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Original Article

Vitamin D supplementation on prediabetic adults with vitamin D deficiency: a double-blind placebo-controlled randomized clinical trial

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Abstract

Hypovitaminosis D (<20 ng/mL) is thought to increase insulin resistance and meta-inflammation contributing to the pathogenesis of diabetes mellitus (DM). Correcting vitamin D deficiency in people with prediabetes might halt its progression to DM. The aim of this study was to examine the effect of vitamin D supplementation on insulin resistance, glycemic status, and inflammation in prediabetic adults with vitamin D deficiency. This double-blind randomized placebo-controlled trial was done among 27 newly detected prediabetic adults with hypovitaminosis D randomly assigned to 60,000 IU of vitamin D weekly for eight weeks followed by monthly for the next four months or placebo along with lifestyle modification in both groups [vitamin D (n= 14) vs. Placebo (n=13). They were comparable in terms of sex, age and borlymass index. Glycemic status, fasting plasma glucose (FPG) and Hemoglobin A1C (HbA1C), insulin resistance (homeostasis model assessment of insulin resistance (HOMA-IR) and inflammatory marker high sensitivity C reactive protein (hs-CRP) were measured at baseline and after six months of intervention. Vitamin D levels (ng/mL) increased in both groups from baseline (vitamin D vs. placebo: 12.2±5.9 vs. 3.9±3.5, mean±SD). FPG (mmol/L) significantly decreased in the Vitamin D group (before vs. after: 5.9±0.6 vs. 5.5±0.7, *P*=0.016, mean±SD), whereas HbA1C (%) and hs-CRP (mg/L) significantly increased in the placebo group (before vs. after-HbA1C: 5.8±0.3 vs. 6.0±0.4, *P*<0.001; hs-CRP: 5.0±4.4 vs. 5.6±4.9, *P*=0.039, mean±SD). Percent changes in glycemic status, HOMA-IR, and hs-CRP were statistically similar between the groups. Our study failed to demonstrate the positive effects of vitamin D supplementation on reducing glucose, insulin resistance, or inflammatory marker in prediabetic adult patients with hypovitaminosis D.

Keywords: Vitamin D, Prediabetes, Insulin resistance, Glycated hemoglobin A1C, HOMA-IR, High sensitivity C-reactive protein

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Introduction

Vitamin D has several extra-skeletal roles, including its contribution to glucose homeostasis. Recent studies suggest that its deficiency is associated with both pancreatic β-cell dysfunction and insulin resistance.[1] Hypovitaminosis D causes activation of the renin-angiotensin system and β-cell apoptosis, low-grade inflammation, inactivation of the insulin gene, and reduced calcium flux leading to reduced insulin secretion. Increased insulin resistance is also a feature of vitamin D deficiency resulting from secondary hyperparathyroidism, meta-inflammation, and reduced expression of the insulin receptor.[2] Many clinical studies found an association of vitamin D deficiency with glucose intolerance, glycemic control, and progression from prediabetes to frank diabetes mellitus (DM), even in prospective studies.[3,4] These attractive findings led researchers to look forward to the role of vitamin D supplementation in preventing the development of DM in vitamin D-deficient patients with prediabetes. However, the results are conflicting.[5,6] One of the possible explanations might be the differences in genetic factors between different races. In a meta-analysis, an association between insulin resistance-related diseases and vitamin D receptor gene polymorphisms (ApaI, BsmI, FokI variant) was more obvious in dark-pigmented Caucasians and Asians but not in Caucasians with white skin.[7] An association was also found between vitamin D receptor gene polymorphisms (ApaI variant) and insulin secretion in Bangladeshi Asians, categorized as at risk for type 2 DM (T2DM).[8] So, there is a possibility of the high prevalence of hypovitaminosis D in our population that may affect insulin secretion and resistance adversely, causing prediabetes and DM. According to International Diabetes Federation, in 2021 around 14.2% of the total adult population had prediabetes and Bangladesh will be the 7th country in the whole world with a number of affected people with DM in 2045.[9] So, the burden is huge and needs urgent preventive measures. Vitamin D deficiency is a modifiable risk factor that can be easily corrected by supplementation. There is no published data on vitamin D supplementation in prediabetic adults with vitamin D deficiency in Bangladesh. The aim of this study was to examine the changes in glycemic status, insulin resistance, and inflammatory marker on vitamin D supplementation.

