

Efficacy of oral vitamin D on glycated haemoglobin (HbA1c) in type 2 diabetics having vitamin D deficiency — A randomized controlled trial

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Abstract

Objective: To study the efficacy of oral vitamin D in improving glycaemic control of patients with type 2 diabetes by reducing glycated haemoglobin levels.

Method: This randomised control trial was carried out at Mayo Hospital, Lahore, from February 5 to August 5, 2016, and comprised type 2 diabetes patients aged 40-70 years visiting the outpatient clinics. They were randomly divided into two groups by using the lottery method. Group A received oral vitamin D along with metformin and group B received metformin only. Blood samples of both the groups were tested for glycated haemoglobin at three months to assess the change. SPSS 21 was used for data analysis.

Results: There were 140 patients divided into two groups of 70(50%) each. Mean age in Group A was 54.80±8.55 years and 58.40±7.98 years in Group B. No significant difference was seen in glycated haemoglobin levels at baseline ($p>0.05$). However, after 3 months post-treatment the levels significantly differed ($p<0.05$) in favour of Group A.

Conclusion: Vitamin D supplementation had a significant effect in lowering glycated haemoglobin level in patients with type 2 diabetes.

Keywords: Vitamin D, HbA1c, Diabetes mellitus, Type 2, Supplementation. (JPMA 68: 694; 2018)

Introduction

One of the most common causes of vitamin D deficiency is reduced exposure to sunlight which ignites the synthesis of vitamin D through skin.¹ Apart from its most commonly understood roles with muscles and bones, vitamin D has numerous other functions.^{2,3} Nearly half of the world's population is vitamin D-deficient⁴ and its daily supplementation is recommended to combat this deficiency.⁵ Vitamin D supplementation is possible from various sources and a number of factors are considered before selecting its route of supplementation. Moreover, there is no fixed recommended dosage till date and it varies with practices and co-morbid conditions.⁶

Vitamin D has recently gained substantial importance in the field of medicine and endocrinology because of the latest research on new receptors at tissue level on which it particularly acts and exerts its multiple metabolic effects besides on bones and muscles.⁷ Pertaining to diabetes mellitus (DM), vitamin D has a significant role in maintaining glucose homeostasis. Decreasing vitamin D levels in serum have proven to increase insulin resistance (IR) and development of type 2 diabetes mellitus (T2DM).⁸

Studies have proved that vitamin D affects insulin

secretion and tyrosine phosphorylation of the insulin receptor.⁹ Observational studies all over the world have inferred an association between hypovitaminosis D and IR. Also, studies have observed inverse relationship between glycated haemoglobin (HbA1c) levels and vitamin D status in diabetics.¹⁰

A meta-analysis proved that vitamin D supplementation was associated with reduction in fasting blood sugar and HbA1c levels among type 2 diabetics having vitamin D deficiency.¹¹ One more trial also exhibited that with vitamin D supplementation, mean HbA1c was controlled to 6.76±0.18% as compared to metformin-only to 7.73±0.23% ($p=0.002$) after 12 weeks.¹² But one trial has reported that there was no difference whether vitamin D supplementation was given or not ($p=0.52$). With vitamin D supplementation, mean HbA1c was controlled to 7.85(6.6-9.8%) compared to metformin-only 6.95 (6.7-7.5%) after 12 weeks.¹³

Deficiency of vitamin D is common in diabetics which may lead to uncontrolled diabetes. However, vitamin D supplementation in diabetics can be helpful in achieving adequate glycaemic level. Multiple studies have conflicting results and conclusions. Literature has exhibited that replacing vitamin D decreases HbA1c level and maintains euglycemic status. The current study was planned to answer these conflicting roles of vitamin D in diabetics.

Patients and Method

This randomized control trial was carried out at Mayo Hospital Lahore's East Medical Ward from February 5 to August 5,

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2016, and comprised diabetics visiting the outpatient clinics. Sample size was calculated with 95% confidence level, 80% power of test and taking magnitude of HbA1c as $7.8 \pm 1.3\%$ with vitamin D and $8.5 \pm 1.6\%$ with metformin-only diabetics.

Those included were patients aged 40-70 years of either gender who were clinically asymptomatic with diagnosis of T2DM, taking only metformin and with an HbA1c range of 7.5-9.0 and 25-Hydroxy Vitamin D levels (25[OH]D) $< 20\text{ng/ml}$. Those excluded were patients having any inability or unwilling to participate; serum calcium levels $> 10.5\text{mg/dl}$; clinical proximal myopathy; intake of vitamin D, calcium or omega-3 supplements within the past 3 months; use of medications that could potentially influence vitamin D metabolism, notably oestrogens and calcitonin, within the past 3 months; any other concomitant clinical disease that could influence vitamin D metabolism; renal, hepatic, other endocrinological disorders; malignancies diagnosed on the basis of history; and use of insulin or any change in the type or dosage of current hypoglycaemic medications during the intervention period. Withdrawal criteria for premature termination of the trial depended upon the onset of hypercalcaemia, hypersensitivity to cholecalciferol, onset of urolithiasis, or any change in hypoglycaemic agents.

