

The Effect of Vitamin D Supplementation on the Glycemic Status and the Percentage of Body Fat Mass in Adults with Prediabetes: A Randomized Clinical Trial

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Abstract

Background: Low serum levels of vitamin D are supposed to contribute to the incidence of diabetes; therefore, vitamin D supplementation may reduce the incidence of diabetes in individuals with prediabetes.

Objectives: The aim of this current study was to examine the effect of vitamin D supplementation on the glycemic status and percentage of body fat mass in adults with prediabetes.

Methods: In a 3-month randomized placebo-controlled supplementation trial, 120 eligible subjects were randomly assigned in a vitamin D or placebo group. They were stratified according to the percentage of body fat mass into four blocks to receive 1000 IU/daily vitamin D or an identical placebo tablet respectively, for 3 months. The study was conducted from January to March of 2016 in Urmia in the North West of Iran. Participants were adults aged 18 to 70 with prediabetes. The fasting blood sugar (FBS), glycated hemoglobin (HbA1c), homeostasis model assessment of insulin resistance (HOMA-IR), serum 25(OH)D levels, and percentage of body fat mass were assessed before and after the intervention.

Results: The comparison of changes from baseline between two groups showed a significant inverse association between the changes in serum 25(OH)D and changes in FBS (-4.64 ± 11.38 compared with -2.11 ± 9.15 for placebo; $P = 0.03$), HOMA-IR (-0.73 ± 4.2 compared with 0.44 ± 4.4 for placebo, $P = 0.01$) and serum insulin (-1.98 ± 15.25 compared with 2.47 ± 15.85 for placebo; $P = 0.007$) but not in the percentage of body fat mass (-0.28 ± 0.77 compared with -0.39 ± 2.82 for placebo; $P = 0.39$).

Conclusions: The study demonstrated that 1000 IU vitamin D supplementation for 3 months can decrease the insulin resistance in individuals with prediabetes; however, it has no significant effect on body fat mass percentage.

Keywords: Prediabetes, Vitamin D Supplementation, Percentage Body Fat Mass, Glycaemic Status, Randomized Placebo-Control Trial

1. Background

Prediabetes is an intermediate condition in which glucose levels raise above the normal range but do not reach the diabetes markers threshold. Results indicating prediabetes are FBS between 100 - 125 or HbA1c between 5.7% - 6.4% (1-3). Prevalence of prediabetes as an early stage of type 2 diabetes increases dramatically and it is estimated that there will be more than 470 million pre-diabetics globally by the year 2030 (4, 5). Increasing prevalence of prediabetes is a relatively major public health concern with considerable costs, morbidity and mortality (6, 7). In recent years, different strategies for prevention of diabetes in high-risk populations have been recommended but in most cases these approaches failed to prevent the progression of prediabetes into becoming type 2 diabetes (8).

Epidemiological studies in diabetic adults provide relatively consistent evidences that glucose levels are in-

versely related to serum 25(OH) D concentrations, however, the results from interventional studies examining the effect of vitamin D supplementation on glycemic control were inconsistent (1, 9, 10). Recent studies on the relationship between percentage of body fat mass and serum vitamin D level showed that there is a strong inverse association between obesity and serum concentration of vitamin D and suggested that vitamin D supplementation may indirectly affect the incidence of diabetes through reducing body fat mass (11-13).

The prevalence of vitamin D deficiency is extremely high. Studies showed that 72.1% of men and 75.1% of women in Iran are vitamin D deficient (14), while a cross-sectional study in Urmia showed that 85% women in Urmia have vitamin D deficiency (15).

Evaluating the effect of vitamin D supplementation on glycemic status and the percentage of body fat mass may help researchers understand whether vitamin D directly

affects the glycemic status or indirectly through lowering weight or the percentage of body fat mass. The current clinical trial was conducted to examine the effect of vitamin D supplementation on the glycemic status and percentage of body fat mass in adults with prediabetes.