Methods

This double-blind placebo-controlled trial was done during the period of July 2018 to August 2019 in the department of Endocrinology, BSMMU among newly detected prediabetic adults with vitamin D deficiency (<20 ng/ml).[10] The study protocol was approved by the institutional review board of Bangabandhu Sheikh Mujib Medical University (No. BSMMU/2018/6240). Informed written consent was taken from each participant.

Using the following formula [$n=\{(Z_\alpha + Z_\beta)^2 \times (\sigma_1^2 + \sigma_2^2)\} \div(\mu_1 - \mu_2)^2$], taking the mean and SD differences of vitamin D (0.5±0.6) and placebo (0.32±0.1) groups from a previous study for HOMA-IR, at 80% power (0.85) and 95% confidence interval (1.96), the minimum sample size was 29.[11,12] At first 103 newly detected adults with prediabetes diagnosed based on American Diabetes Association, 2018 criteria attended in the Endocrinology outpatient department were screened for eligibility.[13] Five patients with body mass index ≥35 kg/m^2 or a history of intake of vitamin D or calcium within 120 days were excluded. Serum vitamin D (high-performance liquid chromatography), intact parathormone, calcium, albumin, phosphate, and alkaline phosphatase (all by chemiluminescent immunoassay) were done in the remaining 98 patients in the fasting state. A total of 57 patients with vitamin D levels ≥20 ng/mL (insufficient and sufficient vitamin D status) and seven patients with high iPTH (>65 pg/mL) were excluded. Meanwhile, two patients became pregnant and two declined to participate in the study. Finally, 30 patients with vitamin D deficiency were included in the intervention **(Figure 1)**.

After taking baseline clinical data (demographic information, height, weight, blood pressure, acanthosis nigricans, skin tag), fasting blood for measurement of glucose (glucose oxidase), insulin (chemiluminescent microparticle immunoassay), high sensitivity C reactive protein (hs-CRP) (immunoturbidimetric assay) and HbA1C (turbidimetric inhibition immunoassay) and 2-hours glucose after oral glucose tolerance test (OGTT), the study participants were randomized into two groups by internet based calculator (Link: https://www.graphpad.com/quickcalcs/randMenu/).

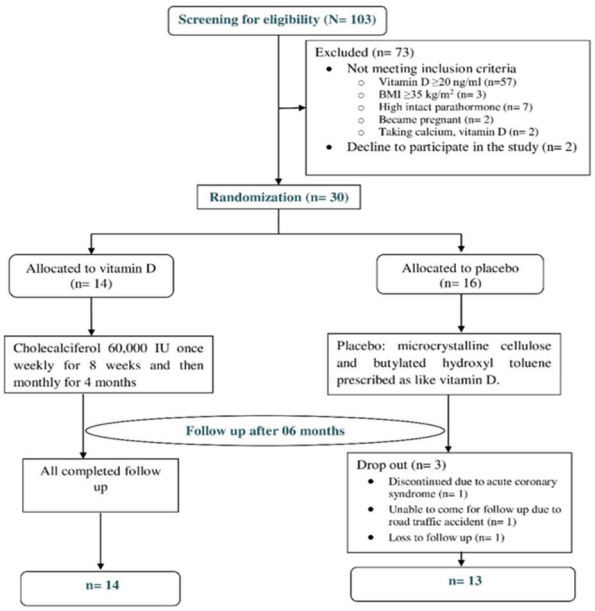


FIGURE 1 The study flow chart

Investigator's code number was given for each subject which acted as their identification number (ID). It is worth mentioning that each individual investigational product (IP)/placebo box (allocated for a single subject) carried a unique code-number (blinded for patient and investigator) and the same code-number was also held by each blister-strip containing box. A common container held all of these unique code numbers labeled stickers for the purpose of lottery. On a lottery basis a sticker was drawn from the common-box by the patient and the sticker holding IP/placebo-code was written on the data sheet of the particular patient. A written prescription form was given to each subject containing their ID, the IP/placebo code number, the mobile phone number of the investigator and the schedule of IP/placebo to be taken. All through the study period, the patient was being dealt with against this particular ID and code number. Each capsule in the IP box contained the excipients with either vitamin D or placebo (blinded to the patient and the investigator). The study medication was cholecalciferol 60,000 IU prescribed once weekly for eight weeks and then monthly for four months and the placebo contained microcrystalline cellulose and butylated hydroxyl toluene prescribed as like vitamin D. Standard life style modification was advised to all participants. It included weight-based calorie intake and a daily walking of at least 30 minutes/day for at least 5 days a week. The first dose of IP/placebo was taken by the participant in front of the investigator and immediate side effects were observed. Patients were given full course of IP/placebo to carry in home. They were instructed to report any adverse events. Drug compliance and any side effects were monitored by telephone conversation. Patients were asked for a follow-up visit after six months with 14 days window period with the prescription form and blister-containing box. A total of 27 patients completed the final visit. Empty blisters were counted; compliance and side effects were asked. Relevant clinical information was taken and fasting venous blood was collected to measure glucose, insulin, hs-CRP, and HbA1C. Insulin resistance was calculated by homeostasis model assessment of insulin resistance (HOMA-IR) with the following formula [HOMA-IR= (fasting insulin in μIU/ml × fasting glucose in mmol/L) ÷ 22.5].[14] On unblinding, 13 were in the placebo group and 14 were in the vitamin D group. Three patients from the placebo group dropped out.

