Relationship of Vitamin D level with insulin dosage required based on insulin therapy protocol

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Abstract

The deficiency of vitamin D amongst Iranian people is high and also is related on hyperglycemia. This study aims to evaluate the association of vitamin D levels with the required dose of insulin prescribed based on an insulin therapy protocol in critical condition patients admitted to intensive care unit (ICU), in an investigation based in Iran. This cross-sectional study was performed on patients who required insulin due to hyperglycemia. The relationship between serum vitamin D level and the required dose of insulin prescribed based on insulin therapy protocol in this group of patients was investigated. A total of 172 patients with a mean age of 46.93 ± 31.9 years were included in this study. Across the included participants, 78.8% of patients had vitamin D deficiency, 11.9% had insufficient vitamin D and 9.3% had normal vitamin D levels. There was a significant difference in mean blood sugar between the vitamin D deficiency group and the normal group. Vitamin D levels were also significantly higher in men than women. Furthermore, the HbA1C hemoglobin level in patients with Vitamin D deficiency was significantly higher compared to the group with normal levels of vitamin D. Our findings suggest that decreased vitamin D is associated with increased blood sugar and insulin requirements in patients admitted to ICU. Women are at a higher risk for vitamin D deficiency. We hope that these findings may help inform relevant treatment strategies.

Key Words: Vitamin D; insulin; iyperglycemia; intensive care unit (ICU).

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Hyperglycemia is common in patients admitted to the intensive care unit (ICU) and is associated with deleterious consequences such as increased length of hospital stay in the ICU, increased risk of infection and increased death and complications.[1] It may arise in ICU patients because of a number of supportive therapies such as: Total Parenteral Nutrition, dextrose supplementation, surgery, and glucocorticoid use.[2] The risk of hyperglycemia arising among patients receiving dextrose infusion, especially those receiving intravenous feeding, is at the highest rate. Additional risk factors for the development of hyperglycemia are: a history of diabetes, acute pancreatitis, obesity, catecholamine vasopressors such as, dopamine, norepinephrine, and immunosuppressants such as tacrolimus and cyclosporine.[3] In patients admitted to the ICU, intravenous infusion of insulin is the preferred method of administration. Based on the available evidence, insulin infusion should be used to control hyperglycemia in most patients admitted to the ICU when their blood sugar is 180 mg/dL or more. When intravenous insulin therapy is started, blood glucose levels should be maintained at 140-180 mg/dL.[4] Although there is no strong evidence to keep the target glucose at a low level, achieving a lower blood glucose target level seems reasonable only in some patients. Intravenous infusion of insulin should be changed to a subcutaneous administration when patients start a routine diet or are transferred to a ward.[4] Vitamin D is a steroid hormone which has major effects on calcium and phosphorus homeostasis, as well as exerting several known effects on the body surface. Vitamin D deficiency reduces intracellular calcium levels, thereby result in reduction of insulin secretion and beta cell

SOFA score	1	2	3	4
Respiration[a]				
PaO_2/FIO_2 (mm Hg)	<400	<300	<220	<100
SaO_2/FIO_2	221-301	142-220	67-141	<67
Coagulation				
Platelets $\times 10^3/mm^3$	<150	<100	<50	<20
Liver				
Bilirubin (mg/dL)	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular[b]				
Hypotension	MAP <70	Dopamine ≤5 or dobutamine (any)	Dopamine >5 or norepinephrine ≤0.1	Dopamine >15 or norepinephrine >0.1
CNS				
Glasgow Coma Score	13-14	10-12	6-9	<6
Renal				
Creatinine (mg/dL) or urine output (mL/d)	1.2-1.9	2.0-3.4	3.5-4.9 or <500	>5.0 or <200

MAP, mean arterial pressure; CNS, central nervous system; SaO_2, peripheral arterial oxygen saturation.

[a] PaO_2/FIO_2 ratio was used preferentially. If not available, the SaO_2/FIO_2 ratio was used

[b] vasoactive mediations administered for at least 1 hr (dopamine and norepinephrine µmg/kg/min).

