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### RESEARCH ARTICLE

#### VITAMIN D STATUS AND DIABETIC CONTROL: EGYPTIAN MULTICENTER STUDY

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#### Abstract

Vitamin D (Vit D) deficiency may be linked to the development of type 1 and type 2 diabetes mellitus (DM). Specific Vitamin D receptor (VDR) allelic variants have been linked to type-1 diabetes mellitus (T1DM) in many countries. However, in type 2 DM, Vitamin D deficiency leads to impaired insulin action and secretion in both animal models and humans. This study aims to determine the effect of low vitamin D on glycemic control in Egyptian patients with type 1 and type 2 DM.

**Patients and Methods:** This is a retrospective multi-centers study included 280 diabetic patients (140 patients with type 1 DM, and 140 with type 2 DM). The patients' data were collected from the patients' medical files in the Diabetic Clinics and Internal Medicines Departments of 3 University hospitals (Benha, Helwan, and Assiut) in Egypt, including age, sex, BMI, onset and duration of DM, LDL-C, vitamin D, and HbA1c.

**Results:** 50 (35.7%) type 1 diabetic patients had low vitamin D versus 110 (78.6%) type 2 diabetic patients. The study revealed a significant inverse correlation between the serum vitamin D level and HbA1c level in patients with type 1 DM; but, in patients with type 2 DM, there was no significance correlation between serum vitamin D level and HbA1c level.

**Conclusion:** Low serum vitamin D level correlated inversely with the degree glycemic control in type 1 DM; but, such correlation had been failed to prove in patients with type 2 DM. Whether giving vitamin D supplementation to already vitamin D deficient diabetics will help to modulate the disease progression remains a debate.

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#### Introduction:-

With its discovery in 1920, the molecule vitamin D had been recognized as an essential vitamin for calcium homeostasis, mostly in the intestine and bone; then in 1969, the discovery of the nuclear vitamin D receptor (VDR) for 1, 25-dihydroxy vitamin D<sub>3</sub> [1,25 (OH)<sub>2</sub>D<sub>3</sub>] defined the existence of the VDR in over 30 tissue/organs of man(1). Vitamin D (Vit D) deficiency may be linked to the development of diabetes mellitus (DM). In type 1DM, 1,25(OH)<sub>2</sub>D<sub>3</sub> has a role as an immunomodulator in the suppression of the disease, through the VDR found in the antigen presenting cells, the activated T cells (2), and the islet  $\beta$ -cells of the pancreas(3). Certain VDR allelic

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variants have been linked to type 1DM, as well as the variability of vitamin D levels can be partially explained by the variation in the season and latitude (4). Meanwhile, in type 2 DM, vitamin D deficiency leads to diminished secretion of insulin in both animal models and humans. It induces glucose intolerance, type 2 DM (5) and metabolic syndrome (6). Vitamin D is recognized to have anti-inflammatory plus immunomodulatory effects, and might decrease insulin resistance. Moreover, insulin excretion and insulin sensitivity are both calcium dependent mechanisms (7). With this in mind, vitamin D is possible to have a role in type 2 DM and its control (8). Nonetheless, the relationship between serum 25-hydroxy-vitamin-D [25-(OH)-D] and glycemic control in diabetics has not been extensively studied. Previous studies were conflicting regarding this issue. Thus, this study aimed to highlight the effect of vitamin D deficiency on glycemic control in Egyptian patients with diabetes (either type 1 or type 2 diabetes).

