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Assessing the relationship of vitamin D and Glycosylated haemoglobin to establish better therapeutic guidelines in type 2 diabetes mellitus

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***Abstract*---**Type 2 diabetes mellitus affects millions of people worldwide. It is a disease considered a major public health problem in India. Vitamin D deficiency was found to be more prevalent in India despite having sunny weather. Its deficiency was found to be correlated with glycosylated hemoglobin. We conducted this study in an effort to better understand the relationship between vitamin D and glycosylated hemoglobin in non-obese. A total of 119 type 2 diabetes patients were recruited in this cross-sectional study. Patient details and biochemical parameters were collected. Participants were divided into groups with vitamin D deficiency 25(OH) D <20 ng/ml and without vitamin D deficiency 25(OH) D >20 ng/mL, Further subgrouping was done into male and female-only groups. Next, the subjects were divided into male and female groups according to their 25(OH)D levels. The finding showed a significantly higher level of

HbA1c (8.02±0.35%) in the vitamin D deficiency group compared to (7.32±0.41%) without vitamin D deficiency (p <.001). And it was also true for creatinine (0.94±0.14 vs. 0.82±0.17) (p<.001) HbA1c and fasting plasma glucose both were significant negatively correlated with vitamin D deficient group only (r = - 0.49, p <.001), (r = - 0.40, p = 0.001). Moreover, liner regression model showed predictability of vitamin D deficiency for high HbA1c (p = 0.002) in type 2 diabetes. Our study suggests to maintaining the level of vitamin D is important to improve glycemic control. Hence vitamin D supplementation should be used in type 2 diabetes with vitamin D deficiency regardless of non-obese patients.

***Keywords*---**25 hydroxyvitamin D, fasting plasma glucose, basal metabolic index.

Introduction

There are 77 million individuals living with diabetes in India. Unfortunately, around 57% of these individuals are still undiagnosed, making it difficult for the Indian health care system to prevent and control this disease. Since the type 2 diabetes mellitus (T2DM) burden is growing globally each year, the study of its pathogenesis is ongoing for decades [1]. There are two main pathophysiological defects of T2DM: insulin resistance and beta-cell destruction, which are caused primarily by both genetics and environmental factors. The prevalence of T2DM varies geographically owing to differences in lifestyle and risk factors. Vitamin D deficiency is now being recognized as an increasingly important factor in the pathogenesis of T2DM along with other known environmental factors such as obesity, sedentary lifestyles, high-calorie foods, and stress [2]. A comprehensive meta-analysis reported that vitamin D deficiency is widespread in Indians. The prevalence of vitamin D deficiency was found to be 40 to 99 percent [3]. According to the evidence from various studies, Vitamin D appears to play a role in blood glucose homeostasis and its deficiency may lead to the development of T2DM [4.5]. Vitamin D is implicated in several mechanisms, including that it activates vitamin D receptors on pancreatic -cells and increases insulin sensitivity in tissues [6]. It also protects beta-cell mass from apoptosis by modulating the activity of cytokines [7]. Pittas et al. [8] According to the study, insulin sensitivity increases by 60% when 25-Hydroxyvitamin-D3 levels increase from 25 to 75 nmol/L. Vitamin D enhances insulin secretion by stimulating beta cells or by facilitating the conversion of pro-insulin to insulin [9].

Vitamin D deficiency is still being debated as a factor in T2DM development Likewise, there is no established guideline for vitamin D screening in patients with type 2 diabetes. However, it may influence glycemic control in T2DM. Vitamin D would be a novel strategy for reducing long-term complications of T2DM for patients in the health care system. Currently, very few studies have been conducted in India regarding the association between vitamin D deficiency and diabetes mellitus. We conducted this study to better understand the relationship between vitamin D and glycosylated hemoglobin to prevent further complications due to diabetes and whether vitamin D deficiency is an

independent risk factor for high levels of HbA1c in the non-obese north Indian semi-urban population.