2. Methods

The study was designed as a 3-month randomized placebo-controlled clinical trial and was conducted at a single site (Imam Khomeini teaching, governmental, referral, Hospital of Urmia University of Medical Sciences) from January to March of 2016 in North West Iran. According to the mean and standard deviation of Hb A1C ($S_1 = 0.88$, $S_2 = 0.82$, $\mu_1 = 8.94$, $\mu_2 = 8.46$) with a type 1 error (α) of 5% and a power ($1-\beta$) of 80%, the sample size was calculated with a 20% of drop outs and 60 patients in each group (16) (Equation 1).

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 (S_1^2 + S_2^2)}{(\mu_1 - \mu_2)^2} \quad (1)$$

2.1. Study Design

The study was designed as a 3-month randomized placebo-controlled clinical trial in which 120 participants were stratified by the percentage of body fat mass in four blocks from January to March 2016 in North West Iran. Randomization was performed by an independent researcher by the use of computer-generation randomization of study participants (Microsoft Excel). The samples were provided from the clinical laboratory of Imam Khomeini teaching hospital of Urmia University of Medical Sciences according to their FBS test.

2.2. Participants

As shown in Figure 1, from the 795 potential participants obtained from the clinical laboratory of Imam Khomeini teaching hospital of Urmia University of Medical Sciences with regards to the FBS test result being between 100 - 125, 539 participants were excluded because of diseases and medications influencing vitamin D and glucose metabolism, pregnancy or lactation and smoking within the first phone call. 256 eligible subjects were invited to the nutrition and diabetic clinic of Imam Khomeini hospital of Urmia University of Medical Sciences for the first visit.

The inclusion criteria were individuals between the ages of 18 to 70 and had two fasting blood sugar tests (FBS) between 100 to 125 mg/dL but did not have type 2 diabetes. The excluding criteria were based on the following: unwilling to participate, any diseases that may influence vitamin D metabolism and status or blood glucose control,

use of medication that could potentially influence vitamin D metabolism, such as type 1 or type 2 diabetes, pregnancy and lactation, smoking and drinking alcohol, having the threshold serum 25(OH)D of either < 10 nmol/ml or > 150 nmol/mL and also patients who consumed less than 90% of the tablets given to take during the study (11, 17, 18). The objective and protocol of the study were described to the subjects before they signed the written informed consent. The participants underwent screening for FBS and percentage of body fat mass. After the second FBS test and confirmation of prediabetes, 120 participants who met the study criteria were randomly assigned in the intervention or placebo group and stratified into four distinct blocks based on the percentage of body fat mass. The study protocol was approved by the ethic committee of Urmia University of Medical Sciences (ID: umsu.rec.1393.212).

2.3. Intervention

Participants in the intervention group received a single daily dose of vitamin D3 (a tablet of 1000 IU vitamin D3 from the Jalinous pharmaceutical company) whereas the placebo group received an identical placebo tablet daily (Keyhan Darou pharmaceutical company) for 3 consecutive months (19). All tablets were in the same shape and color and all 90 tablets were packed in the same bottles by an independent researcher. The compliance of supplementation was enhanced by monthly phone calls. During these calls participants were also asked about their potential symptoms of side effects and toxicity of the supplementation. Participants completed a general questionnaire on their demographic data, medication use and history of diseases by the second admission.

2.4. Diet, Sun Exposure and Physical Activity

Dietary intake was assessed at the beginning and at the end of the 3-month intervention period by using a validated 24-h recall questionnaire for 3 days (including a weekend) (20). The International Physical Activity Questionnaire (IPAQ) was used to estimate the physical activity habits over the last week (21) and the categorical indicator of physical activity was used for the analysis of IPAQ. According to the categorical score, participants were classified in three levels (low physical activity, moderate physical activity and high physical activity). Participants were also asked about the duration of their sun exposure between 10am and 4pm during the previous week.

