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Print ISSN: 2085-3297 Online ISSN: 2355-9179

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RESEARCH ARTICLE

Effect of Three and Six Months of Vitamin D Supplementation on Glycemic Control and Insulin Resistance in Type 2 Diabetes Mellitus: Randomized Placebo-controlled Trial

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Received date: Apr 7, 2023; Revised date: Jun 12, 2023; Accepted date: Jun 21, 2023

Abstract

BACKGROUND: 25(OH)D level is correlated with insulin secretion and tissue sensitivity to insulin. Administration of vitamin D supplements may reduce tissue resistance to insulin in type 2 diabetes mellitus (T2DM), but a number of studies found conflicting results. The present study was to measure the results of administration of vitamin D supplements for 3 and 6 months regarding HbA1c, fasting blood glucose (FBG), insulin and tissue resistance to insulin in T2DM cases.

METHODS: A randomized double-blind placebo-controlled trial was conducted in T2DM patients with ≤3 years duration. Subjects were randomly divided into two groups: 47 subjects received daily 5000 IU vitamin D supplementation and 47 subjects received daily placebo as control. After supplementation for 3 and 6 months, homeostatic model assessment for tissue resistance to insulin (HOMA-IR), insulin, HbA1c, and FBG were examined.

RESULTS: Supplementation of daily 5000 IU vitamin D for 3 months increased 25(OH)D level in the vitamin D group from 12.50±5.28 to 43.57±17.14 ng/mL, and after 6 months the 25(OH)D level was 38.38±17.64 ng/mL. Both groups showed significant differences after 3 and 6 months regarding HOMA-IR (p=0.033 and p=0.031), insulin (p=0.034 and p=0.013), but not FBG (p=0.296) and HbA1c (p=0.360). In both groups, HOMA-IR and insulin increased although the increase in the control group was greater than in the vitamin D group. The difference between the control and vitamin D groups was significant.

CONCLUSION: Vitamin D supplementation for 3 and 6 months may lead to improvement HOMA-IR but not for FBG and HbA1c in the vitamin D group as compared with the control group in T2DM cases.

KEYWORDS: vitamin D, T2DM, HbA1c, blood glucose, insulin, tissue resistance to insulin

Indones Biomed J. 2023; 15(3): 287-95

Introduction

Type 2 diabetes mellitus (T2DM) constitutes a defect in carbohydrate metabolism with the greatest number of cases in the world that has developed into a global pandemic. The two important factors that combine to cause T2DM are defective insulin secretion and high tissue resistance to insulin. Environmental changes may interfere with the epigenetic mechanism of metabolic homeostasis that also

govern T2DM development.(1,2) Low-grade inflammation plays a role in the occurrence of insulin resistance, while T2DM pathogenesis is frequently associated with low-grade inflammation. An inadequate anti-inflammatory response results in chronic low-grade inflammation in T2DM.(3)

Deficiency of vitamin D is one of a number of T2DM risk factors, apart from obesity, sedentary lifestyle, and eating habits, and interferes with insulin release and the sensitivity of tissues to insulin. The Langerhans islet beta cells possess vitamin D receptors and binding proteins, which fact supports the role of vitamin D in insulin secretion. Vitamin D increases the sensitivity of tissues to insulin by stimulating insulin receptors and/or peroxisome proliferator activated receptor-δ (PPAR-δ) inactivation in striated muscle and adipose tissue associated with fatty acids. Vitamin D regulates the activity of the calcium-binding protein calbindin that is located in the cytosol of ß-cells. Calbindin regulates intracellular calcium level by modulating the insulin release that is stimulated by membrane depolarization. Therefore, vitamin D may indirectly result in insulin secretion by regulating calbindin. There is a hypothesis stating that vitamin D consumption may augment insulin release and tissue sensitivity to insulin, thereby reducing T2DM risk.(4-6)

An analytical study of several randomized controlled trials (RCTs) on the effect of vitamin D supplementation on glucose homeostasis concludes that vitamin D supplements do not affect glucose balance and do not prevent T2DM.(7) Vitamin D may be beneficial in T2DM with poor glycemic control, but there is no convincing evidence of its effects in heterogeneous T2DM cases.(8)

Vitamin D3 supplements given in doses of 400000 IU to T2DM cases with deficiency of vitamin D does not affect tissue sensitivity to insulin and insulin release.(9,10) On the other hand, there is also an RCT study stating that vitamin D supplements significantly increase tissue sensitivity to insulin in T2DM or in individuals at risk of diabetes, and reduce HbA1c and homeostatic model assessment for tissue resistance to insulin (HOMA-IR) in T2DM cases with vitamin D deficiency.(11-14) Deficiency of vitamin D in adults is treated with daily 6000 IU vitamin D2 or D3 doses, thereby attaining a level of more than 30 ng/mL, after which daily 1500-2000 IU doses are administered.(15)

T2DM treatment has improved and developed in the past decades, but new T2DM insights are still needed, in view of the continually increasing prevalence of T2DM. Although a large number of investigators have demonstrated that vitamin D improves glucose homeostasis, there are still inconsistent RCT results and not many Indonesian RCTs are investigating the role of vitamin D supplements. Therefore, we conducted this study to determine the effectiveness of vitamin D supplements and to remove the inconsistencies in the results of previous studies in reducing tissue resistance to insulin, and levels of fasting blood glucose (FBG), insulin and HbA1c.

Methods

Study Design

This study was conducted at Mampang district Public Health Center, South Jakarta, Indonesia. Subjects were randomized into two different group by using block permuted randomization with block size of 4. The first group received daily supplements of 5000 IU of vitamin D orally for 6 months, while the second group or the control group received daily placebo tablets for 6 months.

Randomized allocation codes were given to the pharmaceutical personnel to be used as labels on the bottles containing the drugs. The investigators, the personnel connected with the study, and the subjects did not know the type of supplementation given, up to the completion of the study. All subjects involved in the study were to receive standard health services from the responsible physician at the Public Health Center. During the study the clinical condition of the subjects was to be monitored with regard to any complaints (such as nausea, vomiting, constipation, and headache). The monitoring was done for 3 and 6 months, respectively, starting from the administration of the first supplement. Nutritional monitoring of vitamin D was to be performed using the Semi Quantitative Food Frequency Questionnaire (SQ-FFQ) at baseline, and at 3 and 6 months after supplementation to determine the nutritional intake during the study. Sunbathing habit was evaluated from the interview results on subject characteristics and habits.

This study was in accordance with the Helsinki Declaration, and the study protocol was approved by The Health Research Ethics Committee, Faculty of Medicine, Universitas Indonesia and Cipto Mangunkusumo Central General Hospital (No. 1139/UN2.F1/ETIK/PPM.00.02/2021). This study had also been registered in *clinicaltrials.gov* (No. NCT05596383). Written informed consent from each subject was obtained prior to the commencement of the clinical trial activities.

Subjects Recruitment

T2DM subjects were recruited from January to May 2022, among those attending the non-communicable disease

polyclinic at Mampang Public Health Center for treatment. The supplements were administered for 6 months from June to December 2022. The inclusion criteria were: T2DM subjects aged >18 years old, having T2DM for ≤3 years, and a history of taking one type of antidiabetic drugs. The exclusion criteria were: subjects receiving insulin therapy, pregnant or lactating (in case of women), having hepatic and renal function disorders, having a history of allergy, having a history of hypercalcemia, and taking vitamin D supplements in the past 3 months. The drop-out criteria were: subjects who did not participate in the follow-up study, experienced nausea, vomiting, and headaches after taking the tablets, and did not taking >80% of the provided drugs. After calculation, the total minimum number of samples obtained was 90, with minimum number of samples in each group was 45.

