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Evaluation of vitamin D status and its correlation with glycated haemoglobin in type 2 diabetes mellitus.

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Abstract

Background: The role of Vitamin D in various non-skeletal disorders including Diabetes Mellitus has been explored. The role of Vitamin D in peripheral utilization of glucose has been studied.
Aim: This study evaluates the correlation between Vitamin D status and Glycated Haemoglobin in Type 2 Diabetes Mellitus.
Subject and methods: The present study was a retrospective case control study with 78 cases and 69 controls. Mann-Whitney Test was used to study difference in Vitamin D levels between cases and controls. Spearman correlation was used to study the correlation between Vitamin D levels and Glycated Haemoglobin in cases of Type 2 Diabetes Mellitus.
Results: The mean Vitamin D values in cases were 16.1 ng/ml and mean Vitamin D values in controls were 17.3 ng/ml. Though the mean values of Vitamin D in cases were lower than that of controls, the difference was not statistically significant (p=0.31). Vitamin D insufficiency was observed in both cases and controls. Spearman correlation showed there was no statistically significant correlation between Vitamin D levels and Glycated haemoglobin (p value 0.741) in cases of Type 2 Diabetes Mellitus.
Conclusion: Hypovitaminosis D and its correlation with Glycaemic control could not be established.

Keywords: Vitamin D, Diabetes mellitus, Glycated haemoglobin, Glycaemic control.

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Introduction

Type 2 Diabetes Mellitus is a major health concern globally. The total number of Diabetics is expected to reach 366 million by 2030 [1]. In spite of innovative methods in the management of Diabetes Mellitus, the morbidity and mortality continues to be high [2]. Efforts should also be made in preventing Diabetes Mellitus. Vitamin D supplementation to prevent Diabetes Mellitus has been explored [3]. The primary source of Vitamin D is exposure to sunlight which results in the formation of Cholecalciferol in the skin [4]. The epidemiology of Diabetes Mellitus and Vitamin D deficiency is related. The incidence of Diabetes Mellitus is higher in ethnic groups who are more prone for Vitamin D deficiency and Diabetes Mellitus is more common in older age group where in the chances of Vitamin D deficiency increases [5]. Diabetes Mellitus, psoriasis, cancer, multiple sclerosis, cardiovascular diseases and metabolic syndrome are some of the non-skeletal diseases where in Vitamin D deficiency has been implicated to play a role [4,6-10]. Many studies indicate, calcium and Vitamin D homeostasis may play a role in development of Diabetes Mellitus [11]. There are various mechanisms proposed to relate the role of Vitamin D with the development of Diabetes Mellitus. Some of these mechanisms include Expression of Vitamin D receptors in the beta cells of Pancreas, location of Vitamin D response element in human insulin gene, role of Vitamin D in maintenance of normal calcium homeostasis which plays a major role in insulin secretion, Presence of Vitamin D receptor in skeletal muscle, improvement of insulin mediated glucose utilization following Vitamin D therapy, role of cytokines like Interleukin 6 and Tumour Necrosis factor alpha (TNF alpha) in causing insulin resistance and down regulation of cytokine production by Vitamin D [11-14]. The benefits of Vitamin D supplementation in Type 1 Diabetes Mellitus has been widely accepted [15,16]. The role of Vitamin D in Type 2 Diabetes Mellitus is not yet established. There are very few studies in India on correlation between Vitamin D status and glycaemic control in type 2 Diabetes Mellitus. Hence the present study was taken up.

Materials and Methods

The present study was a retrospective case control study with 78 cases and 69 controls. The study was approved by the

institute ethics committee (Reference Number: IEC:RC/14/124). The clinical features and laboratory investigations (Vitamin D levels, Fasting Blood glucose (FBG), Post prandial blood glucose (PPBG), Glycated haemoglobin (HBA1C)) values were collected from the patient's records.

