Original Article

Effect of Vitamin D supplementation on glycemic parameters and progression of prediabetes to diabetes: A 1-year, open-label randomized study

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ABSTRACT

Background: Whether Vitamin D supplementation in prediabetes subjects prevents the development of diabetes is a matter of debate, and the results are inconsistent. This open-label, randomized study in subjects with prediabetes evaluated the effect of 12 months of Vitamin D supplementation on glycemic parameters and progression of prediabetes to diabetes in an ethnically homogeneous Kashmiri population. **Materials and Methods:** A total of 147 subjects were diagnosed as prediabetes out of which 137 subjects were randomized to receive in addition to standard lifestyle measures, either Vitamin D 60,000 IU weekly for 4 weeks and then 60,000 IU monthly ($n = 69$) or no Vitamin D ($n = 68$). Fasting plasma glucose (FPG), 2-h plasma glucose and A1C levels were estimated at 0, 6 and 12 months. Changes in FPG, 2-h plasma glucose, A1C level and the proportion of subjects developing diabetes were assessed among 129 subjects. **Results:** At 12 months, A1C levels were significantly lesser (5.7% ± 0.4%) in the Vitamin D supplemented group when compared with non-Vitamin D supplemented (6.0% ± 0.3%). Similarly, FPG (97 ± 7) and 2-h plasma glucose (132 ± 16) were significantly less in Vitamin D supplemented group as compared with non-Vitamin D supplemented group (FPG = 116 ± 6 and 2-h plasma glucose = 157 ± 25) at 12 months. Nine out of 65 in non-Vitamin D supplemented and seven out of 64 in the Vitamin D supplemented group developed diabetes. **Conclusions:** Vitamin D supplementation in prediabetes subjects significantly lowered FPG, 2-h plasma glucose and A1C levels.

Key words: Diabetes, prediabetes, Vitamin D

Introduction

Diabetes mellitus and Vitamin D deficiency are prevalent worldwide. Several large studies have suggested a relationship between hypovitaminosis D and the prevalence of diabetes.[1-3] Prediabetes is an intermediate stage between normal glucose tolerance and type 2 diabetes mellitus. Many large studies have revealed a higher likelihood of progression of prediabetes to diabetes among Vitamin D deficient subjects.[4,5] Whether intervention with Vitamin D will decrease the progression of prediabetes to diabetes is not yet clear. Only a few, small and short term, studies in humans have analyzed the impact of Vitamin D supplementation on progression of prediabetes to diabetes.[6,7] The few recent studies of adequate sample size and duration also revealed mixed results. Pittas *et al.* reported a significant decrease in fasting plasma glucose (FPG) and homeostatic model assessment-insulin resistance (HOMA-IR) with calcium and Vitamin D supplementation over a period of 3 years in people with prediabetes, but not in those with normal glucose tolerance.[8] Another recent study, however, revealed that Vitamin D supplementation for 1-year in individuals with prediabetes and Vitamin D deficiency did not affect insulin sensitivity or development of diabetes

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.152783

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though A1C levels significantly decreased.[9] A recent Indian study revealed a significant decrease in FPG, IR and systemic inflammatory markers in people with Vitamin D deficiency and prediabetes after Vitamin D and calcium supplementation over a period of 1-year.[10] The Kashmir valley of the Indian subcontinent is situated at an altitude of 1574–5425 feet above the sea level in the Northern mountainous regions of India. Vitamin D deficiency is endemic in the valley and is seen in about 83% of healthy adults and 80–91% of people with diabetes.[11-13] The present study was designed to study the effect of Vitamin D supplementation on glycemic parameters (FPG, 2-h plasma glucose and A1C levels) over a period of 12 months in an ethnically homogeneous Kashmiri population with prediabetes.

