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Research Article

To study the efficacy and safety of Vitamin D as an add-on therapy in patients of Type 2 diabetes mellitus on oral antidiabetic drugs

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ABSTRACT

Background: Predominance of Type 2 diabetes mellitus (DM) is increasing globally at an alarming rate. Therapies for Type 2 DM have improved but still there is a need for new insights to limit the progression of the disease. Vitamin D deficiency has been associated with many non-skeletal disorders including Type 2 DM, suggesting a role in pathogenesis of Type 2 DM. Therefore, the present study was designed to investigate the effect of Vitamin D as an add-on therapy in patients of Type 2 DM whose glycemic status was uncontrolled with oral antidiabetic drugs.
Methods: This was a before and after, open labeled study of 12 weeks duration, conducted on 50 patients of Type 2 DM and Vitamin D deficiency. These patients were given 60,000 IU of Vitamin D_3 orally/week for 12 weeks in addition to oral antidiabetic drugs. Effect of Vitamin D was observed on HbA_{IC}, fasting blood glucose (FBG), 25(OH)D and calcium levels.
Results: At the end of 12 weeks, a highly significant reduction ($p<0.001$) was seen in FBG levels and HbA_{IC} decreased significantly ($p<0.05$). Highly significant ($p<0.001$) increase was observed in 25(OH)D levels and calcium levels increased significantly ($p<0.05$). No untoward side effect was observed in any of the patients.
Conclusion: It establishes that Vitamin D therapy improves glycemic status thereby, delays the progression and consequently the complications of Type 2 DM. Therefore, supplementation of Vitamin D is a promising and safe adjuvant therapy in Vitamin D deficient Type 2 DM patients.

Keywords: Diabetes mellitus, Vitamin D deficiency, Vitamin D

INTRODUCTION

Diabetes mellitus (DM) is the most common condition of all non-communicable diseases globally. Nowhere is the diabetes epidemic more pronounced than in India. It had approximately 50.8 million persons affected by diabetes in 2010, which is expected to rise up to 87 million by 2030.[1] Type 2 DM is more predominant form of diabetes worldwide, accounting for 90% of all diabetes cases and is the main driver of the diabetes epidemic.[2] New cases of Type 2 DM are increasing worldwide in every nation with 80% of affected people living in developing countries. Therefore, Type 2 DM has become a very serious public health problem with a huge socio-economic burden to each country but developing countries like India bear the highest burden.[3]

The goals of therapy for Type 2 DM are to alleviate the symptoms related to hyperglycemia and to prevent or reduce the acute and chronic complications. The mainstay of management for Type 2 DM includes lifestyle and dietary changes. Pharmacological treatment is indicated when diet and lifestyle changes fail to achieve acceptable glycemic control.[4]

In last few decades, although therapies for Type 2 DM and its co-morbidity have improved but still there is a need for new insights for the prevention and management of Type 2 DM as there is increased the impact of the disease. There is enough evidence which suggests that Vitamin D plays a vital role in many non-skeletal disorders including Type 2 DM.[5] Vitamin D is found to exert both direct and indirect effects on various mechanisms related to the pathophysiology of Type

2 DM. This evidence gives a ray of hope for a new path for prevention and management of Type 2 DM.[6]

Vitamin D also known as "Sunshine Vitamin" is a fat-soluble vitamin existing in two forms, i.e., Vitamin D_2 (Ergocalciferol) and Vitamin D_3 (Cholecalciferol). Plants synthesize Vitamin D_2, whereas Vitamin D_3 is synthesized in skin when exposed to ultraviolet B rays from sunlight. Both Vitamin D_2 and Vitamin D_3 are biologically inactive. Thus, for activation various forms of Vitamin D require conversion in liver and kidney, to generate 25(OH)D (calcifediol), and 1, 25(OH)2D (Calcitriol), respectively, latter being the active form. This calcitriol binds to Vitamin D receptors (VDR's) present on various tissues to exert biological actions.[7,8]

Due to lack of exposure to sunlight and lack of dietary sources, Vitamin D deficiency is a pandemic these days. The prevalence of Vitamin D deficiency is increasing with an estimated number of one billion Vitamin D deficient people worldwide.[9] Most accurate way to determine Vitamin D deficiency is to measure 25(OH)D levels as it has a slower rate of clearance and longer biological half-life.[10] Serum 25(OH)D < 30 ng/ml is considered to be insufficient, concentrations between 30 and 150 ng/ml are sufficient and >150 ng/ml are usually toxic.[8]