Fig 1. *The sequential organ failure assessment (SOFA) score.*

dysfunction, resulting in impaired glucose tolerance.[5,6] The deficiency of Vitamin D is a major problem in societies, so much so that it is occurring at an epidemic level, and studies of the last two decades across several countries have shown an increase in the prevalence of vitamin D deficiency.[7] According to the literature, the prevalence of this deficiency is estimated at 18 to 97% .[8] An estimated 29% of the Iranian population is deficient in vitamin D.[9] The reason for the difference in prevalence depends on various factors, one of which is the type of culture and religion of the communities, so that the prevalence of vitamin D deficiency is higher in communities that use special coatings.[10] Vitamin D deficiency can cause many chronic diseases including: type I and II diabetes, infectious diseases, autoimmune diseases, various cancers, hypertension, and cardiovascular diseases.[11] Hyperglycemia has different effects on body organs and mortality and morbidity of patients admitted to the ICU. The role of vitamin D in the dysfunction and secretion of insulin is an important clinical consideration.

Due to the high prevalence of vitamin D deficiency in Iran, this study was performed to investigate the relationship between vitamin D levels and the required dose of insulin prescribed (on a basis of protocol), to critical patients in the ICU.

Materials and Methods

The study was a cross-sectional design which involved patients with critical illness who received insulin due to hyperglycemia (either diabetic or non-diabetic). Patients were hospitalized in the ICU of Rasoul Akram Hospital, Iran, from the beginning of January 2020 to the end of October 2021. A series of inclusion and exclusion criteria were applied to select the final cohort of patients for the study as follows. The inclusion criteria were: patients with high blood glucose (hyperglycemia) who were admitted to the ICU and require insulin administration. The exclusion criteria were: patients who took drugs that interfere with vitamin D metabolism such as corticosteroids, estrogen, oral contraceptive pills, anticonvulsant drugs.

Sample size

The sample size required for the study was calculated according to the following formula as 172 patients:

$n = [z^2 (1 – alpha/2)S^2]/d^2]$,

where:

alpha = 0.05, z(1 – alpha/2) = 1.96, sd = 23.7, sd^2 = 561.69, d(%) = 3.55.

Based on these values, the final value of n was found to be n = 171.21.

Procedure

All patients with hyperglycemia (blood sugar > 180 mg/dL were included in the study and treated with insulin according to the ICU insulin therapy protocol. At the same time, a blood sample was sent to the laboratory to check the level of vitamin D. Patient information including: height, weight, age, gender, name, Acute Physiology And Chronic Health Evaluation (APACHE) and sequential organ failure assessment (SOFA) scores were also recorded in the questionnaire. If hypoglycemia fell below 180 insulin infusions, it was temporarily stopped. Serum levels of vitamin D were measured using an enzyme linked immunosorbent assay (ELISA) kit, with a normal range of 30 to 50 ng/mL. Patients whose level of vitamin D was normal were considered as vitamin D deficiency group. (patients with vitamin D levels between 21 and 29 ng/mL) and vitamin D deficiency (patients with serum concentrations below 20 ng/mL).

The SOFA system is a widely used tool to estimate patient-related outcomes by assessing organ failure through evaluation of the liver, lungs, blood platelets, cardiovascular system, kidneys, and nerves (Figure 1). Each system is assigned a score between 4-1, so that the total minimum scores are 0 and 2 and the maximum score is 24. In this system, higher scores are associated with higher mortality.

Data analysis

For descriptive analysis, statistical indices of frequency, frequency percentage, mean, and standard deviation were used. The chi-square test was used to compare qualitative variables and, *t*-test or Mann-Whitney test was used to compare quantitative variables. SPSS version 26.0 was used to perform data analysis. The *p*-value less than 0.05 ($p \leq 0.05$) was used as the threshold for statistical significance.

Ethical considerations

To introduce the university officials to the research centers, a written introduction letter was received from them. The objective of the present study was described to all units participating in the research and then a written consent was obtained from them. The manager of project kept the information of all participants confidential. Research ethics committee of the Iran University of Medical Sciences and ethical Declarations of Helsinki were considered in all stages of research. At first, Research Council of the Medical School approved the project and after assigning ethics code, the project was performed.