### **Patients and Methods:-**

This is a retrospective multi-centers study conducted at Behna, Helwan and Assiut University Hospitals, during the period from December 2018 to August 2019, including 280 diabetic patients, 140 with type 1 DM and 140 with type 2 DM. Following the ethical committee of the Benha, Helwan and Assiut University Hospitals and after obtaining an informed written consent form the patients to obtain their medical data from their files. The available medical data were collected from the patients' medical files, including age, sex, body mass index (BMI), type of diabetes mellitus (DM), onset and duration of DM, lipid profiles, including low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride levels, serum uric acid level, glycosylated hemoglobin (HbA1c) level, serum vitamin-D level. The inclusion criteria for the patients including: fulfilling the medical data required for study, both sexes, patients categorized as type 1 or type 2 DM (based on clinical data, C-peptide level, insulin level, and specific antibodies if available), the duration between the time at which the selected HbA1c level is performed and the time of at which serum vitamin-D is performed should be within 2 weeks (to avoid gradual improvement of low HbA1c with therapy), and compliance of patients regarding dietary instruction and their dietary diabetic treatment. The patients whose data were not fulfilling the required criteria were excluded from the study. Based on the type of DM, the patients were categorized into patients with type-1 DM patients (140 patients) and those with type-2 DM (140 patients). Based on the serum vitamin D levels and according to the American Society of Endocrinology, the patients were categorized into 3 groups: those with sufficient vitamin D level (i.e., vitamin D level of 30-100ng/mL), those with insufficient vitamin D levels (i.e., serum vitamin D level of 21-29 ng/mL), and those with low vitamin D level (i.e., serum vitamin D levels of 20 ng/mL or less) (9).

### **Statistical Analysis:**

The statistical analyses were completed using SPSS (statistical package for social science) version 16. The data were expressed as number, ratio, percentages, means and standard deviation (SD). The correlation between variables were analyzed using Spearman bivariate correlation. P values of less than 0.05 ( $P < 0.05$ ) are considered significant.

### **Result:-**

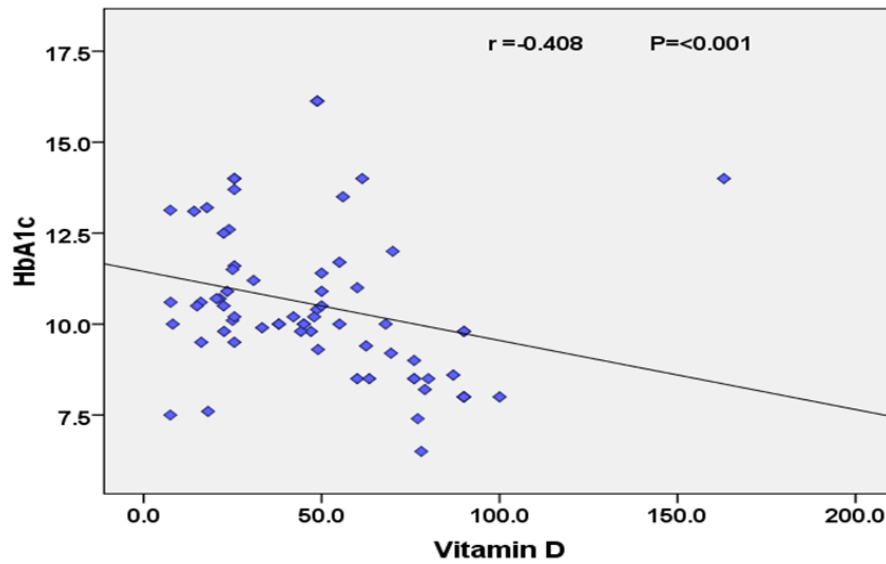
This multicenter study included 280 adult diabetic patients, divided into 140 patients have type 1 DM (group 1) and 140 patients have type 2 DM (group 2). The demographic and laboratory findings of the studied groups were demonstrated in table [1]. In this study, low vitamin D levels were observed in 50 (35.7%) patients with type 1 DM versus 110 (78.6%) patients with type 2 DM. Table 2 showed the features of patients with low vitamin D levels in both type 1 and type 2 DM groups. The correlation between serum vitamin D level and HbA1c in both groups showed a significant inverse correlation between vitamin D level and HbA1c in patients with type 1 DM, but the correlation between serum vitamin D level and HbA1c in patients with type 2 DM was not significant, as shown in figure 1 and figure 2, respectively.

