

Effectiveness And Safety Of Low Dose Vitamin D As An Adjunct Therapy In Patients With Type 2 Diabetes Mellitus: A Double-Blind, Randomised, Controlled Study

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Abstract

Background: The metabolic condition Type 2 Diabetes Mellitus causes insulin resistance and beta-cell malfunction. The presence of low-grade inflammation caused by an elevation in the cytokine's tumour necrosis factor-alpha and interleukin-6 in the blood is the most crucial indicator of T2DM. Given its potent immunosuppressive properties, specific pro-inflammatory cytokine genes, including interleukin-2, interleukin-12, and tumour necrosis factor-alpha, can be inhibited by vitamin D.

Methodology: Participants who satisfied the inclusion criteria and were already getting treatment for type 2 diabetes mellitus were screened from the general medicine outpatient department of a Tertiary Care Hospital in South India for this double-blind, randomised, controlled trial. Participants were split into two groups at random, with group 1 getting capsule vitamin D 6,000IU once a week for 16 weeks while group 2 got a placebo.

Results: Low Dose vitamin D proved to be more effective and safer in controlling HbA1c after 16 weeks compared to placebo.

Conclusion: Vitamin D is proven safe and cost-effective addition to anti-diabetic medicines

Keywords: Type 2 diabetes mellitus, Vitamin D, Anti-diabetic medications.

INTRODUCTION

One of the commonest metabolic disorders, type 2 diabetes mellitus, causes insulin resistance and beta-cell malfunction. 90% of all diabetes cases belongs to T2DM. Diabetes prevalence has been on the rise in India during the last ten years. Type 2 Diabetes Mellitus prevalence in India grew from 7.1% in 2009 to 8.9% in 2019. In India, there were 77 million diabetics as of the year 2019, and by the year 2045, it is predicted that there will be around 134 million. [1,2,3] Most important hallmark of T2DM is the occurrence of low-grade inflammation due to rise in the cytokine's interleukin-6 and tumour necrosis factor-alpha in the blood. This contributes to the development of insulin resistance, particularly in the muscles and adipose tissue. [4] Vitamin D, also known as "sunshine vitamin" is fat-soluble, that controls bone metabolism and aids in maintaining calcium equilibrium. Deficiency of this vitamin can aggravate many diseases. It is crucial for the development of diabetes as well as the tendency to it. [5] Being a robust immunosuppressant, vitamin D3 has the ability to reduce transcription of discrete pro-inflammatory cytokine genes, like interleukin-2, interleukin-12 and tumour necrosis factor-alpha. [6] Vitamin D stimulates beta cells of pancreas thereby increases secretion of insulin and also helps in the conversion of pro-insulin to insulin. [5] Till now, the effect of low dose vitamin D in diabetes stay behind, unexplored and only very few studies in India has been done. Hence this study

was done to assess glycaemic control (HbA1c) at 4 months after supplementing vitamin D in lower doses as an adjunct therapy to type 2 diabetes mellitus patients.

Methodology:

After obtaining ethical committee approval, participants meeting the inclusion criteria were screened from out-patient department of general medicine who were already on therapy for type 2 diabetes mellitus from a tertiary care hospital in South India. Participants with age > 50 years, Male / Female, type 2 diabetes mellitus on treatment, vitamin D < 35ng/ml were included in the study. Participants with age <50 years, vitamin D >35ng/ml, history of kidney stones, history of neurological diseases, history of psychiatric illness, history of hypothyroidism, electrolyte disturbances, history of consumption of drugs which have psychoactive effects such as benzodiazepines, tranquilizers, anti-depressants, current alcohol, or substance use disorder, history of severe renal or hepatic impairment or any critical illness. Sample size was estimated using the formula: $n = (Z^2 \sigma^2) / d^2$ $d = z \sigma(\sqrt{n})$, $Z = 1.96$ (Constant) $n = 30$ $\Sigma = 15$ (Standard Deviation) $d = 5$ (Standard Error)

After obtaining informed consent, data was collected which included demographic profile, past medical history, family history, drug history, personal history, blood pressure, heart rate, blood Investigations - HbA1c & vitamin D. Two groups of participants were randomly assigned, with group 1 receiving 6,000 IU of vitamin D in a capsule once a week for 16 weeks and group 2 receiving placebo. Participants were reviewed on week 1 and then at every 4 weeks till 16 weeks. The possible side effects of the vitamin D supplement such as nausea, vomiting, weakness, frequent urination, bone pain etc were explained to the participant and asked to report immediately. If any adverse effects of vitamin D reported, participants were excluded from the study. With the aid of Microsoft Excel, the data was coded and entered on a computer.

