ISSN: 0975-766X
CODEN: IJPTFI
Available Online through
Research Article
www.ijptonline.com

THE EFFECT OF VITAMIN D SUPPLEMENTATION ON INSULIN RESISTANCE AND GLYCEMIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES

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Received on 12-03-2016 *Accepted on 30-03-2016*

Abstract

Background and Objective: Low vitamin D status has been linked with impaired glycemic control in patients with type 2 diabetes. The purpose of our study was to figure out the effect of vitamin D supplementation on insulin resistance and glycemic control in patients with type 2 diabetes.

Materials and Methods: This study was a randomized, double-blind, placebo-controlled trial. A total of 120 patients with type 2 diabetes were selected and initial fasting blood glucose, two-hour postprandial, calcium, phosphorus, BUN, creatinine, HbA1C, 25 (OH) D and fast serum insulin test levels were measured. Then, based on block randomization design 50,000 IU of vitamin D was given every two weeks to 60 patients of the study group and up to 60 people in the placebo group. After 12 weeks (3 months), fasting blood glucose, two-hour postprandial, HbA1C, fasting serum insulin and vitamin D levels were measured.

Results: Out of 120 patients, 94 patients completed the study. The participants in the study group were 48 persons and in the placebo group were 46 cases. The average age of the participants in men was 47.04±7.98 years and in women was 47.09±7.38 years, respectively. Serum levels of vitamin D before the start of treatment was 16.21±17.38 ng/ml (deficiency). Variations of FBS, 2hpp and HbA1C between the two groups before and after treatment was not statistically significant (P= 0.86, P= 0.09, P= 0.93, respectively). Variations of HOMA-IR and HOMA- β% among study group and placebo group before and after treatment were not statistically significant (P= 0.069, P= 0.07, respectively).

Conclusions: Vitamin D supplementation did not improve glycemic control and insulin resistance. However, HOMA- β% in the study group compared to the placebo group had significantly greater improvement.

Keywords: Type 2 diabetes, Glycemic control, Insulin resistance

Introduction

Diabetes mellitus is an important metabolic disease that its prevalence is increasing. The prevalence of disease in Iran in the years 1995, 2000 and 2025 has determined and predicted 5.5, 5.7 and 6.8 percent, respectively (1). In addition to the genetics that make people prone to diabetes, several environmental factors to the great extent involve in its creation, including a lack of mobility, poor nutrition and obesity (2). Recently, vitamin D due to the potential benefits to health has dramatically got its importance (3).Vitamin D can be obtained through food sources or androgen (4). However, food sources have the capacity to generate approximately 30% of vitamin D (5). Exposure to ultraviolet B (UVB) radiation in sunlight is the most efficient way of obtaining vitamin D (5, 6). Vitamin D is produced by synthesizing photochemical process of 7-dehydrocholesterol through the two stage hydroxylation in the liver and kidneys, converted to its active form (1, 25-dihydroxyvitamin cholesterol) (7). The 1, 25-(OH) 2D3 plays an important role in maintaining calcium homeostasis and there is evidence that may be involved in immune function and has recently introduced its role in type 2 diabetes (3, 8, 9). Due to rapid clearance of 1, 25 (OH) 2D3, the best method for assessing vitamin D status is the measurement of serum 25 (OH) D3 and not1, 25 (OH) 2D3 (10). Reference values for vitamin D levels vary widely depending on ethnic background, age, geographic location, and the sampling season (11). The normal level of 25 (OH) D is between 30-60 ng/ml. Vitamin D insufficiency has been reported to range from levels of 16-30 ng/ml. Vitamin D level less than 20 ng/ml is considered a vitamin D deficiency (12). Based on research evidence, vitamin D deficiency can predispose individuals to diabetes type 1 and 2 (3). Recent data suggest that vitamin D receptor exists on the pancreatic islets β -cells and pancreatic islets are able to express 1-α-hydroxylase, so can activate 25 (OH) D (13, 14). Recent evidences have shown that people with type 2 diabetes and vitamin D deficiency may correlate to CRP increase, high fibrinogen (inflammatory markers) and HbA1C level compared to diabetic patients who have not more vitamin D deficiency (15). In addition, genetic variations in the vitamin D receptor may be associated with an increased risk of diabetes (16, 17). Patients with type 1 and 2 diabetes are at the significant risk of vitamin D deficiency or insufficiency. The causes of this issue are due to diet, insufficient exposure to sunlight, obesity, renal failure and genetics (2). Cross-sectional studies have shown that the level of 25 (OH) D is inversely associated with insulin resistance. While the direct measurement of sensitivity to insulin is required for confirmation, prospective studies support the idea of a protective effect for high 25 (OH) D on the risk of type 2 diabetes (2). Given the high prevalence of diabetes and its complications, the present prospective