Materials and Methods

This study was carried out in a Tertiary Care Teaching Hospital in North India. The sample size was calculated for moderate effect size, that is, $d = 0.5$ to detect the change in FPG, 2-h plasma glucose or A1C levels between the study groups with 80% power of study ($1\text{-}\beta = 80\%$) and $\alpha = 5\%$ between the groups with the help of statistical software for sample size calculation (G - power 3.1.5 and N master 2). The sample size for the two groups was calculated as 128 that is 64 in each group. A total of 147 subjects were diagnosed as prediabetes on the basis of elevated A1C levels, FPG and 2-h plasma glucose during an oral glucose tolerance test (OGTT); out of whom, 137 agreed to participate in the study. Prediabetes was diagnosed using the recent American Diabetes Association criteria: FPG between 100 and 125 mg/dL, 2-h plasma glucose after an OGTT between 140 and 199 mg/dL and A1C level between 5.7% and 6.4%. Informed consent was obtained from all the participants before randomization; the study was approved by institutional Ethics Committee and was carried out in accordance with the principles of the Declaration of Helsinki.

After an overnight fast, a baseline blood sample was obtained; another blood sample for plasma glucose was obtained 2 h following the ingestion of 75 g of anhydrous glucose in water. Plasma glucose concentration was measured by an enzymatic method using glucose oxidase and peroxidase on an automated analyzer (HITACHI 912). Serum 25-hydroxyvitamin D (25-OHD) level was measured by radioimmunoassay (RIA) in the baseline sample. The subjects were randomized by a computer generated code to receive, in addition to standard lifestyle measures and dietary advice, either Vitamin D (the Vitamin D supplemented group, $n = 69$) or nothing (the non-Vitamin D supplemented group, $n = 68$). Vitamin D (cholecalciferol IP) in the dose of 60,000 IU weekly for 4 weeks and then 60,000 IU monthly was given in the form of a chewable tablet (Eris Lifesciences, Ahmadabad, India). This loading dose of Vitamin D (60,000 IU weekly for 4 weeks) corrects Vitamin D deficiency rapidly in most Vitamin D deficient patients, followed by maintenance dose of 60,000 IU monthly.[14] All the subjects in the intervention group who completed 12 months of study took Vitamin D as prescribed as ascertained from the number of empty strips returned at each visit. Subjects were reminded each month telephonically to take the medication.

Subjects were seen monthly for the first 3 months and subsequently every 3 months for a total of 1-year. FPG, 2-h plasma glucose, and A1C levels were measured at baseline and at 6 and 12 months. A1C level was measured with high-performance liquid chromatography standardized to the diabetes control and complications trial assay. Vitamin D was measured at baseline and at 12 months using a RIA kit (Dia Sorin, Stillwater, Minnesota USA). The intra and inter-assay coefficient of variation ranged between 11.7–12.5% and 9.4–11.0% respectively. Vitamin D status was graded as deficiency <20 ng/mL (<50 nmol/L), insufficiency 20–30 ng/mL (50–75 nmol/L) and sufficiency >30 ng/mL (>75 nmol/L) as recommended by lips.[15]

Statistical analysis

All the continuous variables have been expressed in terms of mean ± standard deviation. The two groups of interest have been analyzed in terms of student's independent *t*-test after confirming the normality conditions of the distribution. People who developed diabetes were excluded from the analysis. Furthermore, the categorical variables have been analyzed with Chi-square test. All the results were discussed at 5% level of significance that is $P < 0.05$ considered as significant. Statistical Package for Social Sciences version 21.0 (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) was used for statistical analysis of the data.

Results

The results of FPG, 2-h plasma glucose, A1C level, randomization and completion rates are shown in the flow diagram [Figure 1]. Of 137 subjects with prediabetes, randomized into two groups, eight dropped out before 6 months follow-up leaving 65 in the non-Vitamin D supplemented and 64 in the Vitamin D supplemented group for an intention-to-treat analysis. The age at recruitment, body mass index, FPG, 2-h plasma glucose, A1C and Vitamin D levels were similar in the two groups. The mean

age of our study population was 47 ± 11 years that was comparable in the two groups [Table 1]. At baseline, 54.3% subjects had serum 25-OHD levels below 20 ng/mL (50 nmol/L), while 21.3% had levels of 20–30 ng/mL (50–75 nmol/L) and only 24.4% had above 30 ng/mL (75 nmol/L). Also at baseline 96 (75.6%) study subjects had 25-OHD levels below 30 ng/mL (75 nmol/L). The mean serum 25-OHD levels were 8.2 ng/mL (20.5 nmol/L), 24.7 ng/mL (61.7 nmol/L) and 39.4 ng/mL (98.5 nmol/L) in the deficiency, insufficiency and sufficiency group, respectively. Vitamin D supplementation in the doses used improved serum 25-OHD status significantly such that 68.2% subjects attained 25-OHD levels above 30 ng/mL (75 nmol/L), 17.4% subjects attained levels between 20 and 30 ng/mL (50–75 nmol/L) while the level was below 20 ng/mL (50 nmol/L) in only 14.2% at 12 months. Most of the patients who continued to be Vitamin D deficient after supplementation had baseline 25-OHD <10 ng/mL. In the nonsupplementation group, serum 25-OHD levels did not change significantly at 12 months compared with baseline.

