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ORIGINAL ARTICLE

The association between vitamin D levels and glycemic control in type 2 diabetic patients in Najran Area, Saudi Arabia.

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ABSTRACT

Background: Recently there are various non-skeletal diseases associated with vitamin D deficiency such as type 2 diabetes mellitus (T2DM). The main target of this study is to investigate whether there is any relationship between serum Vitamin D levels and the glycemic control in type 2 diabetic patients. **Methods:** The study was carried out in Najran University Hospital, this study involved 275 type 2 diabetic patients and 136 healthy control. Fasting blood glucose (FBG), HbA1c and 25(OH) vitamin D were analyzed. **Results:** The results showed (8%) of diabetic patients presented with severe Vitamin D deficiency, (27. 6%) presented with moderate deficiency, (19.6%) presented with insufficiency and (44.7%) presented with sufficient levels. HbA1c % and FBG were negatively correlated with Vitamin D levels. The mean levels of vitamin D showed a highly significant difference $p > 0.001$ between diabetic patients (27.84 ± 14.847 ng/ml) and healthy control subjects (53.99 ± 11.401 ng/ml), Also results showed a highly significant difference $p > 0.001$ in vitamin D level between controlled and uncontrolled diabetic patients the level of vitamin D was (46.4 ± 17.5; 28.2 ± 14.9) respectively. **Conclusion:** The findings suggested that there was a high incidence of vitamin D deficiency in type 2 diabetic patients and there was an inverse relationship between Vitamin D and FBG and HbA1c.

Keywords: Type II diabetes; 25 hydroxycholecalciferol; HbA1c

INTRODUCTION

Several emerging studies have highlighted the crucial association between vitamin D deficiency and metabolic disorders like, diabetes mellitus. The main culprit behind the development of diabetes and vitamin D deficiency will be brought into attention in our study.

The relationship between vitamin D and diabetes has received substantial interest. Recent theoretical developments have revealed that there are various diseases associated with vitamin D deficiency that are non-skeletal in origin .These diseases include type 2 diabetes mellitus (T2DM) that has been reported with vitamin D deficiency [1]. Several evidence suggests that vitamin D (25Hydroxy (OH) D]

may play role in development of T2DM and insulin resistance [1]. We aim is to investigate the association between serum 25(OH) D levels with insulin resistance.

We will review the main approaches to the actions of vitamin D that correlate with vitamin D deficiency and development of diabetes mellitus. The foremost mechanisms of actions of vitamin D are highlighted here and they include the following.

Vitamin D, as a critical and essential micronutrient for the human health has achieved an ample and global attention , It exhibits a variety non-skeletal effects that includes but not limited to its potential in secretion and action of insulin .It increases insulin sensitivity that might be mediated via binding of 1,25(OH)2D to vitamin D receptor (VDR). In addition, it causes induction of insulin receptors (IRs) expression on target tissues as well as activation of peroxisome proliferation activated receptor δ (PPAR-δ). Moreover, it stimulates IRs in target insulin-responsive tissues [2].

In humans as well as animals it has been shown that type 2 diabetes mellitus, decreased insulin secretion and increased insulin resistance are all associated with vitamin D deficiency [3]. Moreover, as shown per studies a pivotal functional role in the glucose tolerance has been exhibited by vitamin D effects on insulin secretion and insulin sensitivity [4]. Mechanism of action of vitamin D is via the stimulation of the synthesis of insulin, the pancreatic β cells protection, reduction in the insulin resistance in muscles and the regulation of the adipogenesis mechanism during adipocyte differentiation. Consequently vitamin D is a crucial factor in the development of T2DM [5]. Recently, the role of Vitamin D has highlighted a widespread interest in the pathogenesis and clinical presentations of diabetes [6]. Been a major calcium homeostasis regulator vitamin D can both directly and indirectly via the activation of calcium-dependent endopeptidases improve insulin exocytosis [7]. Vitamin D as an efficient antioxidant plays a role in the prevention of T2DM and it is complications as well [8]. The vitamin D steroid hormone form plays a role in the promotion of suppressor cell activity and the inhibition of cytotoxic T lymphocytes (Tc), macrophages, delayed hypersensitivity type, and the generation of natural killer (NK) cells. It exerts its action in various organs and biological systems via mediating several non- calcemic functions through the regulation of cellular proliferation, differentiation and replication, and as a mediator of autoimmune reactions as well [8]. Deficiency of 25(OH) cholecalciferol has been implicated in the pathogenesis of diabetes although exact pathophysiological pathways remain unclear [9].

