ORIGINAL ARTICLE

Association of Vitamin D and magnesium levels with severity and mortality in patients with COVID-19

Asociación de los niveles de vitamina D y magnesio con la gravedad y la mortalidad en pacientes con COVID-19

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Abstract

Objective: *The study aimed to determine the association between serum magnesium and Vitamin D levels with the severity and mortality by coronavirus disease 19 (COVID-19) in hospitalized patients.* **Method:** *Men and women over 18 years of age with probable COVID-19 were enrolled in a case–control study. Patients with a positive or negative test for Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were allocated into case or control groups, respectively. Vitamin D deficiency was defined by concentrations < 20 ng/mL and hypomagnesemia by serum levels < 1.8 mg/dL.* **Results:** *A total of 54 patients, 30 women and 24 men, were enrolled and allocated into the groups with (n = 27) and without (n = 27) COVID-19. The logistic regression analysis showed that Vitamin D deficiency (odds ratio [OR] = 6.13; 95% confidence intervals [CI]: 1.32-28.34) and insufficiency (OR = 0.12; 95% CI: 0.02-0.60) are significantly associated with hospitalization. However, Vitamin D disorders and hypomagnesemia were not associated with mortality.* **Conclusions:** *The results of the present study revealed that Vitamin D disturbances, but not hypomagnesemia, are associated with the severity of SARS-CoV-2.*

Keywords: *Coronavirus disease 19. Magnesium. Mortality. Severity. Vitamin D.*

Resumen

Objetivo: *Determinar la asociación entre los niveles séricos de vitamina D y de magnesio con la gravedad y la mortalidad de la COVID-19 en pacientes hospitalizados.* **Método:** *Hombres y mujeres mayores de 18 años con probable COVID-19 fueron enrolados en un estudio de casos y controles. Los pacientes con una prueba positiva o negativa para SARS-CoV-2 fueron asignados en los grupos de casos y de controles, respectivamente.* **Resultados:** *Un total de 54 pacientes, 30 mujeres y 24 hombres, fueron enrolados y asignados a los grupos COVID-19 (n = 27) y control (n = 27). El análisis de regresión logística mostró que la deficiencia de vitamina D (odds ratio [OR]: 6.13; intervalo de confianza del 95% [IC95%]: 1.32-28.34) y la insuficiencia de vitamina D (OR: 0.12; IC95%: 0.02-0.60) se asocian significativamente con hospitalización. Sin embargo, las alteraciones de la vitamina D y la hipomagnesemia no se asociaron con mortalidad.* **Conclusiones:** *Los resultados del presente estudio revelaron que las alteraciones de la vitamina D, pero no la hipomagnesemia, se asocian con la gravedad de la COVID-19.*

Palabras clave: *COVID-19. Magnesio. Mortalidad. Gravedad. Vitamina D.*

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a multiorgan disease with inflammatory and prothrombotic characteristics[1,2]. The number of SARS-CoV-2 cases increased rapidly worldwide and, in Mexico, hospitals and emergency services were modified for the specialized treatment of coronavirus disease 19 (COVID-19) patients[3,4]. Through the angiotensin-converting enzyme 2 (ACE-2) receptor, this virus infects lung epithelial cells and macrophages, leading to the activation of macrophages, neutrophils, and T cells, causing sustained elevations of pro-inflammatory cytokines such as interleukin-1, 6 and tumor necrosis factor alpha. In this context, the "cytokine storm," a hyperinflammatory state triggered by SARS-CoV-2, is responsible for some of the most severe complications of COVID-19, including acute respiratory distress syndrome (ARDS). Although the inflammatory response initially helps to eliminate pathogens, it also damages the alveolar endothelial-epithelial barrier, resulting in edema and thrombosis, which in turn causes apoptosis of Type 2 pneumocytes and, in some patients, ARDS[2].