Vitamin D Supplementation and Intervention Evaluation

For a period of 6 months, subjects in the intervention group received 5000 IU vitamin D3 chewable tablets (Batch No. AHA 13303; PT Imedco, Tangerang, Indonesia) daily, while subjects in the control group received placebo tablets (PT Ikapharmindo, Jakarta, Indonesia) daily. The placebo tablets contained microcrystalline cellulose, calcium carbonate, sodium starch glycolate, and magnesium stearate. To ensure blinding, the placebo tablets were made similar to the vitamin D tablets in form, size, and color, and packaged in identically appearing bottles. The pharmaceutical personnel labelled each bottle according to the randomized codes. The investigators distributed the labelled bottles containing the tablets to subjects, while providing instructions on how to take them. Compliance of the subjects in taking the tablets was evaluated by a monthly check on the remaining tablets in each bottle. The subjects were also asked about adverse effects or complaints experienced during the intervention and were instructed to maintain their ordinary dietary pattern during the study. The evaluation of the intervention and of the adverse effects was conducted at 3 months and 6 months post-intervention.

Measurement of HOMA-IR, Insulin, HbA1c, FBG and 25(OH)D

The subjects fasted for approximately 10 hours, to subsequently undergo drawing of venous blood samples of 3 tubes, consisting of one tube with EDTA anticoagulant for the determination of HbA1c, one tube with sodium fluoride (NaF) anticoagulant for determination of FBG, and one tube without anticoagulant for determination of fasting insulin and 25(OH)D.

Tissue resistance to insulin was computed as the HOMA-IR value by multiplying serum FBG in mg/dL with fasting insulin in µIU/mL and dividing by 405. The fasting insulin level was measured by enzyme-linked immunosorbent assay (ELISA) using Roche reagents (Lot No. 45221LP99, Roche Diagnostic GmbH, Penzberg, Germany), and the results were expressed in µIU/mL. HbA1c was measured by high-performance liquid chromatography (HPLC) using Abbott reagents (Lot No. 60880UQ10, Abbott Laboratories, Wiesbaden, Germany), with the results expressed in %. FBG was determined with the hexokinase method using Roche reagents (Lot No. 61202UQ12, Roche Diagnostic GmbH), with the results expressed in mg/dL. The 25(OH)D levels were determined by direct competitive chemiluminescent microparticle immunoassay (CMIA), with Abbott reagents (Lot No. 45712UD00, Abbott Laboratories) and expressed in ng/mL.

Statistical Analysis

The basic characteristics of the intervention (vitamin D) and control groups were analyzed using descriptive statistics. The statistical tests used to compare the outcomes of both groups were the Student t-test for two independent groups and the Mann-Whitney test. The general linear repeated measurement ANOVA test was conducted to compare the outcomes and the supplementation periods in the two groups. If in the ANOVA test a significant difference was found, it was followed by a post-hoc multiple comparison analysis to determine which supplementation period yielded significant differences. A statistical level of $p<0.05$ was considered as significant. The data were analyzed using statistical software SPSS version 20 (IBM Corporation, Armonk, NY, USA).

Results

Subjects and Basic Characteristics

Among 195 individuals of the accessible population, there were 114 subjects who met the inclusion criteria and subsequently were randomized to yield 2 groups of 57 subjects each (Figure 1). During the 3 and 6 months of supplementation, several subjects dropped out because they declined to participate, departed to their home village and did not return, experienced nausea and vomiting, or did not comply with the study protocol, such that the final number of subjects who participated from the baseline stage up to the completion of the study and were analyzed, was 47 subjects in each group.

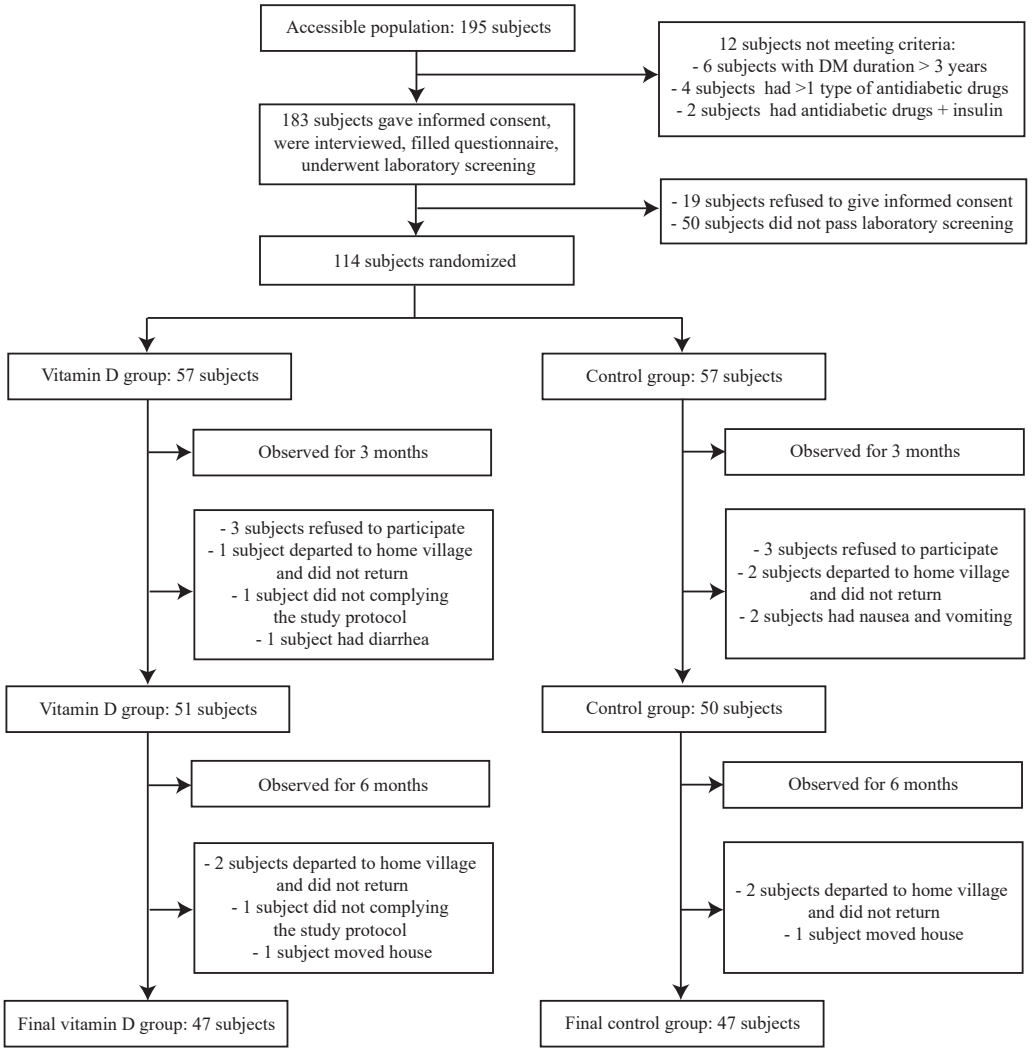

Figure 1. Flow of study respondent participation, allocation and analysis.

In terms of basic characteristics and initial laboratory parameters of 94 respondents, there were no significant differences between groups regarding gender, age, education, occupation, body mass index, DM duration, DM treatment, sunbathing habit, use of long-sleeved clothing, HOMA-IR values, and serum levels of 25(OH)D, FBG, HbA1c, insulin, ALT, albumin, creatinine, and calcium (Table 1).

25(OH)D Level After Administration of Supplements for 3 and 6 Months

After 3 months of daily vitamin D supplements, the 25(OH) D level was raised in the vitamin D as well as the control groups from 12.50±5.28 to 43.57±17.14 ng/mL and from 13.07±5.19 to 15.73±7.80 ng/mL, respectively. There was a significant between-group difference (p=0.000), with a large rise in 25(OH)D level in the vitamin D group. After receving supplements for 6 months, both groups had reduced 25(OH)D levels with statistically significant between-group differences (p=0.000) (Table 2). Statistically significant between-group differences were also seen between 25(OH) D levels at baseline and after the groups had received supplements for 3 months and 6 months, respectively (p=0.000 for both) (Table 3).

