The effect of vitamin D deficiency on glycemic control in patients with type 2 diabetes mellitus

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Abstract

Multiple factors are involved in the development of type 2 diabetes mellitus (T2DM), but an imbalance between free radical formation and antioxidant removal is the main cause of diabetic complications. Micronutrients with antioxidant properties may have a role in the development of diabetes mellitus (DM) and its complications. Vitamin D has recently been found to have membrane antioxidant effect and a relationship to the development of T2DM, as it can modify its risk. Whether vitamin D deficiency has an effect on hyperglycemia in diabetic patients or not need further study. Our aim was to examine the effect of vitamin D deficiency on glycemic control in T2DM. We examined the vitamin D levels of 100 patients with T2DM and correlated them with fasting blood sugar and glycated hemoglobin A1c (HbA1c) levels. High levels of fasting blood sugar and HbA1c levels were significantly associated with vitamin D deficiency. Vitamin D deficiency negatively affects glycemic control in patients with T2DM.

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Introduction

Type 2 diabetes mellitus (T2DM) is highly prevalent worldwide, especially in developing countries. It is caused by pancreatic β-cell dysfunction and insulin resistance, it places a burden on health care institutions due to its many macrovascular and microvascular complications, which lead to high morbidity and mortality.[1] Some humoral substances, such as adipokines increase incidence of diabetic complications. One of these adipokines is Pasma omentin -1, which has an anti-diabetogenic effect and its level is reduced in diabetic patients with high insulin resistance, as it is found that plasma level of omentin -1 is much lower in diabetic patients with complications than in diabetic patients without complications.[2] Another adipokine is neuregulin-4, which has an important role in regulating energy balance, and metabolism of glucose and lipid. It also helps in chronic inflammation down-regulation and it is a good predictor of microvascular complications in diabetic patients.[3]

T2DM is associated with chronic low grade of inflammation, and many inflammatory markers are produced. These lead to free radical formation that needs removal by antioxidant. One new cytokine produced in DM is Cardiothrophin-1 (CT-1), which is composed of 201 amino acid, and has protective effects against apoptosis. Aktas *et al*., found that there are increased levels of CT-1 in diabetic patients independently of hypertension and heart failure. The cause of elevation of CT-1 in type 2 diabetes is that pancreatic beta cell volume and function progressively dimensioned and CT-1 protect pancreatic beta cells from apoptosis. However, the elevated levels lead to left ventricular failure as they cause structural modification of myocytes.[4]

Another set of markers of inflammation derived from hemogram in diabetic patients are neutrophil/lymphocyte ratio and mean platelet volume/lymphocyte ratio (MPVLR). They are found to be associated with frailty in diabetes and are considered to be independent predictors of gestational diabetes.[5,6] Another novel marker of inflammation increased in diabetes, especially

those with diabetic nephropathy, is CRP to albumin ratio. This marker is found to be elevated in those patients (according to the ROC curve, a level higher than 0.82% presents the best sensitivity and specificity in the association with diabetic nephropathy).[7]

Many predictors of diabetic control have emerged to help in differentiating well from poorly controlled diabetes. One of them is uric acid/HDL cholesterol ratio, which has a strong association with fasting blood sugar and HbA1c.[8]

Vitamin D is a fat soluble vitamin that is produced through the effect of ultraviolet B radiation on the epidermis of the skin. It is also found in food substances like fish oil and egg yolk. To become active, it needs two hydroxylation processes, one in the liver that produce 25-hydroxyvitamin D, and the other in the kidney that produce 1, 25-hydroxyvitamin D.[9]

Vitamin D receptors are present in the pancreatic β- cells as vitamin D is involved in regulation of insulin secretion, that's why some hypothesis postulated that vitamin D is involved in the pathogenesis of diabetes mellitus.[10]

Many studies have been conducted to determine the relation between vitamin D deficiency and progression of diabetes, especially its macrovascular complications. Vitamin D deficiency is associated with high inflammatory burden, and many inflammatory markers have been found to be elevated in vitamin D deficiency patients.[11]

Other studies have found a significant effect of vitamin D supplementation on improving fasting blood sugar and glycated hemoglobin A1c.[12] However, more studies are needed to determine the relationship between vitamin D deficiency and glycemic control in diabetic patients and whether vitamin D supplement is going to help in controlling the disease progression.

Materials and Methods

Study design

This study was a prospective randomized clinical trial conducted on 100T2DM patients. The participants 'vitamin D level, fasting blood sugar and HbA1c were measured, all patients were treated with oral hypoglycemic medications. The study was conducted at Medical Research Institute, Alexandria University, between June 2021 to September 2021. Patients enrolled in the study were selected from diabetic population routinely attending the outpatient clinic or admitted to the inpatient wards for follow up and treatment of their diabetes. All patients provided written informed consent, and the study was approved by the Ethics Committee of the institute.