2.5. Anthropometric Measurements

Weight was measured to the nearest 0.1 kg, without shoes and in light clothing, using an electronic YAOHUA calibrated scale. Height was measured to the nearest 0.1

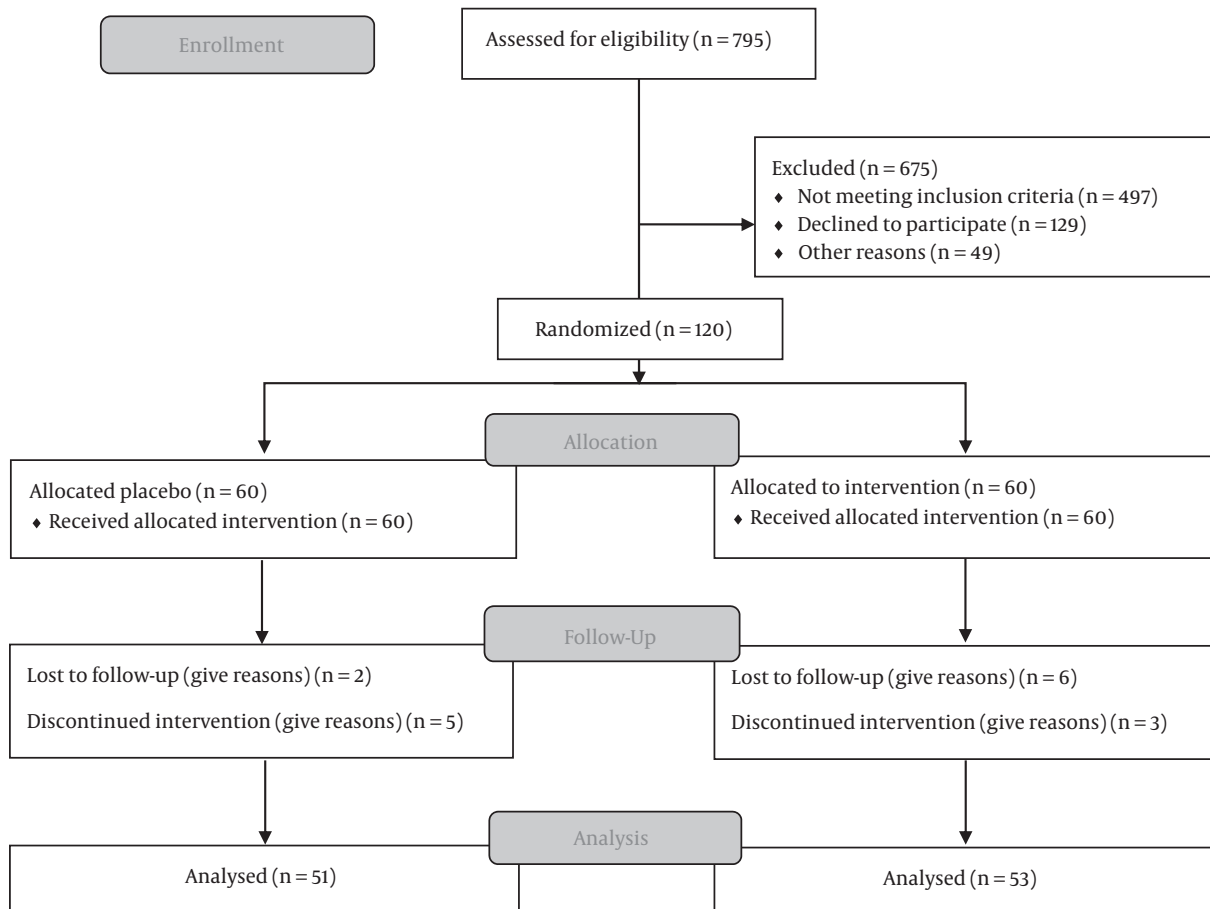


Figure 1. The Study Flow Diagram

cm using a wall mounted standard stadiometer. The percentage of body fat mass was measured with a standard calibrated caliper (SEHAN, Model SH5020/ Korea) in four sites of the body including: biceps, triceps, suprailiac and subscapular areas (22). The tables of percent fat estimation were used for estimating the percentage of body fat mass according to the age and sex of the individual. The body composition tables according to the percentage of body fat mass were used to estimate the percentage of body fat mass. The percentage of body fat mass in non-obese individuals was defined as 17% - 32% of body fat mass in women and 12% - 26% of body fat mass in men and the fat mass in obese individuals was defined as $\geq 32\%$ of body fat mass in women and $\geq 26\%$ of body fat mass in men (22). Waist circumferences were measured in two times to the nearest 0.5 cm using a measuring tape placed at the midpoint between the lower rib and the upper iliac crest, at the end of a normal expiration. For all measurements, the average of multiple measurements was calculated (23).

2.6. Laboratory Measurements

After 12 hours of overnight fasting, blood samples were collected. All collected samples were kept in room temperature for 30 minutes and then centrifuged at 2000 g. FBS and HbA1c were measured at bleeding day but serum insulin and serum 25(OH)D were kept until the last day of sampling at baseline and at the end of the study. FBS was measured using an enzymatic photometric method (Pars Azmoon Co, Tehran, Iran). Serum 25(OH)D concentration was measured by using the ELISA method (DiaSource 25(OH)D Total KAP1971) test,. The percentage of glycated hemoglobin (HbA1C) was measured by the latex enhanced Immunturbidimetric method, fasting serum insulin was measured by the ELISA method (Insulin-R monobind, Lake Forest, CA 92630, USA) and the HOMA-IR was calculated as $[\text{fasting insulin (mU/L)} * \text{FBS (mmol/L)}] / 22.5$ (1, 23).