HbA1c, FBG, Insulin and HOMA-IR After Administration of Supplements for 3 and 6 Months

No significant between-group differences were found in HbA1c and FBG levels at baseline and after receiving supplements for 3 and 6 months (p=0.360 for HbA1c and p=0.296 for FBG) (Table 2). However, between-group differences in insulin levels and HOMA-IR values were statistically significant after the groups received supplements for 3 and 6 months (Table 2).

Dietary Vitamin D, Carbohydrate, Fat, and Protein After Administration of Supplements for 3 and 6 Months

For dietary vitamin D, carbohydrate, fat, and protein intakes no significant between-group differences were found at baseline (p=0.542; p=0.219; p=0.110; p=0.172), after the groups received supplements for 3 months (p=0.615;

Table 1. Basic characteristics and baseline examination of subjects.

Characteristics	Group		*p*-value
	Control (n=47)	Vitamin D (n=47)	
Gender, n (%)			
Male	11 (23.4%)	8 (17%)	0.441*
Female	36 (76.6%)	39 (83%)	
Age (years), mean±SD	54.0±9.3	55.6±9.5	0.411#
Education, n (%)			
Low	11 (23.4%)	21 (44.7%)	0.520*
Middle	12 (25.5%)	10 (21.3%)	
High	24 (51.1%)	16 (34%)	
Employment, n (%)			
Employed	4 (8.5%)	8 (17%)	0.216*
Unemployed	43 (91.5%)	39 (83%)	
BMI (kg/m^2), mean±SD	27.4±4.3	25.8±4.0	0.064#
DM duration, n (%)			
<1 year	16 (34%)	16 (34%)	0.691*
1 year	4 (8.5%)	2 (4.3%)	
>1-3 years	27 (57.5%)	29 (61.7%)	
Medications for diabetes, n (%)			
Metformin	43 (91.5%)	39 (83%)	0.216*
Other medications	4 (8.5%)	8 (17%)	
Sunbathing habit, n (%)			
Yes	8 (17%)	7 (14.9%)	0.778*
No	39 (83%)	40 (85.1%)	
Wearing of long-sleeved clothing, n (%)			
Frequent, n (%)	36 (76.6%)	38 (80.8%)	0.587*
Occasionally, n (%)	11 (23.4%)	9 (19.2%)	
25(OH)D (ng/ml), mean±SD	13.07±5.19	12.50±5.28	0.803#
FBG (mg/dL), mean±SD	156±66.8	167±88.1	0.751#
Insulin (µIU/mL), median (min-max)	2.3 (0.2-53.9)	2.2 (0.1-25.4)	0.552$
HOMA-IR, median (min-max)	1.01 (0.1-26)	1.0 (0.02-8.22)	0.612$
Calcium (mg/dL), mean±SD	9.1±0.4	9.0±0.4	0.353#
Albumin (g/dL), mean±SD	4.5±0.3	4.3±0.3	0.061#
ALT (U/L), median (min-max)	16 (6-52)	17 (6-47)	0.727$
Creatinine (mg/dL) mean±SD	0.72±0.16	0.72±0.16	0.958#

*Tested with Chi-square; # Tested with Independent t-test; $Tested with Mann-Whitney. Level of significance $p<0.05$.

p=0.853; p=0.237; p=0.634) and after the groups received supplements for 6 months (p=0.226; p=0.356; p=0.630; p=0.206) (Table 4).

Discussion

Daily 5000 IU vitamin D supplements for 6 months in T2DM cases raised the 25(OH)D level to a large extent in the vitamin D group. After the groups received vitamin D supplements for 3 months the 25(OH)D level in the vitamin D group was 3 times that at baseline, but after 6 months of vitamin D supplements the 25(OH)D level was equal to or lower than at 3 months. Similar results were found in a study on an African American population with overweight and vitamin D deficiency showing increased 25(OH)D concentration after receiving 1000 IU, 2000 IU, 3000 IU vitamin D supplementation for 3 months and a study on a healthy population with vitamin D deficiency showing increased 25(OH)D concentration after receiving 50000 IU or 100000 IU vitamin D supplementation per week for 12 weeks.(16,17) The increased 25(OH)D level after the groups received supplements for 3 months indicated compliance of the T2DM cases in taking the supplements and triggering of a strong 25(OH)D response by a low baseline 25(OH)D level. This was also found in the study on the African American population with low baseline 25(OH) D levels showing a large increase in 25(OH)D concentration

Table 2. Outcome variables before and after intervention.

Parameters	Group		*p*-value
	Control (n=47)	Vitamin D (n=47)	
25(OH)D (ng/mL), mean±SD			
Baseline	13.07±5.19	12.50±5.28	
After 3 months of intervention	15.73±7.80)	43.57±17.14	0.000*
After 6 months of intervention	13.11±6.09)	38.38±17.64	
HbA1c (%), mean±SD			
Baseline	8.47±2.40	9.18±3.28)	
After 3 months of intervention	8.41±3.02	8.31±2.77)	0.360*
After 6 months of intervention	8.21±2.63	8.34±2.73)	
FBG (mg/dL), mean±SD			
Baseline	156±66.8	167±88.1	
After 3 months of intervention	175±86.6	169±86.4	0.296*
After 6 months of intervention	177±84.2	187±119.2	
Insulin (µIU/mL), median (min-max)			
Baseline	2.3 (0.2-53.9)	2.2 (0.1-25.4)	0.552#
After 3 months of intervention	7.0 (0.9-57.8)	6.1 (1.9-16.4)	0.034#
After 6 months of intervention	8.7 (3.4-55.7)	6 (1.9-14.5)	0.013#
HOMA-IR, median (min-max)			
Baseline	1.01 (0.1-26)	1.00 (0.02-8.22)	0.612#
After 3 months of intervention	2.79 (0.4-31.1)	1.95 (0.6-8.4)	0.033#
After 6 months of intervention	3.22 (0-31.4)	2.28 (0-7.95)	0.031#

*Tested with general linear repeated measurement ANOVA; #Tested with Mann-Whitney. Level of significance $p<0.05$.

with vitamin D supplementation.(18) The baseline 25(OH) D level determines the effectiveness of the supplementation in raising 25(OH)D levels, with a strong 25(OH)D response to vitamin D supplements triggered by a low baseline 25(OH)D. The lower or nearly identical 25(OH)D level after 6 months of supplements may have been caused by the slow 25(OH)D response due to the 25(OH)D level having become relatively high after 3 months. The increase in circulatory 25(OH)D level when receiving vitamin D supplements follows a biphasic curve, *i.e.*, a rapid increase in response when the 25(OH)D level is extremely low and a slow response when the 25(OH)D level is already higher. (19) The fact that the nutrient intake during supplementation showed no significant differences between the two groups, demonstrates that the increase in 25(OH)D concentration during supplementation was not due to nutrient intake, but may have been due to the supplementation.

The deficiency of vitamin D in this study may have been caused by the lack of sunbathing habits, by the habit of wearing long-sleeved clothing all day long, and low nutrient intake. Vitamin D deficiency can aggravate diabetes in obese young women.(20) The nutritional intake of vitamin D in this study was extremely low, which was presumably caused by the low consumption of vitamin D-rich foods. The nutritional requirement for vitamin D from foods that is recommended by the Institute of Medicine (IOM), for females and males aged 51-70 years is 15 µg per day, whereas for females and males aged >70 years it is 20 µg per day.(15) In North Sumatran females it was also found that low vitamin D intake results in deficiency of vitamin

Table 3. Post-hoc multiple comparison analysis of differences in the 25(OH)D level at baseline, and after 3 and 6 months of supplementation.