This study constitutes a relatively new area which has emerged to detect whether there is any correlation between vitamin D and T2DM or not.

METHODS

The study included 275 diabetic patients (166 Male 60.4% and 109 Female 39.6%) attending the outpatient clinic of Najran University Hospital and 136 healthy controls (76 Male 55.9% and 60 Female 44.1%) from Najran area between August 2016 and October 2017. FBG was measured by COBAS INTEGRA 400 and a Roche diagnostics commercial kits, HbA1c was estimated using the Nycocard HbA1c method. While 25(OH) vitamin D was measured using the ELISA technique by kits manufactured by Abcam Company. Weight and height were measured using a standardized scale for weight and height and then BMI was calculated as weight in kilograms divided by the square of height in meters.

We classified the participant according to 25(OH) vitamin D deficiency into four main categories: severe deficiency, <10 ng/ml (25 nmol/l); moderate deficiency, 10-19.9 ng/ml (25-49.9 nmol/l); insufficiency, 20-29.9 ng/ml (50-74.9 nmol/l); sufficiency, ≥30 ng/ml (75 nmol/l) [10 - 11].

All patients were assured that all their obtained information will be handled in a confidential atmosphere and it will not affect their life after taking verbal and written consent. Ethical clearance and protocol approval was obtained

from the research and ethics committee of Najran University, KSA. All procedures followed were following the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in Brazil 2013.

Statistical analysis: Results of this study were statistically analyzed using (SPSS) program. Significant differences between groups were assessed by one-way ANOVA and t-test. Correlation matrix was done and the r values were obtained with the level of significance.

RESULTS

This study involved 275 diabetic patients (166 Male 60.4% and 109 Female 39.6%) and 136 Healthy individuals as a control group (76 Male 55.9% and 60 Female 44.1%).

The study results showed 55.3% of diabetic patients suffering from vitamin D deficiency. Chi Square test was highly significant ($p < 0.001$) and the results showed that 22 (8%) of diabetic patients had severe 25(OH) vitamin D deficiency (<10 ng/ml), whereas, 76 (27. 6%) of diabetic patients with moderate deficiency (10 to 19.9 ng/ml), 54 (19.6%) of diabetic patients presented with insufficiency (20 to 29.9 ng/ml) and finally 123 (44.7%) presented with sufficient levels of 25(OH) vitamin D (≥30 ng/ml) (Table 1).

FBG concentration in Table 2 shows a highly significant different $p > 0.001$ between diabetic patients and healthy control subjects, the higher concentration was for diabetic patients with mean concentration (203.6 ± 81.5 mg/dl) and (79.0 ± 12.6 mg/dl) for healthy control.

Results presented in Table 2 showed a highly significant different $p > 0.001$ in HbA1c percent between diabetic patients and healthy control subjects, the levels were (9.7 ± 2.3 %) and (5.5 ± 0.7%) respectively.

25(OH) vitamin D showed a highly significant difference between studied groups $p > 0.001$. The higher levels were shown in the healthy control group (53.99 ± 11.401 ng/ml) followed by diabetic patients with mean (27.84 ± 14.847 ng/ml) table 2.

HbA1c % in table 3 shows a highly significant difference $p > 0.001$ among studied groups, the higher percentage was shown in insufficiency group (10.1 ± 2.0 %), and severe deficiency (10.1 ± 2.8 %), followed by sufficiency group (9.8 ± 2.3 %), moderate deficiency (9.2 ± 2.3 %), and finally control group was the lowest percentage (5.5 ± 0.7 %).

Figure 1 shows that there is a highly significant deferent in 25(OH) vitamin D level between controlled and uncontrolled diabetic patients the highest levels was shown in patients with HbA1c less than 7%, the level of 25(OH) vitamin D was (46.4 ± 17.5; 28.2 ± 14.9 respectively with significant level less than 0.001.

25(OH) vitamin D levels was shows highly significant difference $p > 0.001$ in studied groups, the highest concentration shown in control group, followed by sufficiency group, followed by insufficiency group, followed by moderate deficiency and finally severe deficiency, and the concentration as follow (54.0 ± 11.4 ng/ml), (41.9± 9.3 ng/ml), (23.1 ± 2.7 ng/ml), (14.6 ± 2.4 ng/ml) and (6.6 ± 1.4 ng/ml) respectively (Figure 2).