Material and Methods

This cross-sectional observational study was conducted on 119 patients with type 2 diabetes of either sex at the Mayo Institute of Medical Sciences, Barabanki, India. The Institutional Ethics Committee approved this study (MIMS/EX/2020/63). And written informed consent was obtained from all participants before starting the study. Patients were recruited from the Department of General Medicine Outpatient Clinic (OPD) as per the inclusion and exclusion criteria. Patients aged between 30 to 75, with type 2 DM, and those willing to give informed consent were included and those who typed 1 DM, pregnant women, liver, and kidney disease were excluded from the study. We gathered demographic data, including age, gender, height, weight, and duration of disease. 5 ml venous blood was drawn after overnight fasting for estimation of biochemical parameters including HbA1c, 25- hydroxyvitamin D (25(OH) D) Fasting blood sugar, creatinine, blood urea nitrogen, total calcium & postprandial blood sugar were measured as per protocol

Statistical analysis

Statistical software, Jamovi (version 2.0) was used for analysis. An independent t-test was performed to compare all participants with and without vitamin D deficiency including males and females. The relationship between 25(OH) D and HbA1c was determined by linear correlation analysis. A linear regression analysis was used to determine the effect of 25(OH) D levels on HbA1c if the correlation was confirmed significantly. A < 0.05 significance level was used as a cut-off point.

Result

A total of 119 participants mean age 52.85 ±8.78 years were included in the study. Of which 69 (58%) and 50 (42%) were male and female respectively. where HbA1c was found to be (7.67±0.52). Basal metabolic index (BMI) was (24.25±2.32) kg/m^2 in the total population of the study (Table no. 01).

Table 1
Demographic and biochemical characteristics of the population. (n = 119)

S. No.	Variables	(Percentage%)and mean±SD
1.	Duration of diabetes-1-2 (years) 3-5 (years)	33 (27%) participants 87 (73%) participants
2.	Age	52.85 ±8.78
3.	Gender – male female	69 (58%) 50 (42%)
4.	BMI (Kg/m^2)	24.25±2.32
5.	HbA1c (%)	7.67±0.52
6.	Fasting plasma glucose (mg/dl)	147.17±9.12
7.	Postprandial plasma glucose (mg/dl)	247±9.15

8.	Blood urea nitrogen (mg/dl)	9.81±0.84
9.	Serum creatinine (mg/dl)	0.88± 0.16

The mean HbA1c was compared in all participants with and without vitamin D deficiency, we found significantly higher HbA1c (8.02±0.35%) in the group with vitamin D deficiency, and in the group without vitamin D deficiency, it was (7.35 ±0.45%) (p <.001) (Figure no. 1(a), 1(b), 1(c).

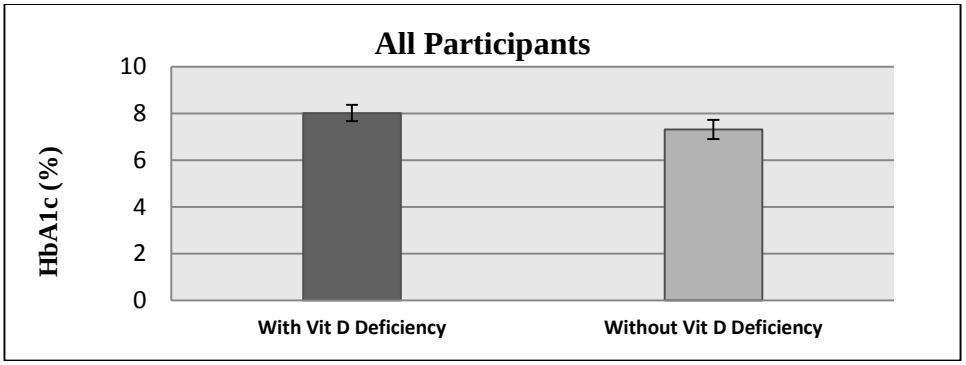
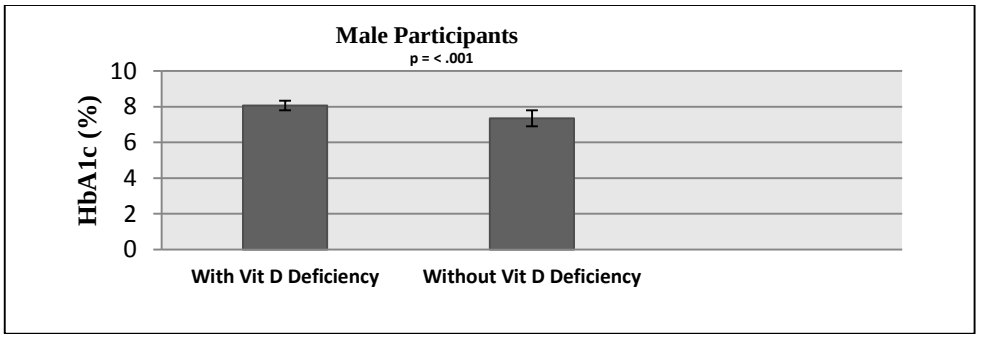


