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Original Article

Biochemistry Section

Correlation of 25-Hydroxycholecalciferol and Glycaemic Status in Recent Onset Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: Type 2 Diabetes Mellitus (T2DM) is a non communicable disease caused by increased insulin resistance and beta cells dysfunction. Recently vitamin D has sparked wide spread interest in pathogenesis of diabetes by playing a role in insulin resistance. As a major regulator of homeostasis of calcium, vitamin D directly and/or indirectly improves insulin exocytosis and glucose tolerance.

Aim: To estimate the serum 25 hydroxy cholecalciferol level and also to correlate with fasting, two hour postprandial blood glucose and Glycated Haemoglobin (HbA1c) values in recent onset T2DM patients.

Materials and Methods: This cross-sectional study was conducted at Government Kilpauk Medical College, Tamil Nadu, India from November 2017-April 2018. One hundred and thirty nine recently diagnosed T2DM patients aged between 30-60 years of both sex, who were on oral hypoglycaemic drugs for less than three months duration were included in the study. The patients were grouped into three groups according to their vitamin D levels, Group 1- Vitamin D deficient- 52 patients (≤20 ng/mL), Group 2- Insufficient Vitamin D- 33 patients (>20-30 ng/mL), Group 3- Vitamin D sufficient- 54 patients (>30 ng/mL). Fasting and two hour postprandial glucose, 25 hydroxy cholecalciferol and HbA1c were estimated. Statistical analysis was performed using analysis of variance (ANOVA) and Pearson's correlation.

Results: Out of 139 participants, 64 were males and 75 were females. The mean age of the study population was 50.64±5.343 years. The mean fasting blood glucose values among the three groups were 168.13, 129.61, and 125.33 mg/dL, respectively. The mean two hour postprandial blood glucose values among the three groups were 269.44, 212.45, and 194.11 mg/dL, respectively. The mean HbA1c among the three groups were 7.481±1.16, 6.027±0.31, and 5.86±0.19, respectively. Decreased 25 hydroxy cholecalciferol level in patients of T2DM showed a statistically significant inverse correlation with fasting and two hour postprandial blood glucose and HbA1c with p-value <0.001.

Conclusion: The study suggested that hypovitaminosis D was prevalent in T2DM. The study showed that decreased vitamin D level in T2DM patients was associated with increased fasting, postprandial blood sugar, and HbA1c. So, vitamin D screening in diabetics and supplementation can improve the glycaemic status.

Keywords: Calcium, Glycated haemoglobin, Hypovitaminosis D, Insulin resistance, Vitamin D

INTRODUCTION

Diabetes mellitus is a metabolic, non communicable disease, characterised by chronic hyperglycaemia with disturbance in the carbohydrate, protein and fat metabolism, resulting from defects in insulin secretion, insulin action or both [1]. The incidence of diabetes mellitus increases globally and national wide. According to the International Diabetes Federation (IFD), worldwide incidence of diabetes mellitus in 2019 was 463 million individuals [2]. In India, 77 million individuals are affected, and expected to increase 153 million by 2045 in South East Asia [2]. Effective preventive measures are therefore needed and modifiable risk factors should be identified and explored. Few studies have shown a relationship between vitamin D and T2DM [3,4].

Vitamin D is a fat soluble vitamin, a hormone, synthesised in the skin on exposure to sunlight. It's function is mainly to maintain the skeletal integrity. It's deficiency manifestations are rickets in children, osteomalacia in adults, and osteoporosis. Extra skeletal effects are Diabetes mellitus, hypertension, metabolic syndrome, atherosclerosis, myocardial infarction, and stroke [5]. Hypovitaminosis D is widespread, the prevalence of Vitamin D deficiency is 44% according to The European Journal of Clinical Nutrition [6]. The prevalence of hypovitaminosis D in south India in 2017 was 40% in males and 70% in females [7].

The T2DM is multifactorial and various factors such as inflammatory factors, reactive oxygen species and autoimmune reactions are the major pathogenic effectors [8]. There has been considerable interest in identifying new factors that may lead to the disease. Recently vitamin D has sparked widespread interest in pathogenesis of diabetes by playing a role in Insulin resistance. Type 2 diabetes and Vitamin D deficiency have common risk factors like race, obesity, ageing, and low physical activity. Vitamin D receptors has been identified in pancreatic islets and Vitamin D dependent calcium binding protein is present in pancreatic tissue [8]. As a major regulator of homeostasis of calcium, Vitamin D directly and/or indirectly improves insulin exocytosis and glucose tolerance [9]. Vitamin D decreases insulin resistance by the upregulation of the insulin receptor gene and also by it's effect on calcium and phosphorus metabolism [10].