All data were entered, edited, and analyzed by the SPSS program (version 22.0). Data were expressed in mean±standard deviation (SD) or frequency (percentages, %) as appropriate. Comparison between the study groups was done by independent samples t-test or Pearson's chi-square/Fisher's exact test as applicable. Comparison within the group (before-after) was done by paired t-test or McNemar test as appropriate. A two-tailed P-value <0.05 was considered statistically significant.

Results

This double-blind randomized placebo-controlled trial was done among 27 newly detected prediabetic adults with vitamin D levels below 20 ng/mL, where 14 patients were randomly allocated to receive vitamin D and 13 patients received a placebo.

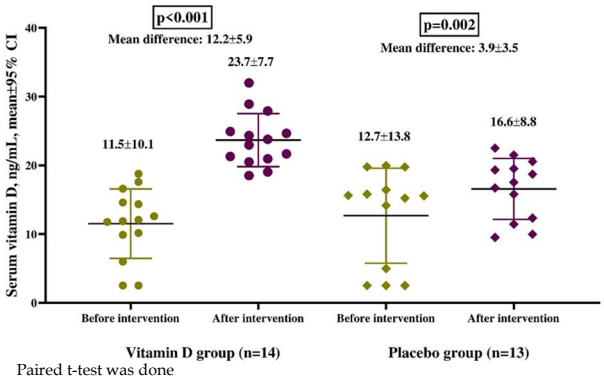
All the baseline variables were statistically similar between the intervention groups (NS for all) except the family history of DM, which was significantly higher in the vitamin D supplementation than in the placebo group (vitamin D vs. placebo: 92.9% vs. 53.8%, *P*=0.033). None of the study participants had any history of alcohol consumption or use of any sunscreen lotion **(Table 1)**.

TABLE 1 Background characteristics of the study population (n= 27)

Variables	Vitamin D (n=14)	Placebo (n=13)	*P**
	Mean±SD or frequency (%)		
Age in years	37.6±8.9	38.5±8.0	0.786
Sex			
Male	03 (21.4)	04 (30.8)	0.678
Female	11 (78.6)	09 (69.2)	
Residence			
Urban	12 (85.7)	10 (76.9)	0.648
Rural	02 (14.3)	03 (23.1)	
Occupation			
Housewife	11 (78.6)	09 (69.2)	0.678
Others	03 (21.4)	04 (30.8)	
Educational status			
Illiterate to below SSC	07 (50.0)	09 (69.2)	0.310
SSC and above	07 (50.0)	04 (30.8)	
Socioeconomic status†			
Low	06 (42.9)	07 (53.8)	0.568
Middle and high	08 (57.1)	06 (46.2)	
Physical activity†			
Light	06 (42.9)	07 (53.8)	0.706
Moderate	08 (57.1)	06 (46.2)	
Smoking status†			
Smoker (present/ past)	01 (7.1)	01 (7.7)	1.00
Nonsmoker	13 (92.9)	12 (92.3)	
Sunlight exposure time†			
Adequate	2 (14.3)	3 (23.1)	0.648
Inadequate	12 (85.7)	10 (76.9)	
Family history of DM			
Present	13 (92.9)	7 (53.8)	0.033
Absent	1 (7.1)	6 (46.2)	

†Definitions taken from a previous study[14]
*Pearson's chi-square/ Fisher's exact test or independent samples-t test were done, as appropriate.

Serum vitamin D levels were overall increased in both groups after the intervention. None except one case of vitamin D supplementation could achieve sufficient vitamin D level (≥30 ng/mL) after six months of therapy **(Figure 2)**.



