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Original Article

Vitamin D Deficiency Implications in Orthostatic Hypotension Among Diabetic Patients

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ABSTRACT

Background: Orthostasis is more common in people with diabetes, especially the elderly, and vitamin D receptors are present in vascular smooth muscles, endothelium, and cardiac cells, which may influence cardiac as well as motor responses during orthostasis. This work aimed for evaluation of the vitamin D status and its correlation with orthostatic hypotension among diabetic patients.

Methods: This pospective cohort study was carried out on 106 type 2 diabetic patients from internal medicine department, at Zagazig University Hospital. Patients were split into the following groups: Group I: cases with vitamin D deficiency(n=50), and Group II: cases with vitamin D insufficiency (n=56). Vitamin D level was assessed using ELISA, and the assessment of orthostatic hypotension via measurement of Blood pressure (BP) after 15 minutes of rest in the supine position.

Results: Both HbA1c and 25(OH) D levels showed high statistically significant differences between group II compared to group I (P = 0.001 for each). A statistically significant difference was found between pre- and post-vitamin D supplementation (P=0.001). Group I had a higher significant orthostatic hypotension than Group II did (P = 0.001). There was an improvement in orthostatic hypotension among the studied groups after vitamin D supplementation. At a cut-off value ≤72.1 nmol/L vitamin D can predict orthostatic hypotension in diabetic patients with a specificity of 97.83%, Sensitivity of 100%, PPV of 93.3%, and NPV of 100%.

Conclusion: Orthostatic hypotension and vitamin D levels were found to be strongly correlated among diabetic patients.

Keywords: Vitamin D, Orthostatic Hypotension, Diabetic Patients.

INTRODUCTION

When a person's blood pressure decreases by more than 20 mm Hg or their diastolic pressure decreases by more than 10 mm Hg upon standing, this is known as orthostatic hypotension (OH). Symptoms often include dizziness and fainting (sometimes called syncope) [1]. People with diabetes, especially the elderly, are at increased risk for orthostatic hypotension. This prolonged BP recovery is typically attributed to diabetes-related autonomic dysfunction, which hinders the body's natural response to hypotension via the baroreflex. Peripheral neuropathy and lower plasma renin activity may have a role, in addition to preexisting heart disease as well as hypertension [2].

Orthostatic hypotension treatment options currently available are inadequate. Stockings, and a head-up sleeping positions as well as abdominal compression are considered non-pharmacological methods that are either ineffective, impractical, or unsupported by evidence [3]. Pressor drugs like fludrocortisone and midodrine are

commonly used in pharmacological interventions to raise blood pressure in both the supine and upright positions. This method may not mitigate the drop in blood pressure associated with an upright position, and it may raise the risk of vascular events. According to a recent systematic review, the evidence supporting these therapies is insufficient to suggest any of them for widespread usage [4]. Several possible health benefits for vascular biology have been linked to vitamin D, including decreased renin secretion, decreased PTH [5]. The presence of vitamin D receptors on vascular smooth muscle, cardiac as well and endothelial cells suggests that vitamin D may modulate the cardiovascular system's response to orthostasis [6]. Taking vitamin D has been shown to have a beneficial effect on endothelial function. Furthermore, an observational study shows a connection between low 25OHD levels and orthostatic hypotension, suggesting that vitamin D may help to alleviate orthostatic hypotension by enhancing vascular and cardiac function via a variety of potential pathways [3].

At the time that we started our research, there were some researches that discussed the relation between Vitamin D and orthostatic hypotension and other researches that discussed the relationship between Vitamin D and diabetes mellitus, with very few researches that were done to assess the relation between Vitamin D and patients who have both diabetes and orthostatic hypotension, that's why we did this work.

Therefore, we did this work for evaluation of the vitamin D status and its correlation with orthostatic hypotension among diabetic patients.

SUBJECTS AND METHODS

This Prospective cohort study was performed on 106 type 2 diabetic patients in the internal medicine department, Zagazig University Hospital during the period from March 2022 to March 2023.