2.7. Statistical Analysis

All data is illustrated as mean \pm standard deviation (SD) or percentages. The normality of data distribution was tested using the Kolmogorov-Smirnov test. The vitamin D and placebo groups were compared using the Student t-test or Mann-Whitney U test for continuous variables and Pearson's chi-square or Fishers test for the categorical variables. The within group differences (before and after the intervention) were assessed using the paired t-test or Wilcoxon test for continuous variables. All statistical analyses were performed using the SPSS 20 (Statistical Package for Social Science for Windows) software. P-values of less than 0.05 were assumed statistically significant. As withdrew participants data were not available at the end of the study to consider the changes, the supplementation effect analysis were conducted per protocol.

3. Results

Of the 120 eligible participants in the study, 86.7% completed the whole process of the study, 51 in the vitamin D group and 53 in the placebo group. The number and reasons of withdrawals were as follows: in the vitamin D group: lost to follow up (n = 6), newly diagnosed breast cancer (n = 1) and taking less than 90% of tablets (n = 2) and in the placebo group those who took less than 90% of tablets (n = 3), lost to follow up (n = 2) and going on a diet for weight loss (n = 2).

3.1. Subjects General Characteristics

The compliance of the study was 86.7%. The subjects were 54 women and 50 men and the mean age of the subjects was 48.1 (interquartile range 25.3 to 65.2) years. We did not detect any side effects related to the intervention. General characteristics of the study population are shown in Table 1. There were not any significant differences between groups for any measurements at baseline (Tables 1 and 2). There were no side effects associated with treatment declared by the participants during the study.