On the other hand 25(OH) vitamin D was non-significantly correlated to HbA1c ($r = 0.044$; $p = 0.470$) (figure 3), and it was non-significantly negatively correlated to FBG ($r = -0.032$; $p = 0.603$) (Figure 3 and 4).

Table 1. The distribution of study population among studied groups.

Study groups	Diabetic Patients	Healthy Control
Severe deficiency	22 (8%)	0
Moderate deficiency	76 (27.6 %)	0
Insufficiency	54 (19.6 %)	0
Sufficiency	123 (44.7 %)	136 (100%)
Total	**275 (100 %)**	**136 (100%)**

Table 2. Mean of some parameters in diabetic patients and healthy control subjects.

parameters	Mean ± SD		sig
	Diabetic patients	Healthy Control	
BMI	34.0 ± 6.7	26.1 ± 2.7	0.000
Systolic BP	125.9 ± 15.3	119.3 ± 4.8	0.000
Diastolic BP	72.74 ± 15.0	81.0 ± 4.2	0.000
FBG mg/dl	203.6 ± 81.5	79.0 ± 12.6	0.000
HbA1c%	9.7 ± 2.3	5.5 ± 0.7	0.000
25(OH)cholecalciferol ng/ml	27.8 ± 14.9	54.0 ± 11.40	0.000

Table 3. HbA1c % in study groups

Status	Study groups	Mean ± SD
Diabetic	**Severe deficiency**	10.1 ± 2.8
	Moderate deficiency	9.2 ± 2.3
	Insufficiency	10.1 ± 2.0
	Sufficiency	9.8 ± 2.3
	Total	**9.7 ± 2.3**
Healthy control	**Control Subjects**	5.5 ± 0.7
	Total	**5.5 ± 0.7**

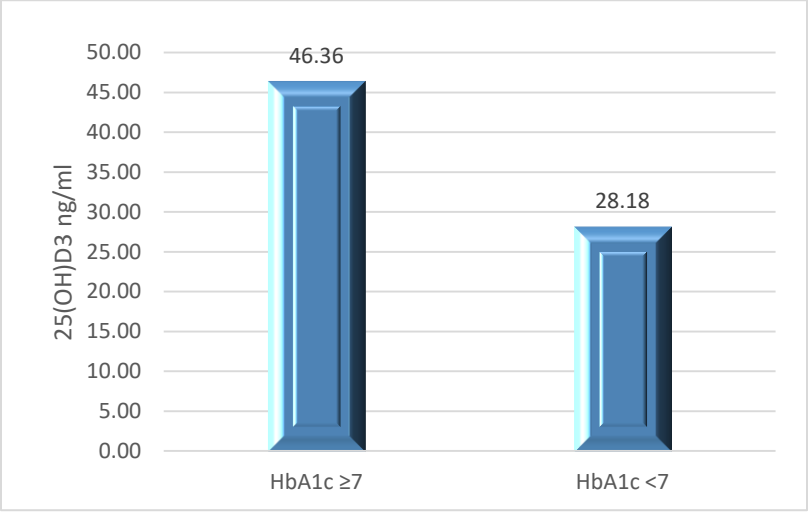

Figure 1. Comparing 25- (OH) cholecalciferol levels in controlled and uncontrolled diabetic patients.