Results

In the final cohort, there were a total of 172 patients, of which 49 (28.4%) were male and 123 (71.6%) were female. Out of the 49 male patients, 22 (45%) were diabetic and out of 123 females, 63 (51%) were diabetic. Means of quantitative variables (length of hospital stay, age, height, weight, and APACHE score) are listed in Table 1. Serum vitamin D levels were measured in patients. It was found that 78.8% of patients had vitamin D deficiency (serum level less than 20 ng/mL), 11.9% of patients exhibited insufficiency of vitamin D (serum level between 21 and 29 ng/mL), and 9.3% had normal levels of vitamin D (serum levels above 30 ng/mL). The mean of vitamin D in the groups were as follows – normal: 36.9 ± 5.95 ng/mL, vitamin D deficiency: 25.0 ± 2.93 ng/mL and insufficient vitamin D: 11.8 ± 5.09 ng/mL. One-way analysis of variance (one-way ANOVA) was used to assess the relationship between age and vitamin D status. The results showed that people with normal vitamin D levels had a mean age of 45.17 ± 15.72 years, people with insufficient vitamin D had a mean age of 46.8 ± 13.18 years and people with vitamin D deficiency showed a mean age of 46.62 ± 18.27 years. There was no statistically significant difference in terms of age ($p = 0.761$). Due to the lack of significant differences between vitamin D levels at different ages, it seems that age cannot be considered as a confounding factor in the relationship between vitamin D levels and prescribed insulin dose. The chi-square test was used to evaluate serum vitamin D levels by gender (Table 2). It showed that vitamin D deficiency in women was significantly higher than men ($p < 0.05$). The mean length of hospital stay and APACHE scores based on patients' vitamin D status were computed, and shown in Table 3. One-way ANOVA was applied to compare these parameters in patients and there was no significant difference in terms of hospitalization time and APACHE score based on vitamin D status ($p > 0.05$). The mean level of blood sugar was evaluated based on the vitamin D status of patients. It was found that people with normal vitamin D had a blood sugar of 183.3± 2.52 mg/dL, people with vitamin D deficiency had a blood sugar of 214.2± 35.82 mg/dL and people with an insufficient vitamin D had a blood sugar of 228.6 ±33.15 mg/dL, where the differences were statistically significant ($p < 0.05$). Since the differences between the two in the one-way ANOVA was significant, they were compared using Tukey post hoc test. The results showed that the mean non-fasting blood sugar in patients with vitamin D

Table 1. *Mean and standard deviation of quantitative variables.*

	Number	Min	Max	Mean	SD
Age (years)	172	39.00	83.00	46.93	31.91
Apache (score)	172	7.00	37.00	23.41	9.11
Duration of hospitalization (days)	172	1.00	82.00	32.69	14.38
Height (cm)	172	139.00	192.00	164.72	10.12
Weight (kg)	172	48.00	115.00	73.48	9.60

Table 2. *Evaluation of patients' vitamin D status by gender.*

Parameter	Normal	Insufficiency of vitamin D	Vitamin D deficiency	*p*-value
Male	4 (2.32%)	9 (5.23%)	36 (20.93%)	0.019
Female	11 (6.39%)	12 (6.97%)	100 (58.13%)	

Table 3. *Apache scores and the median length of hospital stay based on the vitamin D status patients.*

Parameter	Normal	Insufficiency of vitamin D.	Vitamin D deficiency	*p*-value
Duration of hospitalization	26.31 ± 5.41	31.12 ± 21.07	36.11 ± 24.99	0.107
APACHE II	21.09 ± 8.91	23.31 ± 2.14	25.14 ± 12.38	0.181

Table 4. *Comparison of mean blood glucose by vitamin D status of patients.*

	Vitamin D normal	Insufficiency of vitamin D	Vitamin D deficiency	*p*-value
Blood sugar (mg/dl)	183.3 ±2.52	214.2 ±35.82	-	0.047
	183.3 ±2.52	-	228.6 ±33.15	0.01

Table 5. *Comparison of blood glucose at the onset of study and the end of study by vitamin D status of patients.*

Vitamin D normal	Insufficiency of vitamin D	Vitamin D deficiency	Blood sugar (mg/dL)
184.8±3.75	218.3 ±7.68	231.0 ±34.64	Bs (Entry)
183.1 ±2.33	207.1 ±10.48	220.3 ±30.22	Bs (Exit)

insufficiency or deficiency were significantly different from the group with normal amounts of vitamin D ($p < 0.05$).