and interventional study is conducted to investigate the effect of prescribed vitamin D supplements on glycemic control in patients with type 2 diabetes. The present study aimed to respond to some uncertainties, including duration of supplementation, as well as the necessary dose of vitamin D supplementation. A total of 50,000 IU Vitamin D3 was prescribed for every two weeks and totally twelve weeks (3571 units a day) in the case that the risk of poisoning (even in case of insufficiency) is limited and patient acceptance is improved. The target group of this study was poorly controlled type 2diabetic patients treated with oral hypoglycemic drugs.

Materials and Methods:

The current study was a randomized, double-blind, placebo-controlled study. Patients with type 2 diabetes treated with poorly controlled oral medications and referred to outpatient clinics were enrolled in the study. Diagnosis of diabetes was performed using ADA criteria (7). The aim of the study and the possible adverse side effects were explained to all patients and written informed consent was obtained. During the treatment the patients were asked to continue their medications and diet and physical activity in accordance with the opinion of the treating physician, as well as the patients were asked to refrain from taking any other vitamin or mineral supplements. According to a questionnaire that included the name, age, sex, height and weight, BMI, duration of diabetes and oral hypoglycemic drugs, the profile of the patients were recorded; similarly a history of other diseases and taking medications and vitamin supplements, occupation, physical activity, diet, location of life and education were included; as well as to estimate the amount of incoming calories (energy from carbohydrate, protein and FAT), fiber, vitamin D, calcium, and phosphorus the 24-hour dietary recall questionnaire was completed at the early and end of the study. Then, analysis and estimation of the intake of nutrients were calculated using NUT4 software. Initially, fasting blood glucose, 2-hour postprandial test, calcium, phosphorus BUN, creatinine, HbA1C, 25 (OH) D and baseline serum insulin of all the participants were measured. Based on the baseline serum 25(OH) D level patients were divided into two groups:

Group 1: patients with 25 (OH) D≥ 20 ng/ml

Group 2: patients with 25 (OH) D< 20 ng/ml (vitamin D deficiency)

Then for each group randomized block designs was created and in each group six categories of patients were ranked in blocks of four and the supplement or placebo was determined by a draw for researchers. Finally, for a second time, the FBS, 2-hour postprandial test, HbA1C, vitamin D serum 25 (OH) D, and fasting serum insulin were measured. Then, according to the following formula and based on the fasting serum insulin and FBS, the index of HOMA-IR

and HOMA-β% was calculated. Homeostasis Model Assessment of B—Cell function= 20×Fasting insulin (mu/lit)/Fasting Glucose (mmol/lit)-3.5

Inclusion criteria included the presence of type 2 diabetes under treatment with oral hypoglycemic drugs, baseline HbA1C lower or equal to 8.5%, age range of 20-60 years, and BMI higher than 20. The exclusion Criteria included having internal diseases such as chronic renal and hepatic diseases, -GFR<30 ml/min, hypercalcemia and kidney stones, diagnosed primary hyperparathyroidism, coronary heart disease, including ischemic and valvular disease, heart and cardiomyopathy failure, Sarcoidosis, TB and cancer, IBD history, Pregnancy, SBP/DBP>175/104, taking a vitamin D supplement more than 400 IU a day two months before the start of the study. The minimum sample size for this study was calculated 58 using the Eq.(1) and we use 60 patients in each group.

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})\ (\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2} \qquad (1)$$

Out of 120 participants, 94 patients completed the study and were referred for further testing. The final number of participants in the study group was 48 patients and in the placebo group was 46 patients. Data were analyzed by descriptive statistics (mean, standard deviation); graphs and independent t-test were used to compare the differences in the fasting blood glucose level, 2-hour postprandial test, HbA1C, HOMA- β% and HOMA-IR between the two groups. The repetitive measure test was used for the comparison of the mean of fasting blood glucose, 2-hour postprandial test, (25 (OH) D) serum, HbA1C, HOMA-IR and HOMA- β% in the study and placebo group before and after taking vitamin D. The significance level for all tests was 0.05. Data were analyzed using SPSS17.