Figure 1. (a)



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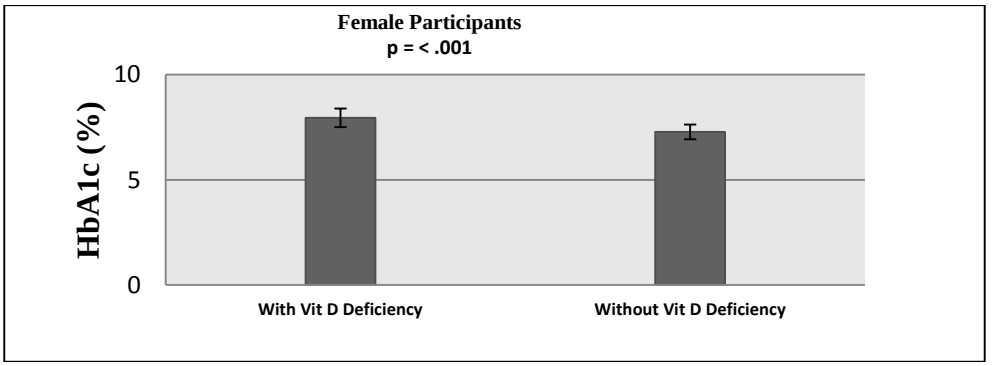

Figure 1. (c)

Figure1. (a) Comparisons of glycated haemoglobin levels among participants in type 2 diabetes mellitus with and without vitamin D deficiency. Figure no. 1(b) Comparisons of glycated haemoglobin levels in male type 2 diabetes mellitus with and without vitamin D deficiency. Figure no.1(c) Comparisons of glycated

haemoglobin levels in female type 2 diabetes mellitus with and without vitamin D deficiency

There was no difference in the BMI in all participants with and without vitamin D deficiency (p = 0.179). Total calcium (8.85±0.70) vs. (9.58±0.49) significantly decrease in the vitamin D deficiency group than in the no vitamin D deficiency group (p <.001). Fasting plasma glucose was significantly higher (150.56±10.60 vs. 143.84±5.75) (p <.001) in the vitamin D deficient group in comparison to the without vitamin D deficient group. And it was also true for creatinine (0.94±0.14 vs. 0.82±0.17) (p<.001) (Table 2).

Table 2
Clinical Characteristics of Studyparticipants with and without vitamin D Deficiency

Variables	All Participants			Male participant			Female participants		
	Without Vitamin D Deficiency	With Vit D Deficien	P-value	Without Vitamin D Deficiency	With Vitamin D Deficiency	P-value	Without Vitamin D Deficiency	With Vit D deficiency	P-value
n = 119	60	59		35	34		25	25	
BMI(kg/m^2)	23.57± 2.03	24.54±	0.164	24.15±1.81	25.04±2.26	0.077	23.72±2.32	23.88±2.84	0.831
TCa(mg/dl)	9.58±0.49	8.85±0.	<.001	9.65±0.48	9.13±0.61	<.001	9.49±0.50	8.46±0.63	<.001
PPG(mg/dl)	245.31±4.74	248.88±	0.033	246.31±5.26	249.85±11.44	0.102	243.91±3.55	247.57±12.55	0.167
FPG (mg/dl)	143.84±5.75	150.56±	<.001	146.03±4.47	152.16±10.36	0.002	140.75±6.00	148.04±10.75	0.003
Cr (mg/dl)	0.82±0.17	0.86±0.	<.001	0.82±0.14	0.94±0.13	0.953	0.81±0.15	0.93±0.15	0.037
BUN(mg/dl)	9.52±0.91	9.53±1.	0.055	9.56±0.95	9.25±1.78	0.363	9.46±0.87	9.78±0.70	0.119