The mean level of insulin in patients based on the status of vitamin D is shown in Figure 2. The mean level of insulin in patients with normal vitamin D was 48.11 ± 8.11. The mean level of insulin in patients with insufficient vitamin D was 59.02 ± 11.17 and the mean level of insulin in patients with vitamin D deficiency was 65.11 ± 10.27 (U/h), which was statistically significant ($p = 0.027$). Due to the significant difference between the groups in the one-way ANOVA, Tukey post hoc test was also used for two-by-two comparison. The results indicated that the required insulin dose in patients with normal levels of vitamin D was significantly lower compared to those with a deficiency of vitamin D. ($p = 0.012$).

Glycated hemoglobin test (HbA1C) was determined to be 6.02 ± 2.87 in patients with normal vitamin D, 7.23 ± 3.09 in patients with insufficient vitamin D, and 8.26 ± 2.12 the patients with vitamin D deficiency. It should be noted that the reported difference was statistically significant ($p = 0.037$). The comparison between the studied groups was done using Tukey post hoc test. The results showed that the level of hemoglobin HbA1C in patients with normal vitamin D levels was significantly lower compared to the patients with insufficient vitamin D and vitamin D deficiency ($p = 0.012$). However, there was not any significant differences between the patients with vitamin D deficiency and those with insufficient vitamin D ($p = 0.097$).

The SOFA score based on the vitamin D status of patient groups were compared (Figure 4). According to the findings, there was a significant difference in SOFA scores between the group with normal vitamin D levels and the vitamin D deficiency group ($p < 0.05$).

Comparison of the effect of underlying factors was carried out using a logistic regression model. These

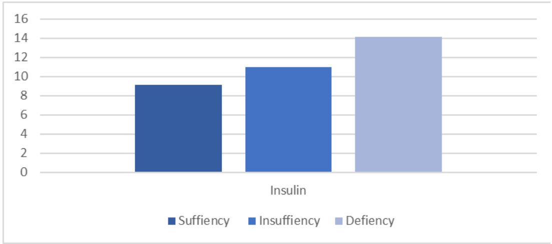

Fig 2. *Mean level of insulin in patients based on the status of vitamin D.*

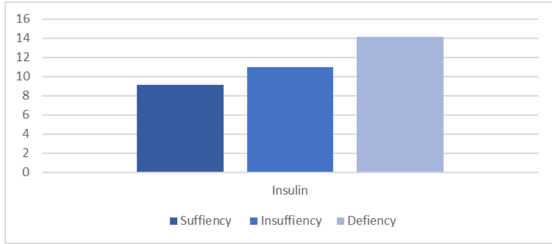

Fig 3. *Comparing the levels of HbA1C hemoglobin based on the status of vitamin D in patients.*

factors included: weight and height on the relationship of vitamin D level with blood sugar. The findings demonstrated that factors such as weight and height were not effective in determining the relationship of the two variables ($p > 0.05$).

Discussion

Due to the hormonal function of vitamin D as a fat-soluble hormone, it can play a significant role in bone metabolism, through the maintenance of phosphorus, and calcium homeostasis. Recent studies have revealed that there are some non-skeletal disorders which lead to vitamin D deficiency.[12] In laboratory animals, vitamin D has been shown to be necessary for the natural release of insulin and the maintenance of glucose tolerance. Pancreatic beta cells have specific receptors for the activity of the 1,25(OH)2D.[13] Based on some studies it has been proposed that vitamin D deficiency is associated with increment of diabetes risk and the development of insulin resistance.[14] The increasing prevalence of type II diabetes has imposed many problems on the health of the community, particularly patients admitted to hospital ICUs. Following this increase, several research studies related to lifestyle, environmental and nutritional factors are attempting to correct and improve the burden of diabetes. Meanwhile, its role in controlling blood sugar in type II diabetes seems necessary due to the various effects vitamin D may have on glucose and calcium metabolism.[15]

In the present study, the prevalence of vitamin D deficiency in patients with hyperglycemia was found to be about 80%. This finding is similar to that of Taheri and colleagues, who found that 82.1% of diabetic patients and 75.6% of healthy individuals were diagnosed with some degree of vitamin D deficiency, in their study of 180 diabetic and non-diabetic individuals.[16] Factors such as lack or deficiency of vitamin D-rich food, low consumption of vitamin D and supplements, clothing habits and full body coverage, and differential exposure to sunlight are the main causes of high prevalence of vitamin D deficiency in the Iranian population.[17]