After 3 months, in the intervention group, mean \pm SD serum concentration of 25(OH) D increased from 19.36 ± 13.51 ng/mL at baseline to 30.48 ± 15.49 ng/mL ($P < 0.001$). Sun exposure ($P = 0.51$) and physical activity ($P = 0.56$) did not change significantly after 3 months of intervention. The comparison of changes from baseline between two groups showed a significant inverse association between changes in the serum level 25(OH)D, changes in FBS (-4.64 ± 11.38 compared with -2.11 ± 9.15 for placebo; $P = 0.03$), HOMA-IR (-0.73 ± 4.2 compared with 0.44 ± 4.4 for placebo, $P = 0.01$) and Serum insulin (-1.98 ± 15.25 compared with 2.47 ± 15.85 for placebo; $P = 0.007$). In addition,

Table 1. Comparison of Age, Gender, Family History of Diabetes, Physical Activity, Daily Sun Exposure and Skin Color Between the Intervention and Placebo Groups^a

Characteristics	Intervention Group (n = 51)	Placebo Group (n = 53)	P Value ^b
Age	48.11 \pm 7.6	48.43 \pm 7.7	0.83
Gender			0.84
Male	24 (47.1)	26 (49.1)	-
Female	27 (52.9)	27 (50.9)	-
Family history of diabetes			0.83
Yes	23 (45.1)	25 (47.2)	-
No	28 (54.9)	28 (52.8)	-
Skin color, %			0.72
Light	30 (58.8)	33 (62.3)	-
Beige	21 (41.2)	20 (37.7)	-
Physical activity			0.67
Low	37 (72.5)	37 (69.8)	-
Moderate	11 (21.6)	10 (18.9)	-
High	3 (5.9)	6 (11.3)	-
Daily sun exposure, h			0.98
< 1	25 (49)	27 (50.9)	-
1-3	21 (41.2)	21 (39.6)	-
> 3	5 (9.8)	5 (9.4)	-

^aValues are expressed as mean \pm SD.

^bChi-square Tests.

there were no significant changes from baseline between the groups in HbA1c (-0.22 ± 0.51 compared with -0.14 ± 0.44 for placebo; $P = 0.65$) (Table 3).

4. Discussion

The aim of the current study was to evaluate the effect of 1000 IU vitamin D supplementation taken for 3 months on the glycemic status and percentage of body fat mass in adults with prediabetes. Our findings showed that 1000 IU vitamin D supplementation for three months has beneficial effects in decreasing insulin resistance. However, we did not find enough evidence to support our hypothesis that increasing 25(OH) D causes the percentage of body fat mass. We evaluated the glycemic status by testing FBS, HbA1c, fasting serum insulin and HOMA-IR.

4.1. Glycemic Status

In recent years several cross-sectional studies demonstrated that serum 25(OH)D levels is inversely associated

Table 2. Baseline and After Intervention Characteristics (Comparison Within and Between Groups)^a

Characteristics	Intervention Group (n = 51)			Placebo Group (n = 53)		P (Between)		
	Before	After	P1 ^b	Before	After	P2 ^c	P3 ^d	P4 ^e
Weight, kg	77.35 ± 13.16	75.96 ± 14.75	0.001 ^f	75.61 ± 14.37	75.24 ± 14.75	0.23 ^f	0.35 ^g	0.56 ^g
BMI, kg/m ²	28.71 ± 4.29	28.24 ± 4.23	0.002 ^h	28.93 ± 4.87	28.81 ± 5.06	0.43 ^f	0.99 ^g	0.67 ^g
WC, cm	93.48 ± 10.5	91.23 ± 14.71	0.11 ^h	94.17 ± 10.28	94.26 ± 10.58	0.97 ^f	0.82 ^g	0.47 ^g
PBFM, %	31.07 ± 5.03	30.79 ± 5.09	0.01 ^f	32.61 ± 5.93	32.21 ± 4.7	0.26 ^f	0.15 ⁱ	0.94 ⁱ
FBS, mg/dL	108.32 ± 7.09	103.68 ± 11.98	< 0.001 ^h	109.28 ± 7.0	107.16 ± 8.5	0.15 ^f	0.4 ^g	0.002 ^g
Serum insulin, mg/dL	14.8 ± 14.92	12.82 ± 7.67	0.87 ^h	12.09 ± 16.56	14.56 ± 8.59	0.001 ^f	0.14 ^g	0.14 ⁱ
HbA1c, %	5.69 ± 0.51	5.46 ± 0.51	0.003 ^f	5.47 ± 0.48	5.59 ± 0.53	0.01 ^f	0.63 ^g	0.22 ^g
MOMA-IR	4.11 ± 3.99	3.37 ± 2.31	0.59 ^h	3.37 ± 4.43	3.81 ± 2.23	0.004 ^f	0.18 ^g	0.12 ^g
Serum 25(OH)D, ng/mL	19.36 ± 13.51	30.48 ± 15.49	< 0.001 ^f	24.16 ± 18.06	22.29 ± 12.75	0.41 ^f	0.17 ^g	0.001 ^g
Energy, kcal/d	2032 ± 329.43	2096 ± 312.05	0.05 ^h	1973.78 ± 396.93	1975.33 ± 395.53	0.97 ^h	0.14 ⁱ	0.88 ⁱ
CHO intake, g/d	251.56 ± 63.03	259.68 ± 59.49	0.46 ^h	232.79 ± 73.58	239.13 ± 50.68	0.46 ^h	0.06 ^g	0.16 ^g
Fat intake, g/d	85.69 ± 29.22	87.19 ± 22.72	0.7 ^f	89.79 ± 26.01	89.99 ± 25.17	0.95 ^f	0.45 ⁱ	0.55 ⁱ
Protein intake, g/d	65.33 ± 18.52	72.76 ± 20.81	0.007 ^f	60.85 ± 16.52	63.27 ± 18.41	0.22 ^h	0.21 ^g	0.01 ⁱ