Abbreviations: BMI, body mass index; T Ca, total calcium; PPBS, postprandial glucose; FBS, fasting plasma glucose; Cr, creatinine; BUN, blood urea nitrogen

It was interesting that HbA1c level remained significantly higher both in male and female with vitamin D deficient group than without vitamin D deficient (8.07±027% vs. 7.35±0.45%) (p <.001), (7.95±0.44% vs. 7.28±0.35%) (p <.001) respectively, and it was also true for fasting plasma glucose level (152.16±10.36 vs. 146.03±4.47) (p = 0.002) (148.04±10.75, 140.75±6.00) (p = 0.003) (Figure 1 B, C, Table 2). But creatinine is seen as significantly higher only in the female vitamin D deficient group than without vitamin D deficient (0.91±0.17 vs. 0.85±0.19) (p = 0.04) Table 2. As we categorized both groups into gender, there was no significant difference in the mean vitamin D levels between males and females in the vitamin D deficiency group (p = 0.705). It was true for both males and females without the Vitamin D deficiency group (p = 0.069). Other variables are shown in Table 3.

Table 3
Clinical characteristics of patients with T2DM according to their sex category

S. No.	Variables	With VitaminD Deficiency 25(OH)D<20ng/mL			Without VitaminDDeficiency25(OH)D >20ng/mL		
		Male	Female	P-value	Male	Female	P-value
1.	Vitamin D (ng/ml)	14.02±2.89	13.75±2.29	0.705	27.07±3.18	25.67±2.39	0.069
2.	BMI (kg/m2)	25.04±2.26	23.88±2.84	0.087	24.15±1.81	23.72±2.32	0.422
3.	Total Ca(mg/ml)	9.13±0.61	8.46±0.63	<.001	9.65±0.48	9.49±0.50	0.243
4.	HbA1c (%)	8.08±0.27	7.95±0.44	0.188	7.35±0.45	7.28±0.35	0.481
5.	PPG (mg/dl)	249.85±11.44	247.57±12.55	0.471	246.34±7.72	243.91±3.55	0.148
6.	FPG (mg/dl)	152.16±10.36	148.40±10.75	0.181	146.03±4.47	140.75±6.00	<.001
7.	Cr.(mg/dl)	0.94±0.13	0.93±0.15	0.736	0.80±0.15	0.85±0.19	0.280
8.	BUN (mg/dl)	10.10±0.80	9.78±0.70	0.128	9.59±0.98	9.78±0.72	0.405

Abbreviations: BMI, body mass index; T Ca, total calcium; PPBS, postprandial Glucose; FBS, fasting plasma glucose; Cr, creatinine; BUN, blood urea nitrogen

As we compared HbA1c between participants with and without vitamin D deficiency, we found it significantly negatively correlated with the vitamin D deficiency group only (r = - 0.49, p <.001). But high HbA1c was not significantly associated in the participants without the vitamin D deficiency group (r = - 0.16, p = 0.212) (Figure 2 A, B).

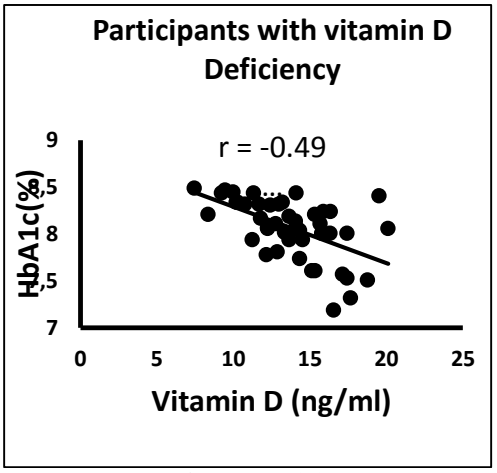

Figure 2. (a)