It has been observed in various studies that risk of Type 2 DM is increased in those with low Vitamin D levels and that addition of Vitamin D improves glucose tolerance and decrease insulin resistance.[11-14] Impaired pancreatic beta cell function, insulin resistance, and systemic inflammation are often indicated for the development of glucose intolerance in Type 2 DM, and there is enough evidence to support that Vitamin D influences these mechanisms.[15] Beta cells in the pancreas have been shown to contain VDR's and 1alpha hydroxylase enzyme.[16,17] Vitamin D plays a significant role in maintaining insulin secretion not only in humans but also in animals. Insulin secretion has shown to be restored in Vitamin D deficient animals with reduced insulin secretion when supplemented with Vitamin D.[18] Vitamin D normalizes extracellular calcium, ensures normal calcium flux through membranes, and indirectly affects insulin secretion. Vitamin D also improves insulin action by stimulating expression of insulin receptors, enhances insulin responsiveness for glucose transport, and improves systemic inflammation by direct action on cytokines.[15]

Therefore, the present study was conducted to observe the effect of Vitamin D supplementation on glycemic profile of patients of Type 2 DM with concurrent Vitamin D deficiency, whose glycemic status was uncontrolled with oral antidiabetic drugs.

METHODS

Study design and settings

The present study was a before and after, open labeled study of 12 weeks duration, to evaluate the effect of Vitamin D supplementation on glycemic profile in patients of Type 2 DM with Vitamin D deficiency. Patients were selected from outpatient Department of Medicine in a tertiary care hospital a constituent of Sri Guru Ram Das Institute of Medical sciences and Research. The approval of ethics committee of the institution was obtained prior to the conduct of the study. Written informed consent was sought from all the patients prior to the study and all risks and benefits were explained to them in their own language. The selection of the patients was done on the basis of the following inclusion and exclusion criteria.

Inclusion criteria

Patients diagnosed with Type 2 DM on regular oral antidiabetic drugs with HbA_{1C} more than 7%. Patient with Vitamin D levels <30 ng/ml.

Exclusion criteria

Patients with history of Type 1 DM, with acute medical emergencies, evidence of metabolic disorder, gastrointestinal, cardiovascular, renal and liver disorders, already on Vitamin D and calcium supplementation, history of surgery in past 6 weeks or likely to undergo surgery during study period, hypersensitivity to Vitamin D, history of drug abuse, any clinical condition necessitating change in treatment, and pregnant and lactating females were excluded from the study.

Intervention

A total of 50 patients meeting inclusion and exclusion criteria were selected and given 60,000 IU of Vitamin D_3 orally/week for 12 weeks in addition to oral antidiabetic drugs. On the start of the study, after detailed patient history and clinical examination, routine investigations were done to exclude any comorbidity. The baseline FBG, HbA_{1C}, serum calcium, and serum 25(OH) D were obtained, and these patients were followed every 4 weekly up to 12 weeks. During the study, signs, symptoms and side effects of patients were recorded. FBG levels were observed after every 4 weeks, whereas HbA_{1C}, serum 25(OH) D and serum calcium levels were recorded at the end of the study, i.e., after 12 weeks. During the study, patients were instructed not to change their oral antidiabetic drugs/drug and diet.

Statistical analysis

Performed by using Microsoft SPSS, Version 17.0. Data were analyzed by descriptive tests and normality of variables was assessed by Shapiro-Wilks test and tabulated as mean ± standard deviation (SD). The effect of Vitamin D supplementation was analyzed by applying Paired Student's t-test. The level of significance was determined as its p value with $p>0.05$ taken as not significant, $p<0.05$ taken as significant at 5% significance level, $p<0.01$ taken as

significant at 1% significance level and p<0.001 taken as highly significant.

RESULTS

About 50 patients (28 males and 22 females) participated in the study. The mean age of the patients was 52.70±9.91 years, with a maximum number of patients in the age group of 51-60 years. The mean weight and height of the patients were 76.88±11.36 kg and 166.82±9.30 cm, respectively. Mean body mass index (BMI) was 27.7±4.05 kg/m^2, and majority of the patients (44%) were overweight having BMI in range of 25-29.9 kg/m^2. All patients were on oral antidiabetic drugs. Majority of these patients were on treatment with a combination of metformin and glimepiride (62%). In the study group, all the patients had normal routine parameters at the baseline.

With supplementation of Vitamin D mean FBG values showed a reduction over 12 weeks period. On comparison with mean baseline FBG values, there was no significant (p>0.05) difference in mean FBG levels after 4 weeks of Vitamin D supplementation, but significant (p<0.05) difference was observed after 8 weeks; whereas after 12 weeks of Vitamin D supplementation difference in mean FBG was highly significant (p<0.001) (Figure 1 and Table 1).

