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Original Article

Effect of oral vitamin D supplementation on glycemic control in patients with type 2 diabetes mellitus with coexisting hypovitaminosis D: A parellel group placebo controlled randomized controlled pilot study

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ABSTRACT

Context: Vitamin D supplementation in type 2 diabetes mellitus patients may lead to improved glycemic control by improving insulin secretion and decreasing insulin resistance.
Aims: To investigate effect of oral vitamin D supplementation on glycemic control, in patients with type 2 diabetes mellitus and coexisting hypovitaminosis D.
Settings and design: Randomized, Parallel Group, Placebo Controlled Trial carried out in a tertiary care hospital of Indian Armed Forces.
Methods and material: Sixty patients with coexisting type 2 diabetes mellitus and hypovitaminosis D were randomized into cases and controls and were supplemented with oral Vitamin D and microcrystalline cellulose respectively for six months. Subjects' HbA1c and vitamin D levels were monitored at the beginning and end of the study, fasting plasma glucose (FPG) & post prandial plasma glucose (PPPG) during monthly OPD visits.
Statistical analysis used: Intra-group comparison was made by paired t test & unpaired t test was used for inter-group (A v/s B) comparisons. Repeated measures ANOVA was undertaken to compare values over time.
Results: The two groups were comparable for all parameters at baseline. Case group showed significant decrease in mean HbA1c levels (7.29% to 7.02%; P = 0.01), mean FPG levels (131.4 to 102.6 mg/dl; P = 0.04) and mean PPPG levels (196.2 to 135.0 mg/dl; P < 0.001). Incidentally, significant improvement in systolic as well as diastolic blood pressure and total cholesterol was also noted in the cases, while for LDL cholesterol improvement tended towards significance (p = 0.05).
Conclusions: We found that oral vitamin D supplementation was associated with improved glycemic control and other metabolic parameters in patients with type 2 diabetes mellitus. Supplementation to achieve normal levels of vitamin D can be a promising adjuvant therapy for T2DM patients & coexisting hypovitaminosis D.

1. Introduction

In the recent past a number of large observational studies have suggested an association between the onset of type 2 diabetes mellitus and vitamin D deficiency. Vitamin D has important effects on insulin action, and may have impact on a number of pathways which may be of importance in the development of type 2 diabetes [1]. Epidemiological studies examining vitamin D status and the risk of hyperglycemia or insulin resistance have thus far been suggestive of inverse associations but are inconclusive. Although there is some evidence to suggest that vitamin D deficiency influences postprandial glycemia and insulin response while supplementation may be beneficial in optimizing these processes, it has not been studied well.

Therefore, we planned this study with the aim to investigate the effect of oral vitamin D supplementation on glycemic control in patients with type 2 diabetes mellitus and coexisting hypovitaminosis D with the hypothesis that vitamin D supplementation will improve the parameters of glycemic control in patients with T2DM with concurrent hypovitaminosis D.

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2. Subjects and methods

2.1. Trial design

It was a randomized, parallel group, placebo controlled trial. Approval for this was granted by our hospital's Review Board for Human Subjects and written informed consent was obtained from all subjects.

2.2. Participants

Newly detected patients attending the endocrinology OPD at Command Hospital, Bangalore (a tertiary care hospital of Indian Armed Forces in South India) between 01 Jan 2012 to 31 Dec 2013 were included in the study.

Inclusion criteria were: patients with type 2 diabetes, aged 21–60 years, on stable dose of metformin for last 3 months, having HbA1c $\leq$ 8.5% & screening vitamin D (D2 & D3 level) $\leq$30 ng/ml.

Exclusion criteria were: hypertension patients, patients with overt features of hypovitaminosis D, abnormal liver function tests (LFTs), history of kidney stones or hypercalcemia. history of drug, alcohol, or illicit substance abuse within the past 6 months, h/o allergy/intolerance to oral vitamin D or microcrystalline cellulose, if taking mineral oil products, using antacids regularly, taking cortisone or other steroids, diuretics, weight-loss drugs, phenobarbital and phenytoin, gallbladder disease or gastrointestinal disorders and taking daily multivitamins, parathyroid disease, uncontrolled thyroid disease and those requiring chronic use of immunosuppressive therapy or corticosteroids, pregnant or lactating women were excluded from the study.

