza A or H1N1 (Spanish flu), H2N2 known as Asian flu and H3N3 defined as Hong Kong flu. In the beginning of 2020, severe pneumonia caused by COVID-19 (SARS-CoV-2) started in Wuhan/China and expanded worldwide, reaching the whole of Northern Italy and more distant countries like Brazil in the following months [2]. Flu-like diseases as COVID-19 cause respiratory disease and spread the same way, human to human via small droplets of fluid from the nose and mouth of someone who is sick, depending on the patient's clinical conditions, cause severe pneumonia [21].

When we analyze the cases of deaths between certain regions in the Chinese province which presented the initial outbreak, it is possible to obtain useful information regarding the pathogenicity of the viruses [2]. In fact, it was observed that in countries such as China, Italy and Brazil, the patients with the highest incidence are male and have a history of comorbidity such as kidney disease

[1] Group of Spectroscopy and Bioinformatics Applied to Biodiversity and Health, School of Medicine, Postgraduation Program in Health and Development in the Midwest Region, Faculty of Medicine, Federal University of Mato Grosso do Sul, Campo Grande, Mato Grosso do Sul, Brazil. E-mail: elizamirandaramos@gmail.com
[2]Federal University of Mato Grosso do Sul, Faculty of Nursing, Campo Grande, MS, Brazil.
[3] Brazil Foundation – CAPES
[4]City Hall of Campo Grande, MS, Brazil.
[5]Postgraduation Program in Health and Development in the Midwest Region, Faculty of Medicine, Federal University of Mato Grosso do Sul, Campo Grande, Mato Grosso do Sul, Brazil.
[6]Group of Spectroscopy and Biodiversity and Health, School of Medicine, Postgraduation Program of Parasitic Infection Diseases, Faculty of Medicine, Federal University of Mato Grosso do Sul, Campo Grande, Mato Grosso do Sul, Brazil;
[7]Ministry of Health, Secretary of Health Surveillance, Department of Strategic Coordination of Health Surveillance, General Coordination of Public Health Laboratories, Brasília-DF, Brazil.

[22], cardiovascular disease, cerebrovascular disease, diabetes and hypertension [22]. Currently, several health professionals have observed in this pandemic that COVID-19 has a direct relationship with comorbidities related to immune deficit and indirectly with secondary bacterial infections [21].

Death cases occurred in patients with lymphopenia and inflammation secondary to pneumonia, that is, the death complication is directly related to the patient's pre-existing diseases [22]. However, it is possible to highlight in this illness process that other patients are able to recover with little or no medical and hospital intervention [21]. Previous studies have presented scientific evidence that flu pandemics that have occurred in the last hundred years including the 20th century are related to the activity cycle of SCHWABE sunspots [29], since the population of several countries has immunological changes related to the induction of vitamin D absorption due to solar cycle [29]. In addition, this study has shown that in the last decade vitamin D controls or improves several viral or bacterial pathologies, with an influential role in the morphology of influenza pandemics including COVID-19 [29]. Deficit of vitamin D is considered the most evident context that brings serious diseases, mainly viral [19]. Since 2005, the use of vitamin has been emphasized as an important immunomodulatory factor, thus, some studies have reported that obesity and changes in vitamin production, either by exposure to sunlight or mainly oral supplementation, are considered important factors in the evolution of flu and mainly to COVID-19 [9].

When we talk about exposure to sunlight, it should be noted that the synthesis of vitamin D by sunlight varies between regions of the Earth due to different geographic latitudes [29]. Thus, it is due to differences in solar incidence between regions that in some countries it is necessary to supplement vitamin D orally, that is, in places where different latitudes develop a greater epidemiological percentage of vitamin D deficits [15,29].

In the past five years there has been a greater understanding of the use of vitamin D and its effects on the human body [16]. Experimental and epidemiological studies carried out in vitro, animal model, ecological profile and with human beings in an experimental and randomized way obtained as a response that vitamin D influences the immune system, pancreas, brain and positive development in the human aging process, mainly in the control cell cycle [29].