Inclusion Criteria:

Cases who aged ≥ 18 years from both sexes, with a high risk of falling or a history of falling in the past year, diabetic patients with orthostatic hypotension, Patients with controlled diabetes, cases who had Vitamin D levels <30 ng/ml (50 nmol/L) and who accepted taking vitamin d supplementation were enrolled in the study.

Patients were split into the following groups based on the patients Vitamin D Level: Group I: cases with vitamin D deficiency(n=50), and Group II: cases with vitamin D insufficiency (n=56) [8].

Exclusion Criteria:

We excluded all cases who had any of the following conditions: metastatic malignancy or sarcoidosis, vitamin D levels ≥30 ng/ml (75 nmol/L0, had History of renal calculi, renal, cardiac or hepatic disorders, hypercalcemia or serum calcium ≥11 mg/dl, those already taking prescription vitamin D supplements, hypertensive patients receive antihypertensive treatment other than ACEIs or ARBs as they do not cause orthostatic hypotension [7], and type 1 diabetes mellitus cases.

After institutional review board approval of IRB (#9335/1-3-2022), written informed consent was obtained from all participants. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

All patients were subjected to the following:

Clinical assessment: Detailed history with special attention to hypertension, cardiovascular disease, dyslipidemia, and diet control among patients. Full general examination: All patients in our study were subjected to full general examinations with the assessment of Body Mass Index.

We measured blood pressure at baseline, 3 months, and 6 months. Recumbent in bed, a mercury sphygmomanometer was used to take the reading.

To have orthostatic hypotension (OH), blood pressure must drop by at least 20 mm Hg in response to standing, or by 10 mm Hg in response to diastole. [1]. Three readings were collected while the subject was lying supine after at least five minutes of rest in a quiet environment, and the average of these two readings was used to determine the subject's supine blood pressure. The participants' blood pressure was then measured at 0, 1, and 3 minutes after they stood. The standard cuff size was from 22 to 32 centimeters, whereas the bigger size ranged from 32 to 42 centimeters for the larger patients.

Routine laboratory investigations included: Complete blood count (CBC), random blood sugar (RBS), hemoglobin A1c (HBA1C), liver and kidney function tests, serum Na, K, Ca, and urinary Na, coagulation profile, and urine analysis.

Special laboratory investigations:

Measurement of serum level of vitamin D(25 hydroxycholecalciferol) by ELISA:

Each subject had four millimeters of peripheral venous blood drawn into a test tube, left to clot, centrifuged at 6000 rpm for 10 minutes, and then their sera were stored at -20^{o}C for 25 OH vit. D until they were tested in the Medical Biochemistry

Department's laboratory at the Faculty of Medicine at Zagazig University. Cobas 6000 was used for the analysis. [8].

The 25(OH)-vitamin D level was measured using a monoclonal antibody selected for its specificity in a competitive ELISA assay. Vitamin D levels lower than 20 ng/ml or 50 nmol/L were defined as 25(OH) vitamin D deficiency, levels ranging from 20 to 29 ng/ml or from 50 to 72 nmol/L was defined as 25(OH) vitamin D insufficiency, and levels equal or higher than 30 ng/ml or 75 nmol/L was defined as sufficiency [8]. Vitamin D level was assesed by ELISA at base line and after 3 months with recording of outcomes with no complications.

All patients were subjected to :

Ingestion of oral vitamin D for three consecutive months in doses of 4000 and 10000 IU/day according to the patient's previous vitamin D level. 10000 IU/day was administered to patients whose serum 25(OH)D levels were below 30 ng/ml, and 4000 IU/day was administered to those whose levels were between 30 and 60 ng/ml [9]. Check for orthostatic hypotension was done by taking a blood pressure reading 15 minutes after lying down. After a three-minute standing period, blood pressure was taken at baseline and 3 months.