Time Period	Time Period	Δ Mean Diff (SE)	*p*-value
Baseline	3 months	- 16.687 (1.639)	0.000*
	6 months	- 12.965 (1.639)	0.000*
3 months	Baseline	16.687 (1.639)	0.000*
	6 months	3.902 (1.639)	0.054
6 months	Baseline	12.965 (1.639)	0.000*
	3 months	- 3.902 (1.639)	0.054

*Level of significance $p<0.05$. SE: Standard error.

Table 4. Dietary intakes before and after supplementations.

Parameters	Group		*p* -value
	Control (n=47)	Vitamin D (n=47)	
Vit D (µg)			
Baseline	2.41 (0-9)	1.50 (0.09-12.44)	0.542*
After 3 months of intervention	1.71 (0-16.8)	2.34 (0.1-39)	0.615*
After 6 months of intervention	1.23 (0.1-12.4)	1.67 (0-12.17)	0.226*
Carbohydrate (g)			
Baseline	33.6 (3.3-169)	28.6 (1.3-93.4)	0.219*
After 3 months of intervention	28.9 (2.8-201.5)	28.3 (2.4-209.8)	0.853*
After 6 months of intervention	35.6 (3.3-109)	35.9 (6.6-207)	0.356*
Fat (g)			
Baseline	33.9 (6.7-169)	29.6 (2.1-187)	0.110*
After 3 months of intervention	15.9 (3.3-89.3)	14 (1.4-56)	0.237*
After 6 months of intervention	21.6 (2.8-68.8)	22.1 (0.6-67.9)	0.630*
Protein (g)			
Baseline	31 (7.2-111)	26.1 (3-109)	0.172*
After 3 months of intervention	26.4 (4.3-101)	24.9 (2.7-75.4)	0.634*
After 6 months of intervention	28.6 (4.1-92)	34.1 (7.4-96.7)	0.206*

Data presented in median (min-max). *Tested with Mann-Whitney. Level of significance $p<0.05$

D.(21) Among the vitamin D-rich foods are salmon, sardines, mackerel, tuna, shiitake mushrooms, cod liver oil, and fortified dairy products (milk, butter, cheese).(22) The inability to purchase vitamin D-rich foods is one of the causes of deficiency of vitamin D.(21) Vitamin D-rich foods, such as salmon and cod liver oil, are relatively expensive, which is also true in Indonesia, such that not all persons in the community consume these foods every day.

Our study found no significant between-group differences in HbA1c level after 3 and 6 months of supplements. These results differ from those of a study on 120 T2DM patients in India with improvement in blood glucose and HbA1c levels in the vitamin D group after receiving 60000 IU vitamin D per week for 2 and 4 months. A study on 60 uncontrolled T2DM patients showed improvement in FBG after receiving 2000 IU vitamin D supplementation for 3 months.(23,24) This may have been caused by differences in the vitamin D dose and duration of supplementation. The baseline 25(OH)D level may presumably influence the effect of vitamin D supplementation, which in turn may result in an extremely low 25(OH)D level.(19) Vitamin D supplementation may not remain effective in persons with more than three years of DM duration, because of fatigue of the pancreatic beta cells.(25) The 25(OH)D had an inverse relationship with HbA1c, probably because of the vitamin D being involved in postprandial insulin rather than basal insulin secretion. In the former condition, an increase in calcium absorption influenced by vitamin D may increase the intracellular calcium level, leading to postprandial insulin secretion and improving HbA1c level without affecting FBG level.(26)

Our study results are in agreement with studies on 140 T2DM patients in Jamshoro and 114 T2DM patients with asymptomatic vitamin D deficiency in Lahore (27,28), where the effects of vitamin D were presumablu much reduced when given in conjunction with oral antidiabetics, since the metformin continued to be taken during their clinical trial (27).

Vitamin D indirectly influences insulin release by regulating intracellular calcium homeostasis and therefore its effect on glucose level is also influenced by the serum calcium level. Although the serum calcium level may be normal, the intracellular calcium level may not be known, whereas abnormal regulation of intracellular calcium may influence insulin secretion and sensitivity.(29) Individual variations in genetic factors, polymorphism of vitamin D receptors (VDR), and baseline vitamin D concentration are several factors that may cause vitamin D to become ineffective.(23) Although insulin was expected to increase only in the vitamin D group, the results showed that there was also an increased insulin level in the control group, which may have been due to the effect of the calcium present in the placebo. Insulin levels between months 3 and 6 are not much different, but the FBG at month 6 is higher than at month 3 in the vitamin D group, this may have been caused by dietary pattern and physical activity, due to the fact that the study subjects were conscious of the laboratory checks, such that in the first 3 months they may have regulated their dietary pattern and physical activity.

Our study found significant between-group differences in insulin levels and HOMA-IR values after 3 and 6 months of supplements, with lower insulin levels and HOMA-IR

values in the vitamin D group than in the control group. However, when compared to the baseline status, HOMA-IR values in both groups increased after 3 and 6 months. The increase in HOMA-IR in the vitamin D group may have been caused by a lack of supervision with regard to the foods consumed by the study subjects, which may have affected the glucose concentrations. This is one of the limitations of the present study. In the study on 90 T2DM patients with 25(OH)D levels of <30 ng/mL in Iran receiving 50000 IU vitamin D for 8 weeks, the increases in HOMA-IR in the vitamin D group were probably caused by changes in FBG and insulin levels after supplementation.(12) HOMA-IR is more a reflection of hepatic insulin resistance. Whole body insulin sensitivity comprises hepatic and peripheral insulin sensitivity. The accuracy of HOMA-IR in predicting whole body insulin sensitivity may vary according to an individual's ethnicity and obesity.(30) After 3 and 6 months of the groups receiving supplements, HOMA-IR values increased in the vitamin D group, but were still lower than in the control group, indicating decreased insulin resistance in the vitamin D group. A study on men with central obesity showed a significant negative correlation between 25(OH) D and HOMA-IR levels. The low 25(OH)D levels are associated with an inceased risk of insulin resistance.(31) Vitamin D Binding Protein (VDBP) and Vitamin D Receptor (VDR) impact on the role of vitamin D in stimulating insulin release.(32)

The increased 25(OH)D level causes a lower insulin resistance, higher insulin sensitivity and a lower fasting insulin level.(33) An increase in 25(OH)D level from 10 ng/mL to 30 ng/mL causes a 60% increase in insulin sensitivity. (24) Vitamin D has a significant influence on tissue resistance to insulin at vitamin D levels of 40-60 ng/mL, whereas at higher or lower vitamin D levels, there is no effect on tissue resistance to insulin.(34) During the study there were no significant adverse effects, indicating that 5000 IU vitamin D is safe for use as supplement for 6 months in T2DM cases. The strength of the present study lies in the use of a double blind RCT. However, the limitations of this study are that it does not differentiate between vitamin D status; that evaluation of tissue resistance to insulin using HOMA-IR is greatly affected by several factors, such as changes in glucose and insulin levels; and the consideration that peripheral insulin response had not been determined, such that it is difficult to find out whether or not the results impact positively on glycemic control. There is a need to conduct further studies that evaluate genetic variation and the effect of oral antidiabetic medications. Further studies are suggested to be conducted in a heterogeneous T2DM population using a larger sample.

Conclusion

Daily 5000 IU vitamin D was able to improve 25(OH)D level. In both groups, HOMA-IR and insulin increased although the increase in the control group was greater than in the vitamin D group. The difference between the control and vitamin D groups was significant, such that it may be concluded that vitamin D supplements for 3 and 6 months may lead to improvement in the vitamin D group as compared with the control group in T2DM cases. There is a need for maintaining an optimal 25(OH)D concentration in patients with T2DM to attain good glycemic control.

Acknowledgements

The authors extend their gratitude to the patients and staff of Mampang Public Health Center and all parties who participated in this study.