According to results of studies by epidemiologists Hope-Simpson, the decrease in solar radiation in seasonal periods influences notably flu epidemics [29]. In addition, the authors Cannel et al., reinforced that the deficit of vitamin D in winter tends to increase exponentially the number of people with flu and other infections in the respiratory tract. In view of the above presented, the objective of this study is to demonstrate, through an analysis of short critical systematic review, that vitamin D supplementation in cases of hypovitaminosis D in risk groups induces an increase changes in the immune system and thus the organism becomes conducive to developing viral diseases, such as COVID-19 [6]. Therefore, methodological techniques were used in meta-analysis and systematic reviews parallel to the FINER strategy in the selection of the included studies to be used in the construction of this critical analysis. In this study, 05 articles [5,6,9,19,29] were selected for inclusion in this critical analysis.

The Vitamin D

Vitamin D is essential in the human diet [5], however, its metabolic absorption by the diet and its metabolism are low and require oral supplementation [7]. Vitamin D is a steroidal and fat-soluble prohormone and has endocrine, paracrine and autocrine functionality [5]. Research has shown that the simplest way found for vitamin D absorption is by exposing the skin to sunlight in which to produce about 10,000 IU (250 mcg/day) of vitamin D per day [20]. However, due to changes in solar incidence in several countries, low levels of vitamin D have been observed in the world population [29]. Thus, the most balanced way to replace this loss in absorption by sunlight has been oral supplementation [28,29]. The other route for the production of vitamin D is exogenous, that is, through food as well as oral supplementation [5].

Immuno-Molecular Action of Vitamin D

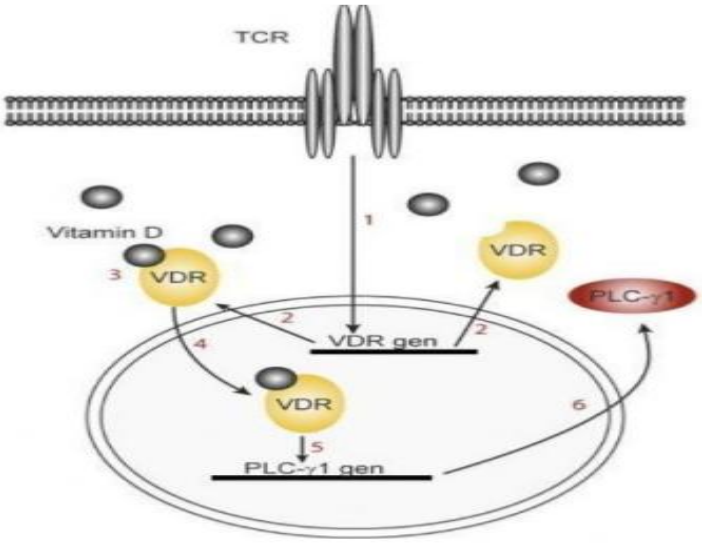
The genetic predisposition in the pathogenesis of diseases related to changes in the immune system is constructed as a mosaic in which it is aggregated to nutritional and environmental factors [11]. In addition, in the quantification of the blood level of vitamin D and in the VDR polymorphism, an important environmental risk factor has been highlighted in the development of diseases in the immune system mainly caused by viruses such as COVID-19 [13].

VDR expression in the activation of defense cells or cytokines is specifically related to polymorphism in genes in Bsml, Apal, Taql, FcγRIIa, CD209, VDR, TNF-α, IL-4, IL-6, IL-8, IL- 10 and INF-γ [9,24]. The Fokl

polymorphism genotypes and their absence have been portrayed by increasing the frequency of diseases in the immune system, mainly viral [15,23].

Thus, there is an important direct relationship of interaction between VDR expression and its biomolecular bonds which produces an endogenous effect on innate cells of the immune system and also (Figure 01) [13] performs a regulatory and immunosuppressive action on immunity adaptive [24].

Figure1 – VDR expression in the activation of T lymphocytes.



Source: DETTOGNI RS. Influence of polymorphisms in the genes FcγRIIa, CD209, VDR, TNF-α, IL-4, IL-6 and INF-γ in the persistence of clinical symptoms of dengue in the convalescence phase. Graduate Program in Biotechnology. 208 f. 2015.

