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The association between vitamin D3 deficiency and acute kidney injury in COVID-19 patients

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ABSTRACT

Introduction: Vitamin D deficiency is a common clinical finding in the general population and hospitalized patients, including patients in the intensive care unit (ICU). Acute kidney injury (AKI) occurs in more than 50% in ICU admitted patients.
Objectives: There are few studies regarding AKI in COVID-19 patients, therefore we investigated the relationship between vitamin D3 deficiency and the occurrence of AKI in COVID-19 patients.
Patients and Methods: This cross-sectional study was conducted on 69 COVID-19 patients who were hospitalized in the ward for 12 months. Their serum vitamin D3 levels were measured in the first 24 hours of hospitalization in the ward. Patients were divided into three groups based on the serum levels of vitamin D3: >50 ng/mL as normal, 20-50 ng/mL as insufficient and <20 ng/mL as deficiency status. The patients were studied until the occurrence of acute renal injury or the occurrence of death.
Results: Out of 69 hospitalized patients in the ward with COVID-19, there were 39 patients in group vitamin D3<20 ng/mL, 21 patients in group vitamin D3 of 20-50ng/mL and 9 patients in group of vitamin D3>50 ng/mL. The frequencies of AKI in groups of vitamin D3<20 ng/mL, 20-50 ng/mL, and >50 ng/mL were 46%, 28%, and 23%, respectively. A significant relationship was observed between AKI and our study groups (P=0.011). Furthermore, there was a significant association between our study groups and mortality (P=0.014), ICU admission (P=0.041) and hospital length of stay (P=0.017). In another division in patients with different levels of vitamin D3 in the presence or absence of AKI, there were significant associations between patients with vitamin D3<20 ng/mL and the presence of AKI and also with mortality (P=0.042), ICU admission (P=0.024) and additionally with hospital length of stay (P=0.027).
Conclusion: Our study showed significant association between vitamin D deficiency and AKI in ICU-admitted COVID-19 patients. Moreover, there were relationships between vitamin D deficiency and mortality, ICU admission and hospital length of stay. These results suggest the correction of vitamin D deficiency may be beneficial to reduce AKI in patient with COVID-19.

Implication for health policy/practice/research/medical education:
In a cross-sectional study on 69 hospitalized patients in the ward with COVID-19, we found significant association between vitamin D deficiency and acute kidney injury. Moreover, there was relationship between vitamin D deficiency and mortality, ICU (intensive care unit) admission and hospital length of stay. These results suggest the correction of vitamin D deficiency may be beneficial to reduce acute kidney injury in patient with COVID-19.

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Original

Introduction

Vitamin D and its metabolites, i.e., hydroxyvitamin D and 1.25 hydroxyvitamin D, are fat-soluble prohormones that are converted into their active metabolites in the body and regulate several functions in all types of cells. Vitamin D nuclear receptors are present in many tissues of the body, and when they are activated, they control calcium metabolism and lead to various biological responses. Among these responses, we can mention cell growth, proliferation, apoptosis and immune system function (1,2). Vitamin D has well-known effects, including anti-inflammatory and immune-regulating effects. In recent decades, prospective studies have shown the relationship between vitamin D deficiency and certain types of cancer, immune system dysfunction, cardiovascular diseases, hypertension and metabolic syndrome (3).

Vitamin D deficiency is a common clinical finding both in the general population and in hospitalized patients, including patients in the intensive care unit (ICU); and is associated with a series of unpleasant clinical consequences, including increased mortality and morbidity. Vitamin D takes part in the regulation of the immune system and interferes in the production of inflammatory cytokines. It is furthermore related to severe acute diseases such as oxidative stress and systemic inflammation (4). So far, the prevalence of vitamin D deficiency in ICU patients has been reported as 26-74%. A prospective study on patients admitted to a surgical ICU showed low vitamin D levels (less than 12 ng/mL) associated with increased mortality (5). In addition, the insufficient level of vitamin D (less than 30) in ICU patients can be associated with a higher risk of clinical complications such as infection, organ failure, increased score of prognostic criteria such as SOFA (sequential organ failure assessment), length of stay in ICU, duration of mechanical ventilation and mortality (6).

