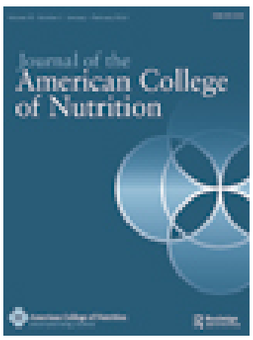

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Vitamin D Status in Hospitalized Chronically Ill Patients

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ABSTRACT

Objectives: Vitamin D deficiency is rarely considered or treated in critically ill patients. Deficiency of 25-hydroxy vitamin D [25(OH)D] prior to hospital admission might be a significant predictor of short- and long-term all cause patient mortality in a critically ill patient. The aim of this work is to investigate the prevalence of vitamin D deficiency in hospitalized patients and its relation to the length of stay and outcome of hospitalization.

Methods: Prospective cohort study performed on 80 patients admitted with acute deterioration of their chronic illness. Four groups of diseases were included, namely, chronic liver diseases (CLD), chronic obstructive pulmonary diseases (COPD), cerebrovascular stroke (CVS), and heart failure (HF). The patients were followed up until their discharge, or transfer, or death. Patients were sampled for their vitamin D level on admission and were divided according to their vitamin D status into sufficient, insufficient, and deficient. Statistical methods and analysis of the present study were conducted using the SPSS V17 program.

Results: Vitamin D level had a significant inverse correlation with length of hospital stay ($r = -0.648$) ($p < 0.001$). In vitamin D-deficient and -insufficient groups, there was a significant difference between survivors and nonsurvivors as regards vitamin D levels and an inverse correlation between vitamin D level and outcome of hospital admission.

Conclusions: Vitamin D deficiency and insufficiency are significantly associated with a longer hospital stay and a poor outcome of hospital admission in comparison to control.

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Vitamin D; hospitalization; chronic diseases

Introduction

Vitamin D is a fat-soluble vitamin that is naturally present in a few food variants, and available as a dietary supplement. It is mainly produced endogenously when ultraviolet rays from sunlight strike the skin and trigger vitamin D synthesis. (1).

Vitamin D promotes calcium absorption in the gut and maintains adequate serum calcium and phosphate concentrations to enable normal mineralization of bone. It is also needed for bone growth and bone remodeling by osteoblasts and osteoclasts (2). More recently, vitamin D was found to play other roles in the body, including modulation of cell growth, neuromuscular function, and reduction of inflammation. Also, benefits on cardiovascular health, metabolism, and prevention of cancer and autoimmune diseases have been described (3). Many genes encoding proteins that regulate cell proliferation, differentiation, and apoptosis are modulated in part by vitamin D. Many cells have vitamin D receptors, and some convert [25(OH)D] to [1,25(OH)2D] (4). Vitamin D receptors are found in nearly all types of immune cells. Its action on innate immunity is stimulatory, while its action on adaptive immunity is mainly considered to be modulatory (5).

Hypovitaminosis D (HVD) is rarely considered in critically ill patients; however, three recently reported cases of life-threatening hypocalcemia secondary to vitamin D deficiency highlighted potential acute complications (6). Deficiency of 25-hydroxy vitamin D prior to hospital admission was found to be a significant predictor of short- and long-term all-cause mortality (7). Patients with [25(OH)D] deficiency in the medical intensive care unit (ICU) have increased hospital mortality, longer mechanical ventilation, and longer ICU stay (8).

Given the endemic nature of HVD in the Egyptian general population, we aimed to explore the prevalence of vitamin D deficiency in hospitalized patients and its impact on the length of hospital stay and outcome of hospitalization.

Patients and methods

Study participants

This study is a prospective cohort study performed on 80 patients admitted to the Department of Internal Medicine at Ain Shams University Hospital between September and December 2016 with acute deterioration of their chronic illness. They were sampled for vitamin D level on admission. Ethical approval was obtained from Ain Shams University, Faculty of Medicine, research Ethics Committee FWA00017858. Informed consent was obtained from all individual participants included in the study.

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Four groups of diseases were included: 20 patients with chronic liver diseases (CLD), 20 patients with chronic obstructive pulmonary diseases (COPD), 20 patients with cerebrovascular stroke (CVS), and 20 patients with heart failure (HF). Patients with CLD were Child-C on the Child–Pugh score, patients with COPD were admitted with infective exacerbation after being diagnosed as COPD by pulmonary function test, and patients with CVS were diagnosed by brain computed tomography (CT), while patients with heart failure were found to have below normal ejection fraction by echocardiography. The patients were followed up until their discharge, transfer to intensive care unit, or death.