Magnesium is an essential mineral for basic biochemical reaction, physiological functions and metabolism in the human body[5-8]. In addition, this element has anti-inflammatory, antioxidant, anti-spasm, vasodilation, and neuroprotection effects[9] and plays an important role in the regulation of the immune response through immunoglobulin synthesis, immune cell adherence, antibody-dependent cytolysis, immunoglobulin M lymphocyte binding, macrophage response to lymphokines, and T helper-B cell adherence, especially in viral infections[10]. Therefore, it has been hypothesized that subjects with hypomagnesemia are at higher risk of developing respiratory tract infections[11].

Magnesium is fundamental in the synthesis, transport, and activation of Vitamin D, since acts as a cofactor for the enzymes involved in its metabolism[12]. Vitamin D confers a protective effect against respiratory tract infections by inhibiting the hyperinflammatory response through the regulation of cytokines and differentiation of T cells[12-14]. Furthermore, some authors have suggested that Vitamin D may downregulate ACE-2 receptors, resulting in a protective effect against fibrosis of COVID-19 by accelerating the healing process in the lung tissue[15]. Thus, the objective of this study was to determine the association between serum Vitamin D and magnesium levels with severity and mortality in hospitalized patients diagnosed with COVID-19.

Materials and methods

With prior approval by the Ethics and Research Committee of the Hospital Salvador Zubirán Anchondo from Chihuahua, México (registration number 0294), and following the principles of the Helsinki Declaration, a cross-sectional and longitudinal study was conducted. Men and women over 18 years of age with probable pulmonary infection were considered to participate in this study after acceptance of the informed consent. After admission in the emergency service, patients were assessed through standardized interviews, clinical examination, and laboratory tests including reverse transcriptase-polymerase chain reaction test for SARS-CoV-2. According to the result of this last test, participants were assigned into the groups with (positive test) or without (negative test) COVID-19. Exclusion criteria were pregnancy, chronic diarrhea, chronic kidney disease, heart failure, cancer, and the supplement intake during the last 4 weeks before the study. Hospitalized patients were followed until discharge due to recovery or death, including the admission to the intensive care unit (ICU).

Definitions

Hypomagnesemia was defined by serum levels < 1.8 mg/dL and Vitamin D deficiency by concentrations < 20 ng/mL, and Vitamin D insufficiency for concentrations 20 and < 30 ng/mL. Finally, hospitalization and admission to the ICU were considered for severity.

Assays

The venous blood samples were obtained following 8-10 h overnight fasting. The serum levels of 25-hydroxyvitamin D were determined by electroluminescence method with a coefficient of variation of 6.7 using a COBAS 6000 analyzer (Roche Diagnostics, Germany). The serum magnesium concentrations were measured with quantitative photometric biochemical analysis with a coefficient of variation of 3.8 using the ADVIA 1800 analyzer (Siemens, Tarrytown, NY, USA).

Statistical analysis

Numerical variables were reported as mean ± standard deviation and categorical variables as proportions. Differences between groups were estimated

using unpaired Student's t-test for numerical variables and the χ^2 test for categorical variables. Multiple logistic regression analysis (adjusted by obesity, diabetes, and hypertension) was performed to assess the association of hypomagnesemia (ordinal variable) and Vitamin D abnormalities (ordinal variables) with SARS-CoV-2 (overall population), severity, and mortality (patients with positive SARS-CoV-2). A 95% confidence interval (95% CI) and $p < 0.05$ were used to establish statistical significance. The data were analyzed with the IBM SPSS Static Version 15.0.

Results

A total of 54 patients, 30 women and 24 men, with a mean age of 53.4 ± 21.8 years were enrolled and allocated into the groups with (n = 27) and without (n = 27) COVID-19.

In the overall population, 78% had low levels of Vitamin D and 55% hypomagnesemia. The most common comorbidities were: diabetes (35%), hypertension (35%), chronic obstructive pulmonary disease 11.1%, liver disease 5%, and asthma 3.7%. However, the distribution of comorbidities between the study groups was similar.

