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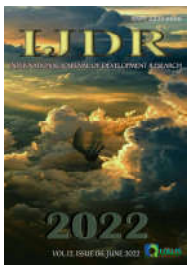

RESEARCH ARTICLE OPEN ACCESS

CORRELATION BETWEEN VITAMIN D ANDCOVID-19 PATIENTS

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ABSTRACT

Vitamin D deficiency is suspected to cause possible complications in COVID-19 patients or they might be provided with a poor prognosis. However, this same vitamin D in excess is capable of causing toxicity. The presentstudy was based on a qualitative/quantitative study carried out from July to September, 2021 .Patients who tested positive for COVID-19 and who sought medical appointment in a private general practice in the city of Caçador,state of Santa Catarina (SC), were selected. The sample consisted of 54 patients who sought ambulatory care and who had a positive diagnosis for COVID-19. Vitamin D levels were found to beeither insufficient or deficient in most patients. However, the plasma concentration of vitamin D in these patients cannot be related to the positivity of the disease or hospitalization. What can be safely concluded is that vitamin D has numerous proven benefits, such as maintaining the cells of the immune system and, thus, preventing infectious diseases.

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INTRODUCTION

At the end of 2019, a new virus emerged in Wuhan, China, later named Sars-Cov-2. In view of its unrestrainedwidespread in several countries, the World Health Organization declared it a pandemic on December 31st, 2019 (SILBERSTEIN, 2020). Classic symptoms related to COVID-19 include cough, fever, headache, shortness of breathethat progresses to pneumonia, in addition to more severe conditions in the respiratory tract (ILIE, et al., 2020). COVID-19 patients have an inflammatory status especially increased in interleukins (IL-1 and IL-6). Thus, research on specific drugs and vitamins to decrease the inflammatory status generate positive expectations for the clinical management of infected patients (SILBERSTEIN, 2020). It is well known that there are countries where the mortality caused by COVID-19 is higher than in others. This is due to several factors, such as social distancing, population health and the number of population. It is worth mentioning that vitamin D deficit could be included as one of these factors. Its supplementation might favor all individuals, since a low serum level has been shown to worsen the symptoms of this disease (MITCHELL, 2020). Vitamin D is related to various clinical outcomes on patients' health and mortality. It is known that the largest fraction of this vitamin in the body is the result of itsproduction in the skin after direct exposure to the sun and ultraviolet rays (HRISBAR, et al., 2020). However, this same vitamin D in excess is capable of causing toxicity, which might result in hypercalcemia (too high concentration of calcium in the blood) and hypercalciuria (excessive urinary calcium excretion). The serum concentration of 25-hydroxyvitamin D (25[OH]D) associated with hypercalcemia is approximately 150 ng/mL. The first signs and symptoms of toxicity include feeding difficulties, polydipsia, polyuria, constipation, irritability, reduced weight gain. Calcium can be deposited throughout the body, especially in the kidneys, and can cause damage (TAYLOR and DAVIS, 2018). Therefore, the present study aimed at assessing the positive cases for COVID-19 in a private general practice. The follow-up of these patients was observed by correlating the need for hospitalization and the concentration of vitamin D, in addition to seeking information about their knowledge on the benefits and harms of vitamin D.

Theoretical foundations: The infection called COVID-19, caused by Coronavirus (SARS-CoV-2), emerged in December, 2019, in China, and became a global public health concern due to its rapid widespread in several countries, which has configured it as a pandemic (PARVEEN, et al., 2020; NANDY, et al; 2020, HUSSAIN, et al; 2020). The degree of struck patients is varied, since although most of them have a mild clinical picture and a favorable prognosis, the elderly and/or those with underlying chronic diseases generally have worse results (PARVEEN et al., 2020). The virus can appear in a symptomatic or asymptomatic form.The symptoms are non-specific ones, such as fever, myalgia and fatigue; or they can be specific to several systems, that is, the respiratory tract, the gastrointestinal tract, the Central Nervous System (CNS), among others. Respiratory