Using SPSS 21.0, analysis was carried out. Descriptive statistics were used in the statistical tests, and the results were presented as mean standard deviation (SD). Statistical significance was defined as a P-value of 0.05 or less.

Results:

Seventy-eight participants were evaluated for eligibility; eight of them were excluded (5 for not fulfilling the inclusion requirements, 3 for declining to participate), and two were unfollowable. (Fig – 1). Baseline characteristics of the population were comparable (Table – 1)

Figure – 1 Consort Flow Diagram

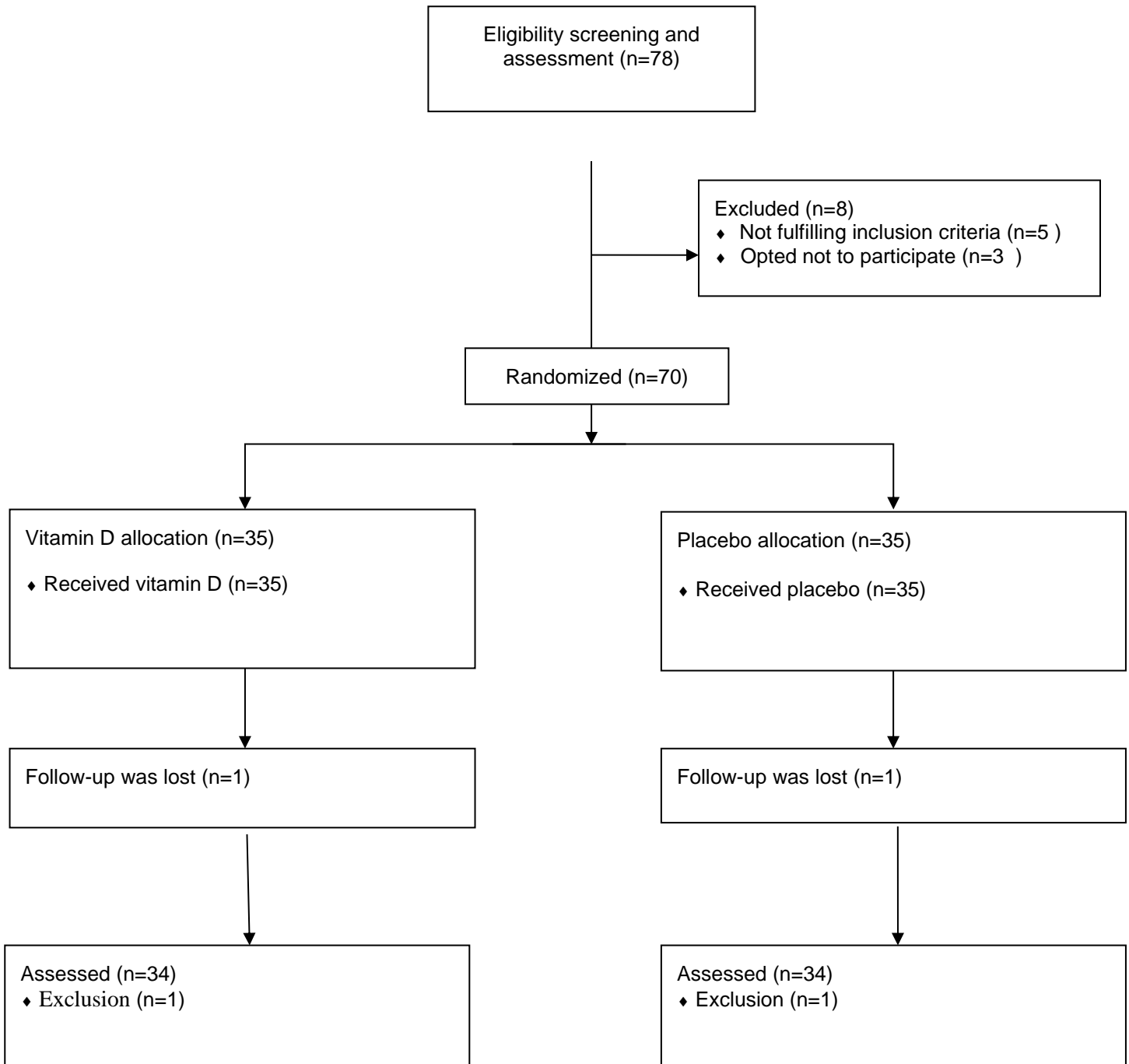


Table 1: Baseline Characteristics

| BASELINE CHARACTERISTICS | GROUP 1 (N=34) | GROUP 2 (N=34) | P VALUE |
|---|-----------------------|-----------------------|----------------|
| MEAN AGE: | 61 ± 6.46 | 60 ± 7.97 | 0.56 |
| SEX: | | | |
| MALE | 19(58%) | 16(46%) | |
| FEMALE | 15(42%) | 18(54%) | |
| MEAN SBP | 131.82 ± 6.05 | 130.02 ± 6.43 | 0.23 |
| MEAN DBP | 80.51 ± 2.40 | 81.6 ± 2.73 | 0.08 |
| MEAN BMI: | 25 ± 3.22 | 24 ± 3.29 | 0.20 |
| MEAN HbA1C: | 9.9 ± 2.69 | 9.1 ± 1.90 | 0.15 |
| MEAN VIT D: | 21.48 ± 0.40 | 21.49 ± 0.38 | 0.91 |
| SBP – Systolic Blood Pressure DBP – Diastolic Blood Pressure BMI – Body Mass Index HbA1C – Glycosylated Hemoglobin VIT D – Vitamin D | | | |

The participants were analysed for mean HbA1C and vit D at 16 weeks. Changes from week 0 to 16 week is depicted in Table 2 and Table 3.

TABLE 2: Change in mean HbA1C from week 0 to week 16

| GROUP | MEAN HbA1C AT WEEK 0 | MEAN HbA1C AT 16 WEEKS | P VALUE |
|--|-----------------------------|-------------------------------|----------------|
| Group 1 | 9.9 ± 2.69 | 5.4 ± 0.98 | 0.01 |
| Group 2 | 9.1 ± 1.90 | 6.2 ± 1.12 | |
| Group 1: Vitamin D receiving participants Group 2: Placebo receiving participants | | | |

TABLE 3: Change in mean vitamin D from week 0 to week 16

| GROUP | MEAN VITAMIN D AT WEEK 0 | MEAN VITAMIN D AT 16 WEEKS | P VALUE |
|--|--------------------------|----------------------------|---------|
| Group 1 | 21.48 ± 0.40 | 25.94 ± 2.45 | 0.01 |
| Group 2 | 21.49 ± 0.38 | 20.85 ± 1.2 | |
| Group 1: Vitamin D receiving participants Group 2: Placebo receiving participants | | | |

Over the course of the 16-week study period, none of the subjects in both the group reported any adverse effect.

Discussion:

The major goal of this double-blind, randomised, placebo-controlled study, which involved 68 patients with type 2 diabetes mellitus, was to see how well HbA1c was managed by taking a low dose of vitamin D supplements. In this comparative study we found that supplementation of vitamin D 6000IU once weekly for 16 weeks improved HbA1c level in participants receiving vitamin D compared to placebo. Participants in the vitamin D group did not report any adverse events, demonstrating the vitamin's safety.