The patients included in the study underwent full clinical case taking and examination and full hospital workup, biochemical and radiological, each according to his or her diagnosis. Samples were withdrawn on admission for vitamin D measurement, as well as Ca, P, alkaline phosphatase (ALP), liver and kidney functions, arterial blood gases, and blood count.

Methods

The 25-OH vitamin D total enzyme-linked immunosorbent assay (ELISA) kit is a solid-phase ELISA, based on the principle of competitive binding. After measurement of vitamin D level, the patients were classified according to their vitamin D status into the deficient group (32 patients with vitamin D level <15 ng/ml), insufficient group (37 patients with vitamin D level from 15 to 29 ng/ml), or sufficient group (11 patients with vitamin D level > 30 ng/ml) (9).

Statistical methods

Statistical presentation and analysis of the present study were conducted using the mean, standard deviation, Student's *t*, chi-squared, linear correlation coefficient, and analysis of variance (ANOVA) tests by SPSS V17. Student's *t*-test (unpaired) was used to compare between two groups with quantitative data. Chi-squared was used to compare two groups as regards qualitative data.

The linear correlation coefficient was used for detection of correlation between two quantitative variables in one group. Analysis of variance (ANOVA) tests were according to the computer program SPSS for Windows; the ANOVA test was used for comparison among different times in the same group with quantitative data.

All quantitative data were correlated with each other using the Pearson correlation coefficient (*r*).

Probability (p) <0.05 was considered significant and <0.01 highly significant. Significant relations were graphically represented by pie and scatter graphs.

Results

The studied groups (when divided according to their vitamin D status) differed in alkaline phosphatase level, which was significantly higher in vitamin D-deficient patients (174.781 ± 32.418 U/L) in comparison to vitamin D-insufficient patients (97.811 ± 36.966 U/L) and vitamin D-sufficient patients (90.182 ± 30.906 U/L), respectively, with $p < 0.001$. Comparisons between these three groups regarding all other laboratory data were nonsignificant. Females had a significantly lower vitamin D level in both deficient and insufficient subgroups (9.700 ± 2.791 ng/ml and 21.000 ± 3.516 ng/ml) than males (11.545 ± 2.041 ng/ml and 24.640 ± 2.722 ng/ml), respectively, and p values were 0.043 and 0.001, respectively.

When studying vitamin D status according to patient's etiology of hospital admission, it was found that in the CLD group (20 patients), 30% were deficient, 55% were insufficient, and 15% were sufficient. In the COPD group (20 patients), 30% were deficient, 50% were insufficient, and 20% were sufficient. In the CVS group (20 patients), 50% were deficient, 45% were insufficient, and 5% were sufficient. In the HF group (20 patients), 50% were deficient, 35% were insufficient, and 15% were sufficient. There was a nonsignificant difference between them in the percentage of patients in the different vitamin D subgroups ($p = 0.237$) and in mean vitamin D levels ($p = 0.237$) (Table 1).

Data about the length of hospital stay showed a significant difference, with the longest duration being in the deficient group ($p < 0.001$) (Table 2). On comparing outcome between different groups, there was a significant difference ($p < 0.001$), with highest percentage of deaths in the deficient group. In the deficient group, 53% of patients were nonsurvivors and 47% were survivors. In the insufficient group, 11% of patients were nonsurvivors and 89% were survivors. In the sufficient group, 100% of patients were survivors.

The comparison between vitamin D levels in survivors and nonsurvivors of different vitamin D status subgroups showed that nonsurviving patients had a significantly lower vitamin D level than surviving patients, where in the deficient group vitamin D level in nonsurvivors was 9.47 ± 2.18 ng/ml, while in the surviving group the level was 12.66 ± 1.29 ng/ml ($p < 0.001$). In the insufficient group, nonsurvivors' level was 17.75 ± 0.5 ng/ml and the survivors' level was 24.15 ± 2.9 ng/ml ($p < 0.001$). In the sufficient group, all were surviving with vitamin D level 36 ± 6.3 ng/ml (Table 3).

Deficient group members (32 patients) were subdivided according to their disease etiology, and in comparing between them as regards length of hospital stay and outcome of admission, comparison shows nonsignificant results ($p = 0.111$ and 0.964), respectively (Table 4).

On correlating different parameters with vitamin D level, there was a significant inverse correlation with length of hospital stay and alkaline phosphatase level ($r = -0.648$, $p < 0.001$; $r = -0.701$, $p < 0.001$, respectively) (Table 5).

Table 1. Comparison between VD levels in the four different groups according to etiology of hospital admission using ANOVA.