Paired t-test was done

FIGURE 2 Individual serum vitamin D levels with mean differences in the study groups at baseline and after intervention (n=27)

All the outcome variables were statistically similar between the study groups both before and after the intervention (NS for all). After six months of intervention, both BMI and WC [before vs. after: BMI (kg/m^2)- vitamin D: 28.8±3.6 vs. 27.7±3.5, P<0.001; placebo: 28.5±2.5 vs. 27.2±3.0, P=0.025; WC (cm)- vitamin D: 99.2±9.4 vs. 94.5±7.6, P=0.004, placebo: 97.1±6.5 vs. 93.4±7.4, P=0.043] significantly reduced in both groups. FPG (mmol/L) significantly reduced in only the vitamin D supplementation group (before vs. after: 5.9±0.6 vs. 5.5±0.7, P=0.016), whereas HbA1C and hs-CRP [before vs. after: HbA1C (%)- 5.8±0.3 vs. 6.0±0.4, p<0.001; hs-CRP (mg/L)- 5.0±4.4 vs. 5.6±4.9, P=0.039] increased in the placebo group. Other clinical and biochemical variables did not significantly change in both groups (NS for all) **(Table 2)**.

There were no statistically significant percent changes in any outcome variables between the intervention groups (NS for all) **(Figure 3)**.

TABLE 2 Outcome variables of the study population (n=27)

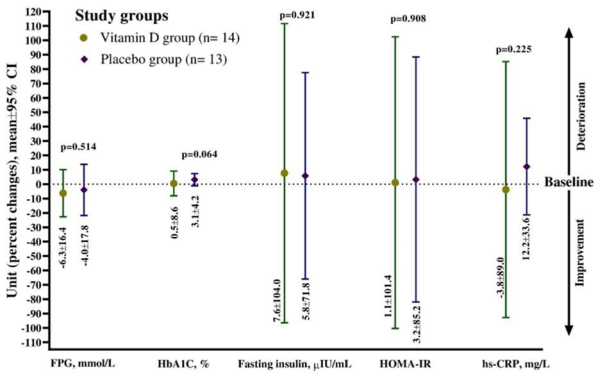
Variables	Before intervention		P^B	After intervention		P^A	P^D	P^P
	Vitamin D (n=14)	Placebo (n=13)		Vitamin D (n=14)	Placebo (n=13)			
	mean±SD or frequency (%)			mean±SD or frequency (%)				
BMI, kg/m²	28.8±3.6	28.5±2.5	0.776	27.7±3.5	27.2±3.0	0.698	<0.001	0.025
WC, cm	99.2±9.4	97.1±6.5	0.511	94.5±7.6	93.4±7.4	0.703	0.004	0.043
SBP, mm-Hg	126.2±13.6	123.1±16.1	0.587	121.8±12.5	120.8±13.1	0.838	0.215	0.529
DBP, mm-Hg	82.3±8.7	85.2±11.0	0.446	80.4±6.9	83.5±7.2	0.264	0.540	0.378
Acanthosis nigricans	5 (35.7)	7 (53.8)	0.449	5 (35.7)	6 (46.2)	0.704	1.000	1.000
Skin tags	7 (50.0)	4 (30.8)	0.440	9 (64.3)	6 (46.2)	0.449	0.500	0.500
FPG, mmol/L	5.9±0.6	5.7±0.6	0.347	5.5±0.7	5.5±0.8	0.805	0.016	0.136
HbA1C, %	5.9±0.4	5.8±0.3	0.678	5.9±0.3	6.0±0.4	0.496	0.752	<0.001
Fasting insulin, µIU/mL	11.8±5.6	12.0±6.0	0.929	11.3±4.7	11.4±4.7	0.937	0.720	0.425
HOMA-IR	3.1±1.5	2.9±1.4	0.786	2.8±1.3	2.7±1.0	0.801	0.508	0.303
hs-CRP, mg/L	9.0±6.7	5.0±4.4	0.084	7.7±5.9	5.6±4.9	0.329	0.300	0.039

BMI (body mass index), WC (waist circumference), SBP (systolic blood pressure), DBP (diastolic blood pressure), FPG (fasting plasma glucose), HOMA-IR (homeostasis model of insulin resistance), hs-CRP (high sensitivity C-reactive protein)
Comparison between groups (before, pB; after, pA) were done by independent samples-t test or Pearson's chi-square test
Comparison within group (p^D, vitamin D; p^P, placebo) were done by paired t test or McNemar test

Discussion

This randomized clinical trial failed to show any significant benefits of the addition of vitamin D with lifestyle modification for any clinical as well as biochemical variables including glycemic profile, HOMA-IR, and hs-CRP in adults with prediabetes and hypovitaminosis D.