Patients

Type 2 diabetic patients were randomly selected from those who were registered at our outpatient clinic or admitted to our inpatient wards. During selection, diabetes was diagnosed and confirmed according to the diagnostic criteria established by the American Diabetes Association at the time of the study,[13] with no change in their diabetes treatment protocol during the study.

Inclusion criteria

T2DM patients above 18 years of age, non-obese with 18.5>BMI <25 kg/m^2 according to WHO criteria.[14]

Exclusion criteria

Individuals with any of the following were excluded: Type 1 DM, gestational DM, chronic kidney disease, chronic liver disease,

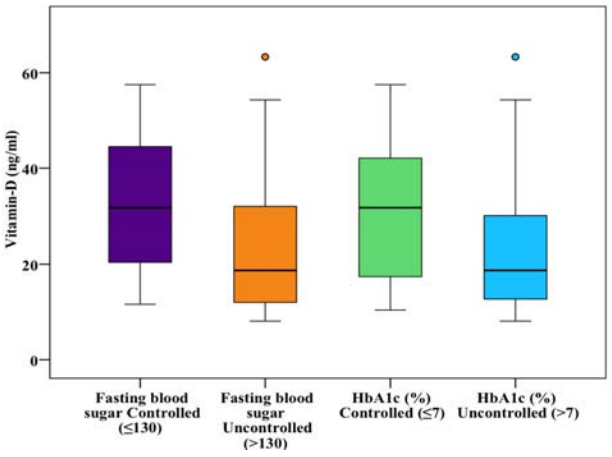

Figure 1. Relation between vitamin-D level and parameters of glycemic control.

Table 1. Distribution of the studied cases according to demographic data and vitamin D level (n=100).

Variable	No. (%)
Gender	
Male	40 (40)
Female	60 (60)
Age (years)	
Mean ± SD.	56.7±12.9
Median (Min. – Max.)	60.5 (25–75)
Vitamin-D (ng/mL)	
Deficient (<30)	60 (60)
Normal (30 – 100)	40 (40)
Mean ± SD.	27.5±15.4
Median (Min. – Max.)	23.5 (8.1–63.3)

SD, standard deviation.

Table 2. Relation between vitamin-D and demographic data (n= 100).

	Vitamin-D (ng/mL) Deficient (<30) (n = 60)	Normal (30 – 100) (n = 40)	Test of Sig.	P
Gender				
Male	28 (46.7%)	12 (30%)	χ^2= 2.788	0.096
Female	32 (53.3%)	28 (70%)		
Age (years)				
Mean ± SD	56.37±14.24	57.3± 0.6	t=0.355	0.723
Median (Min. – Max.)	61 (25–75)	60.5 (27–74)		

SD, standard deviation; t, student t-test, χ^2, Chi square test; *statistically significant at p≤0.05.

Table 3. Relation between vitamin-D level and parameters of glycemic control (n=100).

	Vitamin-D (ng/mL) Mean ± SD.	Median (Min.–Max.)	U	p
Fasting blood sugar				
Controlled (≤130)	32.4±14.7	31.7 (11.6–57.5)	774.0*	0.003*
Uncontrolled (>130)	24.3±15.1	18.7 (8.1–63.3)		
HbA1c (%)				
Controlled (≤7)	31.6±15.3	31.7 (10.4–57.5)	838.0*	0.005*
Uncontrolled (>7)	23.2±14.4	18.7 (8.1–63.3)		

SD, standard deviation; U, MANN Whitney test; *statistically significant at p≤0.05.

and hypoparathyroidism: i) Thorough clinical examination including weight and height; ii) Routine laboratory investigations including: liver function tests, renal function tests, electrolytes, complete blood picture, and lipid profile;[14,15] iii) Glycemic control was assessed by Fasting blood sugar and HbA1c;[13] iv) Vitamin D assessment by high performance liquid chromatography.[16]

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov- Smirnov test was used to verify the normality of distribution of variables. Paired t-test was assessed for comparison between two periods for normally distributed quantitative variables, While Wilcoxon signed ranks test was assessed for comparison between two periods for abnormally distributed quantitative variables. Significance of the obtained results was judged at value <0.05.

Results

According to the inclusion and exclusion criteria, 100 type 2 diabetic patients were involved in the study. Vitamin D was deficient in 60 (60%) of cases, and normal in 40 (40%; Table 1).

The demographic data of diabetic patients at baseline were: 40 (40%) males, 28 (46.7%) had vitamin D deficiency and 12 (30%) had normal vitamin D level. 60 (60%) females, 32 (53.3%) had vitamin D deficiency and 28 (70%) had normal vitamin D level, p= 0.096 (Tables 1, 2).

The mean age of diabetic patients with vitamin D deficiency was 56.7 ± 12.9 years, and mean age of diabetic patient with normal vitamin D level was 57.3 ± 10.6 years, p=0.723 (Table 2).