The clinical and biochemical characteristics of the study population are shown in (Table 1). The cases presented a lower oxygen saturation than the controls. There were other significant differences between the study groups.

In addition, a higher percentage of patients with COVID-19 was admitted to the ICU in comparison with the controls (85.1% vs. 33.3%, $p < 0.001$).

Among COVID-19 patients, the multiple logistic regression analysis showed that Vitamin D deficiency (OR = 6.13; 95% CI: 1.32-28.34) and insufficiency (OR = 0.12; 95% CI: 0.02-0.60) are significantly associated with hospitalization (OR = 0.11; 95% CI: 0.02-0.50). However, hypomagnesemia and Vitamin D abnormalities were not associated with mortality (Table 2).

Discussion

Our results suggest that Vitamin D disorders, but not hypomagnesemia, are associated with the severity of SARS-CoV-2.

Previous studies have reported that low magnesium levels are associated to severity and mortality[16,17], which is in disagreement with our findings. This inconsistency could be explained because these studies were retrospective analyses that only included patients with COVID-19 (comparing severe versus non-severe cases), while we conducted a cross-sectional study comparing patients with and without COVID-19. Furthermore, another possible reason is that the frequency of magnesium deficiency in the target population of our study was very high (46.2%) compared to that reported for the adult Mexican population (31%)[18].

Interestingly, most of our study population had Vitamin D deficiency (74.5%); this finding coincides with another Colombian study where it was found that the male gender and the Fitzpatrick IV phototype were associated with an increased risk of Vitamin D deficiency[19]. Besides, a previous systematic review and meta-analysis revealed that low serum Vitamin D levels are associated with an increased risk of COVID-19 infection[20]. Nonetheless, we observed that Vitamin D deficiency is not associated with the presence of SARS-CoV-2. There are several mechanisms involved in the infection of respiratory viruses by Vitamin D deficiency. In this regard, it has been reported that Vitamin D deficiency affects the immune response, particularly innate immune function. Furthermore, low levels of Vitamin D decrease the active Vitamin D synthesis, leading to the mitigation of the antimicrobial and antiviral properties of this vitamin. Furthermore, Vitamin D regulates the expression of cathelicidin and defensin, molecules that induce the expression of antiviral cytokines and chemokines, resulting in the recruitment of T cells, natural killer cells, neutrophils, monocytes, and macrophages. In addition, Vitamin D induces autophagy in monocytes and macrophages through cathelicidin, Beclin 1, and mTOR pathway[21-23]. Furthermore, Vitamin D stimulates PI3KC3 through upregulation of intracellular calcium and nitric oxide, which promotes autophagy[24]. Therefore, the protective actions of Vitamin D may be mitigated by its deficiency, causing a defective response against respiratory viruses, including SARS-CoV-2[25].

It is noteworthy that the results of our study showed that Vitamin D deficiency was not associated with severity and mortality, which is in contrast with several studies. In this regard, it has been reported that advanced age is an important risk factor for the severity and mortality in patients with COVID-19[26]; however, the target population of our study had a mean age < 60 years, which could explain our results. However, in the sub analysis of patients with SARS-CoV-2, Vitamin D deficiency (n = 18) and insufficiency (n = 4) were associated with hospitalization. Nevertheless, it is important to note that these results were obtained from a smaller sample size, which could explain the direct and inverse association of Vitamin D deficiency

Table 1. Clinical and biochemical characteristics of the study population, n = 54