Generally, decreased blood levels of vitamin D are defined in diseases of the immune system [13], such as flu, patients with HIV and sepsis [23,24].t should be remembered that most of the molecular action of vitamin D is activated and mediated by the nuclear vitamin D receptor (VDR) [9]. Vitamin D has the function of regulating the innate and adaptive immunity system [15,24], because the innate immune response is characterized by the activation of monocytes and macrophages capable of recognizing molecular patterns associated with pathogens and [15], thus providing a first line of defense against external agents by increasing the antimicrobial activity of macrophages, improving chemotactics and phagocytic capacity of these cells [11].Conversely, the deficit of vitamin D impairs the ability of macrophages to mature and cytokines to act [23,24]. In the process of positive regulation of VDR in the activation of the monocyte and macrophage Toll-like receptor, it leads to the induction of catelicidin which is a family of polypeptides found in polymorphonuclear macrophage and leukocyte lysosomes that have a critical function in innate immune defense (Figure 1) [16].The production of catelicidin is increased after infection by viruses and macrophages when recognizing the viral invasion regulates VDR expression by activating the catelicidin gene, thus destroying the viral invader [16, 24]. Monocytes are activated in the presence of [1.25(OH)2D] by sketching a decreased production of TNF-α, IL-1α and IL-6 and an increase in production of IL-10 [14]. Thus, vitamin D has the ability to modulate the immune response in a more regulatory manner [16,24] and active immunity is also influenced by vitamin D in several ways [23].

Vitamin D acts on monocyte-macrophage cells by developing a cell line capable of preventing differentiation of dendritic cells by reducing the expression of co-stimulating molecules on the CD80 and CD86 surface [14,23], affecting the stimulating capacity of T cells [9, 24]. In addition, Vitamin D is able to supply dendritic cells in cell maturation by decreasing the presence of antigens and T and B cell activity [15]. Cytokines derived from dendritic cells and in chemokine expression are modulated by vitamin D, and play the Th1/Th2 balance for a broader Th2 response and regular T lymphocyte compartment [15].

Vitamin D can supply the Th1 and Th17 responses while promoting the expression of the regulatory T cell and the Th2 cell by improving IL-4, IL-5 and IL-10 production [23,24]. Thus, after stimulation of Vitamin D [14], dendritic cells have the ability to reduce and trigger the proliferation of T cells [15].

The dendritic cells of this immune process have a direct action on T lymphocytes and alter the cytokine profile of T cells by inhibiting the proinflammatory action in the production of cytokines such as IL-2, IL-06, IL-8, IL-10, INF -γ, IL-17 and IL-21 [17]. It is noteworthy that vitamin D also influences the production of the B cell population [23,24], since the exposure of B cells can be inhibited [17]. Differentiation of plasma cells, secretion of immunoglobulins (IgG and IgM) and generation of memory B cells induce cell apoptosis with the presence of vitamin D [15].

Ideal Blood Dosage of Vitamin D as an Immunological Protector.

The dosage of vitamin D is difficult, since they are lipophilic molecules that circulate in reduced concentrations [25(OH)D] equivalent to 8 - 60 ng/ml [1.25(OH)2D], that is, from 20 to 60 ng/ml which are strongly adhered to proteins (DBP and Albumin) [15,26]. Serum vitamin D analyzes can be measured using various analytical techniques [4] such as competitive protein binding assays, high performance liquid chromatography (HPLC), radioimmunoassay, automatic immunoassay and liquid chromatography associated with mass spectrophotometry (LC-MS/MS) [4,26]. Methods which use liquid chromatography (LC) and mass spectrophotometry (MS) are more sensitive, specific and are considered "gold standard" techniques [26]. However, the low investment in equipment has limited the use of these techniques in public health in Brazil [4,12]. In Brazil, the "Endocrine Society" [13] and the "Brazilian Society of Endocrinology and Neurology" [24] defined vitamin D deficiency at levels below 20 ng/ml, and insufficiency with [25(OH)D] of 21 - 29 ng/ml and sufficiency with [25(OH)D] greater than or equal to 30 ng/ml [23,24]. These cohort patterns are the most used today to define the blood vitamin D level [4].