Acute kidney injury (AKI) is characterized by a sudden loss of kidney work, coming about in nitrogen maintenance and other squander items that are regularly excreted by the kidneys and it occurs in more than 50% of patients hospitalized in ICU and is an independent risk factor for increased mortality, longer hospitalization, and increased risk of long-term complications such as bone fractures (7). It furthermore causes inflammation due to the damage to tubular epithelial cells. Previous studies have also reported that individuals with kidney dysfunction are four times more likely to face CVDs than those with complete kidney health. On the other hand, an episode of AKI increases the risk of its recurrence in the ward admitted patients. Compared with patients who do not have vitamin D deficiency, in patients admitted to the ward and ICU with vitamin D deficiency, the incidence of AKI and the need for renal replacement therapy is higher. The reason for this association has not yet been fully determined (8).

Objectives

There are very few studies regarding AKI in COVID-19 patients. In this study, we investigated the relationship between vitamin D3 deficiency and the occurrence of AKI in ICU-admitted COVID-19 patients.

Patients and Methods

Study design

This cross-sectional study was conducted on 69 COVID-19 patients who were hospitalized in Shahid Mohammadi hospital for 12 months in 2020. Patients were included in the study based on the inclusion and exclusion criteria. Then serum vitamin D levels were measured in the first 24 hours of hospitalization in the ward. The patients were studied until the occurrence of acute renal failure or the occurrence of death. According to the KDIGO (Kidney Disease Improving Global Outcomes) criteria (9), renal failure is an increase in serum creatinine of more than 0.3 mg within 48 hours, or an increase of more than 1.5 times in the baseline level of creatinine in the last seven days, or a decrease in urinary output to less than 0.5 mL/kg/h for 6 hours and more.

Patients were divided into three groups based on the serum level of vitamin D:

- >50 ng/mL; normal
- 20-50 ng/mL; insufficient
- <20 ng/mL; deficiency

The relationship between different levels of vitamin D serum and mortality in patients admitted to the ward, the occurrence of renal failure, duration of the need for mechanical ventilation, and the duration of hospitalization, as well as the relationship between different serum levels of vitamin D and serum levels of calcium and albumin in these patients were studied separately.

Inclusion criteria were as follows: Age above 18 years, infected with COVID-19, and patients whose serum vitamin D level is measured in the first 24 hours of hospitalization in the ward. And the exclusion criteria were: Pregnancy and breastfeeding, Intravenous nutrition, palliative care, patients who are taking vitamin D supplements, patients needing dialysis, patients with acute renal failure.

Our primary outcome was renal failure, and secondary outcomes included length of stay in ICU, need for mechanical ventilation and duration of mechanical ventilation. Vitamin D level was measured using the chemiluminescence immunoassay (CLIA) method.

Moreover, background information, including age, gender, weight, height, body mass index (BMI), medications and concomitant diseases were recorded in the questionnaire and blood samples were sent to measure blood urea nitrogen (BUN) and creatinine.

Statistical analysis

After gathering the data, it was imported into SPSS software version 25, and chi-square was employed as our statistical test. Besides we conducted one-way ANOVA to compare the means of independent groups and P<0.05 was considered as statistically significant.

Results

A total of 69 patients with COVID-19 hospitalized in the ward were analyzed in this study. The age range of patients was 16 to 89 years old, with the mean age 53±16 years. The frequency percentage of males and females were 46% and 54%, respectively.

Table 1 shows the relationship between the levels of vitamin D3 and the different variables of our study. Patients were divided into three groups based on the measured vitamin D3 levels: <20 ng/mL with 39 patients, 20-50 ng/mL with 21 patients and >50 ng/mL with 9 patients. No significant difference was observed regarding mean age (*P*=0.621). Moreover, in terms of gender, no significant difference between study groups was seen. Therefore, in group vitamin D3<20 ng/mL, there were 58% men, and in groups vitamin D3 of 20-50 ng/mL and vitamin D3 >50 ng/mL, there were 62% and 34% men, respectively (*P*=0.057). The frequencies of AKI in groups of vitamin D3 <20 ng/mL, 20-50 ng/mL, and >50 ng/mL were 46%, 28%, and 23%, respectively. There was a significant relationship between our study groups and AKI (*P*=0.011). About frequency comparison of ICU admission, there were 15 patients (38%) in group vitamin D3 <20 ng/mL, 7 patients (32%) in group vitamin D3 20-50 ng/mL, and there was no ICU admission in group vitamin D3 >50nh/ml, which meant that a statistically significant difference was existed between the study groups (*P*=0.041). In terms of frequency of mortality, 13 out of 29 patients (34%) in group vitamin D3 <20 ng/mL and 6 out of 21 patients (28%) in group vitamin D3 of 20-50 ng/mL expired; however, there was no mortality in group vitamin D3 >50 ng/mL which indicated a statistically significant difference between our study groups (*P*=0.011). Our study showed a statistically significant difference in terms of hospital length of stay in our study groups (*P*=0.017). In group vitamin D3<20 ng/mL, the hospital length of stay was 11±4 days and in group 20-50 ng/mL and >50 ng/mL were 10±9 and 5±3 days, respectively.