Comparison of mean HbA_{1C} before and after 12 weeks of Vitamin D supplementation showed significant (p<0.05) reduction. 12 weeks of Vitamin D supplementation increased mean calcium levels significantly (p<0.05) as compared to mean baseline values. Highly significant (p<0.001) increase was seen in mean 25(OH)D levels when compared to baseline and 92% of patients achieved optimal levels of 25(OH)D after supplementation with Vitamin D (Table 1).

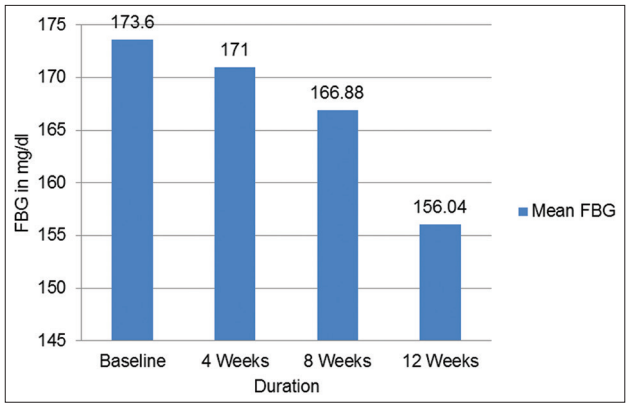

Figure 1: Mean fasting blood glucose levels with Vitamin D supplementation over 12-week period.

Table 1: The effects vitamin D supplementation on biochemical parameters (mean±SD) in Type 2 DM patients; n=50.

Parameters	Baseline	12 weeks	p value
FBG (mg/dl)	173.60±42.75	156.04±45.89	0.0003
HbA_{1C} (%)	9.42±1.59	8.81±1.82	0.010
Calcium (mg/dl)	8.97±0.59	9.11±0.58	0.012
25(0H)D (mg/dl)	17.73±7.04	42.74±11.81	0.0001

FBG: Fasting blood glucose, SD: Standard deviation

We stratified all the 50 patients according to their baseline 25(OH)D levels and divided them into 2 subgroups of 25(OH)D levels <20 ng/ml in 30 patients and 25(OH)D levels in between 20 and 30 ng/ml in 20 patients. Changes after 12 weeks of Vitamin D supplementation compared with baseline were analyzed in both these subgroups. It was seen that patients with lower 25(OH)D levels had higher mean baseline glycemic parameters and lower mean baseline calcium levels (Table 2).

DISCUSSION

The present study was conducted between the period of December 2013 and August 2015. In this study, efficacy and safety of Vitamin D when used as add-on with oral antidiabetic drugs was evaluated by checking glycemic control. 50 patients of Type 2 DM with Vitamin D deficiency not controlled on various oral antidiabetic drugs were included in the study. They were given Vitamin D_3 sachet of 60,000 IU weekly for 12 weeks orally and then glycemic status was compared with baseline values.

The results showed that Vitamin D supplementation of 12 weeks reduces FBG and HbA_{1C} significantly in Vitamin D deficient Type 2 diabetics. Effects of Vitamin D supplementation on glucose homeostasis have been shown by numerous studies. The results of the present study were consistent with many other studies in which FBG and HbA_{1C} improved after Vitamin D supplementation. Talaei et al. conducted a before and after study on 100 Type 2 DM patients and concluded that there was significant improvement in FBG levels after treatment with 50,000 IU of Vitamin D for 8weeks.[11] Lalitha et al. showed significant reduction in HbA_{1C} values in Vitamin D deficient Type 2 diabetics who were treated with Vitamin D as compared to those not on Vitamin D supplementation.[19] Nasri et al. also concluded that Vitamin D supplementation had beneficial effect on glycemic parameters in Type 2 DM male patients.[20]

There were also studies which didnot show reduction in glycemic parameters in patients of Type 2 DM when supplemented with Vitamin D.[10,21] This discrepancy seen in different studies might be related to duration of study and follow-up, study design, sample size, dosage or formulation of intake of Vitamin D and status of Vitamin D levels at the baseline; as the effect of Vitamin D on glucose intolerance is more prominent in patients with Vitamin D deficiency.[22] In a recent meta-analysis conducted by Haroon et al. found that Vitamin D supplementation improved glycemic control in various short-term studies (≤3 months) as compared to long-term studies (≤6 months) which showed no improvement in glycemic parameters.[23]

Table 2: The effects vitamin D supplementation on biochemical parameters (mean±SD) at different baseline 25(OH)D levels in Type 2 DM patients.

