Original Article

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Effect of Vitamin D Replacement Therapy on Glycaemic Control in Type 2 Diabetic Mellitus Patients

Internal Medicine Section

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ABSTRACT

Introduction: Vitamin deficiency has been recently shown to play an important role in the onset and progression of Type 2 Diabetes Mellitus (T2DM). The present study was planned to look for the changes in Serum 25-hydroxyvitamin D [25(OH)D] concentration and subsequent risk of type 2 diabetes levels in diabetic patients after vitamin D supplementation.

Aim: To study the effect of vitamin D therapy on glycaemic control in type 2 diabetes mellitus patients.

Materials and Methods: The present study was conducted in the Department of Pathology, Biochemistry and Endocrinology over a period of one year from November 2010 to December 2011. The study design was open labelled randomised controlled trial. It was a prospective study. The study was approved by the Institutional Ethics Committee and written informed consent was obtained from all the patients.

Oral cholecalciferol in a dose of 60,000 units was administered every 15 days for three months to group of 30 patients selected by simple randomisation technique. Changes in fasting and postprandial sugar levels, HbA1c, routine biochemistry and total vitamin D and Parathyroid Hormone (PTH) were assessed for all patients after three months.

Results: The group supplemented with vitamin D showed a significant improvement in postprandial glucose levels (p= 0.016). Fasting glucose and HbA1c values also showed a decline but it was not statistically significant.

Conclusion: It is concluded that supplementation of vitamin D for three months improved levels of post prandial sugar levels in vitamin D deficient T2DM patients in the present study. Thereby raising the vitamin D levels in patients at risk of T2DM may reduce their risk or slow the development of the disease.

Keywords: Parathyroid hormone, Post prandial glucose, Vitamin deficiency

INTRODUCTION

Diabetes Mellitus is one of the fastest growing non-communicable chronic diseases. Its prevalence continues to increase worldwide [1,2]. Its aetiology is multifold and has both genetic and environmental contribution [3].

Recently, the extra skeletal effects of vitamin D, a hormone involved in bone metabolism, have raised a great interest. Its deficiency has recently been shown to play an important role in the onset and progression of T2DM [2,4]. Vitamin D is thought to affect pancreatic beta cell function (insulin synthesis and secretion) and immune response. Its deficiency leads to impaired secretion of insulin and induces glucose intolerance [3]. Thereby, raising the vitamin D levels in patients at risk of T2DM may reduce their risk or slow the development of the disease.

Few case reports and studies have looked at the effects of v itamin D replacement therapy in patients with T2DM. Therefore, this study is planned to look for the changes in glycaemic levels in diabetic patients after vitamin D supplementation.

MATERIALS AND METHODS

The present study was conducted in the Department of Pathology, Biochemistry and Endocrinology, PGIMER, Dr. Ram Manohar Lohia Hospital, New Delhi, India, from November 2010 to December 2011. The study design was: prospective, open labelled randomised controlled trial. It was a prospective study. The study was approved by the Institutional Ethics Committee and written informed consent was obtained from all the patients.

Inclusion Criteria

Subjects with HbA1c ranging between 7% to 8.5% and vitamin D levels less than 75 nmol/L and subjects ready to give consent for the study.

Exclusion Criteria

Subjects with any metabolic bone diseases, chronic liver and kidney diseases, patients on insulin monotherapy, patients with any change in oral hypoglycaemic drugs during the period of vitamin D supplementation, patients on drugs that interact with oral vitamin D supplements i.e., enzyme inducers like phenytoin, phenobarbitone etc., patients on calcium within last one month, patients with symptomatic osteomalacia or low serum calcium or a high alkaline phosphatase and pregnant females.

A total of 60 Type 2 diabetics with vitamin D deficiency (HbA1c ranging between 7% to 8.5% and Vitamin D levels less than 75 nmol/L) were taken from the diabetic clinic and were divided by simple randomisation into two groups of 30 each. Group I-Those who received vitamin D supplement (oral cholecalciferol in a dose of 60,000 units every 15 days for three months) and Group II-Those who did not receive vitamin D supplement and acted as controls. All these patients were given strict instructions to maintain diet chart and exercise. In the present study, mean duration of diabetes in vitamin D supplemented group was about 10 years.