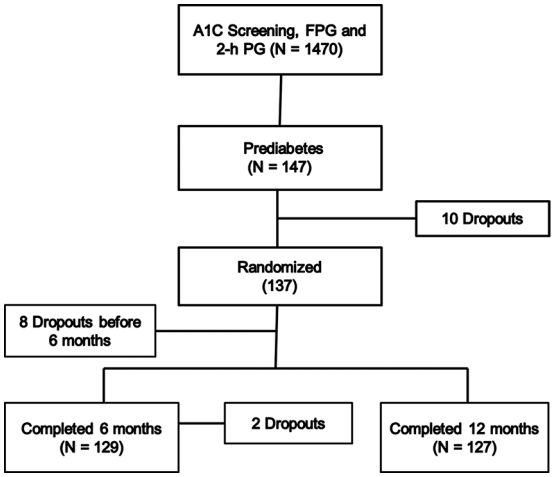

Figure 1 : Flow chart of the study

Table 1: Baseline characteristics (mean±SD) of non-Vitamin D and Vitamin D supplemented group

Parameter	Nonvitamin D supplemented group, (*n*=65)	Vitamin D supplemented group, (*n*=64)	*P*
Age (years)	48.5±11.8	47.6±9.5	0.65
BMI (kg/m^2)	25.2±3.1	25.9±2.6	0.74
FPG (mg/dL)	110±6	109±6	0.55
2 h glucose (mg/dL)	149±23	144±24	0.26
A1C level (%)	5.9±0.2	5.9±0.3	0.92
25-OHD (ng/mL)†	18.9±13.4	19.8±15.5	0.18

SD: Standard deviation, BMI: Body mass index, FPG: Fasting plasma glucose, A1C: Glycated hemoglobin, 25-OHD: 25-hydroxy Vitamin D. †To convert ng/mL into nmol/L, multiply by 2.496

In the non-Vitamin D supplemented group, FPG increased progressively at 6 and 12 months. This increase was significant both at 6 and 12 months [Table 2]. Similarly, 2-h plasma glucose also increased accordingly at 6 and at 12 months. However, this increasing trend was not significant either at 6 months.

In the Vitamin D supplemented group, FPG decreased progressively at 6 and at 12 months. This decrease was significant at 12 months but not at 6 months. 2-h plasma glucose was 144 mg/dL at baseline, 145 mg/dL at 6 months and 133 mg/dL at 12 months. This change also was significant at 12 months, but not at 6 months.

A1C levels in the non-Vitamin D supplemented group progressively increased at 6 and at 12 months. This increase was significant both at 6 and 12 months. In the Vitamin D supplemented group, A1C levels changed from 5.9% at baseline to 6.0% at 6 months and 5.8% at 12 months. This decrease in A1C was statistically significant at 12 months [Table 2].

Comparing the changes in FPG and 2-h plasma glucose between the two groups, the change was significant for both FPG ($P = 0.012$) and 2-h plasma glucose ($P = 0.046$) at 6 months. At 12 months, this change was more significant for both FPG ($P \leq 0.001$) and 2-h plasma glucose ($P < 0.001$). Although there was some decrease in A1C levels at 6 months ($P = 0.539$), but the difference was statistically

Table 2: Comparison of parameters between non-Vitamin D supplemented and Vitamin D supplemented group at 0, 6 and 12 months