Authors Contribution

Alv, SI, DSH, FDS, ARH, and Pr planned and designed the study. Alv collected the data and prepared the manuscript. JP analyzed the data. All authors participated in discussions about the manuscript and approved the final manuscript.

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Effect of Three and Six Months of Vitamin D Supplementation on Glycemic Control and Insulin Resistance in Type 2 Diabetes Mellitus: Randomized Placebo-controlled Trial

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Submission date: 10-Jul-2023 11:36AM (UTC+0700)
Submission ID: 2128913274
File name: InaBj.pdf (1.24M)
Word count: 6677
Character count: 33821

The Indonesian Biomedical Journal, Vol.15, No.3, June 2023, p.194-295 Print ISSN: 2085-3297, Online ISSN: 2355-9179

RESEARCH ARTICLE

Effect of Three and Six Months of Vitamin D Supplementation on Glycemic Control and Insulin Resistance in Type 2 Diabetes Mellitus: Randomized Placebo-controlled Trial

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Received date: Apr 7, 2023; Revised date: Jun 12, 2023; Accepted date: Jun 21, 2023

Abstract

BACKGROUND: 25(OH)D level is correlated with insulin secretion and tissue sensitivity to insulin. Administration of vitamin D supplements may reduce tissue resistance to insulin in type 2 diabetes mellitus (T2DM), but a number of studies found conflicting results. The present study was to measure the results of administration of vitamin D supplements for 3 and 6 months regarding HbA1c, fasting blood glucose (FBG), insulin and tissue resistance to insulin in T2DM cases.

METHODS: A randomized double-blind placebo-controlled trial conducted in T2DM patients with ≤3 years duration. Subjects were randomly divided into two groups: 47 subjects received daily 5000 IU vitamin D supplementation and 47 subjects received daily placebo control. After supplementation for 3 and 6 months, homeostatic model assessment for tissue resistance to insulin (HOMA-IR), insulin, HbA1c, and FBG were examined.

RESULTS: Supplementation of daily 5000 IU vitamin D for 3 months increased 25(OH)D level in the vitamin D group from 12.50±5.28 to 43.57±17.14 ng/mL, and after 6 months the 25(OH)D level was 38.38±17.64 ng/mL. Both groups showed significant differences after 3 and 6 months regarding HOMA-IR (p=0.033 and p=0.031), insulin (p=0.034 and p=0.013), but not FBG (p=0.296) and HbA1c (p=0.360). In both groups, HOMA-IR and insulin increased although the increase in the control group was greater than in the vitamin D group. The difference between the control and vitamin D groups was significant.

CONCLUSION: Vitamin D supplementation for 3 and 6 months may lead to improvement HOMA-IR but not for FBG and HbA1c in the vitamin D group as compared with the control group in T2DM cases.

KEYWORDS: vitamin D, T2DM, HbA1c, blood glucose, insulin, tissue resistance to insulin

Indones Biomed J. 2023; 15(3): 287-95

Introduction

Type 2 diabetes mellitus (T2DM) constitutes a defect in carbohydrate metabolism with the greatest number of cases in the world that has developed into a global pandemic. The two important factors that combine to cause T2DM are defective insulin secretion and high tissue resistance to insulin. Environmental changes may interfere with the epigenetic mechanism of metabolic homeostasis that also

govern T2DM development.(1,2) Low-grade inflammation plays a role in the occurrence of insulin resistance, while T2DM pathogenesis is frequently associated with low-grade inflammation. An inadequate anti-inflammatory response results in chronic low-grade inflammation in T2DM.(3)

Deficiency of vitamin D is one of a number of T2DM risk factors, apart from obesity, sedentary lifestyle, and eating habits, and interferes with insulin release and the sensitivity of tissues to insulin. The Langerhans islet beta cells possess vitamin D receptors and binding proteins, which fact supports the role of vitamin D in insulin secretion. Vitamin D increases the sensitivity of tissues to insulin by stimulating insulin receptors and/or peroxisome proliferator activated receptor-δ (PPAR-δ) inactivation in striated muscle and adipose tissue associated with fatty acids. Vitamin D regulates the activity of the calcium-binding protein calbindin that is located in the cytosol of ß-cells. Calbindin regulates intracellular calcium level by modulating the insulin release that is stimulated by membrane depolarization. Therefore, vitamin D may indirectly result in insulin secretion by regulating calbindin. There is a hypothesis stating that vitamin D consumption may augment insulin release and tissue sensitivity to insulin, thereby reducing T2DM risk.(4-6)

An analytical study of several randomized controlled trials (RCTs) on the effect of vitamin D supplementation on glucose homeostasis concludes that vitamin D supplements do not affect glucose balance and do not prevent T2DM.(7) Vitamin D may be beneficial in T2DM with poor glycemic control, but there is no convincing evidence of its effects in heterogeneous T2DM cases.(8)

Vitamin D3 supplements given in doses of 400000 IU to T2DM cases with deficiency of vitamin D does not affect tissue sensitivity to insulin and insulin release.(9,10) On the other hand, there is also an RCT study stating that vitamin D supplements significantly increase tissue sensitivity to insulin in T2DM or in individuals at risk of diabetes, and reduce HbA1c and homeostatic model assessment for tissue resistance to insulin (HOMA-IR) in T2DM cases with vitamin D deficiency.(11-14) Deficiency of vitamin D in adults is treated with daily 6000 IU vitamin D2 or D3 doses, thereby attaining a level of more than 30 ng/mL, after which daily 1500-2000 IU doses are administered.(15)

T2DM treatment has improved and developed in the past decades, but new T2DM insights are still needed, in view of the continually increasing prevalence of T2DM. Although a large number of investigators have demonstrated that vitamin D improves glucose homeostasis, there are still inconsistent RCT results and not many Indonesian RCTs are investigating the role of vitamin D supplements. Therefore, we conducted this study to determine the effectiveness of vitamin D supplements and to remove the inconsistencies in the results of previous studies in reducing tissue resistance to insulin, and levels of fasting blood glucose (FBG), insulin and HbA1c.

Methods

Study Design

This study was conducted at Mampang district Public Health Center, South Jakarta, Indonesia. Subjects were randomized into two different group by using block permuted randomization with block size of 4. The first group received daily supplements of 5000 IU of vitamin D orally for 6 months, while the second group or the control group received daily placebo tablets for 6 months.

Randomized allocation codes were given to the pharmaceutical personnel to be used as labels on the bottles containing the drugs. The investigators, the personnel connected with the study, and the subjects did not know the type of supplementation given, up to the completion of the study. All subjects involved in the study were to receive standard health services from the responsible physician at the Public Health Center. During the study the clinical condition of the subjects was to be monitored with regard to any complaints (such as nausea, vomiting, constipation, and headache). The monitoring was done for 3 and 6 months, respectively, starting from the administration of the first supplement. Nutritional monitoring of vitamin D was to be performed using the Semi Quantitative Food Frequency Questionnaire (SQ-FFQ) at baseline, and at 3 and 6 months after supplementation to determine the nutritional intake during the study. Sunbathing habit was evaluated from the interview results on subject characteristics and habits.

This study was in accordance with the Helsinki Declaration, and the study protocol was approved by The Health Research Ethics Committee, Faculty of Medicine, Universitas Indonesia and Cipto Mangunkusumo Central General Hospital (No. 1139/UN2.F1/ETIK/PPM.00.02/2021). This study had also been registered in *clinicaltrials.gov* (No. NCT05596383). Written informed consent from each subject was obtained prior to the commencement of the clinical trial activities.