Based on the data achieved from the present study, the prevalence of vitamin D deficiency in men was significantly lower compared to women. As mentioned earlier, too much coverage prevents sunlight from reaching the skin, which causes a decrement in the production of vitamin D in the skin. This is also concurred by a study of Zarooni and colleagues, who found that the coating was associated with deficiency of vitamin D in the study groups.[18]

There are many mechanisms which suggest a relationships of vitamin D with type II diabetes. Diabetes is linked to vitamin D through three mechanisms: (a) inflammation, (b) peripheral tissue resistance to insulin, and (c) modulation of insulin secretion. Vitamin D can modulate the function of the renin–angiotensin system (RAS) by reducing renin gene expression and inhibiting angiotensin I receptors. The incremental activity of the RAS system causes blood pressure, inflammation, and insulin resistance. Another mechanism that has been suggested is the role of vitamin D deficiency in incremental of parathyroid hormone, which can cause obesity, insulin resistance, and elevated lipogenesis.[19]

The findings of our study may be further compared and contrasted with similar research in the field. For example, McKinney et al.[20] reported that the average length of hospital stay in ICU was 16.1 ± 1.1 days, which was much shorter than the present study. A similar study revealed that the length of in-hospital stay in patients with vitamin D deficiency and those with normal vitamin D levels was not significantly different, which is in line with the data achieved from the present study.

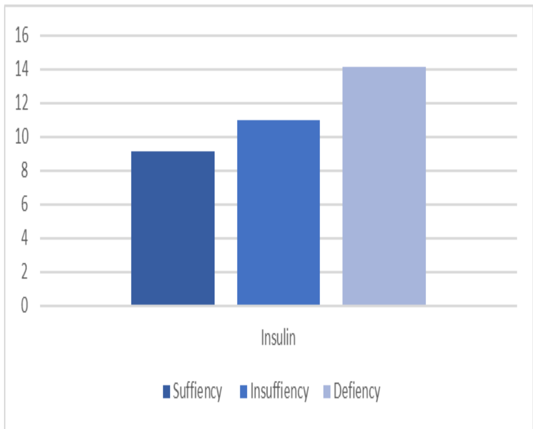

Fig 4. *Comparing the levels of HbA1C hemoglobin based on the status of vitamin D in patients.*

Arnson et al.[21] demonstrated that 82.9% of patients represented vitamin D deficiency, which is similar to the vitamin D deficiency reported in the patients of our study. This may be attributed to their study sample size that was collected during seven months of the year (winter and spring) and did not have a proper distribution across all seasons.

The authors also found that the difference between APACHE Score II and vitamin D level was not significant. Our results are consistent with of that study.

The higher the initial level of vitamin D in a patient was associated with the greater its effect on reducing insulin resistance, as it has a greater effect on the cell genome or elements of the genome that respond to vitamin D. Therefore, the effects of vitamin D on these levels may not be limited to the regulation of calcium levels, but may be capable of producing responses at the receptor level and the level of intracellular messengers by affecting the cellular genome to transmit insulin messages to the cellular system thus, reducing insulin resistance. Vitamin D-mediated increase in cytosolic calcium in muscle tissue appears to be responsible for increased glucose transport to muscle. Vitamin D also can regulate peripheral nuclear receptors, which play an important role in insulin sensitivity.[22] Chiu et al. in California reported that vitamin D levels in patients with type II diabetes had a positive effect on insulin sensitivity index and were inversely related to plasma levels of vitamin D and plasma glucose, which we confirm with the results of this study.[23]

In conclusion, our study report an inverse association between blood sugar level and vitamin D levels. Increasing vitamin D levels in patients reduced blood sugar levels and decreased patients' insulin requirements, which can be assumed to reduce insulin resistance. We also found no significant relationship between vitamin D level and patients age or length of hospital stays or APACHE score.

Though Vitamin D level was not found to be effective in patients' prognosis, we hope that this study can help researchers and clinicians and assist with best practice management of patients.

List of acronyms

APACHE - Acute Physiology And Chronic Health Evaluation
ICU - intensive care unit
ELISA - enzyme linked immunosorbent assay
SOFA - sequential organ failure assessment
HbA1C - Glycated hemoglobin test

Contributions of Authors

All authors have read and approved the final edited typescript.

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Conflict of Interest

The authors declare no conflicts of interest.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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