Glycated haemoglobin (HbA1c) can be interpreted as an average of blood glucose produced over the past 3-4 months. The HbA1c is widely used in the diagnosis of diabetes mellitus and used as a global measure of assessing the management of patients with diabetes, to monitor the long-term glycaemic control and as a measure of the risk for the development of diabetic complications [11].

Various studies have compared the relationship of vitamin D on either fasting or postprandial glucose or HbA1c levels in T2DM separately [12,13]. Recent onset T2DM patients were selected in this study, since chronic elevation of blood glucose levels slowly damages organs and result in microvascular complications like diabetic nephropathy, which in turn will affect the metabolism of vitamin D [11]. The present study was aimed to assess vitamin D levels along with fasting, two hour postprandial blood glucose and

HbA1c among recent onset (duration of less than six months with oral antihyper glycaemic drugs) T2DM patients before complications set in and also to find the correlation of vitamin D levels with fasting, postprandial blood glucose and HbA1c in recent onset T2DM patients.

MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Biochemistry from November 2017-April 2018 in collaboration with Department of Diabetology, Government Kilpauk Medical College, Chennai, Tamil Nadu, India. The study protocol was approved by the Institutional Ethics Committee (IEC) of Government Kilpauk Medical College, Chennai, ID NO- 02/2017 dt-14.11.2017. Study was conducted after explaining the study to the study subjects in their local language and obtaining the informed written consent.

Inclusion criteria: As per the American Diabetes Association (ADA) guidelines [14], 139 cases of recently diagnosed T2DM patients American Diabetes Association (ADA) guidelines [14] of less than six months duration, aged between 30-60 years with both sex who were on oral hypoglycaemic drugs were included in the study.

Exclusion criteria: Patients with Type I diabetes mellitus; pregnant women with gestational diabetes mellitus; patients on treatment with Statin, Insulin, vitamin D, Oral contraceptive pills, and Steroids; individuals with history of alcoholism; known hypo/hyperthyroidism and hypo/hyperparathyroidism, patients with renal impairment, patients with malignancy, patient with hypertension, patients with arthritis and cardiac disease were excluded.

Sample size calculation: Sample size was calculated using the prevalence of vitamin D as 30%, 80% confidence level and at alpha value of 0.05 using a formula $N=Z^2\ pq/d^2$ [15]. The sample size calculated was 139.

After estimating the vitamin D levels, total 139 participants were grouped in to three groups according to the American Association of Clinical Endocrinologist for vitamin D [16] as follows:

- Group 1- vitamin D deficient- 52 patients (≤20 ng/mL),
- Group 2- Insufficient vitamin D- 33 patients (>20-30 ng/mL),
- Group 3- vitamin D sufficient -54 patients (>30 ng/mL).

Detailed history was taken regarding age, sex, education, occupation, h/o of present illness, past, family and drug.

Study Procedure

For the study, 5 mL of fasting venous blood was collected under sterile conditions from the anticubital vein. Blood glucose (fasting-70-109 mg/dL, postprandial 80-139 mg/dL) were analysed using roche Cobas c 311 autoanalyser. HbA1c was estimated by the Turbidimetric Inhibition Immunoassay (TINIA) by using roche Cobas c 311 autoanalyser. 25 hydroxy vitamin D (>30.0 ng/mL) was estimated using Cobas e 411 immunoassay analyser by electrochemiluminescence immunoassay principle [17].

STATISTICAL ANALYSIS

Statistical analysis was performed using International Business Management (IBM) Statistical Package for Social Sciences (SPSS) package-version 20.0. The results obtained were expressed as mean±standard deviation. Comparison of the parameters among the groups were done by Analysis of Variance (ANOVA). Pearson's correlation was used to correlate between parameters done in this study. A p-value of <0.001 was highly significant, <0.05 was significant and >0.05 was insignificant. Chi-square test was used to compare categorical outcomes between study groups and Tukey HSD posthoc tests were used to assess the correlation among multiple comparison groups.

RESULTS

These 139 study participants were grouped into three groups according to their vitamin D levels. In this study out of 139 participants, 64 (46.04%) were males and 75 (53.96%) were females. The study participants were aged between 30-60 years. Out of 139 participants 25 (17.96%) were aged between 30-45 years, 82 (58.99%) were aged between 46-55 years and 32 (23.02%) were between 56-60 years. Mean age of the study population was 50.64±5.343 years.

The mean±standard deviation of the analytes were as follows; vitamin D- 24.9201±13.356, Fasting blood glucose 142.36±28.195, postprandial blood glucose 226.65±60.650 and HbA1c 6.509±1.053 [Table/Fig-1]. There was significant negative correlation between vitamin D and fasting blood glucose was (r-value -0.684), Postprandial blood glucose was (r-value -547), HbA1c was (r-value -0.693) (p-value <0.001) [Table/Fig-2].

