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Original Research

Association between glycated hemoglobin and vitamin D levels in type 2 diabetes mellitus

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Abstract

Background and Aims: Type 2 diabetes mellitus (T2DM) is one of the most common chronic disorders, affecting millions of people around the world. Vitamin D may enhance secretion of insulin from the beta cells of pancreas, increase glucose uptake by the peripheries and decrease systemic inflammation. Hence the study aims to find out the role of vitamin D deficiency in pathogenesis of diabetes mellitus. **Materials and Methods:** A total of 52 T2DM patients were included in the study. The mean level of vitamin D and glycated hemoglobin (HbA_{1c}) were assessed. Fundoscopic evidence was collected to look for evidence of diabetic retinopathy. For that routine urine check was done to look for evidence of proteinuria, which indicating diabetic nephropathy. Statistical analysis was done using SPSS software. **Conclusion:** Our study indicated that there is an inverse relationship between HbA_{1c} and serum vitamin D levels in diabetics. There is increase in the microvascular complications of T2DM with decrease in vitamin D levels.

Keywords: glycated hemoglobin, microvascular complications, type 2 diabetes mellitus, vitamin D

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common chronic disorders, affecting millions of people around the world [1]. It is more common in the developed and developing world owing to obesity, sedentary lifestyle and multiple co-morbidities. Various epidemiological studies suggest individuals with T2DM being asymptomatic, unaware of the symptoms for up to a decade or present with one or more complications of diabetes to health care facilities before a diagnosis of diabetes is made. The most common complications are associated with micro and macro vascular blood vessels, which impair the quality of life significantly, and also increase mortality. Glycated hemoglobin (HbA_{1c}) portrays the high glucose levels led to vascular complications. Challenges were faced to track day-to-day variation in the glucose level and henceforth the control of diabetes. Therefore, HbA_{1c} is a more reliable indicator of the glycemic status over the last 60–90 days. Hemoglobin (Hb) consists of two globin chains attached to a heme molecule. Majority of adult Hb is comprised predominantly of HbA subtype, with small amounts of HbA2 and HbF. HbA is composed of components: A_0, A_{1a}, A_{1b}, and A_{1c}. A_{1c} is the component with majority of glycation [2, 3]. The RBC membrane is very permeable and intracellular glucose rises in hyperglycemia. Non-enzymatic glycation of the N-terminal valine leads to glycation of HbA_{1c}, which is most commonly affected by age, environment, genetic, hematologic and

illness-related factors. This genetic variation is known as "glycation gap".

Vitamin D (calciferol) deficiency has taken a resurgence all around the world in the recent years among the other four fat soluble vitamins (A, D, E, K) [4–6]. Vitamin D is an important micronutrient with hormone like action, which is vital for bone mineralization and calcium and phosphorous metabolism. However, there is a lot of recent evidence in various studies portraying its effects in several disorders like cancer, cardiovascular and respiratory illnesses, autoimmune diseases and infections [4, 5]. Vitamin D may enhance secretion of insulin (an anabolic hormone) from the beta cells of pancreas. Increased glucose uptake by the liver in a chronic setting leads to dysfunction of the beta cells of pancreas and the vicious cycle continues, which eventually decrease the insulin receptor auto-phosphorylation and increase the reactive oxygen species (ROS), all these augmenting the insulin resistance (IR). Vitamin D has been found to play a role in T2DM through altering the mechanisms such as IR, beta cell dysfunction and chronic inflammation (these are the hallmarks of T2DM) [7–12]. Henceforth, vitamin D deficiency has found to have a vital role in pathogenesis of diabetes mellitus [13]. Majority of patients with T2DM may have lower serum vitamin D levels [7–9]. Many studies have shown an inverse relationship between vitamin D levels and glycemic control [10, 14–16]. Also, the presence of microvascular complications has been found to be inversely related to vitamin D levels [17–21]. The purposes of this study were to assess the association between glycated hemoglobin and vitamin D levels in T2DM, and also to determine whether there is any association of the microvascular complications with change in HbA_{1c} and vitamin D levels.

Material and Methods

Study design and patients

This is a clinical, prospective and observational study of patients with T2DM. This study was approved by the Institutional Ethical Committee of NITTE (Deemed to be University). Based on inclusion criteria – patients diagnosed as T2DM, symptoms of diabetes plus RBS≥200 mg/dL or FBS≥126 mg/dL or HbA_{1c} ≥6.5% or 2 hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test, consulting patients; exclusion criteria – patients likely to have vitamin D deficiencies like rickets, osteomalacia, malabsorption, chronic renal failure, cirrhosis of liver, non-consulting patients. The study was conducted in patients with T2DM at the Justice K. S. Hegde charitable hospital, NITTE (Deemed to be university), Deralakatte, Mangalore. A total of 52 study subjects were included in the study.