	Non Vitamin D supplemented (months), (*n*=55)†			Vitamin D supplemented (months), (*n*=56)†			*P**	*P**
	0	6	12	0	6	12	6 versus 6	12 versus 12
BMI (kg/m^2)	25.2±3.1	25.3±2.8	25.4±2.8	25.9±2.6	26.2±2.7	26.3±2.3	-	0.059
FPG (mg/dL)	110±6	114±13	116±6	109±6	108±12	97±7	0.012	<0.001
2 h glucose (mg/dL)	149±23	154±27	157±25	144±24	145±24	132±16	0.046	<0.001
A1C (%)	5.9±0.2	6.1±0.5	6.0±0.3	5.9±0.3	6.0±0.5	5.7±0.4	0.539	<0.001
25-OHD (ng/mL)‡	18.9±13	-	22.4±12	19.8±15	-	43.4±23	-	<0.001
New diabetes *n* (%)	-	-	9 (13.8%)	-	-	7 (10.9%)	-	0.570

*Vitamin D versus non Vitamin D group, †After excluding subjects who developed diabetes, ‡To convert ng/mL into nmol/L, multiply by 2.496. BMI: Body mass index; FPG: Fasting plasma glucose; A1C: Glycated hemoglobin; 25-OHD: 25-hydroxy vitamin D

significant at 12 months ($P \leq 0.001$) [Table 2]. Subanalysis of those subjects having baseline serum Vitamin D levels below 30 ng/mL revealed that FPG, 2-h plasma glucose, and A1C levels changed significantly at 12 months. Those subjects who had baseline serum 25-OHD levels above 30 ng/mL also showed statistically significant change in FPG, 2-h plasma glucose and A1C levels at 12 months. This change was, however, less pronounced in those subjects who had baseline Vitamin D levels above 30 ng/mL [Table 3].

Nine out of 65 subjects (13.8%) in non-Vitamin D supplemented group and seven out of 64 (10.9%) subjects in the Vitamin D supplemented group developed diabetes. Body mass index did not change significantly from baseline in either group.

Discussion

Vitamin D deficiency and type 2 diabetes mellitus are two common disorders throughout the world, including the Indian subcontinent. Ours is an ethnically homogeneous population with high prevalence of diabetes mellitus and Vitamin D deficiency.[11,12] An association has been demonstrated between Vitamin D status and prevalence of diabetes, with low prevalence in people with high Vitamin D status.[16] Prediabetes is the stage of glucose dysregulation ultimately progressing to overt diabetes and many interventions (including metformin and life style modification) have been tried to retard its progression. Life style modification with weight loss of around 5% results in a significant decrease in progression to overt diabetes; maintenance of weight loss over time, however, is difficult.[17] Vitamin D probably has little role in the prevention of diabetes in people with normoglycemia.[8] It has been suggested that in individuals with prediabetes, low serum 25-OHD levels can promote further deterioration in glucose tolerance. Hence, the role of Vitamin D supplementation in progression of prediabetes to overt diabetes is being explored.

Our study revealed that correcting Vitamin D deficiency in people with prediabetes significantly reduces FPG, 2-h plasma glucose and A1C levels at 12 months. Many previous studies revealed no benefit of Vitamin D supplementation in progression of prediabetes to diabetes.[7,18-20] The lack of benefit in those studies may be because of small numbers of subjects and short duration (maximum 6 months) of intervention. In the study by Pittas *et al*.[8] wherein combination of calcium and Vitamin D was studied over a period of 3 years, a significantly lower rise in FPG and decrease in HOMA-IR were seen. The results of the present study confirm the findings of the previous short term studies that no major changes in glycemic parameters (fasting, 2-h plasma glucose and A1C) will be evident at 6 months of Vitamin D supplementation. It is believed that Vitamin D receptors are present in beta cells of islets of Langerhans, which also possess 25-OHD 3-1α hydroxylase enzyme.[21,22] Vitamin D receptors are also demonstrated in skeletal muscle, adipocytes and liver.[23-25] Vitamin D supplementation has been shown to activate Vitamin D receptors on beta cells, and improve insulin secretion,[26,27] cause expression of insulin receptors and increased responsiveness of glucose transport *in vitro*.[28]