**Table 1:-** Demographic and laboratory findings of the studied patients.

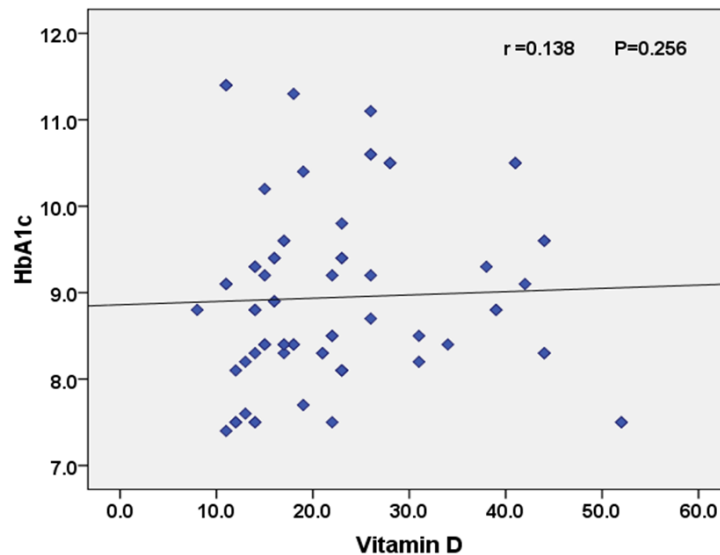
Parameters	Type 1 DM (Number = 140)	Type 2 DM (Number = 140)
Age (years)	18.71±6.64	39.26±8.037
Sex (male/female)	44/96	74/66
Duration of DM (years)	7.23±5.49	17.21±9.47
BMI (kg/m <sup>2</sup> )	23.03±4.46	28.51±3.72
LDL-C (mg/dl)	109.77±35.56	72.90±25.66
HbA1c (%)	10.52±2.14	8.95±1.04
Vitamin D (ng/ml)	48.66±29.13	22.77±11.01
Dyslipidemia (no/yes)	62/78	122/18

**Table 2:-** Characteristic feature of the low vitamin D level diabetic patients.

Variables	Low Vitamin D groups	
	Type 1 DM (Number = 50)	Type 2DM (Number = 110)
Age (years)	18.32±4.89	38.13±7.35
Duration (years)	6.88±3.56	17.82±10.02
Sex (male/female)	24/26	58/52
BMI (kg/m <sup>2</sup> )	23.10±4.10	28.29±3.90
Vitamin D(ng/ml)	19.53±6.39	17.78±5.13
HbA1c (%)	11.12±1.79	8.97±1.08
LDL-C (mg/dl)	106.99±29.58	71.59±27.47
Dyslipidemia (no/yes)	18/32	94/16



