The Effects of Vitamin D Supplementation on Glucose Control and Insulin Resistance in Patients with Diabetes Type 2: A Randomized Clinical Trial Study

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Abstract

Background: Vitamin D deficiency is prevalent in diabetes type 2 and this vitamin may be related to insulin action. This randomized controlled trial study was done to evaluate the effect of vitamin D supplementation on glucose control and insulin resistance in patients with diabetes type 2.

Methods: Participants of this randomized clinical trial study consisted of 28 patients with type 2 diabetes who received 100 microgram (4000 IU) vitamin D and 30 diabetic patients who received placebo for 2 months between September 2012 and February 2013. The effect of vitamin D on glucose control was assessed by measuring HbA1c and insulin resistance as HOMA-IR at the baseline and the end of the intervention.

Results: The results showed a significant decrease in HbA1c (from 7.29 ± 0.22 % to 6.76 ± 0.18 %, P<0.001) and insulin concentration (from 8.24 ± 0.97 μIU/mL to 6.55 ± 0.28 μIU/mL, P=0.048), but a non-significant decrease in HOMA-IR in vitamin D group. Also, HDL-C level increased significantly in both of vitamin D (P=0.046) and placebo groups (P=0.028).

Conclusion: It seems that vitamin D supplementation has beneficial effects on glucose homeostasis and can increases insulin sensitivity in diabetic 2 patients.

Keywords: Vitamin D, Diabetes type 2, HbA1c, Insulin resistance

Introduction

Diabetes type 2 is a worldwide disease and it is estimated that at the end of 2030 more than 550 million people suffer from this disease (1). There are several studies showing that vitamin D deficiency may resulted in developing diabetes type 2 (2-4). Vitamin D may facilitate insulin function by regulating its receptor expression, so it may be increases insulin sensitivity (5). Vitamin D may also regulate glucose homeostasis by stimulating insulin release from pancreatic B-cells (6, 7). Therefore, the correction of vitamin D deficiency may result in improved glucose control and has...
beneficial effects on complications of diabetes type 2 (8). Lower circulating level of calcidiol was associated with the increased risk of coronary artery disease in diabetic patients (9). Vitamin D supplementation increases significantly insulin sensitivity in IGT patients (10). Recently, Malekshah et al. reported high prevalence of vitamin D deficiency in several cities of Iran (11).

Because of the role of vitamin D in insulin function and the prevalence of vitamin D deficiency in Iran, the aim of this study was to examine the effects of vitamin D supplementation on glucose control and insulin sensitivity and lipid profile in patients with type 2 diabetes.

Methods

The participants of this randomized double-blind placebo-controlled clinical trial study consist of 65 diabetic type 2 patients at the age range of 30-60 years old who agreed to take place in our study between September 2012 and February 2013. An informed consent was obtained from all of the participants. Seven patients discontinued the supplements consumption, three from placebo group and four from vitamin D group. The study completed with 58 patients (36 women and 12 men). Patient selected from Iranian Diabetes Association (IDA). This study was approved by the Tehran University of Medical Sciences (TUMS) ethical committee (ID: 17112) and registered on www.clinicaltrial.org as NC 01876563.

The exclusion criteria were consuming vitamin D supplements within 3 months before beginning of the study and having complications of diabetes, thyroid disorders, and using insulin, thiazolidinediones or anti-obesity drugs. None of the women patients were pregnant or breastfeeding. All patients used metformin and/or glibenclamide as anti-diabetic drugs and agreed to maintain their usual dietary and physical activity habits at the time of intervention.

Participants of this study divided into two randomly allocated groups (vitamin D and placebo) by random permuted blocks within the strata (BMI) method. The vitamin D group received 100 microgram or 4000 IU (one tablet of vitamin D) daily and placebo group received one placebo tablet per day for 2 months. Minoo Pharmaceutical, Cosmetic and Hygienic Company made both vitamin D supplements and placebo. Height, hip and waist circumference was measured to the nearest centimeter and weight to the nearest kilogram. BMI was calculated as the weight divided by the square of height. In the beginning of the study and after 2 months, blood samples were taken after 12-14 hours fasting overnight. After centrifuging, serums were separated and stored at -80 C until measuring the concentration of serum calcidiol, lipid profile and insulin. In addition, HbA1c was measured with HPLC columns as long-time control of glucose.

Biochemical measurements: Serum calcidiol was measured using chemiluminescence method with ELECSYS system 2010 with Roche kit (code number: 05894973). Serum insulin was measured by human insulin ELISA kit (Diametra, Italy) with the sensitivity of 0.25 mcIU/ml and an intraassay and interassay of ≤5% and ≤10% respectively. HOMA-IR was calculated using the formula of fasting glucose (mmol/L) x fasting insulin (μIU/mL) / 22.5 (12).