Cases

Inclusion criteria: Age group: 30 to 70 years, Diagnosed cases of Type 2 Diabetes mellitus based on American Diabetes Association (ADA) criteria: HBA1C values ≥ 6.5% OR Fasting blood glucose ≥ 126 mg/dl or Two hour post glucose ≥ 200 mg/dl OR Patients with classical symptoms of diabetes (polyuria, polydipsia and polyphagia) with a random plasma glucose of ≥ 200 mg/dl.

Exclusion criteria: Patients with Type 1 Diabetes Mellitus, Pancreatic disease, Hepatic disease, Renal disease, Bone diseases, Malignancy and any history of use of drugs such as insulin, calcium and vitamin D were excluded from the study.

Controls

Individuals with blood sugar within normal limits were included as controls. Age and gender matched controls were selected for the study. Subjects with Pancreatic disease, Hepatic disease, renal disease, bone disease, malignancy and any history of use of drugs such as calcium and vitamin D were excluded from the study.

Methods

Blood glucose was estimated by Hexokinase method in cobas integra 400 plus from Roche diagnostics, Glycated haemoglobin was measured by immunoturbidimetric method in microlab 300 from merck, 25 hydroxy Vitamin D was measured in cobas e411 by electrochemiluminescence (ECLIA) method.

Statistical methods: Data were entered into Microsoft Office Excel 2007. Categorical data were reported as frequency and continuous data were reported as mean and standard deviation. Mann-Whitney Test was used to test the difference between Vitamin D levels between cases and controls. The level of significance was taken as $p<0.05$. Spearman correlation was used to study the correlation between Vitamin D levels and Glycated haemoglobin in cases of Type 2 Diabetes Mellitus.

Results

Out of 78 cases, 33 were males and 45 were females. Out of 69 controls, 33 were males and 36 were females. The mean age of cases and controls were 48.5 ± 11.9 and 44.0 ± 10.5, respectively. Vitamin D insufficiency was observed in both cases and controls (Table 1). The mean Vitamin D values in cases were 16.1 ± 13.8 ng/ml and mean Vitamin D values in controls were 17.3 ± 12.3 ng/ml (Table 2). Though the mean values of Vitamin D in cases were lower than that of controls, Mann-Whitney Test shows there is no statistical difference in Vitamin D levels between cases and controls as shown in Table 2 and Figure 1.

Table 1. *Distribution of Vitamin D levels in cases and controls.*

Vitamin D levels (in ng/ml)	Cases (n=78)		Controls (n=69)	
	Number	Percentage	Number	Percentage
Deficiency (<6)	25	32.1	17	24.6
Insufficiency (6 to 20)	27	34.6	30	43.4
Sufficiency (21 to 100)	26	33.3	22	31.9

Table 2. *Vitamin D levels (Mean, SD, and Standard error of Mean) in cases and controls.*

Status	Number	Mean Vitamin D levels (ng/ml)	Standard Deviation	Standard error of Mean	p value
Cases	78	16.1	13.8	1.6	0.31
Controls	69	17.3	12.3	1.5	

Spearman correlation showed a negative negligible correlation between Vitamin D levels and HBA1C, which was not statistically significant. Correlation coefficient was found to be 0.003 (p value 0.741) (Table 3).

Table 3. *Vitamin D values in relation with HBA1C levels.*

25 hydroxy Vitamin D	HBA1C < 8 g%	HBA1C >8 g%	Total
Deficiency	15	10	25
Insufficiency	15	12	27
Sufficiency	16	10	26
Total	46	32	78

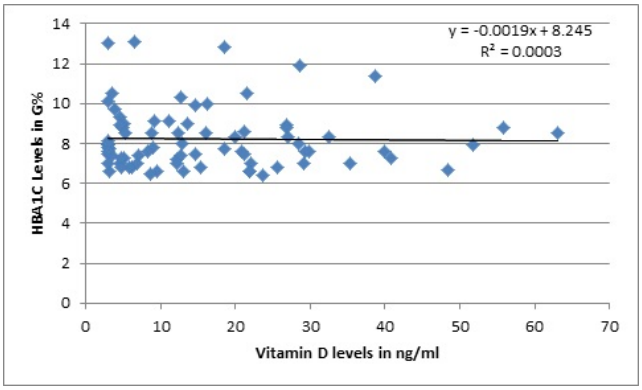

Figure 1. *Scatter plot indicating negative negligible correlation between HBA1C levels with Vitamin D levels (r^2=0.003, r=-0.017).*