**Figure 1:-** Correlation between serum vitamin D level and HbA1c in type 1 DM.



**Figure 2:-** Correlation between serum vitamin D level and HbA1c in type 2 DM.

### Discussion:-

This study appraised the effects of vitamin D deficiency on glycemic control in both type 1 and type 2 DM. It is found that, 35.7% of type 1DM patients have vitamin D deficiency. In the Al-Daghri et al (10) study, the incidence of vitamin D deficiency was 100% in patients with type 1 DM. Another study revealed 63% of type 1 DM was vitamin D deficient (11). Likewise, one study showed the deficiency of Vitamin D was seen in 91.1% of the subjects with T1DM (12). Such variability of the prevalence of deficiency of vitamin D in patients with type 1 DM could be related to the degree and duration of sun exposure, the climate, and the geographical distribution. Similar explanation is reported by Mohr et al. (13) who evaluated the incidence of type 1DM in children younger than 14 years during the period from 1990 to 1994 in 51 areas worldwide; according to their results, the incidence of the disease came near zero in regions with high ultraviolet-B (UV-B) irradiance. Moreover, the seasonal occurrence of type 1 DM at the onset is well known (14). Genetic differences among populations are also one of the reasons responsible for the variability in the incidence of vitamin D deficiency in type 1DM; allelic variations in the VDR genes may affect the immune-modulatory function of the VDR (15). In the current study, a significant negative correlation was revealed between HbA1c and serum vitamin D levels in patients with type 1 DM. Consistent with this results, a study of Elsayed et al., demonstrated a significant inverse correlation between HbA1c and vitamin D ( $r=-0.374$  and  $P=0.003$ ) in type 1 diabetics (16). In contrast, Nwosu et al (17) found a non-significant correlation between 25 (OH) D and HbA1c in patients with type 1 diabetics. Additionally, Nwosu et al (17) found in their later study a statistically significant, but clinically non-significant, increase in HbA1c value following vitamin D supplementation in type 1 diabetics (18). Similarly, Pitocco et al. showed no improvement in C-peptide and HbA1c levels but significantly lower insulin doses in the calcitriol-treated group (19). The study of Aljabri et al. conducted on type 1 diabetics found a significant decrease in HbA1c level following treatment with vitamin D and calcium (20). The explanation of this finding could be the insulin resistance which is found with the onset of type 1 DM and/or the onset of puberty (21). In the present study, type 1 diabetics with a mean age of  $18.71 \pm 6.64$  years were in their pubertal stage. It appears that the type 1 diabetics were affected by a confounder other than vitamin D like hormonal changes during puberty which are associated with insulin resistance. It is also known that vitamin D increases insulin sensitivity by stimulating the expression of insulin receptors and/or by activating peroxisome proliferator activated receptor- $\delta$  (22). So, its deficiency could exacerbate the state of insulin resistance in a subset of patients.

Although, 78.6% of type 2 DM patients in the current design were vitamin D deficient, there was no correlation between glycemic control and vitamin D deficiency in this group. In concordance of Sheth et al. who found no relationship between vitamin D and HbA1c in patients with type 2 DM (8). Another study found, a weak association between HbA1c and vitamin D levels (23). Interventional studies such as SUNNY Trial found that vitamin D supplementation did not improve glycemic control in vitamin D deficient type 2 diabetics (7). A systematic review and meta-analysis of 15 studies concluded that there was inadequate evidence of the beneficial effect of vitamin D supplementation on improving glycemic control or insulin resistance in patients with diabetes (24).

Another key thing to remember is that vitamin D enhances insulin secretion and stimulates  $\beta$ -cell survival by modifying the generation and effects of cytokines, and protect the  $\beta$ -cell against cytokine-induced apoptosis(1). In addition to its indirect actions in insulin secretion, which is a calcium dependent process, low vitamin D status induces secondary hyperparathyroidism which in turn inhibits insulin synthesis(25). But, we could not demonstrate such correlation between the vitamin D deficiency and type 2 DM, and this could be explained according to Luo et al. who stated that the inflammatory processes are extremely initiated by the diabetes or the  $\beta$ -cell dysfunction, and that insulin resistance is more severe and less reversible by the long duration of diabetes (26).

### Conclusion:-

In conclusion, the current study could reveal an inverse negative correlation between low serum vitamin D levels and glycemic control in type 1 DM; but, the study in contrast failed to prove the same relationship regarding to type 2 DM.

Vitamin D status is not the only element responsible for better health of the individuals, but a lifestyle modification, intensification of medications, and dietary changes appear to play a role in improving hemoglobin glycation and insulin resistance. The debate remains on whether giving vitamin D supplementation therapy to the already vitamin D deficient diabetics will help modulate the disease progression or not.

### Limitation of the study:

There were many confounding factors need to be taken into consideration in assessing the relation between serum vitamin D level and HbA1c, including patient's lifestyle, diabetic medication, and genetic background. To obtain a strong evidence for the probable value of vitamin D supplementation as a prevention or therapy for diabetic patients, large prospective trials involving carefully chosen populations and end points are recommended.

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