A systematic review by Z malihi found that taking substantial doses of vitamin D2 or D3 daily, weekly, or monthly for a year or more did not increase the possibility of kidney stones or other negative outcomes considerably[7] A RCT by Z malihi et al, observed that the incidence rate of kidney stone events or hypercalcemia during a median of 3.3 years did not change with a monthly vitamin D3 intake of 100,000 IU[8] Dalgard C et al, discovered that as people age, their vitamin-D levels decrease. The reduction in skin's concentration of 7-dehydrocholesterol and possible decreased absorption of oral vitamin-D as people age could be the cause of this drop in vitamin D production.[9] Lu L et al, [10] and Kotwal SK et al,[11] discovered decreased vitamin D levels in people with rising fasting blood glucose. When vitamin -D levels were compared with post prandial blood sugar, almost all the patients with post prandial blood sugar abnormality had either low or insufficient levels. An inverse and substantial association between circulating vitamin D levels and risk of type 2 diabetes development was seen throughout a broad range of blood vitamin D levels in different populations, according to a meta-analysis of numerous prospective studies.[12] Zoppini G et al from Italy found that in people with type 2 diabetes, blood vitamin D levels are inversely correlated with HbA1c.[13] Buhary BM et al from Saudi discovered an oppositional link between blood vitamin D levels and HbA1c.[14] Sudhir Chandra Jha et al from North India indicated that in people with type 2 diabetes, the relationship between vitamin D and HbA1c was inverse. [15]

Supplementation of vitamin D in low levels will result in reduction of HbA1c in patients with T2DM and improve overall health of the patients. Limitations of our study were small group of participants and shorter duration. Hence, to support our findings, clinical trial with a big sample size and a lengthy duration is required.

Conclusion:

Type 2 diabetes care and management of complications is a challenge for physicians, patients, and their families. At present management standards focus on glycaemic control to reduce risk of long-term complications. Hence anti-diabetic medications can be supplemented with the safe and affordable vitamin D.

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Ethical Consent

Patient included in the study provided informed consent.

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To conduct the study no funding was used.

Conflict of Interest

There were no conflicts of interest, according to the authors.

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