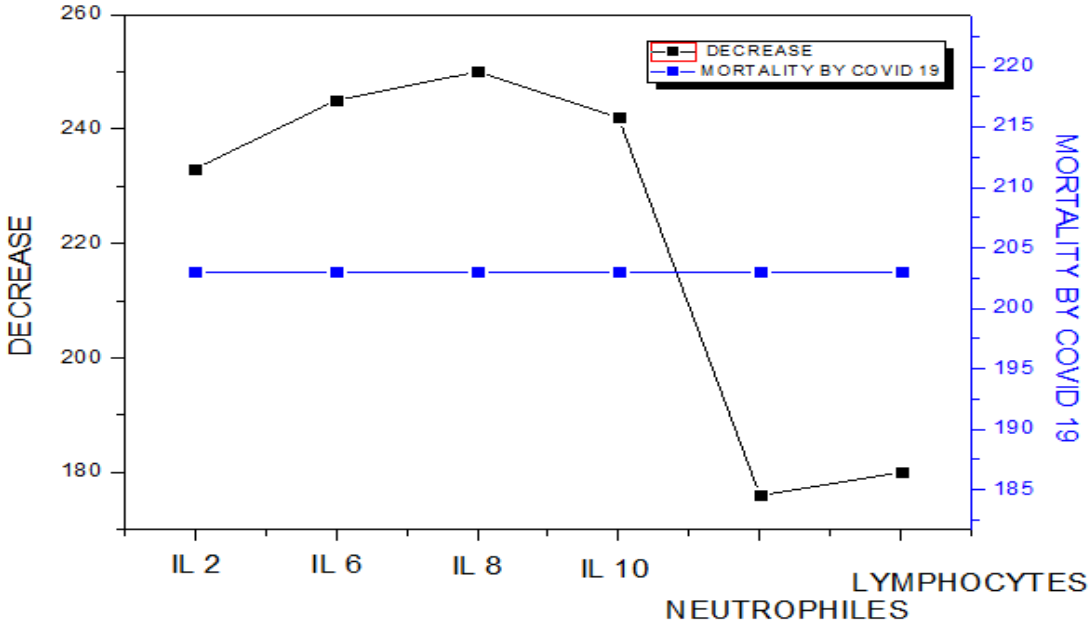
Ideal Dose for Oral Supplementation in Patients Belonging to Risk Groups

Variations in the risks and benefits of using vitamin D have been recorded in relation to the dosage used worldwide [25]. There is a consensus that the daily intake of 50,000 IU/week (1250 mcg/week) of vitamin D by patients does not have toxic effects on the body, which would not cause adverse health effects [11]. Adequate levels of vitamin D play a positive and important role in the prevention and control of respiratory tract infection such as viral flu [5,6].

Results and Discussion

In the three studies analyzed in our study, it was observed that the immune cell parameters, the expression of IL-2, IL-6, IL-8, Il-10, neutrophils and lymphocytes in the serum of patients evaluated with COVID-19 showed a significant decrease (Figure 1) [5,19]. Two studies analyzed in this critical review showed elevated levels of IL-2 and IL-6 expressed in patients with COVID-19 [6,9,21,24]. This increase in some parameters may be due to the main clinical characteristic of COVID-19 [2,21], which is considered severe, in this case, the respiratory distress syndrome related to pneumonia caused by the virus [21].

Figure 1 - Result of the effect of immune cell deficit on COVID-19.



Researchers performed a biopsy in the lung tissue of patients with COVID-19 who progressed to death from pneumonia [21]. According to the researchers' report, the evolutionary characteristics of the COVID-19 pathology are the same as those of other viral diseases known in the world (SARS and MERS) [19,24]. These diseases, like COVID-19, have an aggravation characterized by the desquamation of lung cells and the formation of transparent membranes, that is, the lung tissue presents inflammation with exudative changes, there is the presence of sticky secretion in alveolar sections and fibrous cords in the lung tissue with recent formation and immunological alteration with sudden increase of IL-2 and IL-6 which are related to the worsening of COVID-19 (Table 1) [18,27].The inflammatory process is a protective immune response that helps to clear the source of infection; however the absence of an immune response and control of this excessive inflammatory process causes immunological damage [24,27]. In addition, vitamin D has an effect on the total number with positive immune cell changes in infectious processes such as sepsis and H1N1 [6,24].