2.3. Intervention

Patients were randomized into two groups: vitamin D supplementation group (cases) and placebo group (controls) using a table of random numbers. Seven patient in placebo and 4 in vitamin D arm did not complete the follow up. Subjects were blinded to the study drug and received oral vitamin D (calcirol 60,000 IU every week for first six weeks and then once every 4 weeks till completion of study) and oral placebo (microcrystalline cellulose), both drugs having been given in identical packings. Existing medications including metformin, aspirin and statins were continued. Patients were followed up every four weekly.

Subjects' HbA1c and vitamin D levels were monitored at the beginning and end of the study, fasting plasma glucose (FPG) & post prandial plasma glucose (PPPG) during monthly OPD visits. 10 ml of venous blood was collected for HbA1c estimation, FPG and PPPG to be done at baseline and every 4 weeks for 24 weeks; vitamin D assay drawn at baseline and at end of study and preserved at −20 °C and HbA1c estimation was done at baseline, 12 weeks and 24 weeks. Serum 25(OH) vitamin D estimation was done by radioimmunoassay [fully automated IRMA SR300 using 25 OH- VitaminD RIA CT Kit, AMP 70-R4000 kits manufactured by Asbach Medical Products GmBH, Germany having relative coefficient of variation of 7.2%] and HbA1c estimation was done by HPLC method [RECIPE, Model- VARIENT using Clin Test solutions having relative coefficient of variation of 0.9%] in the Endocrinology lab while, biochemistry was done in central lab of the hospital using [SYSMEX auto analyzer, MODEL-EM 360 using standard reagents].

2.4. Outcomes

Primary outcome was to assess changes in parameters of glycemic control (FPG, PPPG, HbA1c) after vitamin D supplementation at prespecified intervals i.e. FPG, PPPG on monthly and HbA1c on 3 monthly intervals. Secondary outcome was to assess changes in blood pressure and lipid profile parameters after vitamin D supplementation wherein systolic and diastolic BP were checked on monthly and lipid profile measurements were done on 3 monthly basis.

2.5. Sample size

At confidence of interval level of 95%, to get power of study >85% we needed a total of 30 patients in each supplementation and placebo arms to assess the changes in parameters of glycemic control as compared to baseline.

Randomization was carried out using a table of random numbers.

2.6. Statistical methods

Various parameters of both the groups were compared. Data were expressed as mean ± SD. Intra-group comparison was made by paired *t*-test & unpaired *t*-test was used for inter-group (A v/s B) comparisons. Repeated measures ANOVA was undertaken to compare values over time. All *P* values were based on two-sided tests. The cut-off for statistical significance was 0.05. The Statistical Package for the Social Sciences (SSPS) for Windows version 16 was used for statistical evaluation of data.

3. Results

A total of 117 patients were counseled of which 71 gave consent. They were then randomized, into vitamin D supplementation group (cases, n = 30) and placebo group (controls, n = 30) using a table of random numbers. Seven patient in placebo and 4 in vitamin D arm did not complete the follow up (Fig. 1).

Participants' baseline characteristics are given in Table 1. The mean age of patients were 48 years in the supplementation group & 50 years in the placebo group and mean BMIs were 24.5 & 25.5 in the cases & control groups respectively. Both the groups were comparable for all parameters at baseline (Table 1).

As expected, vitamin D supplementations led to significant improvement in serum 25 (OH) vitamin D levels in cases (25.29 ± 8.58 ng/ml to 68.46 ± 10.22, $P < 0.001$) while it remained unchanges in controls. There was significant improvement in measures of glycemic control (HbA1c, FPG and PPPG) at the end of 6 months as compared to baseline in cases while no significant change was noted in controls (Table 2). In the timeline trend, the improvement in FPG and PPPG was seen in initial 3 months that was sustained over next 3 months of the study period as depicted in Figs. 2 and 3.

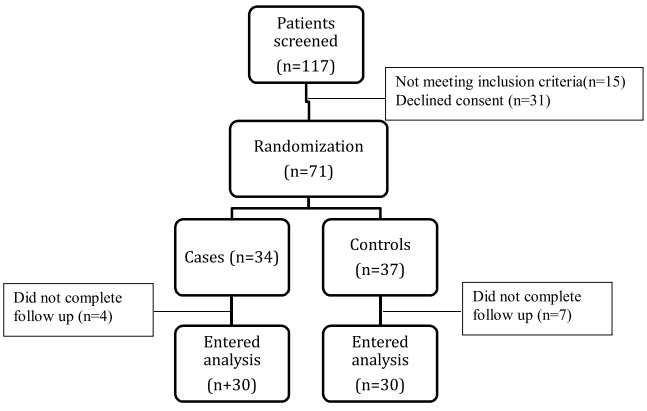

Fig. 1. Flow diagram of study design.

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