STATISTICAL ANALYSIS

The SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA) and the MedCalc 13 for Windows (MedCalc Inc., San Diego, CA, USA) were used to collect, tabulate, and statistically analyze all data (MedCalc Software bvba, Ostend, Belgium). Data were tested using the Shapiro Walk test, Chi-square test ($\chi 2$), Fisher exact, Independent T-test, Mann Whitney and Pearson's and For this study, we compared quantitative variables using Spearman's correlation coefficient tests. The (+) sign was considered as indication for direct correlation i.e. increase frequency of independent lead to increase frequency of dependent & (-) sign as indication for inverse correlation i.e. increase frequency of independent lead to decrease frequency of dependent, also we consider values near to 1 as strong correlation & values near 0 as weak correlation. Receiver operating characteristic (ROC) curve was constructed to permit selection of threshold values for test results and comparison of different testing strategies. Areas under ROC curves and their standard errors were determined using the method of Cantor, and compared using the normal distribution, with correction for correlation of observations derived from the same cases. Value of area under a ROC curve (AUC) indicates: 0.90 – 1 = excellent, 0.80-0.90 = good, 0.70-0.80 = fair; 0.60-0.70 = poor; and 0.50-0.6 = fail. The optimal cutoff point was established at point of maximum accuracy

RESULTS

Differences in gender, age, and BMI were seen between groups, although they were not statistically significant (p = 0.032,0.22, and 0.38 respectively) (Table 1)

There were statistically significant differences in the duration of type 2 diabetes mellitus and diabetes characters between the studied groups (p = 0.001) (Table 2).

Both HbA1c and 25(OH) D levels showed high statistically significant differences between group II compared to group I (P = 0.001 for each) (Table 3).

There was a significant negative correlation between the duration of diabetes and serum 25-hydroxyvitamin D levels, and a significant positive relationship between duration of diabetes and glycated haemoglobin (HbA1c) levels (Table 4).

There was a substantial variation before and after vitamin D supplementation (P = 0.001) (Table 5).

Group I had a significantly higher orthostatic hypotension than Group II (P 0.001). (Table 6).

There was an improvement in orthostatic hypotension among the studied groups after vitamin D supplementation (Table 7).

At a cut-off value ≤72.1 nmol/L vitamin D can predict orthostatic hypotension in diabetic patients with a specificity of 97.83%, Sensitivity of 100%, PPV of 93.3%, and NPV of 100%. (Table S1, Figure S1).

Table 1: Demographic characteristics data for studied groups

	Group I (n = 50)	**Group II (n = 56)**	***F***	***P value***
Gender Male Female	 28 (56%) 22 (44%)	 25 (44.6%) 31 (55.4%)	10.2	0.032
Age (years) $\overline{X}$ ±SD Range	 50.9±8.4 (35 – 68)	 49.8±8.9 (30 – 68)	1.49	0.22
BMI (kg/m^2) $\overline{X}$ ±SD Range	 33.1±6.0 (22.3 – 46)	 35±6.0 (23.5 – 46.8)	1.03	0.38

BMI: Body mass index
N.B: P > 0.05 → non significant *P < 0.05 → significant*
P < 0.01 → highly significant *p < 0.0001 → very high significant*

Table 2: Diabetes characters distribution among studied groups

	Group I (n = 50)	**Group II (n = 56)**	***F***	***P value***
HBA1c mean±SD	**6.64±0.69**	**6.40±0.61**	6.9	0.001**
Fasting blood glucose mean±SD	**194.08±16.08**	**184.08±15.02**	8.7	0.001**
Post prandial blood glucose mean±SD	**259.14±40.15**	**249.74±41.05**	2.6	0.001**
DM duration / years Median (Min- Max)	**9(3-17)**	**7(2-15)**	9.6	0.051

HBA1c: hemoglobin A1c, DM: Diabetes mellitus

Table 3: Comparison of serum 25 (OH) D and HbA1c (%) level in the studied groups

	Group I (n = 50)	**Group II (n = 56)**	***F***	***P value***
HbA1c (%) $\overline{X}$ ±SD Range	6.64±0.69	6.40±0.61	6.9	0.001**
Vit. D (nmol/l) $\overline{X}$ ±SD Range	 38.9±7.4 (27 – 53)	 46.9±6.5 (30 – 52)	95.08	0.001**

HBA1c: hemoglobin A1c
**: p < 0.001 highly significant

Table 4: Correlation between duration and (serum 25-OH vitamin D, HbA1c level in studied groups

	HbA1c%	25OH vit.D (nmol/l)
DURATION	.628**	-.618**

** Correlation is significant at the 0.01 level (2-tailed).
R > 0.5 strong correlation R < 0.5 week correlation

Table 5: Comparison of vitamin D level pre and post treatment among cases with vitamin D deficiency.