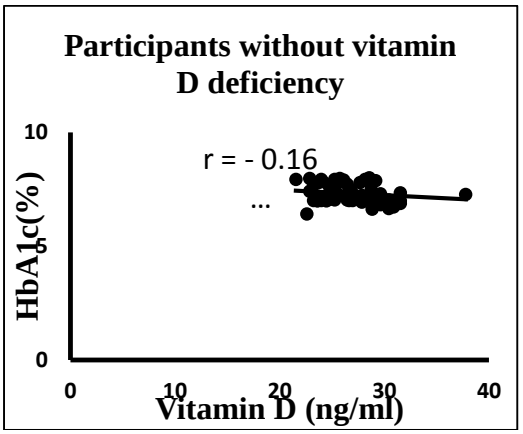

Figure 2. (b)

Figure 2. (a): Correlation of glycated haemoglobin levels in type 2 diabetes mellitus patients with vitamin D deficiency. 2(b) Correlation of glycated haemoglobin levels in type 2 diabetes mellitus patients without vitamin D deficiency

Higher fasting plasma glucose was significantly associated with a lower level of vitamin D in all participants (r = - 0.40, p = 0.001) but this association was not significant in the participants' higher levels of vitamin D (r = - 0.12, p = 0.35) (Figure 3 A, B).

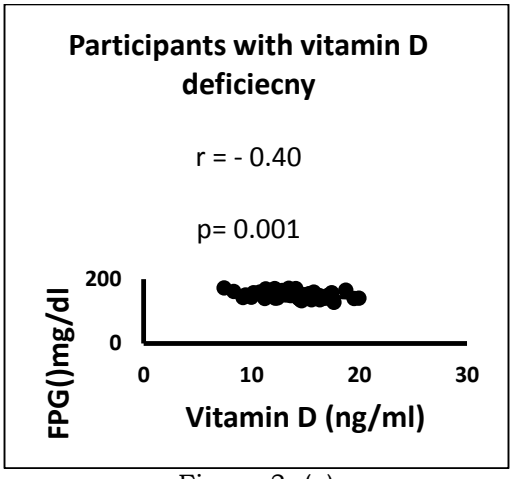

Figure 3. (a)

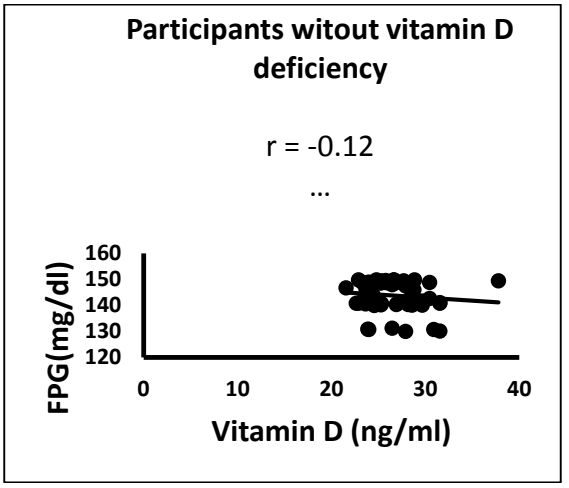

Figure 3. (b)

Figure 3. (a) Correlation of fasting Plasma glucose levels in type 2 diabetes mellitus patients with vitamin D deficiency. 3(b) Correlation of fasting plasma glucose levels in type 2 diabetes mellitus patients without vitamin D deficiency

The linear regression model was performed to access the predictability of vitamin D in the participants in the vitamin D deficiency group, it was seen that high HbA1c significantly ($p = 0.002$) was associated with vitamin D deficiency in the participants after adjusting for BMI, T Ca, PPPG, FPG, BUN, and creatinine (Table 4).

Table 4
Linear Regression Model with Vitamin D Deficiency for HbA1c in Type 2 DM Patients

S. No.	Variables	B	SE	β (Beta)	t	P-value
1.	Vitamin D	-0.062	0.019	-0.464	-3.178	0.003
2.	BMI	0.004	0.017	0.035	0.289	0.777
3.	TCa	0.059	0.066	0.011	0.884	0.383
4.	PPG	0.007	0.003	0.246	1.990	0.052
5.	FPG	0.002	0.004	0.067	0.532	0.539
6.	Cr	-0.307	0.298	-0.124	-1.032	0.308
7.	BUN	-0.048	0.054	0.106	0.888	0.382