Table 1 - Immune cell parameters in COVID-19 patients with evolution to pneumonia.

INCREASE		**MORTALITY FOR PNEUMONIA CAUSED IN COVID 19**
VARIABLE	**n**	**n**
IL 2	106	100
IL 6	105	98
TOTAL ASSESSED PATIENTS	472	472

Cells of the immune system express Toll-like vitamin D receptors (Figure 1) and portray the intracellular mechanisms capable of converting [25(OH)D] into its active formulation [1.25(OH)2D] reflecting in the organism of protective and antimicrobial form [9,24]. According to one study, the use of vitamin D at a dose equivalent to 1250 mcg/week may reduce the risk of severity of COVID-19 [6,24]. In addition, the effectiveness of vitamin D supplementation with high weekly doses was demonstrated in a study in systematic review and meta-analysis, where no cases of vitamin D-induced hypercalcemia were reported [23,24]. This same dose was used to treat sepsis and H1N1 [1,5,6]. The dose of 1250 mcg/week is higher than the dose that can be produced from sun exposure [6,23-24]. On the other hand, vitamin D supplementation necessary for the general population to reach concentrations of 25(OH)D greater than 20 ng/ml occurs specifically in winter [6,24]. Supplementation of vitamin D in doses equivalent to 1250 mcg/week favors the increase in serum IgM levels with respiratory infection in the child population [1], as well as the increase in serum catelicidin which significantly reduces the frequency of hospital complications such as pneumonia, sepsis and H1N1 [6,18].

Vitamin D has several immunomodulatory functions including the regulation of antiviral peptides that are part of human innate immunity and can, for example, inactivate the influenza virus [6,24]. It is interesting to note that vitamin D behaves as a metabolizing hormone capable of contributing to the proper functioning of cardiac and pulmonary tissue in an inflammatory process. In our assessment findings in the articles included for this study [1], the decrease in cytokines (Il-2, Il-6, Il - 8, Il-10 and lymphocytes and neutrophils) was correlated with the severity of the illness process by COVID-19 (Figure 1) [9,19,23]. Our results are similar to those reported by previous authors who evaluated viral diseases such as H1N1 and dengue, which found that the degree of impairment of the immune system was closely related to hypovitaminosis D [9,19,24]. Our data reflect the fact that the disease severity related to COVID- 19 leads to a concern with the patient's nutritional status [11], mainly due to vitamin D deficiency, which, in turn, worsens the patient's clinical condition and changes the regulation of immune system cells (Figure 1) [19,24].

Therefore, maintaining a blood vitamin D level of 20 ng/ml or greater plays a protective role in the immune system of the COVID-19 carrier [24,29]. Vitamin D has a direct relationship with problematization in the worsening of patients with COVID 19, for example, vitamin D deficiency causes an increase in sepsis in patients in viral infectious processes that evolve to complications such as pneumonia and sepsis [1,8,19,23]. In fact, metabolic changes in glucose and especially calcium are altered with vitamin D deficits and thus cause damage such as decreased immune cell production (neutrophils and lymphocytes) [9] and decreased cytokines (IL-2, IL-6, IL -8, IL-10) (Figure 1) [7,9] in the organism, as well as incapacitating the organism to respond to the action of the invading virus [19,24]. From such evidence highlighted above, the hypothesis that must be considered is that Vitamin D supplementation is able to reduce the risk of prevalence and death from COVID-19.According to previous studies that evaluated an immunological cellular population sample in MERS and H1N1 [6], it should be considered and investigated in order to condition the ideal dose in the supplementation of vitamin D orally in times of pandemic in a safe and balanced

way as a preventive form of population worsening [6,23]. Especially at-risk population such as diabetics, hypertension, chronic kidney disease, heart disease, multiple sclerosis, autoimmune diseases and oncological diseases, etc [21,22].