manifestations include dry cough, pneumonia, pulmonary edema, Acute Respiratory Distress Syndrome (ARDS), pulmonary edema, septic shock, metabolic acidosis, coagulation dysfunction, and multiple organ dysfunction syndromes, among other complications. (PARVEEN, et al, 2020; MAVEDDAT, et al; 2020). Approximately 20% of COVID-19 patients develop severe respiratory problems, with an overall fatality rate around 2.3% (SHI Y et al, 2020). The complications of COVID-19 occur mainly in people with a risk factor, that is, diabetes, hypertension, obesity, cardiovascular diseases, cancer, smoking history, vitamin D deficit, since they evolve more seriously, especially if associated with old age. (HAN, et al., 2020). Disease prevention includes a set of care. Considering Covid-19 syndrome, caused by the new corona virus, the best prevention is reducing physical contact, avoiding agglomerations, not sharing personal materials, always washingthe hands correctly with water and soap, besidesusing alcohol gel (BRASIL, 2019). Strengthening the immune system in the fight against infections is another form of prevention by making use of some vitamins, such as A, C, D, iron, zinc and selenium, which can act positively on the immune system. Vitamin A has a main structure in skin cells and the respiratory tract; iron acts on the differentiation of cell growth and on the critical enzymes of immune cells; zinc, on the other hand, is a trace element fundamental for the maintenance of innate and adaptive immune function, since it plays a fundamental role in the process of transcription, translation and replication of DNA, in addition to being an important antioxidant that plays a central role. (WESSELS et al., 2017; MAGGINI et al., 2018).

Vitamin D is a fat-soluble hormone, obtained through food and skin synthesis after sun exposure. Thus, the production of this vitamin is dependent on exposure to ultraviolet rays of type B (UVB) to activate the synthesis of this substance (FERRARINI and MACEDO, 2015). Vitamin D has two main forms: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). D3 is only found in food of animal origin, and D2 is produced by the body through cutaneous synthesis when the skin comes into contact with the sun, in addition to being produced by yeasts, fungi and plants (HOLICK, 2011). Both are effectively absorbed into the bloodstream. However, the liver metabolizes them differently. Both vitamin D2 (ergocalciferol) and D3 (cholecalciferol) need to be processed by the body to reach their metabolically active form, that is, calcitriol. Thus, they undergo a chemical process known as hydroxylation, first in the liver and then in the kidneys (forming calcidiol and calcitriol, respectively). However, studies show that vitamin D2 appears to produce less calcidiol than an equal amount of vitamin D3 (ROMAGNOLI, 2008). Vitamin D, when administered in adequate doses, does not cause any type of toxicity, however, if consumed in high amounts it can be toxic. Symptoms of toxicity include anorexia, dehydration, muscle weakness, migraines, nausea, vomiting, polyuria, and polydipsia (TAYLOR and DAVIS, 2018). In view of several studies on the use of vitamin D in COVID-19 patients, some have shown evidence that low levels of vitamin D could have negative effects on infection with this disease. A large cross-sectional study sought to associate data on morbidity and mortality caused by COVID-19 and mean serum levels of vitamin D in European countries. Such a study showed a strong association of low vitamin D level in patients with a case of coronavirus infection (ILIE, et al., 2020). A retrospective multicenter study carried out in Asia with 212 cases of COVID-19 found a mean vitamin D serum level of 23.8 ng/ml. The results indicated an association between high serum concentrations of vitamin D and the improvement of clinical situations of the worst outcomes (severe to critical), whereas the vitamin deficit might be related to more severe clinical conditions in COVID-19 patients (ALIPIO, 2020).

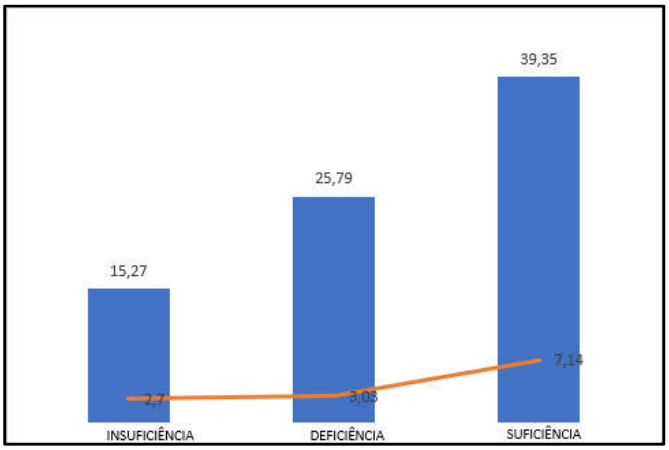
Another observational retrospective study evaluated vitamin D concentrations in 107 patients, and significantly lower levels were found in COVID-19 positive patients compared to negative ones (D'AVOLIO et al., 2020). Based on these findings, the authors of the study hypothesized that supplementation of this vitamin could reduce the risk of contracting COVID-19. Studies also sought to analyze whether good levels of vitamin D would be able to assist in the treatment or improve the prognosis of COVID-19 patients. The authors searched for COVID-19 mortality data compared to vitamin D levels in different European countries. They showed that countries with lower latitudes and high rates of vitamin D deficiency also had the highest rates of infection and death on the European continent (LAIRD et al., 2020). Grant et al. (2020) pointed out that vitamin D might decrease the risk of infections, and the deficiency of this vitamin might worsen acute respiratory distress syndrome. The authors suggested that for preventing and avoiding spread of infections, especially regarding COVID-19, 10,000 International Units (IU) of vitamin D3 per day should be taken for a few weeks to rapidly increase sufficient concentrations of 25-hydroxyvitamin D, followed by 5000 IU/day, in addition to monitoring the serum concentration on a regular basis. Arandomized clinical trial study that included 240 hospitalized patients with moderate to severe COVID-19 did not show improvement in hospitalized patients with a single dose of 200,000IU of vitamin D (ANNWEILER, et al., 2020).