A detailed clinical examination including anthropometric profile, pulse, Blood Pressure (BP), fundus examination, treatment being taken, concomitant illness, body aches and pain was done. Venous blood samples (12-15 mL) were collected in three vacutainers, Ethylenediaminetetraacetic Acid (EDTA) vacutainers for complete haemogram and for glycated haemoglobin (HbA1c) estimation using High Performance Liquid Chromatography (HPLC), fluoride vacutainers for the estimation of fasting and post prandial sugar levels and plain vacutainers for the estimation of Vitamin D and PTH by Enzyme Linked Immunosorbent Assay (ELISA) and other

investigations like Liver Function Test (LFT), Kidney Function Test (KFT) and Calcium/Phosphorous/alkaline phosphatise (Ca/Phos/ALP) by colorimetric method on fully automated biochemistry analyser. Samples were collected in morning for fasting blood sugar and two hours later post prandial. Same time samples were collected for all other tests also.

Follow Up

Fasting and post prandial glucose, HbA1c, Routine biochemistry (LFT, KFT, Ca/Phos/ALP) and total Vitamin D and PTH levels of the patient were measured on the first day. At baseline, patients were enquired regarding general well-being, bodyaches and pain classified as (no pain-0, minimum pain not requiring medication-1, pain requiring medication-2, pain disabling sleep-3). A note of oral hypoglycaemic and other medications was made. During the study period, no change in oral hypoglycaemic was made. Those requiring change in medications were excluded from the analysis; however, in the present study none of the patient required additional medication. Patients were told to keep record of fasting and postprandial sugar every 15 days and a reminder was given telephonically. Three months later, fasting and post prandial sugar levels, HbA1c, routine biochemistry and total vitamin D and PTH were reassessed for all patients.

STATISTICAL ANALYSIS

All data were compiled and a master chart was prepared. Data was double entered and checked for discrepancies. Using a SPSS software version 17.0, statistical analysis was performed. Descriptive statistics, such as “means”, “standard deviation” and “p-value” were used to describe the study sample. Assessment of association of vitamin D supplementation and glycaemic control in T2DM patients was done using the “Student’s paired t- test” and Chi-square test. A p-value of less than 0.05 was considered significant at 95% confidence level.

RESULTS

A total of 98 patients underwent investigations, of which 38 were excluded based on the following criteria:

High HbA1c of >8.5% in 12 patients.

Low HbA1c of <7% in 20 patients.

High vit D levels of >75 nmol/L in one patient.

Already on calcium supplementation in five patients.

A total of 60 Type 2 Diabetics with vitamin D deficiency were included in the study. Out of these 30 were given vitamin D and designated as cases. The other 30 were controls, not given vitamin D. These all patients were followed up for three months and the results obtained were statistically analysed (as shown in flow diagram).

Baseline characteristics of both cases and controls were comparable in relation to age and sex distribution. In both the groups, cases and controls, individual male: female ratio was 1:1. Both the groups had similar weight and glycaemic profile. Levels of Calcium, Phosphorous, ALP, Vitamin D and PTH were also comparable in both the cases and control groups [Table/Fig-1]. Body Mass Index (BMI) was less than 25 in 31 patients (non-obese) and 29 patients in the study were obese. All patients had HbA1c values between 7 to 8.5%. A total of 31 patients were vitamin D deficient using a cut-off value of <25 nmol/L while 29 patients were vitamin D insufficient with values ranging between 25-74 nmol/L. PTH was found to be high in 25 patients using a cut-off value of 75.1 pg/mL [5].

[Table/Fig-2] depicts the evaluation of the weight and biochemical parameters before and after vitamin D supplementation in Group I patients (who received Vitamin D during the study period). Vitamin D levels were significantly raised and PTH levels showed a significant decline at the end of three months. There was significant improvement in post prandial sugar levels after three months of vitamin D supplementation. HbA1c levels and fasting sugar levels also improved in three months however, it was not statistically significant. Calcium levels were significantly elevated while there was no change in phosphorous levels.

Casesdepicts a significant fall in post prandial sugar values (p=0.016) post vitamin D supplementation. No significant change was found in fasting and post prandial sugar levels in controls (baseline and three months follow up). [Table/Fig-3] provides various parameters at baseline and at three months follow up in Group II patients (control group). Total number of controls included were 30