Analytes	Mean±Std. Deviation
Fasting glucose (mg/dL)	142.36±28.195
Postprandial glucose (mg/dL)	226.65±60.650
HbA1c (%)	6.509±1.0538
Vitamin D (ng/dL)	24.9201±13.356

[Table/Fig-1]: Mean values of all the analytes.

Analytes	Vitamin D (ng/dL)	p-value
Fasting glucose (mg/dL)	-0.684	<0.001**
Postprandial glucose (mg/dL)	-0.547	<0.001**
HbA1c (%)	-0.693	<0.001**

[Table/Fig-2]: Correlation of vitamin D with the analytes.
Pearson correlation-(**) denotes the p-value is 0.000 to 0.010- highly significant

The mean fasting blood glucose values among the three groups-vitamin-D level below 20, 20-30 and >30 were 168.13±31.755, 129.61±6.324, 125.33±5.191, respectively and the p-value was <0.001 which was statistically significant. The mean postprandial blood glucose in group 1 was 269.44±69.762, Group 2 was 212.45±38.85 and in Group 3 was 194.11±31.34. The p-value was <0.001** which was statistically significant. The mean HbA1c among the three groups were 7.481±1.1633, 6.027±0.3145 and 5.867±0.1962, respectively. The p-value was <0.001** which is statistically significant [Table/Fig-3].

Analytes	Group 1 (vit-D below 20)	Group 2 (vit-D 20-30)	Group 3 (vit-D above 30)	p-value
Fasting glucose (mg/dL)	168.13±31.755	129.61±6.324	125.33±5.191	<0.001**
Postprandial (mg/dL)	269.44±69.762	212.45±38.854	194.11±31.341	<0.001**
HbA1c (%)	7.481±1.1633	6.027±.3145	5.867±0.1962	<0.001**

[Table/Fig-3]: Comparison of analytes between groups.

By Tukey HSD posthoc tests for multiple comparison of fasting blood sugar between groups 1 and 2 and groups 1 and 3 was highly significant (p<0.001), represents the significance by Tukey HSD posthoc test for postprandial blood glucose. Mean difference of postprandial blood glucose between groups 1 and 2 was 56.99±11.26 and between groups 1 and 3 was 75.3±9.836 and this difference was highly significant (p-value of <0.001). Mean difference between groups 1 and 2 was 1.453±0.1644, and between groups 1 and 3 was 1.614±0.1435 with highly significant p-value of <0.001** [Table/Fig-4].

(I) Vitamin D	(J) Vitamin D	Mean difference (I-J)	Std. Error	Sig.
Fasting blood glucose				
Group 1	Group 2	38.53(*)	4.440	<0.001**
Group 2	Group 3	4.27	4.408	0.598
Group 3	Group 1	-42.80(*)	3.876	<0.001**

Postprandial blood glucose				
Group 1	Group 2	56.99(*)	11.267	<0.001**
Group 2	Group 3	18.34	11.186	0.233
Group 3	Group 1	-75.33(*)	9.836	<0.001**
HbA1c				
Group 1	Group 2	1.453(*)	0.1644	<0.001**
Group 2	Group 3	0.161	0.1632	0.588
Group 3	Group 1	-1.614(*)	0.1435	< 0.001**

[Table/Fig-4]: The mean difference by Tukey HSD posthoc test for multiple comparison of analytes.
(*) denotes the mean difference is significant at the 0.05 level

DISCUSSION

This study was attempted to explore the association of vitamin D with glycaemic status in recent onset T2DM. One hundred and thirty nine recent onset diabetic subjects were selected and grouped into three groups according to their vitamin D level and the biochemical parameters were assessed for all the three groups. Among the parameters, fasting blood glucose, postprandial blood glucose, and HbA1c were statistically highly significant with vitamin D between the groups with p-value of <0.001**.

In this study the prevalence of vitamin D deficiency in recent onset diabetic patients attending Diabetic OPD of GOVT. KMCH was 61% (23.7%insufficient and 37.4% deficient). Only 39% of Diabetics had sufficient vitamin D level. Lack of exposure to the sun is the leading cause of vitamin D deficiency as it is a sunshine vitamin. With modernisation, the number of hours spent outdoor have decreased thereby it leads to an inadequate sun exposure. Other reasons are dark skin complexion and sunscreen use.