METHODOLOGICAL LIMITATIONS

The present study was based on a qualitative/quantitative study carried out from July to September, 2021 (JAVORSKI, 2021).The patients who tested positive for COVID-19 and who sought medical appointment in a private general practice in the city of Caçador, state of Santa Catarina (SC)were selected. At the time of the appointment the medical professional applied a questionnaire to the patients who agreed to participate in the research. Such a questionnaire included closed questions related to the use of vitamin D supplementation, sun exposure habits and the dose of this supplementation.The patients were also questioned whether theyhad needed hospitalization for the follow-up of the disease. Demographic and anthropometric data were obtained by using a standardized questionnaire comprising ethnicity and age; or physical examination, including height and weight. The patients were evaluated at the beginning of the intervention and three months later. The evaluation included clinical aspects relevant to this study, that is, diagnostic criteria, disease duration, body mass index (BMI), use of medications,in addition to the average daily dose of Vitamin D, if any was taken. This research project was approved by the Committee on Ethical Research with Humans under Ordinance number 50843521.8.000.8145.As recommended by Resolution 466/12, CNS/MS, confidentiality of information and names of the participants will be ensured.

RESULTS AND DISCUSSION

The sample consisted of 54 patients, who sought ambulatory care from July 1st to September 30rd, 2021, and who had a positive diagnosis for COVID-19. The age of the patients ranged from 22 to 80 years. 40% of them were women, and 60% were men.The highest age group affected was younger than 60 years (34 patients).



Source: Javorski, 2021

Fig. 1. Results related to vitamin D dosage of the Covid-19 patients

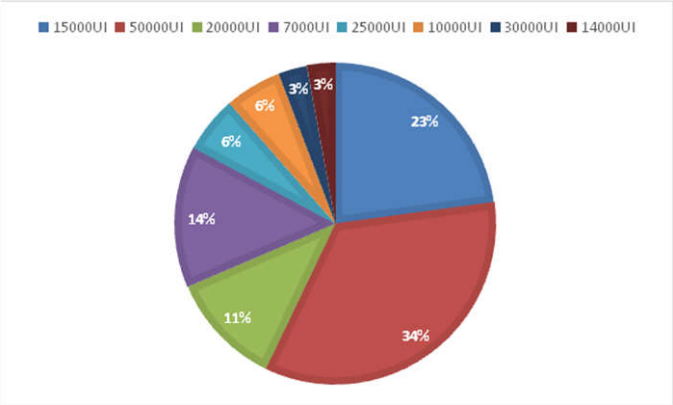
It is worth mentioning that at the beginning of the sample collection (July, 2021) the Ministry of Health had already started the vaccination campaign for people over 60 years old, which might justify the lower demand for this age group with positive disease in the general practice. Figure 1 shows the vitamin D dosage ratio of the patients who sought medical care for COVID-19 follow-up at the first appointment.

Considering the number of patients, 16 of them were dosed at the insufficiency level (mean 15.27 ± 2.70); 10 were vitamin deficient (mean 25.79 ± 3.03), and 22 had a normal dose for vitamin D (mean 39.35 ± 7.14). It I should be highlightedthat 6 patientsdid not perform the dosage before or after COVID-19. Regarding the patients interviewed, 37 of them were already using vitamin D routinely, but none as a way of preventing COVID-19. Vitamin D levels were found to be insufficient or deficient in most patients, however, most of themhad already attended the general practiceand had vitamin D dosage as supplementation routinely. Thus, this was a limiting factor in the sense of correlating the positivity of the disease to the concentration of vitamin D. What can be inferred is that there is a need for monitoring and supplementingthe population with this vitamin. According to the Brazilian Society of Endocrinology, the reference value for vitamin D dosage considered as insufficiency is 20ng/ml; for deficiency it is <20ng/mL, and normal levels are between 30-60ng/m. When above >100ng/mL mL it is considered a risk of toxicity and might cause hypercalcemia and hypercalciuria (MOREIRA et al, 2020).