Vitamin D(nmol/L) mean±SD	Group I (n = 50)	Group II (n = 56)	test of significance
Pre treatment	38.9±7.4	46.9±6.5	t=39.54 p<0.001*
Post treatment	65.97±5.33	75.97±5.33	

t:Paired t test , *statistically significant

Table 6: Orthostatic hypotension in studied groups

	Group I (n = 50)	Group II (n = 56)	*F*	*P value*
Systolic blood pressure Supine. Erect	 154.09±25.62 120.09±26.75	 142.08±15.87 116.81±19.09	3.33 ,	0.04*
Diastolic blood pressure Supine. Erect	 88.18±11.39 62.64±11.39	 73.19±10.22 51.81±4.33	9.69 ,	<0.001*
SBP drop	34.0±4.36	25.28±9.48	5.92 ,	0.009*
DBP drop	26.55±3.42	21.39±10.18	0.783 ,	0.460

SBP: Systolic blood pressure , DBP:Diastolic blood pressure
*statistically significant

Table 7: Relation between vitamin D supplementation and improvement in orthostatic hypotension.

		Before supplementation	After supplementation	test of significance	% improvement
Systolic blood pressure	**Supine.**	**142.08±15.87**	**158.75±22.12**	t=4.42 p<0.001*	11.7
	Erect	**116.81±19.09**	**143.75±22.85**	t=6.80 p<0.001*	23.1
Diastolic blood pressure	**Supine.**	**73.19±10.22**	**85.58±10.66**	t=8.92 p<0.001*	16.9
	Erect	**51.81±4.33**	**75.58±10.45**	t=13.09 p<0.001*	45.9
SBP DROP		**25.28±9.48**	**15.0±8.45**	t=5.81 p<0.001*	40.7
DBP DROP		**21.39±10.18**	**10.0±9.91**	t=5.35 p<0.001*	53.2

SBP: Systolic blood pressure , DBP:Diastolic blood pressure
t: Paired t test , *statistically significant

DISCUSSION

Orthostatic hypotension (OH) happens frequently among elderly people and is strongly linked to an increased risk of falling. Observational studies showed that blood levels of vitamin D are inversely related to OH, and vitamin D is also connected with regulation of the blood pressure via the renin-angiotensin and autonomic nervous systems' interactions. There has been a lack of definitive trial evidence, however one research using intermittent, high-dose oral vitamin D3 demonstrated a temporary reduction in OH at 3 months. It is not known if older people are at risk for falls benefit from larger vitamin D3 supplemental doses or not [10,11].

This was the first investigation on the role of vitamin D deficiency in orthostatic hypotension in diabetic patients, to the best of our knowledge. Most of the previous research mainly emphasized the role of vitamin D in OH among the overall population.

In terms of the relation between HbA1C and vitamin, the present study revealed that; Both HbA1c and 25(OH) D levels showed high statistically significant differences between group II compared to group I (P = 0.001 for each). A strong negative correlation was found between the duration of diabetes and the proportion of serum 25-OH vitamin D, and a strong positive correlation was found between the duration and the proportion of glycated hemoglobin (HbA1c) levels between diabetic groups.

In accordance, Buhary et al [12] performed their prospective observational cohort study on people with type 1 and type 2 diabetes (aged more than twelve years). There was a significant decrease in 25(OH)D levels (below 50 nmol/L) in 73.1% of the individuals. They discovered that HbA1c was lowered with vitamin D intake (from mean HbA1c of 10.55 to 7.70). After supplementation, serum vitamin D levels were inversely correlated with HbA1c (r = -0.16 (P 0.000001) vs. r = -0.14 (P 0.0000002). Recommending testing for vitamin D deficiency in individuals with greater HbA1c is likely to result in better blood glucose control and the patient's overall health.