Laboratory, anthropometric and clinical data collection

All necessary blood tests including HbA_{1c} levels and serum vitamin D level were measured. Fundoscopic evidence was collected to look for evidence of diabetic retinopathy. For that routine urine check was done to look for evidence of proteinuria, which indicating diabetic nephropathy. The sample size and the technique of estimation of proportion was calculated using the below formula.

$$n = \frac{Z^2_{1-\alpha/2} P(1-P)}{d2}$$

Where, α – Level of significance
d – Precision
P – Anticipated Proportion

Statistical analysis

Statistical analysis was performed using SPSS 15.0 and Epiinfo 6 software packages. Frequency tables, pie charts or bar charts were used to display percentage for categorized variables and continuous variables will be shown as mean±SD and error bar charts. To test the significance of association between categorized variables, Chi square test, Mann–Whitney test and ANOVA test were used. p≤0.05 was considered as significant.

Results

A total of 52 patients were included in the study. Of these majority of the patients (31%) were in the age group of 30–40 years, 27% of the patients belonging to 51–60 year age group, 17% belongs to the age group of 61–70 years, 15% were in the age group of 41–50 years followed by 10% in the age group above 70 years (Figure 1). Among them 54% were female and 46% were male. The study found only 6% patients were seen to have normal vitamin D level, where as 94% of the subjects were seen to have low level of vitamin D. Majority of the study subjects had good (40%) and moderate (35%) glycemic control whereas, 25% of them had poor prognosis of glycemic control. The present study also investigates the presence and absence of microvascular complications such as diabetic retinopathy, nephropathy and neuropathy in the 52 study subjects. Among them, 38% of the study subjects (20 patients) had diabetic retinopathy, of which 13 had NPDR (non-proliferative diabetic retinopathy) and 7 had PDR (proliferative diabetic retinopathy). Similarly, 35% of the study subjects (18 patients) had diabetic nephropathy as evidenced by the presence of proteinuria, and 11 patients (21%) were found to have symptoms of diabetic neuropathy. Table 1 detailed the comparison of parameters studied between the study subjects.

The mean level of vitamin D and its association with HbA_{1c} was found significant (Table 2). It has seen that higher the HbA_{1c}, lower the vitamin D level (Figure 2). The significant negative correlation was calculated between vitamin D and HbA_{1c} level, it is found to be –735 (Pearson correlation) (Figure 3). Alongside, the level of HbA_{1c} had an inverse relationship with the presence of microvascular compilation was statistically significant, which is depicted in Figure 4. There was an inverse relationship between the level of vitamin D and presence of microvascular complication (not statistically significant). However, on regression analysis, it was found that inverse association of HbA1c with vitamin D levels was statistically significant.

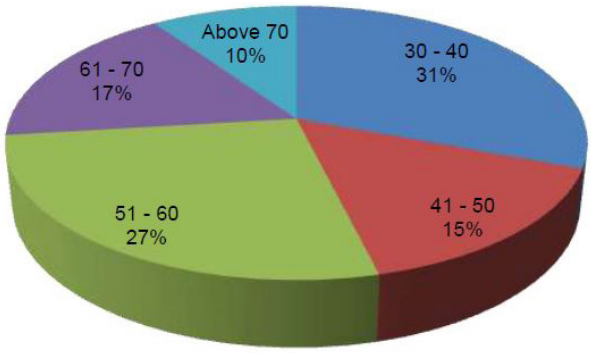

Figure 1: Age wise distribution of patients in percentage.

Table 1: Baseline characteristics of type 2 DM patients.

Parameters	In ratio
Male: Female (in number)	24:28
Vitamin D levels (Normal: Low) (in ng/mL)	3:49
HbA_{1c} level (<7:7–9:>9) (in g/dL)	21:18:13
Diabetic retinopathy (present:absent)	20:32
Diabetic nephropathy (present:absent)	18:34
Diabetic neuropathy (present:absent)	11:41

Table 2: Mean vitamin D level and its association with glyco Hb.

Glyco Hb %	N	Mean Vit D (ng/mL)	Std. dev	95% Confidence Interval for Mean		ANOVA test (p value)	
				LowerBound	UpperBound		
<7	21	25.84	9.04	21.73	29.96	0.000	HS
7–9	18	14.76	4.96	12.29	17.22		
>9	13	8.51	5.07	5.45	11.57		
Total	52	17.67	9.91	14.91	20.43		

Where p value <0.001 is considered as significant.
HS indicates highly significant.

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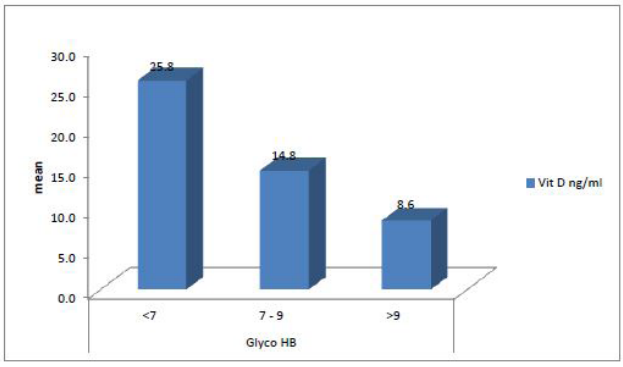