Although the present study has limitations such as the size of the sample, it is carried out in a pandemic moment, being limited to the number of patients who were admitted to hospitalization processes. However, it is possible to observe that the immune system cells and cytokines should be used as a possible marker of support for nutritional status, being correlated to the deficiency of vitamin D [5,24]. In view of the evidence, such cells can be used as a possible support biomarker in the process of vitamin D supplementation in complex viral diseases such as COVID-19 [1,9,24].

Conclusion

Based on the results of this research, it was observed that the decrease in immune defense cells (neutrophils and lymphocytes) and cytokines (Il-2, Il-6, Il-8, Il-10) are related to the deficiency of Vitamin D in the body and has as a consequence the clinical worsening in COVID 19. Furthermore, the decrease in immune cells (neutrophils and lymphocytes) and cytokines (IL-2, IL-6, IL-8 and IL-10) can be used as a biomarker in the process of worsening COVID 19. The momentary increase in Il-2 and IL-6 and subsequently decrease may be due to the laboratory evolution for pneumonia caused by COVID-19 and is directly related to vitamin D deficit.

References

ALAGARASU K, et al. Elevated levels of vitamin D and deficiency of mannose binding lectin in dengue hemorrhagic fever. Virology Journal, v. 9, p. 86, 2012.

BACKER JA, KLINKENBERG D, WALLINGA J. Incubation period of 2019 novel coronavirus (2019-nCoV) infections among traveler from Wuhan, China, 20–28 January 2020.Euro surveillance: bulletin Europeen sur les maladies transmissibles. European communicable disease bulletin 2020, 25(5):2000062.

BIKLE, D.D. Chapter one - Vitamin D regulation of immune function. Elsevier. v. 86. p.1-21. 2011.

BIKLE, D.D et al. Vitamin D assays and the definition of hypovitaminosis D: results from the First International Conference on Controversies in Vitamin D. Br J Clin Pharmacol. v.84. n.10. p.2194-2207. 2018.

BRUM, D. G; COMINI-FROTA, E. R; VASCONCELOS, C. C. F; DIAS-TOSTA, E. Suplementação e uso terapêutico de vitamina D nos pacientes com esclerose múltipla: Consenso do Departamento Científico de Neuroimunologia da Academia Brasileira de Neurologia. Arq. Neuropsiquiatria, v. 72, n. 2 (III –IV), p. 3-7, January. 2014.

CANNELL JJ.; VIETH R; UMHAU JC; HOLICK MF; GRANT WB; MADRONICH S; GARLAND CF; GIOVANNUCCI E. Epidemic influenza and vitamin D. Epidemiol Infect 2006, 134, 1129-1140, doi:10.1017/S0950268806007175.

CAMERON LK.et al. Vitamin D levels in critically ill patients with acute kidney injury: a protocol for a prospective cohort study (VID-AKI). BMJ Open. 2017.

COCCO E; MELONI A; MURRU MR; et al. Elements responsive to vitamin D in the HLA-DRB1 promoterregion in the alleles associated with multiple sclerosis in Sardinia. PloSOne. v.07. n.07. e41678. 2012.

DETTOGNI RS. 1985- D479i Influência de polimorfismos nos genes FcγRIIa, CD209, VDR, TNF-α, IL-4, IL-6 e INF-γ na persistência de sintomas clínicos da dengue na fase de covalescença/Raquel Spinassé Dettogni – 2015. 208 f.: il. Orientador: IúriDrumond Louro. Tese (Doutorado em Biotecnologia) – Universidade Federal do Espírito Santo, Centro de Ciências da Saúde.

DRECHSLER C; PILZ S; OBERMAYER-PIETSCH B; et al. Vitamin D deficiency is associated with sudden cardiac death, combined cardiovascular events, and mortality in hemodialysis patients. Europan Heart Journal, v.31. p.2253-2261. 2010.

HASHEMI R; MORSHEDI M; JAFARABADI I.; et al. Anti-inflammatory effects of dietary Vitamin D3 in patients with multiple sclerosis. Neurology Genetics. 04. 6. 01-08. 2018.

HOLICK MF. Vitamin D deficiency. The New England Journal of Medicine. v.357. n.3, p.266-81. 2007.