After approval was obtained from the review board of King Edward Medical University, Lahore, and informed consent from patients or their attendants, demographic information, body mass index (BMI), duration of DM was noted. Initially, blood sample for assessment of HbA1c was obtained from each patient after which they were randomly divided in two groups by using the lottery method. Group A received oral vitamin D along with metformin and Group B received metformin only. Group A patients were prescribed oral cholecalciferol 50,000 IU/week for 12 weeks after which patients were requested for a follow-up visit when blood sample for HbA1c

assessment were obtained from each patient.

SPSS 21 was used for data analysis. Age, BMI, duration of T2DM and HbA1c levels were presented as means with standard deviation. Gender was depicted as frequency and percentage. HbA1c level amongst the groups was compared using independent sample t-test. Effect-modifiers, like age, gender, BMI and duration of DM, were controlled through stratification. Independent sample t-test was applied by taking $p \leq 0.05$ as statistically significant.

Results

There were 140 patients divided into two groups of 70(50%) each. Mean age in Group A was 54.80 ± 8.55 years

Table-1: Descriptive statistics for HbA1c.

| Group | Base Line | | 3 Months | |
|----------------|-----------|--------|----------|------|
| | A | B | A | B |
| N | 70 | 70 | 70 | 70 |
| Mean | 8.21 | 8.25 | 5.93 | 7.02 |
| Std. Deviation | 0.44 | 0.47 | 0.61 | 0.59 |
| Minimum | 7.5 | 7.5 | 5.0 | 5.7 |
| Maximum | 9.0 | 9.0 | 7.0 | 8.0 |
| t-test | -0.590 | -10.66 | | |
| p-value | 0.56 | 0.000 | | |

Group A: Vitamin D with Metformin Group B: Metformin only
HbA1c: Haemoglobin A1c.

Table-2: Mean Vitamin D levels between both groups.

| | Group | VITAMIN D LEVELS (ng/ml) | | | p-value |
|----------|---------|--------------------------|---------|----------------|------------|
| | | N | Mean | Std. Deviation | |
| Baseline | Group A | 70 | 13.4900 | 3.73 | .320 |
| | Group B | 70 | 13.3971 | 3.36 | |
| 3 months | Group A | 70 | 28.8014 | 6.16 | < 0.0004 |
| | Group B | 70 | 15.1071 | 3.54 | |

Group A: Vitamin D with Metformin Group B: Metformin only.

Table-3: Mean HbA1c levels with different variables of the patients at baseline and 3 months with stratification.

| | | Base Line | | t-test | p-value | 3 Months | | t-test | p-value |
|----------------|--------|-----------------|-----------------|--------|---------|-----------------|---------------------|--------|---------|
| | | Group-A | Group-B | | | Group-A | Group-B | | |
| BMI | 20-25 | 8.20 ± 0.42 | 8.27 ± 0.45 | -0.72 | 0.47 | 5.96 ± 0.62 | 7.08 ± 0.54 | 9.43 | 0.001 |
| | 26-30 | 8.21 ± 0.48 | 8.21 ± 0.53 | -0.004 | 0.99 | 5.84 ± 0.60 | 6.88 ± 0.69 | 5.11 | 0.001 |
| Duration of DM | 1-5 | 8.15 ± 0.46 | 8.28 ± 0.52 | -1.21 | 0.27 | 5.96 ± 0.65 | 6.85 ± 0.64 | 5.87 | 0.001 |
| | 6-10 | 8.29 ± 0.40 | 8.23 ± 0.41 | 0.57 | 0.56 | 5.87 ± 0.56 | 7.18 ± 0.50 | 9.89 | 0.001 |
| Age | 40-55 | 8.20 ± 0.43 | 8.23 ± 0.48 | -0.223 | 0.824 | 6.02 ± 0.64 | 6.89 ± 0.65 | -5.08 | 0.000 |
| | 56-71 | 8.21 ± 0.45 | 8.26 ± 0.47 | -0.500 | 0.618 | 5.82 ± 0.57 | 7.08 ± 0.55 | -9.78 | 0.000 |
| Gender | Male | 8.21 ± 0.46 | 8.16 ± 0.50 | 0.428 | 0.670 | 5.95 ± 0.61 | $6.96 \pm 0.57 \pm$ | -6.59 | 0.000 |
| | Female | 8.20 ± 0.43 | 8.32 ± 0.44 | -1.22 | 0.225 | 5.91 ± 0.63 | 7.06 ± 0.61 | -8.313 | 0.000 |

HbA1c: Haemoglobin A1c

BMI: Body Mass Index

DM: Diabetes Mellitus.

and 58.40 ± 7.98 years in Group B (Table-1). No significant difference was seen in vitamin D levels at baseline ($p > 0.05$). However, after 3 months post-treatment, the levels significantly differed ($p < 0.05$) (Table-2). Mean HbA1c levels were compared with different variables like BMI, T2DM duration, age and gender at baseline and 3 months with stratification between the 2 groups (Table-3).