Variables	Overall n = 54	SARS-CoV-2 (+) n = 27	SARS-CoV-2 (−) n = 27	p-value
Age, years	53.4 ± 22.0	52.5 ± 22.4	54.3 ± 21.9	0.77
Women, n (%)	24 (44.4)	14 (51.8)	16 (59.2)	0.78*
Body mass index, kg/m^2	25.3 ± 32.2	26.2 ± 5.8	24.5 ± 5.0	0.23
Systolic blood pressure, mmHg	113.5 ± 32.2	110.1 ± 6.5	116.8 ± 30.3	0.45
Diastolic blood pressure, mmHg	74.0 ± 20.8	71.1 ± 21.9	77.0 ± 19.5	0.29
Oxygen saturation, %	84.7 ± 7.4	81.5 ± 8.7	87.9 ± 3.9	0.001
Magnesium, mg/dL	1.9 ± 0.9	1.9 ± 0.6	1.8 ± 0.4	0.50
Vitamin D, ng/mL	15.8 ± 7.0	15.1 ± 5.0	16.5 ± 8.6	0.48
Days of hospitalization	6.3 ± 5.9	12.3 ± 9.5	11.1 ± 8.9	0.92
Deaths, n (%)	21 (38.8)	13 (48.1)	8 (29.6)	0.16*
APACHE II score	11.9 ± 9.3	12.3 ± 9.5	11.1 ± 8.9	0.81
SOFA score	5.8 ± 3.6	4.8 ± 3.5	6.7 ± 3.5	0.06

Values are mean ± standard deviation. P value estimated with the Student×s t-test. *p-value estimated with the χ^2 test. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Table 2. Multiple logistic regression analysis that evaluates the association between low levels of magnesium and Vitamin D (independent variables) with SARS-CoV-2 and their outcomes (dependent variables). The normal values of magnesium and Vitamin D were used as reference groups

Independent variables	SARS-CoV-2 (+)*	Hospitalization**	ICU admission**	Death**
	OR (95% CI)†	OR (95% CI)†	OR (95% CI)†	OR (95% CI)†
Hypomagnesemia (< 1.8 mg/dL)	0.54 (0.16-1.77)	0.61 (0.16-2.27)	0.78 (0.25-2.37)	1.08 (0.34-3.39)
Vitamin D deficiency (< 20 ng/mL)	2.36 (0.54-10.30)	6.13 (1.32-28.34)	2.79 (0.70-11.13)	2.87 (0.62-13.20)
Vitamin D insufficiency (20 < 30 ng/mL)	0.51 (0.11-2.24)	0.12 (0.02-0.60)	0.27 (0.06-1.14)	0.20 (0.38-1.15)
Magnesium and Vitamin D deficiencies	0.92 (0.25-3.32)	1.29 (0.27-6.12)	2.04 (0.55-7.54)	2.32 (0.65-8.17)

OR: odds ratio; CI: confidence interval; ICU: intensive care unit. *Analysis conducted in the overall population. **Analysis conducted in patients with SARS-CoV-2 (+). †Analysis adjusted by obesity, diabetes, and hypertension. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

and insufficiency, respectively. Therefore, these findings could be treated with caution.

A previous meta-analysis revealed that Vitamin D supplementation prevents against acute respiratory tract infection[27]. In this context, a randomized controlled trial showed that a high-dose Vitamin D supplementation turned SARS-CoV-2 RNA negative in Vitamin D-deficient individuals with COVID-19 infection[28]. Another randomized clinical trial suggested that a high dose of Vitamin D improves the clinical course of COVID-19 infection through the suppression of cytokine storms[29]. According to the abovementioned, Vitamin D supplementation may be a promising treatment for COVID-19 in vitamin deficient patients. However, larger randomized controlled trials are mandatory to corroborate the potential beneficial effects of this vitamin on outcomes of COVID-19 infection.

This study has some limitations that should be mentioned. First, taking into account the study design, causality cannot be assured. Second, we recognize the small sample size, which may introduce a potential source of bias. Finally, it is important to note that this study was conducted during the winter, resulting in an increased incidence of respiratory tract infections and reduced sun exposure, which could affect our results.

Conclusion

The results of the present study showed that Vitamin D abnormalities are associated with the severity of

SARS-CoV-2. However, low magnesium and Vitamin D levels are not related with the mortality by COVID-19.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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