Two recent studies of sufficient sample size and duration on Vitamin D supplementation in people with prediabetes have been published. Davidson *et al*. demonstrated no differences in insulin sensitivity, insulin secretion, FPG and 2-h plasma glucose after increasing serum 25-OHD levels to 70 ng/mL (175 nmol/L) in people with prediabetes and Vitamin D of <30 ng/mL (75 nmol/L). However, A1C levels were significantly less ($P = 0.004$) at 1-year in people with Vitamin D supplementation.[9] Though no subject experienced increased serum or urinary calcium excretion, the benefits or undesirable effects of increasing 25-OHD levels to >50 ng/mL (125 mmol/L) are not clear as yet, with some even suggesting a U shaped relation between mortality and Vitamin D levels.[29] Another recent study has revealed that best mortality benefits are achieved at serum Vitamin D levels between 30 and 49.9 ng/mL,[30] our study has achieved a mean serum 25-OHD Level of 42.2 ng/mL in the Vitamin D supplemented group. The cut-off for serum 25-OHD levels are recommended mainly for its skeletal outcome, wherein 30–49.9 ng/mL is defined as potentially beneficial and ≥50 ng/mL as potentially harmful.[31] Another study from Eastern India (with high prevalence of Vitamin D deficiency and prediabetes) revealed significant improvement in glycemic parameters (FPG, 2-h plasma glucose and A1C levels) 1-year after supplementation of calcium and Vitamin D as against a group receiving calcium supplementation only. The study also revealed low progression to overt diabetes in Vitamin D and calcium supplementation group.[10] Serum 25-OHD level of >30 ng/mL was achieved in 80% of the group in combined supplementation group,

Table 3: Changes in glycemic parameters at 12 months in vitamin D supplemented group depending on baseline 25-OHD levels

	Subgroup with baseline 25-OHD <30 ng/mL			Subgroup with baseline 25-OHD >30 ng/mL		
	0	12	*P*	0	12	*P*
FPG (mg/dL)	109	97	<0.001	108	98	0.003
2 h glucose (mg/dL)	141	132	0.046	147	131	0.049
A1C (%)	5.9	5.7	0.017	6.0	5.7	0.045

A1C: Glycated hemoglobin, FPG: Fasting plasma glucose, 25-OHD: 25-hydroxy Vitamin D

but exact mean 25-OHD levels achieved are not clear. The differences in the recent studies might be due to differences in the relationship between Vitamin D and glucose metabolism in varied ethnic populations. The Third National Health and Nutrition Examination Survey revealed an inverse relationship between serum 25-OHD levels and FPG in nonhispanic white, but not in nonhispanic black persons.[32] It is believed that a serum 25-OHD level of 15 ng/mL (37.5 nmol/L) or less may be a threshold at which Vitamin D deficiency confers negative effect on insulin sensitivity.[33] In the present study, about 50% of patients with prediabetes had serum 25-OHD levels below 15 ng/mL (37.5 nmol/L). Vitamin D receptor polymorphism, which is racially determined may also affect the relationship between Vitamin D and insulin sensitivity.[34]

In summary, in Kashmiri population with high prevalence of prediabetes and Vitamin D deficiency, Vitamin D supplementation over a period of 1-year resulted in improvement in glycemic parameters, although no effect on the rate of progression to overt diabetes was seen.

Acknowledgments

This study was wholly supported by Sher-I-Kashmir Institute of Medical Sciences (SKIMS), Soura, Jammu and Kashmir, India and provided necessary grant for the study. Authors also acknowledge the help of Dr. Rayees Ahmad Dar for help in statistical analysis. The authors thank Khalid J Farooque, Suman Kotwal, Manzoor Ahmad Bhat, Nazir Ahmad Pala, Mahroosa, Idrees Mubarik, Shahnawaz Ahmad Mir and Hammad-ur-Rahaman for both recruiting and screening subjects; Umar for doing A1C levels, Mohammad Shafi for measuring Vitamin D levels and Rayees Ahmad for doing statistical analysis. Eris Lifesciences Pvt. Ltd., Ahmadabad, Gujarat provided Vitamin D.

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Cite this article as: Kuchay MS, Laway BA, Bashir MI, Wani AI, Misgar RA, Shah ZA. Effect of Vitamin D supplementation on glycemic parameters and progression of prediabetes to diabetes: A 1-year, open-label randomized study. Indian J Endocr Metab 2015;19:387-92.

Source of Support: Nil, **Conflict of Interest:** None declared.