Parameters	Normal Values	Cases (n=30) (Group I)	Controls (n=30) (Group II)	p-value
Age (years)	-	57.13±11.74	53.60±9.98	0.214
Sex (M/F)		15:15	15:15	-
Weight (kg)	-	67.76±10.33	66.19+/-13.57	0.737
Fasting sugar (mg/dL)	60-100	148.70±48.143	141.22±26.72	0.467
PP sugar (mg/dL)	90-160	218.10±73.254	186.93±61.27	0.099
HbA1c (%)	3.5-6	7.78±0.416	7.76±0.40	0.926
Calcium (mg/dL)	8.5-10.5	8.88±0.603	8.62±0.79	0.255
Phosphorous (mg/dL)	3.5-5.5	3.75±0.995	3.67±0.60	0.535
ALP (U/L)	50-300	182.50±45.216	194.15±56.24	0.225
Vitamin D (nmol/L)	47.7-144	25.63±9.941	29.07±14.9	0.361
PTH(pg/mL)	13.9-75.1	81.95±65.978	68.72±32.04	0.249

[Table/Fig-1]: Baseline characteristics of both cases and controls.
Student’s paired t-test. A p-value of less than 0.05 was considered significant at 95% confidence level. PP sugar: Post Prandial sugar; ALP: Alkaline phosphatase; PTH: Parathyroid hormone

Parameters	Pre Vit D	Post Vit D	p-value
Weight (kg)	67.76±10.33	67.30±10.30	0.864
Fasting blood sugar (mg/dL)	148.70±48.143	130.33±24.746	0.091
Post prandial blood sugar (mg/dL)	218.10±73.254	178.97±34.777	0.016 (Significant)
HbA1c (%)	7.78±0.416	7.58±0.735	0.175
Calcium (mg/dL)	8.88±0.603	9.38±0.436	<0.001 (Significant)
Phosphorous (mg/dL)	3.75±0.995	3.77±0.546	0.920
ALP (U/L)	182.50±45.216	181.50±58.836	0.936
Vitamin D (nmol/L)	25.63±9.941	60.26±24.982	0.000 (Significant)
PTH (pg/mL)	81.95±65.978	50.90±27.871	0.002 (Significant)

[Table/Fig-2]: Evaluation of the weight and biochemical parameters before and after vitamin D supplementation in Group I patients.
Student’s paired t-test [L12]. A p-value of less than 0.05 was considered significant at 95% confidence level. Vit D: Vitamin D; ALP: Alkaline phosphatase; PTH: Parathyroid hormone

Parameters	Baseline values	Three months later	p-value
Weight (kg)	66.19±13.57	66.26±13.94	0.944
Fasting blood sugar (mg/dL)	141.22±26.72	135.37±19.85	0.347
Post prandial blood sugar (mg/dL)	186.93±61.27	187.93±22.41	0.934
HbA1c (%)	7.76±0.40	7.6±0.92	0.341
Calcium (mg/dL)	8.62±0.79	8.64±0.91	0.857
Phosphorous (mg/dL)	3.67±0.60	3.64±0.54	0.784
ALP (U/L)	194.15±56.24	165.59±58.62	0.066
Vitamin D (nmol/L)	29.07±14.9	33.97±13.97	0.175
PTH (pg/mL)	68.72±32.04	75.53±39.77	0.370

[Table/Fig-3]: Various parameters at baseline and at three months follow up in Group II patients.
Student’s paired t-test. A p-value of less than 0.05 was considered significant at 95% confidence level. ALP: Alkaline phosphatase; PTH: Parathyroid hormone

however, three were excluded because these patients developed elevated vitamin D level >60 nmol/L at three months follow up due to following reasons. It was found that two patients were prescribed calcium supplementation by an orthopaedician and the third one had goat's milk twice daily. Shostak NA et al., observed that goat milk supplementation in addition to standard osteoporotoic therapy increased concentrations of 1,25(OH)2D and 25(OH)D in the blood serum (by 18, 5-28, 2% in the goat milk supplemented group compared to by 8, 0-17, 9% at the control group) [6]. After excluding these patients, calcium, vitamin D and PTH levels at the end of three months were not statistically different (p=0.175 and 0.370 respectively). There was no change in fasting or postprandial glucose and HbA1c levels.

Parameters	Responders	Non Responders	p-value
Age (years)	57.31±13.68	56.93±9.56	0.931
Sex (M/F)	9:7	6:8	0.464
Weight (kg)	66.38±9.90	69.36±10.96	0.44
Duration of diabetes (years)	10.27±7.19	10.50±6.32	0.927
Neuropathy	five patients	three patients	0.544
Number of OHAs	2.94±1.12	3.07±1.14	0.749
Vitamin D (nmol/L)	26.019±11.579	25.186±8.079	0.823
PTH (pg/mL))	81.163±40.874	82.857±88.212	0.946
Calcium (mg/dL)	8.831±0.530	8.936±0.692	0.644

[Table/Fig-4]: Comparative evaluation of responders and non- responders based on improvement in post prandial sugar levels of >20 mg/dL in the Group I.
A p-value of less than 0.05 was considered significant at 95% confidence level. OHAs: Oral hypoglycaemic Agents; PTH: Parathyroid hormone

The present study shows a significant difference in Vitamin D and PTH values after three months of vitamin D supplementation in Group I. However, there is no significant difference in their values in the control group. We further sub-analysed the responders and non- responders based on improvement in post prandial sugar levels of >20 mg/dL in the vitamin D supplementation group (Group I). We found no significant difference in any of the parameters in both the groups as depicted in [Table/Fig-4].