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 Metabl. v. 96, n. 12, p. 1911-1930. Jul., 2011.

JOANNA J; WŁODZIMIERZS; BŁAŻEJR; PAWEŁM; DANIELAP; KATARZYNAWK; IWONAS. Clinical and immunological effects of vitamin D supplementation during the pollen season in children with allergic rhinitis. Arch Med Sci. January. 2018.

KOUCHAKI E; AFARINI M; ABOLHASSANI J, et al. High-dose *ω*-3 Fatty Acid Plus Vitamin D3Supplementation Affects Clinical Symptoms and Metabolic Status of Patients with Multiple Sclerosis: A Randomized Controlled Clinical Trial. The Journal of Nutrition. 2018.

JANGHORBANI M; SHAYGANNEJAD V; HAKIMDAVOOD M; SALARI M. Trace Elements in Serum Samples of Patients with Multiple Sclerosis. Athens Journal of Health. v. 4, n. 2. p. 145-54, June. 2017.

LEE P. Vitamin D metabolism and deficiency in critical illness. Best & Practice & Research Clinical Endocrinology & Metabolism. v.25. n.05. p.769-81. 2011.

LOEB M; DANG AD; THIEM VD; THANABALAN V; WANG B; NGUYEN NB; TRAN HTM.; LUONG TM; SINGH P; SMIEJA M, et al. Effect of Vitamin D supplementation to reduce respiratory infections in children and adolescents in Vietnam: A randomized controlled trial. Influenza Other Respir Viruses 2019, 13, 176-183, doi:10.1111/irv.12615.

MANION M; HULLSIEK KH; WILSON EMP; RHAME F; et al. Vitamin D deficiency is associated with IL-6 levels and monocyte activation in HIV-infected persons. PLoS One. v.12. 2017.

MOROMIZATOT; et al. Association of Low Serum 25- Hydroxyvitamin D Levels and Sepsis in the Critically Ill. *Critical Care Medicine*. v.42. Issue 1: p.97–107. 2014.

NANSHAN CHEN, MIN ZHOU, XUAN DONG, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel corona virus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395: 507513. https://doi.org/10.1016/S0140-6736(20)30211-7

OPAS, OMS. Folha informativa – COVID-19 (doença causada pelo novo coronavírus). 2020. Acesso:https://www.paho.org/bra/index.php?option=com_content&view=article&id=6101:covid19&Itemid=875.

RAMOS EM, LIMA MD, GONZALEZ JEC, FACCO GG, NASCIMENTO dVA. Vitamin d in intensive therapy in treatment of adult patients: a methanalysis of clinical testing. International Journal of Development Research. v.9. 2019.

RAMOS EM, LIMA MD, GONZALEZ JEC, FACCO GG, NASCIMENTO dVA. Analysis of vitamin d effectiveness of short interventions in the prevention and reduction of sepsis in Brazilian intensive care: a systematic review. International Journal of Development Research.v.9. Issue 02. 2019.

VELDMAN CM; CANTORNAMT; DELUCAHF. Expressão do receptor 1,25-dihidroxivitamina d (3) no sistema imune. Arco. Biochem. Biofísica. v.374. p.334-338. 2000.

VOGESER M. Quantification of circulating 25-hydroxyvitamin D by liquid chromatography – tandem mass spectrometry. J Steroid Biochem Mol Biol. v. 121. n. 16-17. p. 565-73. August. 2010.

ZHOU YF.; LUO BA; QIN LL. The association between vitamin D deficiency and community-acquired pneumonia: A meta-analysis of observational studies. Medicine (Baltimore) 2019, 98, e17252, doi:10.1097/MD.0000000000017252.

ZUGHAIER SM, ALVAREZ JA, SLOAN JH, KONRAD HR, TANGPRICHA V. The role of vitamin D in the regulation of the iron-hepcid in ferroportin axis in monocytes. Journal of Clinical and Translational Endocrinology. v.01. n.01. p.e19-e25. 2014.

HAYES DP. Influenza pandemics, solar activity and Vitamin D. Medical Hypotheses. v. 74. p.831-834. 2010.