Abbreviations: BMI, body mass index; T Ca, total calcium; PPBS, postprandial plasma glucose; FBP, fasting plasma glucose; Cr, creatinine; BUN, blood urea nitrogen

Discussion

Type 2 diabetes is challenging for health care providers as the burden of this disease growing not only in India even in other countries despite having standard treatment. The most well-known lipoprotein hormone with metabolic properties is

vitamin D, which plays a vital role in calcium and phosphorus balance, bone metabolism, and skeletal development [10]. Vitamin D and the immune system are being discussed in great detail and earlier research has shown that it can increase immunity [11]. Recently, research has drawn considerable attention to the relationship between Vitamin D levels and insulin sensitivity, and glucose metabolism, including glycemic control. [12,13]. Vitamin D deficiency is more prevalent in the Indian scenario even with ample sunlight exposure throughout the year, because vitamin D and diabetes are prevalent in India, it is extremely important to explore their relationship [3]. In addition to the bone system, 1,25-dihydroxyvitamin D3 and 1-Alpha-Hydroxylase expression in beta cells of the pancreas significantly contribute to type 2 diabetes pathogenesis [14]. Impaired insulin production, insulin resistance, and systemic inflammation are all key factors in T2DM pathogenesis.[15]. One of the studies reported that vitamin D reduces inflammatory responses by inhibiting the production of cytokines, which contributes to suppressing chronic inflammation in type 2 diabetes [16]. One of the studies described, that it reduces insulin resistance when vitamin D increases the expression of the human insulin receptor gene, which codes for the production of an insulin-binding protein. [17].

In the present study, we observed higher HbA1c levels in all participants with vitamin D deficiency than in a group without vitamin D deficiency in type 2 diabetes mellitus patients. The same is reported by Anyanwu AC et al. in their finding [18]. The same held true for both groups of male and female patients, which is inconsistent with Li Z et al. [19], who find higher HbA1c only in female patients with vitamin D deficiency. Previous studies have found that BMI is associated with vitamin D deficiency [20,21]. Conversely, in our study, BMI was the same in both groups with and without vitamin D deficiency. This could be due to less sample size or because vitamin D deficiency is more prevalent in India regardless of BMI.

Further, as we compared within the group with and without vitamin D deficiency our result showed significantly higher fasting plasma glucose in males without vitamin D deficiency group than that of females. but this difference was insignificant in the vitamin D deficiency group both in males and females. Tran Huu TT et al. [22]. showed in their study individuals with no vitamin D deficiency had lower fasting blood glucose, similar to our study Fasting plasma glucose was found to be lower in all participants without the vitamin D deficiency group. Also, a significant difference was found in the Post-prandial plasma glucose in all study participants with and without vitamin D deficiency. Also, glycosylated hemoglobin levels and vitamin D levels exhibit a significant an inverse relationship with the vitamin D deficiency group only, but we could not establish a significant correlation among participants having no vitamin D deficiency, which implies the vitamin D level may have an impact on glucose control in type 2 diabetes mellitus and this is supported by Juhi A et al, M Yaseen M et al showed an inverse relationship between HbA1c and vitamin D [23,24].

In contrast, other studies have not established a link between HbA1c and vitamin D deficiency. [25,26]. it may be due to genetic variation and/or used other techniques in the study or it may be due to differences in the vitamin D level [27]. Additionally, fasting blood glucose was found to be significantly negatively

correlated with vitamin D deficiency, The results are consistent with previous literature [28,29,18]. Interestingly, in the current study after adjusting BMI, T Ca, FPG, PPPG. Cr, BUN vitamin D significantly affects HbA1c only in participants with the vitamin D deficiency group, which means vitamin D deficiency will remain the only significant predictor for high HbA1c in type 2 diabetes.

Conclusion

From the present finding HbA1c and fasting plasma glucose levels are increased in patients with T2DM who are Vitamin D deficient. HbA1c and Fasting blood glucose both are negatively correlated with vitamin D deficiency. It's important to maintain vitamin D levels to improve glycemic control. Hence vitamin D supplementation should be used in type 2 diabetes with vitamin D deficiency regardless of non-obese patients.

Conflicts of Interest

No conflicts of interest

Acknowledgment

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