Likewise, Children and adolescents with type 1 diabetes may benefit from vitamin D supplementation, according to an Iranian study, even if no changes are made to the insulin dosage [13]. The HbA1c values of African American patients with type 2 diabetes were observed to decrease significantly from year 1 to year 2 and from year 1 to year 3 of a three-year research that was conducted in the United States [14]. Vitamin D - -replete, type 1 DM patients exhibited an effect on glycemic control in further research conducted in Saudi Arabia after 12 weeks of supplementation [15].

Group I had a significantly higher orthostatic hypotension than Group II (P 0.001). Similarly, Gilani. et al [16] have demonstrated that; compared to individuals with adequate vitamin D levels, men with a deficiency were more likely to get OH within 1 minute of standing. There was no link between vitamin D deficiency and the risk of OH. They hypothesized that since vitamin D deficiency was associated with an increased risk of OH, but vitamin D sufficiency was not, this suggested a threshold effect, wherein the risk of OH rose only below a certain level of vitamin D.

Also, Ometto. et al [17] have demonstrated that; 5 cross-sectional studies with 3646 people were meta-analyzed from an original pool of 317 hits (1270 with hypovitaminosis D and 2376 without). Even after controlling for a median of five potential confounders, patients with hypovitaminosis D still showed a greater prevalence of orthostatic hypotension. Serum vitamin D concentrations were considerably lower in people with orthostatic hypotension. Their meta-analysis shows that low vitamin D levels are linked to low blood pressure when standing up, even after controlling for other factors.

In addition, Annweiler. et al [18] have demonstrated that; Women with vitamin D insufficiency were more likely to experience diastolic orthostatic hypotension (19.2% vs. 10.0%; P = 0.03). Diastolic blood pressure fluctuated inversely with 25OHD concentration after 3 minutes of standing (P = 0.046). Orthostatic hypotension was also linked to 25OHD deficit, and diastolic orthostatic hypotension (P = 0.003). Prior research found the same findings [19-21].

On the other hand, Juraschek. et al [10] have displayed that; Mean systolic and diastolic blood pressures were 130 (19) and 67 (11) mm Hg, respectively, at baseline in a group of 688 elderly people with serum 25(OH)D levels of 22.1 (5.1) ng/ml and 2.8% OH. Over the course of two years, 2,136 OH evaluations were performed. Doses of 1,000 IU or more per day had no effect on seated, standing, or orthostatic BP and did not reduce the risk of OH or orthostatic symptoms compared to 200 IU/day. This led them to the conclusion that

higher doses of vitamin D3 supplements should not be used as a preventative measure against OH.

Supplemental vitamin D did not alter the null connection between BP and baseline blood 25(OH)D, according to a separate meta-analysis [22].

The inconsistencies between studies could be attributed to variations in the timeframe within which OH develops, the reference groups used, and the criteria for vitamin D deficiency and OH.

One possible method by which vitamin D protects against falls is through its effect on blood pressure. In mice, vitamin D was found to affect the renin-angiotensin system [23] and lower systolic blood pressure in sedentary individuals [22].

Both animal studies and human observational research have linked vitamin D deficiency to endothelial dysfunction. Furthermore, Blood vitamin D is favourably connected to autonomic nervous system activity, and vitamin D supplementation in humans has been shown to improve cardiac autonomic function [11,24].

Regarding vitamin D supplementation, the current study demonstrated that there was an improvement in orthostatic hypotension among the studied groups after vitamin D supplementation.

Because vitamin D levels are inversely linked with orthostatic hypotension (OH), vitamin D3 supplementation is being evaluated as a potential strategy to reduce OH [10].