Vitamin D has been suggested due to the fact that it acts in several mechanisms and can reduce the risk of infections. Thus, it has aroused the interest of the scientific community in investigating the possible effect on the prevention or treatment of COVID-19. Vitamin D is thought to suppress adenosine deaminase 2 (ADA2), an adhesion molecule for the invasion of COVID-19 host cells (GRANT et al., 2020). According to Glinsky (2020) the observational analyzes also pointed out that vitamin D deficiency might contribute to the high mortality of older people with COVID-19. Therefore, multiple evidences indicate that its deficiency, particularly in the elderly, can be a negative factor for the clinical prognosis of the disease. Thus, the aging process causes not only a reduction in immunity, but also in the synthesis of endogenous vitamin D, which might justify the greater susceptibility of the elderly to complications and mortality from COVID-19 (GIMÉNEZ et al., 2020).

The present survey carried out at the general practice showed that only 4 patients required hospitalization. Their vitamin levels were the following: 17.9 ng/mL, 37.5 ng/mL, 49.9 ng/mL and 22.2 ng/mL, butone of them was not submitted to vitamin D dosage. As mentioned earlier, these patients had already been taking supplementation previously as a medical recommendation. Regarding the patients' knowledge on the synthesis and maintenance of vitamin D, 17% of the interviewed patients reported being exposed to the sun at least twice a day for 10 to 20 minutes. In addition, 22% of the patients reported using sunscreen, which decreases the absorption of vitamin D, since the product prevents the cutaneous synthesis of such a vitamin. In the southern region the incidence of solar rays is lower in winter; this causes a great deficiency of this vitamin in the body. Some individuals at higher risk, such as older people and darker-skin individuals, require vitamin D supplementation even with sun exposure. Considering cutaneous synthesis, during spring, autumn and summer, 10 to 15 minutes of sun exposure between 10 a.m. and 3 p.m. is enough for the synthesis of vitamin D in light-skinned individuals. Living in latitudes beyond 35º to 40º, which reduces the amount of UVB rays (Ultraviolet type B) that reach the earth, and having dark skin interfere in this production, since melanin absorbs UVB photons, functioning as a natural sunscreen. The use of sunscreen with a protection factor greater than 30 can decrease vitamin D synthesis by up to 90%. (ARAÚJO, 2016).

Figure 2 shows the dosage of vitamin D supplemented by the patients and reported at the time of the interview.



Source: Javorski, 2021

Fig. 2. Analysis of data on the weekly doses of vitamin D supplementation related the international units that each patient reported been using at the time of the interview

Gasmi et al. (2020) reported that vitamin D supplementation is efficient when used before the onset of respiratory tract infection. Despite this, for the treatment of patients at risk of COVID-19, it is indicated to increase 25-hydroxyvitamin D concentrations between 40–60 ng/mL (100–150 nmol/L), considering the use of 10,000 IU per day of vitamin D3 for a few weeks in order to rapidly increase concentrations, followed by 5000 IU/day in a monitored manner. Likewise, the protocols followed regarding the dosage of vitamin D for patients in general, but not related to COVID-19, are the following: risk patients must maintain above 30ng/mL, which makes a loading dose replacement of 50,000IU per week under a treatment of 4 to 8 weeks.Then,it should be followed by a maintenance dose, that is, 7,000IU per week in case of insufficiency, andhigher doseshave eventually to be used in case of deficiency. For young patients without any comorbidity, levels above 20ng/ML should be used as a normal value.The recommendation is to exposure to sun for 10 to 15 minutes wearing sleeveless clothes, not making use of sunscreen and without a hat (SBEM, 2020).

FINAL CONSIDERATIONS

Vitamin D levels were found to be insufficient or deficient in most patients. However, this study cannot suggest a correlation with COVID-19 because of the region where the patients live and their lack of routine in exposing themselves to the sun. Likewise, those with satisfactory levels of vitamin Dhad beenpreviously supplementing it due to medical advice received during their routine appointments at the general practice. The need for monitoring vitamin D is reinforced. Patients at risk should maintain the dose of vitamin D above 30ng/mL. In case theyneed, a loading dose, that is, 50,000IU should be used per week for 4 to 8 weeks, followed by maintenance doses. What can safely be concluded is that vitamin D has numerous proven benefits, such as the maintenance of the immune system cells and, thus, prevention of infectious diseases. Several studies have shown a strong correlation between this vitamin deficiency and poor prognosis of COVID-19, especially regarding the elderly and patients at risk. However, the present study found no association, although the majority of the COVID-19 patients herein assessed hadshown doses lower than recommended when searching medical care. The need of monitoring the plasma concentrations of the vitamin D is also highlighted since, as already mentioned, when used in excess might cause toxicity to the organism. Thus, such a vitamin should not be self-medicated.

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