Subjects Recruitment

T2DM subjects were recruited from January to May 2022, among those attending the non-communicable disease

polyclinic at Mampang Public Health Center for treatment. The supplements were administered for 6 months from June to December 2022. The inclusion criteria were: T2DM subjects aged >18 years old, having T2DM for ≤3 years, and a history of taking one type of antidiabetic drugs. The exclusion criteria were: subjects receiving insulin therapy, pregnant or lactating (in case of women), having hepatic and renal function disorders, having a history of allergy, having a history of hypercalcemia, and taking vitamin D supplements in the past 3 months. The drop-out criteria were: subjects who did not participate in the follow-up study, experienced nausea, vomiting, and headaches after taking the tablets, and did not taking >80% of the provided drugs. After calculation, the total minimum number of samples obtained was 90, with minimum number of samples in each group was 45.

Vitamin D Supplementation and Intervention Evaluation

For a period of 6 months, subjects in the intervention group received 5000 IU vitamin D3 chewable tablets (Batch No. AHA 13303; PT Imedco, Tangerang, Indonesia) daily, while subjects in the control group received placebo tablets (PT Ikapharmindo, Jakarta, Indonesia) daily. The placebo tablets contained microcrystalline cellulose, calcium carbonate, sodium starch glycolate, and magnesium stearate. To ensure blinding, the placebo tablets were made similar to the vitamin D tablets in form, size, and color, and packaged in identically appearing bottles. The pharmaceutical personnel labelled each bottle according to the randomized codes. The investigators distributed the labelled bottles containing the tablets to subjects, while providing instructions on how to take them. Compliance of the subjects in taking the tablets was evaluated by a monthly check on the remaining tablets in each bottle. The subjects were also asked about adverse effects or complaints experienced during the intervention and were instructed to maintain their ordinary dietary pattern during the study. The evaluation of the intervention and of the adverse effects was conducted at 3 months and 6 months post-intervention.

Measurement of HOMA-IR, Insulin, HbA1c, FBG and 25(OH)D

The subjects fasted for approximately 10 hours, to subsequently undergo drawing of venous blood samples of 3 tubes, consisting of one tube with EDTA anticoagulant for the determination of HbA1c, one tube with sodium fluoride (NaF) anticoagulant for determination of FBG, and one tube without anticoagulant for determination of fasting insulin and 25(OH)D.

Tissue resistance to insulin was computed as the HOMA-IR value by multiplying serum FBG in mg/dL with fasting insulin in µIU/mL and dividing by 405. The fasting insulin level was measured by enzyme-linked immunosorbent assay (ELISA) using Roche reagents (Lot No. 45221LP99, Roche Diagnostic GmbH, Penzberg, Germany), and the results were expressed in µIU/mL. HbA1c was measured by high-performance liquid chromatography (HPLC) using Abbott reagents (Lot No. 60880UQ10, Abbott Laboratories, Wiesbaden, Germany), with the results expressed in %. FBG was determined with the hexokinase method using Roche reagents (Lot No. 61202UQ12, Roche Diagnostic GmbH), with the results expressed in mg/dL. The 25(OH)D levels were determined by direct competitive chemiluminescent microparticle immunoassay (CMIA), with Abbott reagents (Lot No. 45712UD00, Abbott Laboratories) and expressed in ng/mL.

Statistical Analysis

The basic characteristics of the intervention (vitamin D) and control groups were analyzed using descriptive statistics. The statistical tests used to compare the outcomes of both groups were the Student t-test for two independent groups and the Mann-Whitney test. The general linear repeated measurement ANOVA test was conducted to compare the outcomes and the supplementation periods in the two groups. If in the ANOVA test a significant difference was found, it was followed by a post-hoc multiple comparison analysis to determine which supplementation period yielded significant differences. A statistical level of $p<0.05$ was considered as significant. The data were analyzed using statistical software SPSS version 20 (IBM Corporation, Armonk, NY, USA).

Results

Subjects and Basic Characteristics

Among 195 individuals of the accessible population, there were 114 subjects who met the inclusion criteria and subsequently were randomized to yield 2 groups of 57 subjects each (Figure 1). During the 3 and 6 months of supplementation, several subjects dropped out because they declined to participate, departed to their home village and did not return, experienced nausea and vomiting, or did not comply with the study protocol, such that the final number of subjects who participated from the baseline stage up to the completion of the study and were analyzed, was 47 subjects in each group.

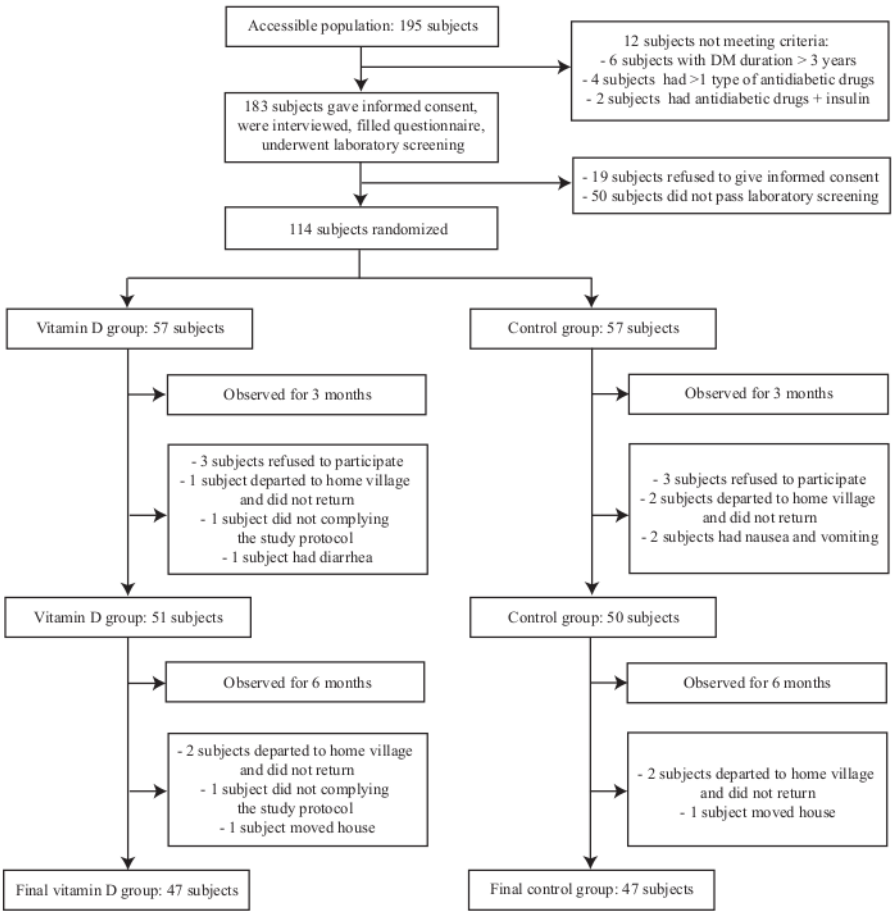

Figure 1. Flow of study respondent participation, allocation and analysis.

In terms of basic characteristics and initial laboratory parameters of 94 respondents, there were no significant differences between groups regarding gender, age, education, occupation, body mass index, DM duration, DM treatment, sunbathing habit, use of long-sleeved clothing, HOMA-IR values, and serum levels of 25(OH)D, FBG, HbA1c, insulin, ALT, albumin, creatinine, and calcium (Table 1).

25(OH)D Level After Administration of Supplements for 3 and 6 Months

After 3 months of daily vitamin D supplements, the 25(OH)D level was raised in the vitamin D as well as the control groups from 12.50±5.28 to 43.57±17.14 ng/mL and from 13.07±5.19 to 15.73±7.80 ng/mL, respectively. There was a significant between-group difference (p=0.000), with a large rise in 25(OH)D level in the vitamin D group. After receving supplements for 6 months, both groups had reduced 25(OH)D levels with statistically significant between-group differences (p=0.000) (Table 2). Statistically significant between-group differences were also seen between 25(OH)D levels at baseline and after the groups had received supplements for 3 months and 6 months, respectively (p=0.000 for both) (Table 3).