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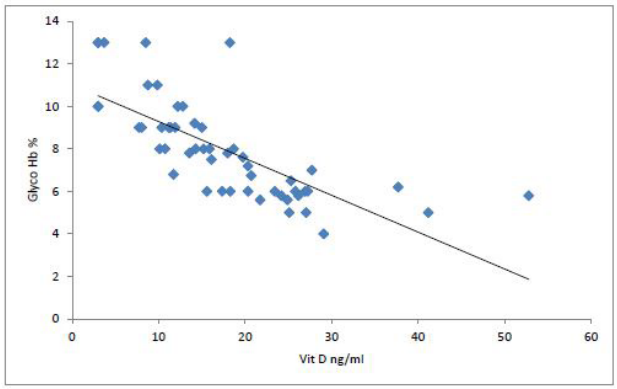

Figure 3: Scatter diagram depicting the association between Glyco Hb and Vitamin D levels.

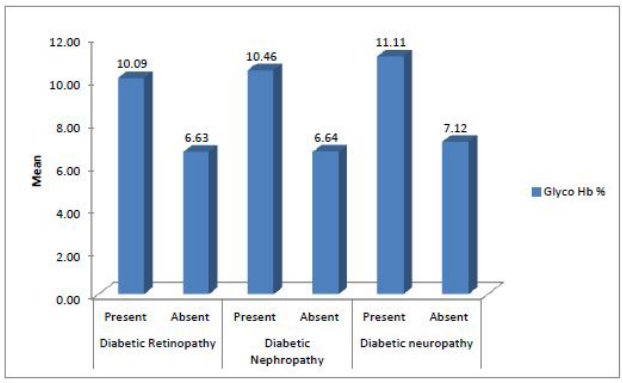

Figure 4: Glyco Hb levels and its association with Micro vascular complications.

Discussion

In our study, 52 patients of T2DM were interviewed and investigated to look for the association between HbA_{1c} and vitamin D levels. We also evaluated their implications on the microvascular complications of T2DM, namely diabetic retinopathy, diabetic nephropathy and diabetic neuropathy. The gender distribution was almost equal in our study and majority of the patients were belonged to the age group of 30–40 followed by 51–60 years. This was similar to a study by Niyati et al. where, correlation between vitamin D and HbA_{1c} in T2DM patients was estimated for over 100 patients, of which 54 were males and 46 were females [22].

In our study, it was found that only 6% of the patients had normal vitamin D level, which majorly effects on HbA_{1c} levels and their correlation between diabetic and non-diabetic adults. A study conducted by Ahlam et al. [16] involved 299 patients of diabetes in different age groups and only 23 (7.7%) were found to have sufficient vitamin D levels. Khalida et al. [23] conducted a study on 165 patients titled association of vitamin D deficiency with poor glycaemic control in diabetic patients of whom 34 (20%) of the patients had adequate vitamin D levels. The main drawback of our study is the lack of control population and a small sample size. However, the very low percentage of population with normal vitamin D levels has to be looked into further [24]. In our study, majority of the patients had good (40.4%) and moderate (34.6%) glycemic control whereas 25% of them had poor glycemic control. A study conducted by Giocomo et al. [15] on 715 patients had 83% of patients with good glycemic control. Our study also shows significant inverse association between HbA_{1c} and vitamin D levels, where HbA_{1c} is inversely related to serum vitamin D levels in T2DM. Similarly, the study by Ahlam et al. [16] showed the inverse relationship on 184 study subjects to see the effect of vitamin D and HbA_{1c} levels, and their correlation between diabetic and non-diabetic adults. Hypovitaminosis D in patients with T2DM – a relation to disease control and complications, a clinical study on 136 patients by Hala et al. showed that serum vitamin D levels correlated negatively with HbA_{1c} [26]. While in our study there was an inverse relationship between the mean vitamin D level and the occurrence of microvascular complications of T2DM, i.e. diabetic retinopathy, diabetic nephropathy and diabetic neuropathy [27–29]. However, the study conducted by Nikhil et al. [19] on 50 patients of which 25 had microvascular

complications, also showed a similar inverse but statistically insignificant relationship between the two. In a study conducted by Celil et al. [25] on 557 patients with T2DM and 112 controls, also found inverse but statistically insignificant association between vitamin D levels and the presence of microvascular complications. However, the report by few studies showed a statistically significant relationship between the microvascular complications of T2DM and serum vitamin D levels [17, 18, 30].

Conclusion

Vitamin D deficiency is highly prevalent among patients with T2DM. Low vitamin D levels were found to be associated with increased microvascular complications of T2DM. So, it is warranted to measure vitamin D levels among diabetics as it is a correctable risk factor. Furthermore, there is also a significant inverse relationship between the levels of HbA_{1c} and vitamin D levels, depicting the importance of glycemic control. Therefore, additional large-scale studies are required to establish if vitamin D supplementation will improve glycemic control among diabetics.

Conflict of interest

The authors declare no conflict of interest.

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