Results

A total of 63 men and 45 women attended at the beginning of the study included 34 men and 20 women in the placebo group and 29 men and 25 women in the study group (P= 0.329). The mean BMI of the primary participants in the placebo group and in the study group was 28.65±2.9 and 28.08±3.46, respectively (P= 0.36). The mean levels of calcium, phosphorus, BUN, and creatinine in patients in the placebo and study groups were similar at baseline. The 2hpp average pre-treatment of the participants in the study group was 190.83±53.46 and after treatment reached to 237.60±80.52 and in the placebo group reached from 203.54±57.76 to 228.74±84.15. Regarding to the P-value, the changes in the two groups before and after treatment was statistically significant (P= 0.00), but in placebo and study groups before and after treatment (P= 0.86) was not statistically significant (P> 0.05). The mean of HbA1C before

treatment in participants in the study group was 7.14±0.92 and after treatment reached to 7.13±1.04 and in the placebo group the variation was from 7.19±0.91 to 6.44±1.20, respectively, and according to the P-value, the changes between the two groups as a whole before and after treatment were statistically significant (P= 0.00), but in terms of placebo and study groups before and after treatment (P= 0.09) variations were not statistically significant (P> 0.05).The mean of HOMA-IR pre-treatment of the participants in the study group was 58.20 ± 31.59 which after treatment reached to 55.88±35, but in terms of placebo and study groups before and after treatment (P= 0.09) variations were not statistically significant (P> 0.05).

Discussion

The present study showed that the mean serum vitamin D levels in diabetic patients before treatment was 16.21±17.38 ng/ml (deficiency) in the condition that Khuzestan province is the tropical area of Iran, so it is important to examine the vitamin D levels in patients with diabetes. The present study examined the effect of vitamin D supplementation in type 2 diabetic patients for 3 months (12 weeks). The result showed that vitamin D supplementation can significantly increase the serum vitamin D levels of participants (the mean levels after treatment in the study group increased up to 26.62±11.17 ng/ml but still was in the range of insufficiency) and partly has been effective in the disease process, although there was no statistically significant relationship in the most indicators of disease control.

The FBS level changes caused by vitamin D supplements between the two groups before and after treatment (P= 0.68) and in the placebo and study groups before and after treatment (P= 0.93) were not statistically significant (P> 0.05). Generally, the 2hpp variations between the two groups before and after treatment (P= 0.00) were statistically significant, but in terms of placebo and study groups before and after treatment (P= 0.86) was not statistically significant (P> 0.05). In general, HbA1C changes between the two groups before and after treatment (P= 0.00) were statistically significant, but in placebo and study groups before and after treatment (P= 0.09) were not statistically significant (P> 0.05) which indicates that the decrease to a large extent was due to factors other than supplementation with vitamin D like activities or taking hypoglycemic drugs. The findings of the present study are consistent with many interventional studies that have been done in this area.

Pittas et al. (2007) examined the effects of daily consumption of 500 mg of calcium citrate and 700 international units of vitamin D or placebo into the 314 people for three years. At the end of the study, based on initial blood glucose, people were evaluated on the two groups of IFG (Impaired Fasting Glucose) and NFG (Normal Fasting

Glucoses). In the NFG group no significant difference was observed in the blood glucose of the study and placebo groups. In the IFG group the increased blood sugar levels in taking calcium and vitamin D supplement group w more than the placebo group. In fact, calcium and vitamin D in the IFG group released the process of IFG hyperglycemia increases and prevent its further increase. It is noteworthy that in this study calcium and vitamin D were given at the same time (13). In a study conducted by Jorde & Schau (2009), 36 diabetic patients treated with metformin and insulin before bedtime was randomly treated by 40,000 IU vitamin D3 (cholecalciferol) per week or placebo for six months.

After six months, FBS and HbA1C levels were not changed significantly compared to a pre-prescribed dietary supplement. In addition to these parameters the difference of parameters compared to the baseline between vitamin D intake and placebo groups was not different. In a study by Shirin Zadeh et al. (2006), the impact of vitamin D supplementation on insulin resistance in patients with type 2 diabetes was analyzed. A total of 57 diabetic patients taking hypoglycemic pills and with vitamin D deficiency (25-OH-D <20 ng/ml) were selected to participate in the study and treated for a month with vitamin D (1500 IU) or placebo. After treatment, only 60% of patients in the group receiving supplementation obtained the sufficient vitamin D level. Fasting glucose and insulin levels decreased in the group receiving vitamin D that these changes were not significant. After intervention the serum C-peptide level in the group receiving supplements increased from 82.0±41.2 ng/ml / to 14.1±78.2 ng which was not statistically significant (P< 0.02).