	Vitamin D (ng/ml)		ANOVA	
Group	Range	Mean ± SD	*F*	*p* Value
CLD	8–40	21.950 ± 8.906	1.443	0.237
COPD	8–53	22.750 ± 10.770		
CVS	8–38	17.650 ± 7.257		
HF	6–35	18.650 ± 9.659		

Table 2. Comparison Between Vitamin D Status Groups as Regards Length of Hospital Stay Using ANOVA.

	Length of hospital stay (days)		ANOVA	
Groups	Range	Mean ± SD	*F*	*p* Value
Deficient	8–36	22.813 ± 6.342	22.778	<0.001**
Insufficient	6–32	14.946 ± 5.312		
Sufficient	5–29	11.091 ± 6.595		

*Significant; **highly significant.

Discussion

Vitamin D deficiency and insufficiency have become pandemic and are now seen in every country around the world. It has been estimated that more than 1 billion people worldwide are either vitamin D deficient or vitamin D insufficient (10). Many epidemiological, clinical, and experimental studies indicate that a compromised vitamin D status plays a major role in the pathogenesis of various chronic diseases (11).

HVD among hospitalized patients is more widespread than realized. It can contribute to poor hospitalization outcome through its effect on musculoskeletal functions and immune competence. In acute illness or acute on top of chronic illness, these functions are essential for recovery. However, the failure to diagnose an underlying deficiency places the patient at risk for continued pain, weakness, secondary hyperparathyroidism, osteomalacia, and fractures (12).

In this work, the authors aimed to correlate vitamin D deficiency in hospitalized patients admitted with acute deterioration of their chronic illness to length of hospital stay and outcome of hospitalization.

On comparing length of hospital stay within different vitamin D status groups, a highly significant difference ($p < 0.001$) was found, with the longest duration of hospital admission being in the deficient group. In general, vitamin D level had a significant inverse correlation with length of hospital stay in all studied patients. These results were in agreement with others (13,14,15), who reported that lower [25(OH)D] levels were significantly associated with longer hospital admission. Other researchers disagree (16); they suggested that [25(OH)D] levels ≤12 ng/ml were not associated with any significant differences in the overall length of hospital stay, according to their results. This may be because Moraes et al. excluded patients with a total length of hospital stay >3 days before ICU transfer in his study, whereas Higgins et al. had no such exclusion criterion.

Concerning the outcome of hospital admission within the studied groups, we found that no-surviving patients had a highly significant lower vitamin D level than surviving patients in the deficient and insufficient groups ($p < 0.001$). These results were in agreement with those of Moraes et al. (16), Melamed et al. (17), and Matthews et al. (18), who reported that low vitamin D levels on hospital admission are an independent risk factor for mortality in critically ill patients. Lee et al. (19), also reported that mortality rate predicted by the simplified acute physiologic scores (SAPS score) was close to 3 times higher in vitamin D-deficient patients compared to those who were sufficient.

Table 3. Comparison of VD level between survivors and non-survivors in the vitamin D status groups using T-Test.

		VIT.D (ng/ml)		*T*-Test	
Groups	Outcome	No.	Mean ± SD	*T*	*p* Value
Deficient	Nonsurvivors	17	9.471 ± 2.183	−4.952	<0.001**
	Survived	15	12.667 ± 1.291		
Insufficient	Nonsurvivors	4	17.750 ± 0.500	−4.314	<0.001**
	Survived	33	24.152 ± 2.927		
Sufficient	Nonsurvivors	0	0.000 ± 0.000	X	X
	Survived	11	36.091 ± 6.316		

*Significant; **highly significant.

On correlating vitamin D state with gender, females were found to have a lower vitamin D level than that of males in each group, with significant difference in the deficient group ($p = 0.043$) and highly significant difference in the insufficient group ($p = 0.001$). These results are in agreement with those of Botros et al. (20), Amr et al. (21), and El Rifai et al. (22), who reported that despite the tropical climate, vitamin D deficiency and insufficiency are highly prevalent among Egyptian females, maybe due to inadequate sun exposure possibly related to cultural/social factors, and insufficient dietary calcium.

When correlating vitamin D level with level of alkaline phosphatase, there was an inverse highly significant correlation ($p < 0.001$, $r = -0.701$). This result was in agreement with that of Mc Kenna et al. (23), who reported that age-related increase in serum alkaline phosphatase activity was significantly less in vitamin D-replete subjects than in vitamin D-depleted subjects in his study. On the other hands, this finding disagrees with results of Shaheen et al. (24), who reported that serum vitamin D levels may not be correlated with increased serum alkaline phosphatase levels.

About corrected serum calcium level in our studied groups, this study found that normal calcium level was maintained even in the deficient group. This result was in accord with Zaloga et al. (25) and Lee et al. (26), who reported that severe hypocalcaemia is an uncommon finding in non-critically ill patients, due to the presence of multiple compensatory mechanisms to maintain normocalcemia.