Discussion

In the present study, Vitamin D deficiency was observed in 32% of cases and 25% of controls. Sheth et al. observed

Vitamin D deficiency in 91.4% of cases of Type 2 Diabetes Mellitus and 93% in the control group. Sheth et al. could not establish any association between Vitamin D deficiency and Glycated haemoglobin which is in agreement with the findings of the present study [17]. In a study done by Athanassiou et al. Vitamin D values were found to be 19.26 ± 0.95 ng/ml in type 2 Diabetes mellitus cases which were in the insufficiency range. The findings of Athanassiou et al. are in agreement with the findings of the present study since the Vitamin D levels of the present study were also in the insufficiency range. In their study, they observed an inverse relationship between Vitamin D levels and Glycated haemoglobin which could not be established in the present study [18]. Three cohort studies observed lower incidence of Diabetes Mellitus in individuals with high Vitamin D levels [19]. Alhumaidi et al. observed low Vitamin D levels in both cases of Type 2 Diabetes Mellitus and controls which were comparable to the findings of the present study. They observed low Vitamin D levels in 98.5% of the study population (including cases and controls) [20].

In the present study, low Vitamin D levels were observed in 66.5% of the study population (including cases and controls). Anderson et al. observed high prevalence of Diabetes Mellitus in individuals with severe Vitamin D deficiency [21]. Dalgard et al. observed deficiency of Vitamin D doubled the risk of development of type 2 Diabetes Mellitus. They also observed an independent association between increase in HBA1C with decrease in Vitamin D levels [22]. Mauss et al. observed severe Vitamin D deficiency was associated with high fasting blood sugar and type 2 Diabetes Mellitus in older working adults [23]. Chiamolera et al. observed a 25 hydroxy Vitamin D of 23.4 ± 8.3 ng/ml in patients with type 2 Diabetes mellitus which was higher than the results of the present study [24]. Lakshmi et al. observed a mean 25 hydroxy Vitamin D values of 16.34 ng/ml in cases. The findings of Lakshmi et al. is in close agreement with the 25 hydoxy Vitamin D levels of the present study which was 16.07 ng/ml. Lakshmi et al. observed a significant difference between 25 hydroxy Vitamin D levels between cases and controls which was not observed in the present study [25].

In the present study, we observed Vitamin D deficiency in 38% of Female Diabetics and 25% of Male Diabetics. Al-Zaharani M observed Vitamin D deficiency in 73.6% of Female Diabetics and 46.9% of Male Diabetics [26]. Ahmadieh et al. observed a negative correlation between 25 hydroxy Vitamin D and HBA1C which was not in agreement with findings of the present study as in the present study, correlation between 25 hydroxy Vitamin D and HBA1C could not be established [27]. Ahbab et al. observed 25 hydroxy Vitamin D levels of 22.38 ± 6.45 ng/ml in total patients with type 2 Diabetes Mellitus, 20.64 ± 6.14 ng/ml in female diabetics and 24.91 ± 6.04 ng/ml in male Diabetics [28]. Kadi observed low 25 hydroxy Vitamin D levels in 83% of Type 2 Diabetes Mellitus cases and 76% of control group and there was no statistical difference in 25 hyroxy Vitamin D levels between cases and controls [29]. In the present study, low 25 hydroxy Vitamin D levels were observed in 67% of cases and 68% of controls.