HbA1c, FBG, Insulin and HOMA-IR After Administration of Supplements for 3 and 6 Months

No significant between-group differences were found in HbA1c and FBG levels at baseline and after receiving supplements for 3 and 6 months (p=0.360 for HbA1c and 0.296 for FBG) (Table 2). However, between-group differences in insulin levels and HOMA-IR values were statistically significant after the groups received supplements for 3 and 6 months (Table 2).

Dietary Vitamin D, Carbohydrate, Fat, and Protein After Administration of Supplements for 3 and 6 Months

For dietary vitamin D, carbohydrate, fat, and protein intakes no significant between-group differences were found at baseline (p=0.542; p=0.219; p=0.110; p=0.172), after the groups received supplements for 3 months (p=0.615;

Table 1. Basic characteristics and baseline examination of subjects.

Characteristics	Group		*p* -value
	Control (n=47)	Vitamin D (n=47)	
Gender, n (%)			
Male	11 (23.4%)	8 (17%)	0.441*
Female	36 (76.6%)	39 (83%)	
Age (years), mean±SD	54.0±9.3	55.6±9.5	0.411#
Education, n (%)			
Low	11 (23.4%)	21 (44.7%)	0.520*
Middle	12 (25.5%)	10 (21.3%)	
High	24 (51.1%)	16 (34%)	
Employment, n (%)			
Employed	4 (8.5%)	8 (17%)	0.216*
Unemployed	43 (91.5%)	39 (83%)	
BMI (kg/m^2), mean±SD	27.4±4.3	25.8±4.0	0.064#
DM duration, n (%)			
<1 year	16 (34%)	16 (34%)	0.691*
1 year	4 (8.5%)	2 (4.3%)	
>1-3 years	27 (57.5%)	29 (61.7%)	
Medications for diabetes, n (%)			
Metformin	43 (91.5%)	39 (83%)	0.216*
Other medications	4 (8.5%)	8 (17%)	
Sunbathing habit, n (%)			
Yes	8 (17%)	7 (14.9%)	0.778*
No	39 (83%)	40 (85.1%)	
Wearing of long-sleeved clothing, n (%)			
Frequent, n (%)	36 (76.6%)	38 (80.8%)	0.587*
Occasionally, n (%)	11 (23.4%)	9 (19.2%)	
25(OH)D (ng/ml), mean±SD	13.07±5.19	12.50±5.28	0.803#
FBG (mg/dL), mean±SD	156±66.8	167±88.1	0.751#
Insulin (µIU/mL), median (min-max)	2.3 (0.2-53.9)	2.2 (0.1-25.4)	0.552$
HOMA-IR, median (min-max)	1.01 (0.1-26)	1.0 (0.02-8.22)	0.612$
Calcium (mg/dL), mean±SD	9.1±0.4	9.0±0.4	0.353#
Albumin (g/dL), mean±SD	4.5±0.3	4.3±0.3	0.061#
SGOT (U/L), median (min-max)	16 (6-52)	17 (6-47)	0.727$
Creatinine (mg/dL) mean±SD	0.72±0.16	0.72±0.14	0.958#

*Tested with Chi-square; # Tested with Independent t-test; $Tested with Mann-Whitney. Level of significance $p<0.05$.

p=0.853; p=0.237; p=0.634) and after the groups received supplements for 6 months (p=0.226; p=0.356; p=0.630; p=0.206) (Table 4).

Discussion

Daily 5000 IU vitamin D supplements for 6 months in T2DM cases raised the 25(OH)D level to a large extent in the vitamin D group. After the groups received vitamin D supplements for 3 months the 25(OH)D level in the vitamin D group was 3 times that at baseline, but after 6 months of vitamin D supplements the 25(OH)D level was equal to or lower than at 3 months. Similar results were found in a study on an African American population with overweight and vitamin D deficiency showing increased 25(OH)D concentration after receiving 1000 IU, 2000 IU, 3000 IU vitamin D supplementation for 3 months and a study on a healthy population with vitamin D deficiency showing increased 25(OH)D concentration after receiving 50000 IU or 100000 IU vitamin D supplementation per week for 12 weeks.(16,17) The increased 25(OH)D level after the groups received supplements for 3 months indicated compliance of the T2DM cases in taking the supplements and triggering of a strong 25(OH)D response by a low baseline 25(OH)D level. This was also found in the study on the African American population with low baseline 25(OH)D levels showing a large increase in 25(OH)D concentration

Table 2. Outcome variables before and after intervention.

Parameters	Group		*p*-value
	Control (n=47)	Vitamin D (n=47)	
25(OH)D (ng/mL), mean±SD			
Baseline	13.07±5.19	12.50±5.28	
After 3 months of intervention	15.73±7.80)	43.57±17.14	0.000*
After 6 months of intervention	13.11±6.09)	38.38±17.64	
HbA1c (%), mean±SD			
Baseline	8.47±2.40	9.18±3.28)	
After 3 months of intervention	8.41±3.02	8.31±2.77)	0.360*
After 6 months of intervention	8.21±2.63	8.34±2.73)	
FBG (mg/dL), mean±SD			
Baseline	156±66.8	167±88.1	
After 3 months of intervention	175±86.6	169±86.4	0.296*
After 6 months of intervention	177±84.2	187±119.2	
Insulin (µIU/mL), median (min-max)			
Baseline	2.3 (0.2-53.9)	2.2 (0.1-25.4)	0.552#
After 3 months of intervention	7.0 (0.9-57.8)	6.1 (1.9-16.4)	0.034#
After 6 months of intervention	8.7 (3.4-55.7)	6 (1.9-14.5)	0.013#
HOMA-IR, median (min-max)			
Baseline	1.01 (0.1-26)	1.00 (0.02-8.22)	0.612#
After 3 months of intervention	2.79 (0.4-31.1)	1.95 (0.6-8.4)	0.033#
After 6 months of intervention	3.22 (0-31.4)	2.28 (0-7.95)	0.031#

*Tested with general linear repeated measurement ANOVA; #Tested with Mann-Whitney. Level of significance $p<0.05$.

with vitamin D supplementation.(18) The baseline 25(OH)D level determines the effectiveness of the supplementation in raising 25(OH)D levels, with a strong 25(OH)D response to vitamin D supplements triggered by a low baseline 25(OH)D. The lower or nearly identical 25(OH)D level after 6 months of supplements may have been caused by the slow 25(OH)D response due to the 25(OH)D level having become relatively high after 3 months. The increase in circulatory 25(OH)D level when receiving vitamin D supplements follows a biphasic curve, *i.e.*, a rapid increase in response when the 25(OH)D level is extremely low and a slow response when the 25(OH)D level is already higher. (19) The fact that the nutrient intake during supplementation showed no significant differences between the two groups, demonstrates that the increase in 25(OH)D concentration during supplementation was not due to nutrient intake, but may have been due to the supplementation.

The deficiency of vitamin D in this study may have been caused by the lack of sunbathing habits, by the habit of wearing long-sleeved clothing all day long, and low nutrient intake. Vitamin D deficiency can aggravate diabetes in obese young women.(20) The nutritional intake of vitamin D in this study was extremely low, which was presumably caused by the low consumption of vitamin D-rich foods. The nutritional requirement for vitamin D from foods that is recommended by the Institute of Medicine (IOM), for females and males aged 51-70 years is 15 µg per day, whereas for females and males aged >70 years it is 20 µg per day.(15) In North Sumatran females it was also found that low vitamin D intake results in deficiency of vitamin

Table 3. Post-hoc multiple comparison analysis of differences in the 25(OH)D level at baseline, and after 3 and 6 months of supplementation.

Time Period	Time Period	Δ Mean Diff (SE)	*p*-value
Baseline	3 months	- 16.687 (1.639)	0.000*
	6 months	- 12.965 (1.639)	0.000*
3 months	Baseline	16.687 (1.639)	0.000*
	6 months	3.902 (1.639)	0.054
6 months	Baseline	12.965 (1.639)	0.000*
	3 months	- 3.902 (1.639)	0.054

*Level of significance $p<0.05$. SE: Standard error.