Abbreviations: BMI, body mass index; CHO, Carbohydrate; FBS, fasting blood glucose; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model of assessment - insulin resistance; PBFM, Percentage of body fat mass; WC, waist circumference; ; 25(OH)D, 25- hydroxy vitamin D.

^aValues are expressed as mean ± SD or %.

^bP values of within group comparison in intervention group.

^cP values of within group comparison in placebo group.

^dP values of between vitamin D and placebo group at baseline.

^eP values of between vitamin D and placebo group after the intervention.

^fP values for paired t-test.

^gP values for Mann-Whitney U test.

^hP values for Wilcoxon test

ⁱP values for Student t-test.

Table 3. FBS, HbA1c, HOMA-IR, Serum Insulin and Percentage of Body Fat Mass Changes From Baseline in Vitamin D and Placebo Group^a

Characteristics	Changes from Baseline Intervention Group	Changes from Baseline Placebo Group	P Value
FBS	-4.64 ± 11.38	-2.11 ± 9.15	0.03 ^b
HbA1c	-0.22 ± 0.51	-0.14 ± 0.44	0.65 ^c
HOMA-IR	-0.73 ± 4.2	0.44 ± 4.4	0.01 ^b
Serum Insulin	-1.98 ± 15.25	2.47 ± 15.85	0.007 ^b
25(OH)D	11.11 ± 12.11	-2.39 ± 11.6	0.001 ^{>b}
Body fat mass, %	-0.28 ± 0.77	-0.39 ± 2.82	0.39 ^b

Abbreviations: BMI, body mass index; CHO, Carbohydrate; FBS, fasting blood glucose; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model of assessment - insulin resistance; PBFM, Percentage of body fat mass; WC, waist circumference; 25(OH)D, 25- hydroxy vitamin D.

^aValues are shown as Mean ± SD or %.

^bMann-witheny U test.