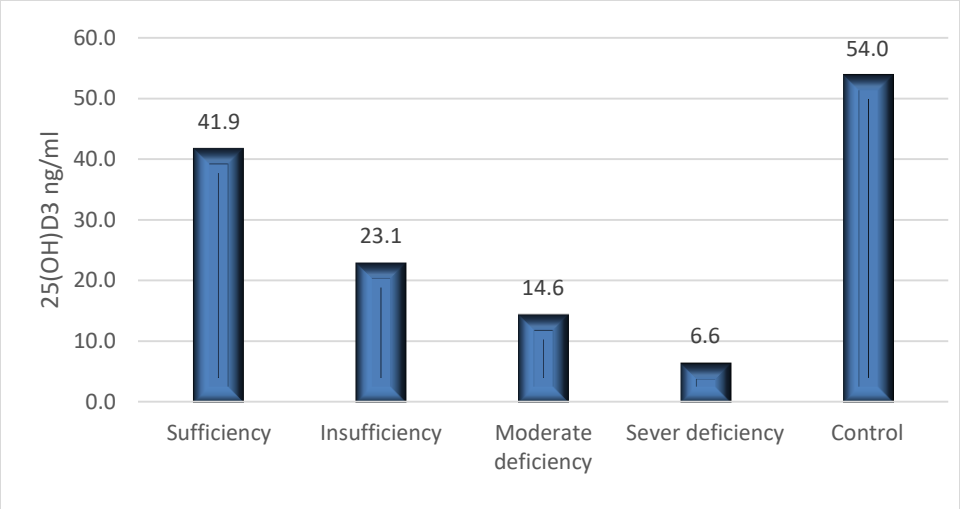

Figure 2. Comparing 25(OH) vitamin D levels various studied groups.

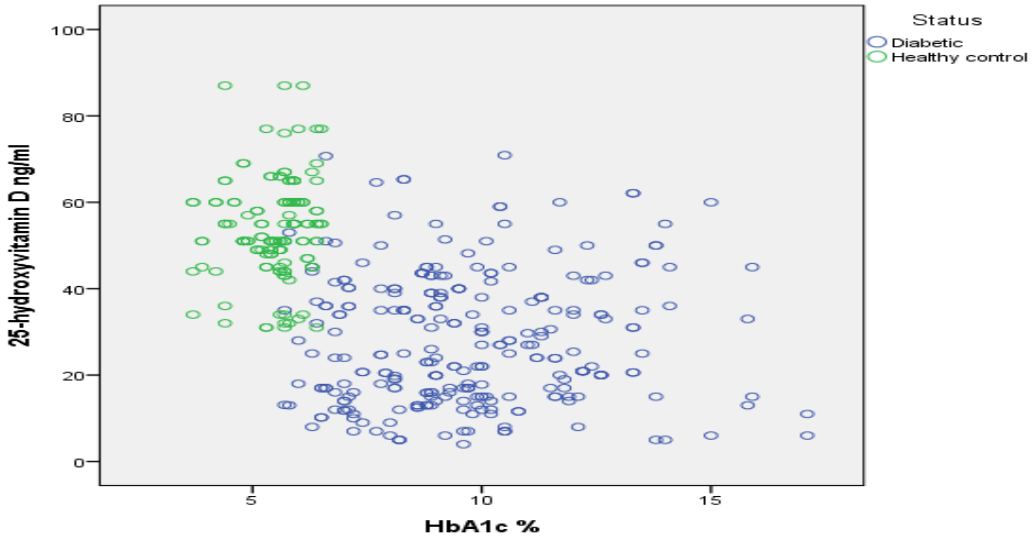

Figure 3. Correlation of 25(OH) vitamin D with HbA1c% in diabetic and healthy control subjects

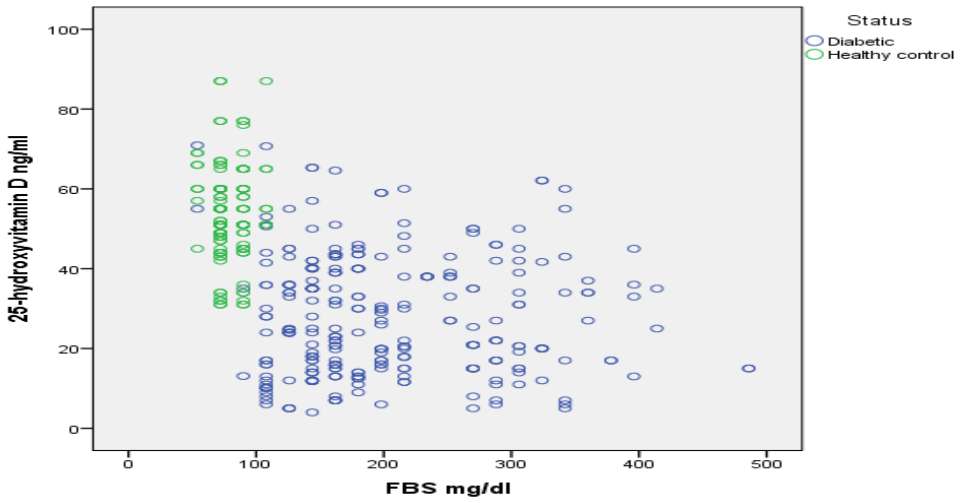

Figure 4. Correlation of 25(OH) vitamin D with fasting blood glucose in diabetic and healthy control subjects.