Each vitamin D group was divided into two groups based on the presence or absence of AKI, then these groups were compared in terms of mortality, hospital length of stay, and ICU admission (Table 2). In this division in patients with different levels of vitamin D3 in the presence or absence of AKI, there were significant associations between group of patients with vitamin D3<20 ng/mL in presence of AKI and mortality (*P*=0.042), ICU admission (*P*=0.024) and hospital length of stay (*P*=0.027).

Discussion

To the best of our knowledge, few studies examined the relationship between vitamin D deficiency and AKI in COVID-19 patients, and their results were inconsistent (10,11). The current study aimed to assess whether the vitamin D3 level at the beginning of hospitalization in COVID-19 patients was correlated to AKI. Our results showed the frequency of AKI in patients with vitamin D3 <20 ng/mL was significantly higher than in other patients. Our results were inconsistent with the Orchard et al study, which examined the relationship between ICU outcomes and vitamin D levels in critically ill patients of COVID-19 and showed no significant relationship between AKI and vitamin D levels (11).

Orchard et al (11) tested only patients with recorded vitamin D levels and other COVID-19 patients were excluded. Therefore this condition could explain their contrary results with our findings. Furthermore, the cut-off scales for defining vitamin D sufficiency and insufficiency were different in their study.

In other studies, in non-COVID-19 patients hospitalized in ICU, the results were similar to our findings. In the study by Braun et al, including two thousand seventy-

Table 1. The relationship between the levels of vitamin D3 and the different variables of the study

Variables		Levels of vitamin D3 (ng/mL)			*P* value
		<20	20-50	>50	
Age		52±17	55±14	57±8	0.621
Gender, n (%)	Male	16 (58)	13 (62)	3 (34)	0.057
	Female	23 (42)	8 (38)	6 (66)	
Length of Hospital stay		11±4	10±8	5±3	0.017
ICU admission, n (%)	Yes	15 (38)	7 (33)	0 (0)	0.041
	No	24 (62)	14 (67)	9 (100)	
Expire, n (%)	Yes	13 (34)	6 (28)	0 (0)	0.014
	No	26 (66)	15 (72)	9 (100)	
AKI, n (%)	Yes	18 (46)	6 (28)	2 (23)	0.011
	No	21 (54)	15 (72)	7 (77)	

AKI, acute kidney injury; ICU, intensive care unit.

Table 2. Comparison of mortality, ICU admission and hospital length of stay in different vitamin D groups according to the presence or absence of AKI

Variables		Vitamin D3 (ng/mL)								
		<20			20-50			>50		
		AKI			AKI			AKI		
		Yes	No	*P* value	Yes	No	*P* value	Yes	No	*P* value
ICU admission, n (%)	Yes	8 (44)	7 (34)	0.024	4 (66)	3 (20)	0.014	0 (0)	0 (0)	1
	No	10 (56)	14 (66)		2 (34)	12 (80)		2 (100)	7 (100)	
Expire, n (%)	Yes	7 (39)	6 (28)	0.042	4 (66)	2 (14)	0.011	0 (0)	0 (0)	1
	No	11 (61)	15 (72)		2 (34)	13 (86)		0 (0)	7 (100)	
Length of hospital stay		13±7	9±4	0.027	12±5	8±4	0.031	5±2	4±2	0.712

AKI, acute kidney injury; ICU, intensive care unit.

five patients in ICU, it has been shown vitamin D deficiency prior to hospitalization is associated with AKI and mortality (6). In addition, a study in Spain which conducted on 135 critically ill patients in ICU supported this hypothesis (12). In a prospective observation study, including six hundred and ten patients with severe sepsis in ICU, it has been shown that AKI and the requirement for renal replacement occurred more in patients with vitamin D deficiency compared to those patients who did not have vitamin D deficiency (8).