After the intervention, the mean changes of QUICKI in the group receiving supplements were significantly higher than the placebo group (P< 0.03) which indicate that the insulin resistance in a group receiving vitamin D supplementation decreased compared to the placebo group (18). Bonakdaran et al. (2010) studied the effects of daily 5.0 mg calcitriol for 8 consecutive weeks on the 58 diabetic patients administered in the Mashhad Ghaem Hospital. They reported that the fasting blood glucose, glycosylated hemoglobin and insulin resistance decreased, but the changes were not statistically significant (P> 0.05) (19). Eftekhary et al. (2011) studied the impact of calcitriol on glucose and insulin levels in patients with type 2 diabetes.

A total of 70 patients with type 2 diabetes were investigated for 12 weeks in the intervention and placebo groups. The study group received daily 0.5 mg calcitriol (two capsules 0.25 mg) and the placebo group received two placebo capsules. Fasting blood glucose level at weeks zero, 6, and 12 in the study group had any significant changes, but in the placebo group significantly increased (P= 0.03).In the study and placebo groups, the mean of

HbA1C at week 12 compared to week zero showed a significant increase (P= 0.013 and 0.0004, respectively), but the rate of increase in the study group was almost twice the placebo group. Insulin resistance was increased in both groups (P= 0.023 and 0.0001). HOMA-% B, indicator of beta cells activity were unchanged in the placebo group, but significantly increased in the study group (P= 0.009) (20).

Borrissoua et al. (2003) studied the effects of supplemental cholecalciferol (vitamin D3) on insulin resistance and insulin secretion in type 2 diabetic women treated for one month with daily 1332 IU vitamin D, respectively. The first phase insulin secretion was significantly increased (34% with P <0.05), while there was no significant change in the second phase insulin secretion (20% with P> 0.8). It is noteworthy that the first phase insulin secretion affects the glucose postprandial level (21). Hurst et al. (2010) in a randomized and placebo-controlled trial by in New Zealand studied the effect of vitamin D3 on insulin sensitivity and insulin secretion and insulin resistance in 80 women with vitamin D deficiency. After six months of treatment with vitamin D3, the level of 25 (OH) D3 of 21nmol/L increased to 75nmol/L. A vital recovery in insulin sensitivity and a decrease in fasting insulin were observed in the group that had received the supplement, compared to the placebo group and after supplementation the level of 25 (OH) D3 increased to the extent of 25%. The difference between this study and other studies was that supplementation in people with vitamin D deficiency and insulin resistance was carried out for six months. However, in the case of glucose 2hhp as an indicator of insulin resistance, the result of the study was further strengthened (22).

In a study by Nagpal et al. (2009), the effect of three oral doses of 120,000 IU of vitamin D3 with placebo over a period of six weeks on the HOMA-IR, insulin sensitivity, OGIS, and insulin secretion on the healthy non-diabetic men with central obesity was investigated. Vitamin D3 supplementation improved the OGIS compared with placebo (Intention-To-Treat analysis P= 0.055); however, no change was found in the other results (Out Come measures), including HOMA, HOMA-2 (quantitative insulin sensitivity index) and insulin secretion (HOMA% B, HOMA2-% B) (23). According to the results of the present study and similar studies on vitamin D levels regarding the effect of vitamin D supplementation can be concluded that vitamin D supplementation has no effect on the decrease of HbA1C levels in diabetic patients, but it can decrease the processing speed. Regarding the effect of vitamin D on insulin resistance and beta cell function indices, the HOMA-IR changes in general between the two groups before and after treatment (P= 0.069) and in the placebo and study groups before and after treatment (P= 0.069) were not statistically significant (P> 0.05). As well as changes in HOMA- β% in both groups before and

after treatment (P= 0.51) and in the placebo and study groups before and after treatment (P= 0.07) were not statistically significant (P> 0.05).

Finally, in the present study, however the effect of vitamin D supplementation on measures of glycemic control, insulin resistance and beta cell function was not statistically significant, but given that HOMA-IR in the study group compared to the placebo group had no change and in the placebo group increased and HOMA- β% in the study group compared to the placebo group had significantly greater improvement. Vitamin D could decrease the pathophysiological process of the disease, though if more time was available to study its effects on diabetes control were more pronounced. Limitations of the present study included the reducing number of patients in the course of the study; short-time study; the simultaneous presence of patients with vitamin D deficiency; and normal vitamin D levels in the study.

Conclusions

The present study showed that vitamin D deficiency is an important problem among diabetic patients in the province, which this can contribute to the escalation and lack of disease control, and considering the problem diagnosis and treatment of vitamin D deficiency that is also affordable, it is necessary to evaluate the diabetic patients.

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