DISCUSSION

Saudi Arabia has been ranked by the World Health Organization as having the second highest rate of diabetes in the Middle East with an estimated population of 7 million suffering from diabetes and more than 3 million with pre-diabetes [12], on the other hand Vitamin D deficiency has been proven to be common in Saudi adults especially among females and in the younger age groups [13].

This study explored the relationship between vitamin D deficiency and T2DM. We found a significant bivariate association of T2DM with vitamin D deficiency. In diabetic patients, it was found that 25 (OH) vitamin D3 deficiency prevalence is around 55.3 %; Serdar Olt found that 8.4% of the diabetic patients had insufficient vitamin D levels [5]. On the other hand 89.2% of diabetic patients had insufficient vitamin D levels as demonstrated by Bayani et al [14], in comparison to the Mehta et al study whereby 68% of diabetic patients had insufficient vitamin D levels [8]. As shown by the study there was a significantly low 25(OH) Vitamin D3 level in diabetic patients; this finding is consistent with results from previous studies, as Bayani et al. demonstrated that the mean vitamin D values were significantly lower in diabetic patients as compared to the healthy control group [14]. In the Antalya study it was shown that vitamin D deficiency was detected in around 70.85% of type 2 diabetic patients compared to the level of non-diabetic healthy control subjects [15].

The study revealed that 8% of all diabetic patient had severe 25(OH) vitamin D3 deficiency, 27.6 % were moderately deficient, 19.6 % had insufficient value, this result is slightly lower than the results of Mauss et al who found that 13% of all participants were having a severe deficiency whereas 33% were moderately deficient [11].

Results of several previous studies revealed a non-significant and even an inverse correlation between 25(OH) D3 with HbA1c %levels in diabetic patients. In a cohort study, in patients with T2DM when compared to the control group it was found that there was an inverse relationship between glycosylated hemoglobin levels and 25(OH) D3 levels in. These results imply that 25(OH) D3 levels may exert an effect in the control of glucose in diabetes mellitus type 2 [16 - 17]. Our study has demonstrated a non-significant negative correlation with the fasting blood sugar.

The reported associations between T2DM, and vitamin D deficiency are highlighted earlier moreover, the role of vitamin D in the insulin pathway is still a matter of debate. Based on preclinical studies, vitamin D appears to play an essential regulatory role in calcium influx into β

cells, insulin secretion, and β cell survival. Vitamin D deficiency impairs glucose-mediated insulin secretion in rat pancreatic beta cells, whereas supplementation with vitamin D seems to restore such glucose-stimulated insulin secretion [18 - 19].

As stated above, diabetes was found to be significantly correlated with vitamin D deficiency, which is congruent with other studies. Those studies already had described the mechanisms through which vitamin D can affect the glucose metabolism. The binding of the circulating active form, 1,25(OH)2D, to vitamin D receptor, is expressed in pancreatic β cells [20], furthermore, a vitamin D response element was found to be present in the insulin gene [21], presence of vitamin D receptor in skeletal muscle [22] and the fact that the transcription of insulin receptor genes is increased via 1,25(OH)2D [23], moreover, there is suppression of the renin gene with subsequent reduction in the hyperglycemic induced renin levels increase within the pancreatic β cells .The renin-angiotensin activity blockade has been proposed as a novel target for diabetes treatment [21].

Until further confirmatory causation studies are available, it is recommended that greater global attention be devoted to assessment of vitamin D levels, to reduce the risk for developing T2DM which, in turn, may affect the vitamin D levels. This can act as a guide for practitioners in their treatment and management.

CONCLUSION

In conclusion, the findings of our study suggest that there is a high incidence of vitamin D deficiency in diabetic patients in the Najran area. Vitamin D is inversely correlated with FBS and HbA1c, finally, the uncontrolled diabetes is associated with low level of vitamin D.

Contributors: ABE: Concept and design of the study, data collection, laboratory investigations, statistical analysis and literature search. WGB: Data collection, clinical studies and data acquisition, revision of the manuscript. MIA: Data collection, clinical studies and data, revision of the manuscript acquisition. OEF: Laboratory investigations, revision of the manuscript and literature search.

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