The mechanism for the increased risk of AKI in vitamin D deficiency may be due to the pleiotropic functions of vitamin D, which inhibits smooth muscle cell proliferation of vessels, protects the function of normal endothelial cells, and modulates the inflammatory process (6). In vitamin D deficiency, macrophage functions seem to be suppressed, including chemotaxis, phagocytosis, and pro-inflammatory cytokines production (13). Furthermore, evidence shows vitamin D can stimulate innate immunity and induce T-regulatory cells by dendritic cells and can have a therapeutic effect on pro-inflammatory cytokines(14). In addition, this vitamin can suppress nuclear factor kappa B (NF-κB) activation, which it is related to oxidative stress and pro-inflammatory factors which it is activated in tubular cells of kidney during AKI in experimental models(15). To interpret another reason, we can point to the effect of vitamin D in the hampering of leukocytes' adhesion to the endothelium (16). In one review article, Hsieh et al explained the role of vitamin D in the AKI and COVID-19 and supported our hypothesis (10).

Moreover, we found that the frequency of mortality, ICU admission, and hospital length of stay was significantly higher in the group with vitamin D deficiency than in other groups. A retrospective study demonstrated that lower vitamin D levels were associated with much worse prognosis, including mortality, lung involvement, and hospital length of stay, which was consistent with our results (17). Additionally, another study supported our findings and indicated the presence of an association between vitamin D deficiency and mortality of COVID-19 infection (18). In one systematic review article, it has been argued that vitamin D supplementation ameliorated ICU admission, ventilator requirements and mortality rates in patients with COVID-19 (19). In other studies, it has been shown a relationship between vitamin D deficiency and ICU admission (20, 21).

Nonetheless, some studies showed no significant relationship between vitamin D levels and clinical outcomes such as ICU admission, mortality and mechanical ventilator requirements (22-24). It may be due to different cut-off scales for defining vitamin D sufficiency and insufficiency. In another study, Orchard et al illustrated no signal of association between vitamin D deficiency and clinical outcomes such as AKI and hospital length of stay. The authors interpreted these findings to mean that there may be other variables, including patient-specific risk factors, interventions in ICU and bacterial co-infections, that may affect the general clinical outcomes more than the serum levels of vitamin D alone (11). Furthermore, our findings were still in contrast with the study by Szeto et al, including 700 COVID-19 hospitalized patients, which demonstrated no association between prehospitalization vitamin D levels and clinical outcomes (mortality, intubation status, length of stay in hospital and renal replacement). The authors explained it might occur due to the small subset of patients who have available prehospitalization vitamin D, and those with available vitamin D levels differed from those without vitamin D levels in underlying comorbidities (25). To the best of our knowledge, no studies investigated the frequencies of mortality, ICU admission, and hospital length of stay in COVID-19 patients with both vitamin D deficiency and the presence of AKI. We demonstrated in our study that the frequencies of these clinical outcomes were significantly higher in the group with the presence of vitamin D deficiency and AKI simultaneously. To justify this issue, we can point to the mutual effects of AKI and vitamin D deficiency in COVID-19 patients, which we discussed in detail in our articles.

Conclusion

Our study showed a significant association between vitamin D deficiency and AKI in ICU-admitted COVID-19 patients. Moreover, there was relationship between vitamin D deficiency and mortality, ICU admission and hospital length of stay. These results suggest the correction of vitamin D deficiency may be beneficial to reduce AKI in patient with COVID-19. More studies with a larger sample size are needed further to confirm the role of vitamin D in AKI.

Limitations of the study

Our study has some limitations. First of all, our study is single-center and our sample size was small, which caused a decrease in the power of statistical analysis of outcomes in patients with COVID-19. In addition, we only investigated vitamin D levels in hospitalized COVID-19 patients and did not include outpatients of COVID-19. Moreover, due to the inherent observational study design, it cannot allow us to infer causality. Furthermore, other unmeasured variables may affect AKI independently of vitamin D, which can cause biased estimates. The specific habits of patients, diet, lifestyle and exposure to sunlight were not examined in our study.

Authors' contribution

Conceptualization: MA. Methodology: HS, FKM, MKJ and AM. Validation: ASA, SB and MA. Formal Analysis: HS, AM and SB. Investigation: MKJ. Resources: ASA, FKM and MA. Data Curation: MKJ and MA. Writing—Original Draft Preparation: FKM, SB and ASA. Writing—Review and Editing: FKM, SB and HS. Visualization: ASA, HS and AM. Supervision: AM, FKM and HS. Project Administration: MA and MKJ.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

At each research stage, we followed the principlesof the Declaration of Helsinki and the Ethics Committee of the Ministry of Health. Each participant signed the informed written consent form. This project was also confirmed by the Ethics Committee of the Hormozgan University of Medical Sciences (ethical code #IR.HUMS.REC.1398.394). All participants signed the written informed consent. Besides, ethical issues (including plagiarism, data fabrication and double publication) have been completely observed by the authors.

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