Table 4. Dietary intakes before and after supplementations.

Parameters	Group		*p*-value
	Control (n=47)	Vitamin D (n=47)	
Vit[illegible] (µg)			
Baseline	2.41 (0-9)	1.50 (0.09-12.44)	0.542*
After 3 months of intervention	1.71 (0-16.8)	2.34 (0.1-39)	0.615*
After 6 months of intervention	1.23 (0.1-12.4)	1.67 (0-12.17)	0.226*
Ca[illegible]hydrate (g)			
Baseline	33.6 (3.3-169)	28.6 (1.3-93.4)	0.219*
After 3 months of intervention	28.9 (2.8-201.5)	28.3 (2.4-209.8)	0.853*
After 6 months of intervention	35.6 (3.3-109)	35.9 (6.6-207)	0.356*
Fa[illegible])			
Baseline	33.9 (6.7-169)	29.6 (2.1-187)	0.110*
After 3 months of intervention	15.9 (3.3-89.3)	14 (1.4-56)	0.237*
After 6 months of intervention	21.6 (2.8-68.8)	22.1 (0.6-67.9)	0.630*
Pro[illegible]n (g)			
Baseline	31 (7.2-111)	26.1 (3-109)	0.172*
After 3 months of intervention	26.4 (4.3-101)	24.9 (2.7-75.4)	0.634*
After 6 months of intervention	28.6 (4.[illegible]2)	34.1 (7.4-96.7)	0.206*

Data presented in median (min-max). *Tested with Mann-Whitney. Level of significance $p<0.05$

D.(21) Among the vitamin D-rich foods are salmon, sardines, mackerel, tuna, shiitake mushrooms, cod liver oil, and fortified dairy products (milk, butter, cheese).(22) The inability to purchase vitamin D-rich foods is one of the causes of deficiency of vitamin D.(21) Vitamin D-rich foods, such as salmon and cod liver oil, are relatively expensive, which is also true in Indonesia, such that not all persons in the community consume these foods every day.

Our study found no significant between-group differences in HbA1c level after 3 and 6 months of supplements. These results differ from those of a study on 120 T2DM patients in India with improvement in blood glucose and HbA1c levels in the vitamin D group after receiving 60000 IU vitamin D per week for 2 and 4 months. A study on 60 uncontrolled T2DM patients showed improvement in FBG after receiving 2000 IU vitamin D supplementation for 3 months.(23,24) This may have been caused by differences in the vitamin D dose and duration of supplementation. The baseline 25(OH)D level may presumably influence the effect of vitamin D supplementation, which in turn may result in an extremely low 25(OH)D level.(19) Vitamin D supplementation may not remain effective in persons with more than three years of DM duration, because of fatigue of the pancreatic beta cells.(25) The 25(OH)D had an inverse relationship with HbA1c, probably because of the vitamin D being involved in postprandial insulin rather than basal insulin secretion. In the former condition, an increase in calcium absorption influenced by vitamin D may increase the intracellular calcium level, leading to postprandial insulin secretion and improving HbA1c level without affecting FBG level.(26)

Our study results are in agreement with studies on 140 T2DM patients in Jamshoro and 114 T2DM patients with asymptomatic vitamin D deficiency in Lahore (27,28), where the effects of vitamin D were presumablu much reduced when given in conjunction with oral antidiabetics, since the metformin continued to be taken during their clinical trial (27).

Vitamin D indirectly influences insulin release by regulating intracellular calcium homeostasis and therefore its effect on glucose level is also influenced by the serum calcium level. Although the serum calcium level may be normal, the intracellular calcium level may not be known, whereas abnormal regulation of intracellular calcium may influence insulin secretion and sensitivity.(29) Individual variations in genetic factors, polymorphism of vitamin D receptors (VDR), and baseline vitamin D concentration are several factors that may cause vitamin D to become ineffective.(23) Although insulin was expected to increase only in the vitamin D group, the results showed that there was also an increased insulin level in the control group, which may have been due to the effect of the calcium present in the placebo. Insulin levels between months 3 and 6 are not much different, but the FBG at month 6 is higher than at month 3 in the vitamin D group, this may have been caused by dietary pattern and physical activity, due to the fact that the study subjects were conscious of the laboratory checks, such that in the first 3 months they may have regulated their dietary pattern and physical activity.

Our study found significant between-group differences in insulin levels and HOMA-IR values after 3 and 6 months of supplements, with lower insulin levels and HOMA-IR

values in the vitamin D group than in the control group. However, when compared to the baseline status, HOMA-IR values in both groups increased after 3 and 6 months. The increase in HOMA-IR in the vitamin D group may have been caused by a lack of supervision with regard to the foods consumed by the study subjects, which may have affected the glucose concentrations. This is one of the limitations of the present study. In the study on 90 T2DM patients with 25(OH)D levels of <30 ng/mL in Iran receiving 50000 IU vitamin D for 8 weeks, the increases in HOMA-IR in the vitamin D group were probably caused by changes in FBG and insulin levels after supplementation.(12) HOMA-IR is more a reflection of hepatic insulin resistance. Whole body insulin sensitivity comprises hepatic and peripheral insulin sensitivity. The accuracy of HOMA-IR in predicting whole body insulin sensitivity may vary according to an individual's ethnicity and obesity.(30) After 3 and 6 months of the groups receiving supplements, HOMA-IR values increased in the vitamin D group, but were still lower than the control group, indicating decreased insulin resistance in the vitamin D group. A study on men with central obesity showed a significant negative correlation between 25(OH)D and HOMA-IR levels. The low 25(OH)D levels are associated with an inceased risk of insulin resistance.(31) Vitamin D Binding Protein (VDBP) and Vitamin D Receptor (VDR) impact on the role of vitamin D in stimulating insulin release.(32)

The increased 25(OH)D level causes a lower insulin resistance, higher insulin sensitivity and a lower fasting insulin level.(33) An increase in 25(OH)D level from 10 ng/mL to 30 ng/mL causes a 60% increase in insulin sensitivity. (24) Vitamin D has a significant influence on tissue resistance to insulin at vitamin D levels of 40-60 ng/mL, whereas at higher or lower vitamin D levels, there is no effect on tissue resistance to insulin.(34) During the study there were no significant adverse effects, indicating that 5000 IU vitamin D is safe for use as supplement for 6 months in T2DM cases. The strength of the present study lies in the use of a double blind RCT. However, the limitations of this study are that it does not differentiate between vitamin D status; that evaluation of tissue resistance to insulin using HOMA-IR is greatly affected by several factors, such as changes in glucose and insulin levels; and the consideration that peripheral insulin response had not been determined, such that it is difficult to find out whether or not the results impact positively on glycemic control. There is a need to conduct further studies that evaluate genetic variation and the effect of oral antidiabetic medications. Further studies are suggested to be conducted in a heterogeneous T2DM population using a larger sample.

Conclusion

Daily 5000 IU vitamin D was able to improve 25(OH)D level. In both groups, HOMA-IR and insulin increased although the increase in the control group was greater than in the vitamin D group. The difference between the control and vitamin D groups was significant, such that it may be concluded that vitamin D supplements for 3 and 6 months may lead to improvement in the vitamin D group as compared with the control group in T2DM cases. There is a need for maintaining an optimal 25(OH)D concentration in patients with T2DM to attain good glycemic control.

Acknowledgements

The authors extend their gratitude to the patients and staff of Mampang Public Health Center and all parties who participated in this study.

Authors Contribution

Alv, SI, DSH, FDS, ARH, and Pr planned and designed the study. Alv collected the data and prepared the manuscript. JP analyzed the data. All authors participated in discussions about the manuscript and approved the final manuscript.

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