A study conducted by Nishchitha K et al., [18] involved 299 patients of diabetes in different age groups. Only 23 (7.7%) were found to have sufficient vitamin D levels. Khalida I et al., [19] 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 presence of comparatively higher prevalence of hypovitaminosis D in diabetic patients in general and in patients with poor glycaemic control in particular is in agreement with the results documented in previous Asian study by Iqbal K et al., [19]. In 2013, an Indian study done by Daga RA et al., for comparison of concentration of 25(OH)D in newly detected youth onset diabetic subjects with non diabetic healthy subjects the mean±SD of 25 (OH) D was significantly low-7.88±1.20 ng/mL in subjects with diabetes against 16.64±7.83 ng/mL in controls [20]. A observational study by Pittas AG et al., showed a relatively consistent association between low vitamin D status and prevalence of type 2 Diabetes [21].

Previous cross-sectional and case control studies proved an inverse association between vitamin D and type 2 diabetes as well as the markers of adverse glucose homeostasis [22,23]. According to the observation of the study, when the vitamin D deficiency in Type 2 Diabetes patients were severe, fasting blood glucose of those patients were more than the controlled fasting glucose and the patients with sufficient vitamin D had controlled mean fasting glucose level.

According to another observation of the study, in vitamin D deficient group, the mean postprandial blood glucose was 269±69.76, which was higher than the controlled postprandial blood glucose. This means the patients with deficient vitamin D had high postprandial blood glucose level than other two groups.

Based on the available clinical and epidemiological data, when the fasting blood glucose was more than 125 mg/dL the positive effects of vitamin D is primarily related to its action on insulin secretion, action or both and secondarily due to its role on inflammation. The mechanisms of the effect of vitamin D in T2DM include, (i) improvement of beta cell function and enhanced insulin release by direct effect on vitamin D receptors of pancreatic beta cells and by increasing the intracellular ionised calcium. (ii) increases insulin sensitivity and increase glucose utilisation by enhancing expression of insulin receptor and by regulation of peroxisome proliferative activated receptor or via calcium dependent pathways in target cells, (iii) several genetic polymorphism in genes related to vitamin D metabolism such as DBP and VDR may predispose the subjects to type 2 Diabetes. (iv) Beta cell apoptosis is inhibited due to VDR transcription factor mediated inhibition of cytotoxic cytogene expression. (v) The 1,25(OH)D increases transcription of insulin receptor gene and also suppresses the renin gene [24-26].

Results from a study by Kumar H et al., observed that vitamin D level was inversely related to fasting blood sugar in patients with Type 2 Diabetes Mellitus [27]. Kayaniyil S et al., longitudinal study in 2013 showed a significant inverse association of vitamin D with fasting glucose [28]. According to present study there was a statistically significant inverse correlation between serum vitamin D and HbA1c. In Group 1 of present study with vitamin D level below 20 ng/dL had mean HbA1c of 7.48±1.16 and Group 2 with vitamin D level between 20-30 ng/dL had HbA1c of about 6.02±0.31 and Group 3 with vitamin D level above 30 ng/dL had HbA1c of about 5.86±0.196. p-value is <0.001**, which is highly significant. This may be due to the fact that vitamin D is a factor for the insulin secretion and sensitivity as discussed earlier.

The study by Nishchitha K et al., [18] showed an inverse relationship on 184 study subjects between vitamin D and HbA1c 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 by Ahamadieh H et al. showed that serum vitamin D levels correlated negatively with HbA1c [22]. The study by Kumar H et al., showed that serum vitamin D levels correlated negatively with HbA1c with 50 diabetic patients [27]. These finding suggest the need of screening of vitamin D deficiency in elevated HbA1c level patients and vice versa. The low level of vitamin D in diabetic patients and inverse relationship between vitamin D level and HbA1c supports an active effect of vitamin D in pathogenesis of type 2 DM. Vitamin D prevalence of 61% of our study implies the necessity for more research and implementation of preventive measures related to vitamin D deficiency. In present study serum 25hydroxy vitamin D was measured as vitamin D status 'Total D' which measures both D2 and D3.

Limitation(s)

Confounding factors for vitamin D like duration of exposure, complexion of skin, etc, were not evaluated in this study. Prediabetic and impaired diabetic patients were not included in the study.

CONCLUSION(S)

The study suggests that hypovitaminosis D is prevalent in T2DM. The study showed that hypovitaminosis D in T2DM patients was associated with increased fasting, postprandial blood sugar and HbA1c. Thus an inverse correlation was present between vitamin D and blood sugar, HbA1c. Vitamin-D could be one of the risk factor in development of diabetes and may be a major independent predictor of complication of diabetes mellitus. So it is reasonable to include vitamin D screening in the diabetic patients on a regular basis to improve the vitamin D level to prevent or delay the development of complications of diabetes mellitus. Large well designed randomised controlled interventional study is needed to clarify the relationship of vitamin D and Diabetes.

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