Statistical analysis: Statistical analysis was performed by using SPSS version 18. All data were shown as mean ± SE. The Kolmogorov smirnoff test was used for determining normality of the parameters and Wilcoxon test and mann-whitnes test were used to analysis of non-normal distribution variables within and between groups. Independent sample t-test and paired t-test were used for comparison between groups before and after supplementation and within groups for analysis of normal distribution variables. In all analysis, P-value <0.05 was considered statistically significant.

Results

Vitamin D group consisted of 28 patients (15 men and 13 women) and placebo group consisted of 30 patients (21 men and 9 women) and there was not significant differences in the sex distribution between 2 groups (P=0.154). In addition, there

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was no significant differences in times at sun exposure between two groups ($P=0.580$).

Table 1 illustrates the baseline characteristics of 2 groups participated in this study. As it demonstrated, there are no significant differences between anthropometric parameters and duration of disease between 2 groups.

Table 1: Baseline characteristics of anthropometric parameters in vitamin D and placebo groups before the intervention

| Variable                  | Vitamin D group (n=28) | Placebo group (n=30) | P-value |
|---------------------------|------------------------|----------------------|---------|
| Age (yr)                  | 50.03                  | 49.90                | 0.924   |
| Weight (kg)               | 75.73 ± 3.09           | 82.32 ± 2.90         | 0.125   |
| BMI (kg/m$^2$)            | 27.94 ± 0.92           | 28.75 ± 0.95         | 0.541   |
| Waist circumference (cm)  | 92.56 ± 2.33           | 96.53 ± 2.23         | 0.223   |
| Hip circumference (cm)    | 104.19 ± 1.88          | 106.40 ± 1.47        | 0.356   |
| WHR                       | 0.89 ± 0.014           | 0.90 ± 0.012         | 0.348   |
| Duration (year)           | 5.98 ± 0.84            | 6.07 ± 0.73          | 0.877   |

Data are expressed as mean ± SE, t-test was used to detect differences between the groups

Table 2 illustrates Fasting biochemical characteristics of two groups at baseline and Post intervention. The results show that supplementation with vitamin D caused a significant decrease in HbA1c ($P<0.001$) and it was still significant after removing the baseline effect ($P<0.001$, ANCOVA). Serum insulin concentration decreased significantly in vitamin D group ($P=0.048$), it was not significant between two groups at the end of the study but after adjusting for the baseline values the difference got statistically significant ($P<0.001$, ANCOVA). There was not any significant difference in HOMA-IR between two groups at the end of the study or after adjusting for the baseline values the difference got statistically significant ($P<0.001$, ANCOVA). There was not any significant difference in HOMA-IR between two groups at the end of intervention, but it got statistically significant ($P=0.036$, ANCOVA) after adjusting for the baseline values. HDL-C concentration increased significantly in both vitamin D ($P=0.046$) and placebo receiving groups ($P=0.028$). In addition, mean concentration of FBS and TC increased significantly in placebo group. For TC concentration, the difference between two groups was statistically significant after removing the effect of baseline values ($P=0.021$, ANCOVA). Serum calcidiol was still significantly different between two groups after removing baseline amounts ($P<0.001$, ANCOVA).

Discussion

The results of this study showed that vitamin D supplementation decreased serum insulin concentration and had beneficial effects in decreasing HbA1c in diabetic type 2 patients. There are several studies with similar results supporting this idea that vitamin D is an important nutrient in control of glucose homeostasis (13, 14). Vitamin D intake decreased prevalence of diabetes type 2 in long-time (15). One mechanism that plausible for relating vitamin D to diabetes may be its action on insulin receptor in beta cells. Vitamin D can stimulate gene expression of insulin receptor and increases glucose transport from the intestine (5). Another mechanism is that 1,25 (OH)$_2$D3 involves in calcium absorption from the gut and calcium is necessary for insulin release from beta-cells (16, 17). Recently, it has been cleared that beta-cells have receptors for 1,25 (OH)$_2$D3, the active form of vitamin D and this cells can convert calcidiol to this form of vitamin (17). One study showed that whether calcium is used or not, vitamin D supplementation improves glucose control in adults at high risk of diabetes type 2 (18).
### Table 2: Fasting biochemical characteristics of vitamin D and placebo groups at baseline and Post intervention