Critical illness is characterized by different degrees of local and systemic inflammation, as well as metabolic and immune dysfunction; functions over which vitamin D exerts important regulatory actions. In states of normal circulating vitamin D level, individual target tissues are possibly able to increase local formation of [1,25(OH)2D] to meet tissue demand during critical illness. Also, failure to upregulate the parathyroid hormone (PTH)–vitamin D axis due to circulating vitamin D insufficiency may contribute to metabolic and immune dysfunction and ultimately multiple-organ failure, which is the cause of morbidity and mortality in intensive care patients (27).

Possible mechanisms by which vitamin D level affects morbidity and mortality include its roles in immunity, muscular strength, and bone health and its other alleged actions on cardiometabolic homeostasis. We found a nonsignificant difference on comparing length of hospital stay or outcome of hospital admission between the four different disease groups in the vitamin D-deficient group.

We couldn't find also a difference between the different etiologies of hospitalization as regards vitamin D level, although the deficiency in vitamin D was explained in each disease

Table 4. Comparison Between Different Disease Etiology Groups as Regards Outcome of Hospital Admission Within Deficient Group Using Chi-Squared Test.

		Outcome of hospital admission		Length of hospital stay (days)
Deficient group (32)		Survivors	Nonsurvivors	Mean ± SD
CLD	Number	3	3	19.667 ± 6.683
	%	50.00	50.00	
COPD	Number	3	3	27.167 ± 9.174
	%	50.00	50.00	
CVS	Number	6	4	20.700 ± 4.832
	%	60.00	40.00	
HF	Number	5	5	24.200 ± 4.158
	%	50.00	50.00	
Total	Number	17	15	22.813 ± 6.342
	%	53.13	46.88	
		Chi-squared		ANOVA
	χ^2	0.276		F 2.190
	p Value	0.964		p Value 0.111

etiology. Thus, hospitalization due to acute deterioration of chronic illness of different etiologies is associated with poor hospital outcome and longer hospital stay in those with vitamin D deficiency and insufficiency in comparison to those with sufficient levels of vitamin D, regardless of the cause of admission.

This study showed that vitamin D sufficiency may be a significant confounder in patients admitted to a hospital with acute deterioration of their chronic illnesses. Significantly better outcome regarding morbidity and mortality in vitamin D-sufficient patients urges the medical staff to pay attention to that poorly recognized albeit important problem.

In this study, vitamin D level below 15 ng/ml was used as a cutoff value for vitamin D deficiency to improve statistical significance of the results by combining them into 3 groups rather than 4, because of the limited number of patients in each of the 4 studied groups (20 patients).

Table 5. Correlation of Vitamin D Level and Different Parameters in All Studied Patients (80).

	Vitamin D	
Correlations	r	p Value
Length (days)	−0.648	<0.001**
Age (year)	−0.085	0.456
WBC (10^3/ul)	−0.042	0.714
HGB (g/dl)	0.003	0.980
PLT (10^3/ul)	−0.028	0.804
BUN (mg/dl)	0.075	0.508
Cr (mg/dl)	0.214	0.056
Na (mmol/L)	−0.148	0.189
K (mmol/L)	0.034	0.768
ALT (IU/L)	−0.098	0.388
AST (IU/L)	−0.081	0.478
T.prot (g/dl)	0.013	0.906
AlB (g/dl)	−0.046	0.683
T.Bil (mg/dl)	0.015	0.893
ALK.P (U/L)	−0.701	<0.001**
PO4 (mg/dl)	0.153	0.175
Mg (mg/dl)	0.101	0.374
Ca (mg/dl)	0.145	0.200
PH	0.080	0.481
HCO_3 (mmol/L)	0.052	0.645
PO_2 (mm Hg)	−0.074	0.517
PCO_2 (mm Hg)	0.092	0.418

*Significant; **highly significant.

Conclusion

Vitamin D deficiency and insufficiency are significantly associated with a longer hospital stay and a poor outcome of hospital admission. We couldn't find a difference between the different etiologies of hospitalization as regards vitamin D level. Awareness by the general public, health care providers, and health insurance systems of the importance of vitamin D adequacy could have an impact on the length of hospital stay and outcome of hospital admission. Vitamin D supplementation might be recommended as a routine procedure in hospitalized patients, with the exception of hypercalcemic and hyperphosphatemic patients, knowing that vitamin D has a wide therapeutic window.

Ethical approval

This study has been approved by Ain Shams University, Faculty of Medicine, Research Ethics Committee, FWA 00017858. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest

The authors declare no conflicts of interest.

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