While Witham. et al [3] have demonstrated that, after controlling for baseline age, 25-hydroxyvitamin D, SBP, and orthostatic fall, there was no discernible treatment effect 3 months into the study when comparing the vitamin D group to the control group (3 mmHg for systolic fall, 95 percent CI -1 to 8; 1 mmHg for diastolic fall, 95 percent CI -1 to 3). After 12 months of intermittent high-dose oral vitamin D3, they found that older persons with isolated systolic hypertension did not significantly improve their orthostatic hypotension.

Vitamin D's effect on muscle strength and balance may explain why vitamin D intake lessens the danger of falling [25,26]. It is unclear, however, what other mechanisms might be at play here. Insufficient evidence suggests that vitamin D does not contribute to orthostatic hypotension. Vitamin D has been linked to increased risk of cardiovascular disease, stroke, and diabetes [27,28]. Other possible explanations for this reduced risk of falling are unknown. Although data is weak, It's possible that vitamin D contributes to orthostatic hypotension. Low levels of vitamin D have been related to increased risk of cardiovascular disease, stroke, and high blood pressure [29].

Limitations:

The current study was done in one center on a relatively small sample size, it is required to do additional research, including longer follow-up and multicenter practice.

CONCLUSION

Orthostatic hypotension and vitamin D levels were found to be strongly correlated among diabetic patients.

Conflict of Interest

None

Financial Disclosures

None

Individual author's contribution:

Elhosiny E.E: collecting data,samples and labaroratory results with doing most of interperetations. **Abdel-Hai A.R:** Suggesting the idea of research with continuous supervision on whole work and guidance of selection of cases and broad instructions. **Gad S.A:** Direct supervision on the work with help in statistics, and assement of the writing of thesis and the manuscript.

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Table (S1): Sensitivity, specificity and accuracy for vitamin D to predict orthostatic hypotension in diabetic patients:

	Cut off	Sensitivity	specificity	NPV	PPV
Vit. D (nmol/L)	**≤ 72.1**	**100.0**	**97.83**	**100.0**	**93.3**

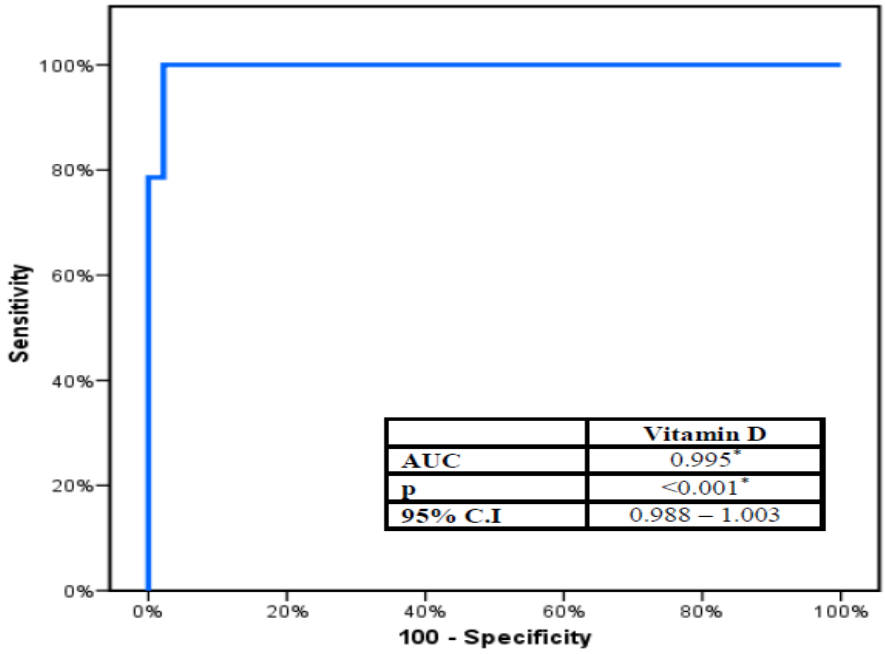

Figure (S1): ROC curve for vitamin D to predict orthostatic hypotension in diabetic patients.

Citation

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