^cT-test.

with the glycemic status (24-26). However the interventional studies, evaluating the effect of vitamin D supple-

mentation on glycemic control showed inconsistent results (9, 12, 17, 27, 28). The results from a systematic review of 15 studies on vitamin D supplementation in individuals with diabetes and prediabetes could not confirm the beneficial effects of vitamin D supplementation on improving the glycemic status or insulin resistance in patients with diabetes, normal fasting glucose or impaired glucose tolerance (27). In contrast, some studies concluded that an increase in serum vitamin D, results in improving glycemic control (1, 11). In a randomized clinical trial the results from Tomi Pekka et al. showed that vitamin D supplementation for 5 months caused a dose dependent increase in serum 25(OH)D levels but this elevation in serum vitamin D levels did not result in any changes in glucose metabolism (2). Vitamin D supplementation caused a significant improvement in insulin resistance and sensitivity in a more recent study conducted by Anthony M Blenchia et al. giving 4000 IU vitamin D3/daily for 6-month (29). Pitas et al. in the largest and in a duration of seven years in a randomized clinical trial on 314 non-diabetic adults, showed that vitamin D and calcium supplementation affects glucose metabolism and insulin resistance only in

participants with prediabetes but a supplementation with a combination of vitamin D and calcium make it difficult to clarify that whether vitamin D affects the glycemic parameters or calcium (30). In another randomized clinical trial, Nikooye et al. showed that yogurt drink whether with or without calcium resulted in improving the glycemic status in diabetic adults. The decrease in weight and percentage of body fat mass in this study may affect the glycemic status (1). In the current study, in order to minimize the effect of percentage of body fat mass on the glycemic status and vitamin D metabolism, participants were randomized into a vitamin D and placebo group, which were stratified according to their percentage of body fat mass. In contrast with results from the Nikooye study, our results showed that vitamin D supplementation did not affect the percentage of body fat mass but improved the glycemic status (1, 9). In the previous clinical trials there were several limitations which may affect the results, these limitations include small sample size (31), poorly controlled confounding factors such as the effect of vitamin D on percent of body fat mass (17) as well as a lifestyle including dietary habits and outdoor physical activity (32, 33). The results from the current study are in agreement with the results of those concluded that vitamin D supplementation can improve glycemic insulin resistance (1, 9, 11, 12, 34).

4.2. Anthropometric Measurements

Our findings showed that vitamin D supplementation had no effect on Anthropometric measurements including BMI, waist circumference and the percentage of body fat mass. However, cross-sectional studies showed that serum 25(OH)D level is associated with the regulation of body fat mass and increasing in lean body mass (1, 29, 35, 36). However, results from clinical trials are inconsistent (36, 37). Results from the meta-analysis of 12 clinical trial showed that vitamin D supplementation without calorie restriction could not decrease the weight or the percentage of body fat mass (38). In a recent randomized clinical Sadiya et al. resulted that vitamin D supplementation in obese diabetics do not affect the percentage of body fat mass or waist circumference (17). Findings from the current study were in contrast with the findings of those who concluded that vitamin D supplementation could result in decreasing weight, body fat mass or waist circumference (35, 36, 39). It also concluded that vitamin D supplementation with 1000 IU vitamin D for three months has no impact on BMI, waist circumference and percentage of body fat mass.

One of the limitations of the current study was that all of our laboratory measurements were based on the fasting plasma analysis instead of the accurate glucose clamp method as well as using the ELISA method instead of HPLC method in measuring serum 25(OH)D. Nevertheless, one

of our main efforts was to reduce the confounders to minimum, because the origin of the patient record questionnaires, changes in life style, physical activity and sun exposure may have varied during the intervention period. The other limitation of the study was the short duration of intervention and the insufficient dose of vitamin D, which could only raise the 25(OH)D to the optimum levels in only 37% of participants. The study was designed in a way to consider the percentage of body fat mass as one of the most important confounding factors. All of our subjects were at the same stage of the disease and did not use medication for glycemic control.

4.3. Conclusion

In conclusion, supplementation with 1000 IU vitamin D for 3 months improved insulin resistance in adults with prediabetes. Some recommendations for future studies can be; long term RCTs of vitamin D supplementation focusing on individuals with prediabetes, examining glycemic status, using gold-standard measurements and following up the incidence rate of type 2 diabetes. These are required to ascertain whether vitamin D supplementation could be a safe and effective strategy to prevent type 2 diabetes in the prediabetic population or not.

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Footnote

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