Improvement in glucose control as depicted by decline in HbA1c was achieved in Group A ($p = 0.000$).

Discussion

All over the world there are diabetics and their number is ever increasing.¹⁴ Currently, more than 280 million diabetics are estimated and the anticipation is that it will cross 438 million by the year 2030. Clinical trials have inferred mixed results regarding association of low vitamin D and development of diabetes even though epidemiological studies have established strong linkages between hypovitaminosis D and impaired glucose tolerance (IGT).¹⁵ Some epidemiological studies also advocate a relationship between low vitamin D and microvascular diabetic complications.¹⁶

Besides, 1, 25 dihydroxycholecalciferol exerts its action in maintaining euglycaemic environment in multiple ways. Activated vitamin D acts on beta cells of pancreas to impart insulin receptor gene expression.¹⁷ Moreover, vitamin D after its activation causes increase in serum calcium levels by enhancing its small intestinal absorption and calcium is a prerequisite for the insulin release from beta cells of pancreas.

In the recent past, studies on beta cells of pancreas have discovered that they have receptors for active form of vitamin D and these receptors have intrinsic capacity to convert inactive form of vitamin D to its active form.¹⁸ Researchers studied the role of vitamin D on glucose homeostasis and IR in T2DM patients and concluded that vitamin D replacement significantly declines HbA1c.¹² Results of the present study are consistent with the findings of that particular report. Another research contrarily exhibited no significant difference in the change of HbA1c between the groups.¹³ The study on the effect of vitamin D supplementation on glycaemic control in T2DM (SUNNY Trial) also endorsed that mean baseline HbA1c was same in both groups even after 6 months.¹⁹ Another interventional study done amongst 129 Korean patients failed to prove a therapeutic role of vitamin D in improving HbA1c or IR despite achieving its physiological serum levels.²⁰

A team of researchers did meta-analysis to see the results of vitamin D supplementation and improved vitamin D

status on blood sugar levels and IR in diabetic patients. They concluded that supplementation of Vitamin D, a minimum dose of $100 \mu\text{g/d}$ (4000 IU/d), significantly reduces fasting blood glucose, HbA1c, and homeostatic model assessment of insulin resistance (HOMA-IR) index, and helped to control glycaemic response and improve insulin sensitivity in T2DM patients.²¹ These conflicting conclusions led to some more interventional clinical trials and a landmark meta-analysis reported that there is no substantial or statistical evidence to date that vitamin D in its active form has a clinical and therapeutic role in treatment of T2DM patients in addition to the conventional anti-diabetic medicines.²²

On the contrary, a substantial number of observational studies established impaired glucose tolerance and hypovitaminosis D. Many ongoing studies have made the observations that deficiency of vitamin D is an independent risk factor for development of type 2 diabetes.²³ It still is a question to be answered that if vitamin D insufficiency and IR are a cause and effect phenomenon as both these entities are explicit among diabetics.

There can be many reasons why so many conflicting conclusions are made in different interventional studies about the therapeutic role of active vitamin D in improving glycaemic levels in diabetic patients. The variables under study in different studies were in contrast. Moreover, the follow-ups that were done in these studies and the time duration at which the outcome variables were measured were different. Finally, the formulations and dosage of vitamin D along with its route of administration and sample size all had an impact in the conclusion and are responsible for these varied results.

The conflicting observational and interventional results should compel the researchers to find the answers to all those unclear areas.

Considering its sampling size, relevant methodology and statistical analysis the results of the current study can be generalised to the population of T2DM patients having vitamin D deficiency on metformin. However, whether the results can be generalised to type 1 diabetics or to patients taking multiple medicines for the control of diabetes including those on insulin and HbA1c levels beyond 9%, needs to be proven by conducting more researches using varied samples and methods.

The present study has some limitations. Firstly, it is not a multicentre trial and the sample size was limited depending upon the study design and prerequisites. Moreover, sample of the diabetic patients was not

heterogeneous. Placebo was not given to metformin-only group so the difference could also be attributed to the psychological effect of additional pills in the intervention group. Further interventional studies are required which should try to answer all these conflicting conclusions.

Conclusion

Vitamin D supplementation along with the conventional anti-diabetic medicines in T2DM patients improved their glycaemic status as evidenced by reduction in HbA1c levels.

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