FPG was significantly reduced in the vitamin D supplementation group and HbA1C significantly increased in the placebo group. However, percent changes in these glycemic values between the groups were not statistically different. Similar findings were also observed by other authors.[16-19] Two open-label randomized trials done in India found a significant reduction of glycemic values in the vitamin D supplementation group with progression to DM. They did not compare the percent changes of glycemic values with the placebo group.[12,20] Another study did not find a significant change in FPG but a small lower value of HbA1C in the vitamin D supplementation group.[21]



FPG (fasting plasma glucose), HOMA-IR (homeostasis model of insulin resistance), hs-CRP (high sensitivity C-reactive protein)
Independent samples-t test was done

FIGURE 3 Percent changes of outcome variables of the study groups (n=27)

In our study, fasting insulin and insulin resistance did not significantly change after vitamin D supplementation. Improvement of insulin resistance was not observed in several studies also.[16-18,21] On the contrary, others found improvement in insulin resistance in vitamin D supplementation group.[12,19]

In this study inflammatory marker hs-CRP reduced in the vitamin D group but in placebo group it significantly increased. However, the difference between the intervention groups were not statistically significant. Similarly, Sollid et al. had found no significant differences in hs-CRP, inflammatory and metabolic markers between or within groups.[16] Similar findings were also found by Gagnon et al..[18] On the other hand Dutta et al. and Niroomand et al. found significant improvement in hs-CRP.[12,19]

Systematic reviews and meta-analyses also showed mixed results. Some authors found no improvement in glucose and insulin indices.[5,6] Others found some small benefits without significant effects on DM prevention. So, they did not recommend vitamin D supplementation for the improvement of glucose or insulin resistance.[22,23]

In this study, both BMI and WC improved significantly in both vitamin D and placebo groups from baseline. But between groups, there were no significant changes. So these changes are not due to vitamin D supplementation but rather due to therapeutic lifestyle management.

Although serum vitamin D levels improved in both groups after the intervention, even the vitamin D supplementation group could not achieve a sufficient mean vitamin D levels. On the contrary, most of the studies showed marked improvement in vitamin D levels in the treatment group. It has been shown that ingesting 100 IU/day (2.5 microgram/day) of vitamin D increases serum 25(OH)D approximately by about one ng/mL. Therefore, the dose of 60,000 IU per week used in our study is expected to cause a rise of about 70 ng/mL in serum 25(OH)D levels.[24] It is indeed well known that obese individuals need larger doses of vitamin D, which is possibly due to the sequestration of vitamin D in adipose tissue. We could not assess the possibility of lower content of vitamin D in the IP than the manufacturer's claim.[17] Some individuals with VDR polymorphisms may be poor responders to vitamin D supplementation in terms of improvement in serum 25 (OH)D concentrations, insulin sensitivity and inflammation.[25,26]

The strength of this study was its design (double blind randomized placebo controlled clinical trial) and low number of loss to follow up (total three). We have also some limitations. First, the sample size was small. It is thus possible that our study did not have the power to find an effect of treatment. We could not reach the target vitamin D level of ≥30 ng/mL, so the actual effect may not be found. We did OGTT during recruitment only, it was not repeated and literature shows that repeat OGTT in IGT confirms the diagnosis in only half. We did not assess dietary vitamin A intake, which could potentially interact with vitamin D to alter its efficacy. Another limitation of our study is a short duration of follow-up (six months). Finally, this study was out-patient-based, so lifestyle, diet, sunlight exposure, and other medication or confounder that may influence vitamin D or blood glucose could not be controlled.

Conclusion

The study findings failed to show the beneficial roles of vitamin D supplementation in vitamin D deficient adults with prediabetes in the prevention of DM. Small sample size, short duration of follow-up, and failure to achieve sufficient vitamin D levels after supplementation were the major limitations of this study. A longer duration of follow-up with maintaining of sufficient serum vitamin D levels might be required to find the beneficial effects of vitamin D supplementation in prediabetic people with low vitamin D levels.

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Author Contribution

Protocol writing (MHG, MSM, TH, SS, MAK, MFH, MAH, & MF); data collection (MHG, MSM, MHR, AY, IF, AKS, & MFH); data analysis (MHG, MSM, TH, MM, & MFH); manuscript writing (MHG, MSM, & TH); critical review (SS, MAK, MM, MAH, & MF); approval (all).

Conflict of Interest

None of the authors has any conflict of interests to declare

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