The finding of the present study was comparable with the findings of Kadi as statistical difference in 25 hydroxy Vitamin D between cases and controls could not be established. Cimbek et al. observed low Vitamin D levels in both cases of Type 2 Diabetes Mellitus and controls [30]. Krul-Poel et al. observed Vitamin D deficiency in 38% of Type 2 Diabetes Mellitus patients and there was no statistical significant difference in HBA1C levels between Type 2 Diabetes Mellitus patients with Vitamin D deficiency and Type 2 Diabetes Mellitus patients without Vitamin D deficiency [31]. Doddamani et al. observed Vitamin D deficiency in 70% of cases of newly diagnosed type 2 Diabetes Mellitus cases. They also observed an inverse relationship between HBA1C and Vitamin D levels [32]. Brijesh et al. observed 25 hydroxy Vitamin D levels of 23.63 ± 3.71 ng/ml in patients with Type 2 Diabetes Mellitus with HBA1C levels less than 7 g% and 25 hydroxy Vitamin D levels of 19.41 ± 4.76 ng/ml in patients with Type 2 Diabetes Mellitus with HBA1C levels more than 7 g%.

They also observed a negative correlation between 25 hydroxy Vitamin D levels and HBA1C levels in Type 2 Diabetes Mellitus patients [33]. Shanti et al. observed 25 hydroxy Vitamin D levels to be in the insufficiency range (18.492 ± 3.49 ng/ml) in cases of Type 2 Diabetes Mellitus which was in agreement with the findings of the present study. They also observed a negative correlation between 25 hydroxy Vitamin D levels and HBA1C which was not statistically significant [34]. Taheri et al. observed Vitamin D deficiency in 26.3% of type 2 Diabetes Mellitus cases and 18.6% of healthy controls [35]. Mohapatra et al. observed a 25 hydroxy Vitamin D level of 19.94 ± 2.41 ng/ml in cases of Type 2 Diabetes Mellitus which is in agreement with 25 hydroxy Vitamin D levels of the present study since its in the insufficiency range. They observed a statistically significant negative correlation between 25 hyroxy Vitamin D levels and HBA1C [36]. Kotwal et al. observed 81% of patients with type 2 Diabetes Mellitus had either Vitamin D deficiency or Vitamin D insufficiency in comparison to 67% of controls. They also observed a significant negative correlation between 25 hydroxy Vitamin D levels with HBA1C [37]. Mangukiya et al. observed 25 hydroxy Vitamin D levels to be in the insufficiency range (18.492 ± 3.49 ng/ml) which was in agreement with the findings of the present study. They also observed a negative association between 25 hydroxy Vitamin D and HBA1C which was not statistically significant [38]. Saha et al. observed significantly lower Vitamin D 3 levels in patients with type 2 Diabetes Mellitus in comparison to healthy controls [39]. Kandi et al. observed significantly lower Vitamin D levels in cases of Type 2 Diabetes Mellitus in comparison to healthy controls [40].

Sadiya et al. conducted a randomized controlled clinical trial on Vitamin D deficient obese type 2 Diabetes Mellitus group and observed no improvement in metabolic control in these patients on Vitamin D supplementation. In their study, they also observed high C reactive protein in most of their subjects which supports the inflammatory process in the pathogenesis of Type 2 Diabetes Mellitus [41]. Cangoz et al. stated administration of Vitamin D for management of Type 2

Diabetes Mellitus is not evidence based [42]. Sabherwal et al. observed a significant decrease in HBA1C levels in south Asian type 2 Diabetes Mellitus patients after Vitamin D administration which indicates a role of Vitamin D in glycaemic control [43]. Nikooyeh et al. observed improvement in glycaemic control (decrease in HBA1C) after Vitamin D administration in Type 2 Diabetic patients. They also concluded daily intake of Vitamin D with or without calcium will result in improvement of glycaemic control [44]. Yiu et al. observed there was no significant change in HBA1C after Vitamin D supplementation in Type 2 Diabetes Mellitus patients [45].

Limitation of the study

Since the study was a retrospective study, the confounding factors for Vitamin D levels like duration of sun exposure and complexion of the skin could not be evaluated in the subjects.

Conclusion

Hypovitaminosis D and its inverse association with Glycated Haemoglobin in type 2 Diabetes Mellitus have been established in many studies. Such a finding could not be demonstrated in the present study which could be due to low sample size.

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