DISCUSSION

In the present study, the group supplemented with vitamin D showed a significant improvement in post prandial glucose levels (p=0.016). Improvement in glucose levels occurred independent of change in weight. Fasting glucose and HbA1c values also showed a decline but it was not statistically significant.

Most of the observational studies indicate that concentration of serum vitamin D has inverse association with the risk of T2DM [7-11] or most of the diabetics have low serum concentration of vitamin D [12-16]. In an observational study by Athanassiou IK et al., an inverse relationship was observed between HbA1c levels and 25(OH)D3 levels in the patient group, implying that 25(OH)D3 levels may affect glucose control in diabetes mellitus type 2 [4].

Few of the studies found inverse association of vitamin D with fasting glucose [17-19], HbA1c [3,8,20] or Oral Glucose Tolerance Test (OGTT) [21]. However, some studies found no association of vitamin D with fasting glucose [21-23]. Few studies observed that subjects with higher intake of vitamin D are less likely to have diabetes mellitus than others [11,24]. In a study done by Mattila C et al., significant inverse association between serum 25(OH)D and T2DM was found [25].

We observed improvement in postprandial blood glucose levels in the group supplemented with vitamin D. However, clinical studies involving supplementation with vitamin D have not shown much benefit in glycaemic control. Most of these studies except few, were done for a shorter period of time ranging from few days to few weeks [22,26,27]. The vitamin D levels were either adequate or not done in most of these studies and patients were supplemented with activated form of vitamin D-1,25 dihydroxycholecalciferol. Also, most of the patients analysed were either healthy volunteers or patients with impaired glucose tolerance. In the present study, all our patients were diabetics and their serum vitamin D levels were low (than 75 nmol/L). Hence, it is possible that improved glycaemic levels after vitamin D supplementation were in relation to patients with already low levels of vitamin D.

The present study corroborates with the findings of Borrisova AM et al., who supplemented vitamin D in females with baseline vitamin D of 35.3±15.11 and found decrease in levels of fasting glucose but it was not statistically significant [28]. Gedik O and Akalin S, found that after vitamin D supplementation in vitamin D deficient group (vitamin D levels of 29.7±3.3 nmol/L), fasting glucose levels have improved [29]. Ismail A and Namala R, supplemented the subjects with either Vitamin D or high calcium, and found that insulin sensitivity was enhanced in vitamin D deficient group compared with normal controls [17].

In the present study, mean duration of diabetes in vitamin D supplemented group was about 10 years and there was no association found with the duration of diabetes in the patients responding to the treatment. Orwoll E et al., demonstrated that duration of diabetes did not influence the response of fasting indices to 1,25(OH)2D (glucose, insulin, C-peptide, and glucagon) but there was a correlation between the duration of diabetes and the response of 1,25(OH)2D treatment in maximal insulin secretion (p= 0.05) and in integrated insulin secretion (p= 0.052) [22]. Aksoy H et al., found negative correlation with duration of Diabetes Mellitus [15].

In the present study, patients were supplemented with 60,000 IU of cholecalciferol every 15 days for three months. In most of the previous studies, either the vitamin D levels were not done or patients were supplemented with activated form of vitamin D for shorter periods. It may be possible that longer period of supplementation gives better results. Gedik O and Akalin S, supplemented oral 2000 IU/day cholecalciferol for six months and found improved blood glucose levels [29].

All our patients were diabetics and their serum vitamin D levels were low (less than 75 nmol/L). In western studies showing no improvement, vitamin D levels were not done. It is possible that improved glycaemic levels after vitamin D supplementation were due to supplementation in patients with already low levels of vitamin D.

LIMITATION

Insulin sensitivity was not done. Sample size was small and the study was performed for shorter period of time.

CONCLUSION

It is concluded that supplementation of vitamin D for three months improved levels of post prandial sugar levels in vitamin D deficient T2DM patients in the present study. However, a larger study with more number of patients done for a longer duration would be helpful to determine the role of vitamin D in glycaemic control in T2DM.

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