| Treatment group | Vitamin D group (n=28) | Placebo group (n=30) | P.value* |
|-----------------|------------------------|----------------------|---------|
| FBS (mg/dl)     | baseline               | 147.07±10.11         | 151.23 ± 7.48 | 0.740 |
|                 | Post-intervention      | 147.74 ± 10.16       | 161.27 ± 7.69 | 0.288 |
|                 | difference             | 2.70 ± 9.66          | 10.03 ± 4.61 | 0.483 |
|                 | P.value*               | 0.782                | 0.038      |
| TG (mg/dl)      | baseline               | 158.25 ± 12.41       | 167.43 ± 16.10 | 0.656 |
|                 | Post-intervention      | 145.33 ± 10.28       | 178.20 ± 14.80 | 0.080 |
|                 | difference             | -13.07 ± 13.15       | 10.76 ± 14.45 | 0.231 |
|                 | P.value*               | 0.329                | 0.462      |
| TC (mg/dl)      | baseline               | 201.82 ± 7.91        | 184.53 ± 6.73 | 0.100 |
|                 | Post-intervention      | 189 ± 7.04           | 200.87 ± 8.70 | 0.301 |
|                 | difference             | -12.88 ± 7.25        | 16.33 ± 6.93 | 0.005 |
|                 | P.value*               | 0.087                | 0.025      |
| HDL-C (mg/dl)   | baseline               | 42.29 ± 1.84         | 41.17 ± 2.15 | 0.697 |
|                 | Post-intervention      | 49.63 ± 3.28         | 49 ± 3.03 | 0.888 |
|                 | difference             | 6.81 ± 3.25          | 7.83 ± 3.39 | 0.830 |
|                 | P.value*               | 0.046                | 0.028      |
| LDL-C (mg/dl)   | baseline               | 88.93 ± 7.23         | 97.37 ± 7.64 | 0.427 |
|                 | Post-intervention      | 88.37 ± 6.94         | 98.67 ± 7.22 | 0.311 |
|                 | difference             | 0.56 ± 7.19          | 1.30 ± 8.65 | 0.971 |
|                 | P.value*               | 0.903                | 0.882      |
| HbA1c (%)       | baseline               | 7.29 ± 0.22          | 7.84 ± 0.28 | 0.132 |
|                 | Post-intervention      | 6.76 ± 0.18          | 7.73 ± 0.23 | 0.002 |
|                 | difference             | -0.53 ± 0.08         | -0.11 ± 0.08 | 0.001 |
|                 | P.value*               | <0.001               | 0.176      |
| Insulin (μIU/mL)| baseline               | 8.24 ± 0.97          | 7.49 ± 0.58 | 0.505 |
|                 | Post-intervention      | 6.55 ± 0.28          | 7.96 ± 0.94 | 0.171 |
|                 | difference             | -1.68 ± 0.81         | 0.47 ± 0.51 | 0.027 |
|                 | P.value*               | 0.048                | 0.367      |
| MOMA-IR         | baseline               | 2.50 ± 0.19          | 2.55 ± 0.16 | 0.841 |
|                 | Post-intervention      | 2.38 ± 0.18          | 2.78 ± 0.19 | 0.134 |
|                 | difference             | -0.14 ± 0.14         | 0.22 ± 0.13 | 0.056 |
|                 | P.value*               | 0.307                | 0.092      |
| Calcidiol (ng/ml)| baseline               | 15.55 ± 1.91         | 14.64 ± 2.22 | 0.759 |
|                 | Post-intervention      | 27.50 ± 2.04         | 15.95 ± 2.20 | <0.001 |
|                 | difference             | 11.95 ± 1.44         | 1.92 ± 0.89 | <0.001 |
|                 | P.value*               | <0.001               | 0.040      |

Data are expressed as mean ± SE, * Independent samples t-test, # Paired t-test.

Supplementation with vitamin D was only related to improved glucose control in diabetic patients with vitamin D deficiency and this nutrient had not any beneficial effect in patients with normal range of serum calcidiol (19). Supplementation of 1000 IU vitamin D combined with or without calcium in the form of fortified yogurt resulted in decreased HbA1c (20). However, vitamin D supplementaion although can normalize the calcidiol concentration in diabetic patients; it has no long-term effect on glycemic control in this people (21).
In our study, vitamin D supplementation did not change serum lipid profile in diabetic patients significantly except for HDL-C. However, the concentration of LDL-C and FBS increased significantly in placebo receiving group. One previous study showed that supplementation with vitamin D did not result in significant reduction in plasma glucose, TC, LDL-C and TG (19). Moreover, vitamin D supplementation had not significant effect in reducing serum FBS or insulin resistance in one systematic review (22).

Unlike our results, in the study of Al-Daghri et al. supplementation with vitamin D had decreased significantly serum TC and LDL-C concentration (23).

One of limitations of our study is the number of patients participated in the study. Maybe, if we used more patients, we could achieve better results such as reduction in some fractions of lipid profile.

Conclusion

Supplementation with UL dose of vitamin D could improve glucose control in diabetic type 2 patients, but did not exhibit any beneficial change in lipid profile except for HDL-C concentration. Therefore, it seems that vitamin D supplementation might be used as a strategy for control of glucose control in these people.

Ethical considerations

Ethical issues (including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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