Parameters	25(OH)D<20 ng/ml (n=30)			25(OH)D 20-30 ng/ml (n=20)		
	Baseline	12 weeks	p value	Baseline	12 weeks	p value
FBG (mg/dl)	180.77±48.97	162.13±51.66	0.005	162.85±29.16	146.90±34.80	0.024
HbA_{1C} (%)	9.59±1.80	9.12±2.02	0.085	9.17±1.21	8.35±1.38	0.064
Calcium (mg/dl)	8.93±0.61	9.11±0.63	0.010	9.05±0.57	9.11±0.53	0.435
25(0H)D (mg/dl)	13.16±4.91	39.25±11.46	0.0001	24.59±2.93	47.96±10.56	0.0001

FBG: Fasting blood glucose, SD: Standard deviation

The addition of Vitamin D significantly increased calcium levels as compared to baseline. Calcium levels were basically done to rule out hypercalcemia due to hyperparathyroidism or Vitamin D toxicity after supplementation. The mean levels of calcium remained within the normal range at the baseline and also at the end of the study (ref. range: 8.5-10.1 mg/dl). These results were consistent with a study conducted by Al-Daghri et al.[24] which showed significant increase in calcium levels as compared with baseline after supplementation of Vitamin D for 18 months.

Highly significant increase was observed in 25(OH)D levels, and 92% patients achieved optimal levels of 25(OH)D after 12 weeks of Vitamin D supplementation. Studies conducted by Nasri et al.[20] and Al-Daghri et al.[24] also showed highly significant change in 25(OH)D levels after Vitamin D supplementation and studies conducted by Heshmat et al.[22] and Talaei et al.[14] showed significant change in levels of 25(OH)D after Vitamin D supplementation. Patel et al.[10] conducted a study in Vitamin D deficient Type 2 DM patients supplemented with subtherapeutic doses of Vitamin D for 4 months and showed no difference in glycemic parameters and serum calcium levels when compared to baseline. Though 25(OH)D levels significantly increased but none of the patient achieved optimal levels of 25(OH)D after 4 months of treatment. This shows that optimal dosage and proper schedule of Vitamin D is necessary to show its effects. Moreover, the amount of Vitamin D deficiency matters in concern to its effects.

Subgroup analysis was done to observe the change in glycemic parameters at different levels of 25(OH)D. It was seen that mean baseline FBG and HbA_{1C} was higher in the group which was more deficient in 25(OH)D. Similar findings were also present in a study conducted by Krul-Poel et al.[21] and Talaei et al.[16] pointing out that Vitamin D levels play a vital role in the degree of glucose intolerance, i.e., lesser levels will cause more glucose intolerance. Though significant decrease in levels of FBG was observed in both the subgroups but mean change from the baseline was higher in patients having 25(OH)D levels <20 ng/ml, which shows that greater effect of Vitamin D will be seen in the group having lower levels of 25(OH)D. In present study, HbA_{1C} changes were not significant in both the subgroups individually whereas, significant change was observed in the group as a whole. Contrarily, in the study conducted by Krul-Poel et al.,[21] no effect was seen on glycemic parameters after Vitamin D supplementation when analysis was done in whole group but significant reduction was seen in HbA_{1C} levels in a subgroup having Vitamin D <15 ng/ml. This difference may be due to small size of the group, non-existence of placebo group, short duration of the study, and different dose regimen of Vitamin D and inclusion of only Vitamin D deficient patients.

The mean baseline calcium levels were lower in subgroup having 25(OH)D levels <20 ng/ml. After 12 weeks of Vitamin D supplementation, significant change in levels of calcium was observed in subgroup having low levels of 25(OH)D but in the other subgroup change was not significant change was seen. It shows that Vitamin D in therapeutic doses also increases calcium levels.[25] In case of low levels of Vitamin D the calcium levels can be decreased because with Vitamin D deficiency, only 10% of ingested calcium may be absorbed.[26] After 12 weeks of Vitamin D supplementation in both the subgroups, Vitamin D increased to highly significant levels. At 12 weeks, 100% patients in the subgroup of 25(OH)D levels between 20 and 30 ng/ml had optimal levels of 25(OH)D; whereas in the subgroup of 25(OH)D levels <20 ng/ml 86.7% patients had optimal levels and 13.3% patients had levels below 30 ng/ml.

Regarding the safety and tolerability of Vitamin D, no untoward side effects or any signs of Vitamin D toxicity were recorded during or after Vitamin D supplementation in the present study, which may be due to the fact that only Vitamin D deficient patients were enrolled in this study and given Vitamin D supplementation for 12 weeks duration.

CONCLUSION

It establishes that Vitamin D therapy improves glycemic control thereby delays the progression and consequently the complications of Type 2 DM in Vitamin D deficiency; so supplementation with Vitamin D is a promising adjuvant therapy in these patients. Doses of 60,000 IU orally a week for 12 weeks are quite safe in Vitamin D deficient Type 2 diabetics so Vitamin D supplementation needs to be included in the treatment of Type 2 DM.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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