Mean vitamin D level in diabetic patients with controlled fasting blood sugar was 32.4±14.7ng/ml, while the mean vitamin D level in diabetic patients with uncontrolled fasting blood sugar was 24.3±15.1ng/mL, p= 0.003*(Table 3, Figure 1).

The mean vitamin D level in diabetic patients with controlled HbA1c level was 31.6±15.3ng/ml, while the mean vitamin D level in diabetic patients with uncontrolled HbA1c level was 23.2±14.4ng/ml, p=0.005* (Table 3, Figure 1).

Discussion

Vitamin D deficiency is a common finding in diabetic patients, and prevalence varying between regions. For instance, a study conducted in a referral hospital in Kenya reported lower prevalence rates of vitamin D deficiency and insufficiency among diabetic patients (38.4% and 21.9% respectively), compared to other countries in Asia, Europe, and North America.[17]

However, in a study conducted in Saudi Arabia found higher rates of prevalence of vitamin D deficiency (59.8%) and insufficiency (38.6%) among diabetic patients, which is similar to our findings where 60% of diabetic patients were vitamin D deficient.[18]

Gender may also play a role in the prevalence of vitamin D deficiency among diabetic patients, as recent research has shown that female diabetic patients are more deficient in vitamin D than male diabetic patients.[19] In our study, we found that 53.3% of female diabetic patients were vitamin D deficient, while 46.7% of the male diabetic patients were deficient, but this was not statistically significant. The difference may be attributed to factors such as poor sun exposure, poor dietary vitamin D, obesity and sedentary life in Middle East females.

In addition, elderly people, including diabetic patients, are more susceptible to vitamin D deficiency, especially in European countries with low sun exposure, decreased synthesis, absorption, and metabolism because of aging.[17] However, in our study, there was no significant difference in the mean age between diabetic patients with or without vitamin D deficiency, probably because the study population had mean age of 56.7 years, and diabetes is more common in old age group.

As diabetes continues to pose a major health problem, researchers have explored other pathogenic mechanisms that contribute to its development and progression, such as the relationship between vitamin D deficiency and progression of diabetes. This is due to the presence of vitamin D receptors in pancreatic B cells and other tissues such as liver and muscle tissue, suggesting that vitamin D may be involved in glucose homeostasis.[20]

Studies have shown that optimum level of vitamin D in serum reduces insulin resistance, and HbA1c level and leading to more control of hyperglycemia.[21] In another case control study, HbA1c found to be higher in the group with vitamin D deficiency than the group with no vitamin D deficiency.[22]

A recent study done by Erkus E, et al. involved a controlled group of diabetic patients and uncontrolled group, assessing vitamin D levels in both controlled and uncontrolled groups. They found that vitamin D levels were much lower in the uncontrolled group of patients and suggested that vitamin D could be used as a treatment modality for diabetes in the future.[23]

Another interventional study used a vitamin D supplement 4500 IU/Day for 2 months and assessed fasting blood sugar and HbA1c at baseline and after giving the supplement was given. They found a reduction in fasting blood sugar from a mean of 133 mg/dL to mean of 127 mg/dl and reduction of mean HbA1c from 7.7% to 7.2%.[24]

In a double-blind, placebo- controlled study conducted by Lemieux *et al*.,[25] on 96 subjects at risk to develop diabetes or with early diabetes, they found a significant increase in peripheral insulin sensitivity and B cell function after administrating 5000 IU vitamin D daily for 6 months. However, some authors, such as Kumar *et al*.[26] in a retrospective case-control study, did not find any relation between vitamin D deficiency and glycemic control. They evaluate 78 cases and 69 controls for vitamin D and HbA1c levels and found no significant correlation between them.

In our study, we found that the mean vitamin D level was 32.4ng/mL in patients with controlled fasting blood sugar, while it was 24.3ng/mL in patients with uncontrolled fasting blood sugar levels. Regarding HbA1c, the mean vitamin level was 31.6ng/mL in patients with values ≤ 7 and 23.2ng/mL in patients with HbA1c values >7. These results suggest that vitamin D deficiency is associated with higher levels of fasting blood sugar and HbA1c.

These results may be attributed to the postulated role of vitamin D in glycemic control where it reduces systemic inflammation by modulating the immune response and decreasing insulin resistance at the peripheral tissue.[27] Moreover, vitamin D increases insulin secretion via direct mechanism in which it increases intracellular calcium through calcium channel leading to increase insulin secretion or indirectly through mediating B- cell calcium – dependent activation which enhance conversion of pro insulin to insulin.[28] These results lead us to consider evaluation of vitamin D in diabetic patients and to correct the deficiency if present, together with optimizing diet, exercise and medications for better glycemic control.

Conclusions

In conclusion, higher levels of fasting blood glucose, and HbA1c levels were associated with Vitamin D deficiency that may affect glycemic control in type 2 diabetic patients. This may call for correction of vitamin D deficiency in patients with uncontrolled DM.

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