Effect of Therapeutic Dose of Vitamin D on Serum Adiponectin and Glycemia in Vitamin D-Insufficient or Deficient Type 2 Diabetic Patients

Nima Baziar1; Kurosh Jafarian1; Zhaleh Shadman2; Mostafa Qorbani3,4; Mohsen Khoshniat Nikoo2; Mahshid Abd Mishani2

1Department of Clinical Nutrition and Dietetics Therapy, Faculty of Nutrition Sciences and Food Technology, Tehran University of Medical Sciences, Tehran, IR Iran
2Research Center of Endocrinology and Metabolism, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, IR Iran
3Department of Community Medicine, Alborz University of Medical Sciences, Karaj, IR Iran
4Non Communicable Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, IR Iran

*Corresponding Author: Mohsen Khoshniat Nikoo, Research Center of Endocrinology and Metabolism, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, IR Iran. Tel: +98-2188220094; Ext: 5; Fax: +98-2188220052, E-mail: khoshniatmohsen@yahoo.com

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Background: Lower vitamin D status has been reported in diabetic patients. Serum 25-hydroxyvitamin D and adiponectin were inversely associated with type 2 diabetes and insulin resistance. Vitamin D may involve in regulation of the adiponectin levels, which is directly related to insulin sensitivity.

Objectives: The aim of this study was to investigate the effect of therapeutic dose of vitamin D on serum adiponectin and insulin resistance in vitamin D-insufficient or deficient type 2 diabetic patients.

Materials and Methods: This double-blind, randomized, clinical trial was conducted on 81 type 2 diabetic patients with vitamin D level of 10-30 ng/mL. Intervention was 50000 IU vitamin D or placebo once a week for 8 weeks. At the beginning and end of the study, blood samples were collected after 12 hours of fasting and serum glucose, insulin, 25-hydroxyvitamin D, and adiponectin were measured. Insulin resistance was calculated by homeostasis model assessment (HOMA-IR).

Results: After 8-week intervention, serum 25-hydroxyvitamin D significantly increased and reached the normal levels in patients receiving vitamin D (P < 0.001) and the levels of fasting serum glucose, insulin, and HOMA-IR were significantly decreased (P = 0.04, 0.02 and 0.007, respectively). No significant changes were observed in these levels in the placebo group. Significant differences were observed in mean changes in the above-mentioned variables between the two groups (P = 0.01, 0.04 and 0.006, respectively). No significant changes were found in serum adiponectin in the vitamin D and placebo groups (P = 0.83).

Conclusions: Therapeutic dose of vitamin D can improve vitamin D status and glycemic indicators. But it seems that an 8-week intervention period was not sufficient to reveal the possible effects of vitamin D on serum adiponectin levels.

Keywords: Diabetes Mellitus; Vitamin D; Insulin Resistance; Adiponectin

1. Background

The association between the several non-skeletal diseases and vitamin D deficiency has been recently reported (1, 2). Some risk factors of vitamin D deficiency and type 2 diabetes are similar (e.g. ethnicity, obesity, age and low physical activity level). A low level of vitamin D status has been reported in diabetic patients (1, 3-5). Vitamin D may be involved in the pathways of insulin production, secretion, and possibly insulin signaling in insulin-sensitive tissues (6). It may be effective in reducing the risk of type 2 diabetes (4, 7, 8) and its management (3, 6). Vitamin D deficiency was associated with insulin resistance (4, 7, 9, 10) and considered as a risk factor for type 2 diabetes (2, 7, 10). Adiponectin is one of the suggested mechanisms by which vitamin D may affect insulin sensitivity (5, 11) and epidemiological studies have shown that adiponectin is inversely associated with obesity, insulin resistance, diabetes, metabolic syndrome, cardiovascular disease and hypertension (12-21). In comparison to healthy people, the lower plasma concentrations of adiponectin have been reported in type 2 diabetic patients and obese people (7, 22, 23). Thiazolidinediones-induced improvement in insulin sensitivity may be related to an increase in serum adiponectin (23).

Reported positive association between vitamin D and adiponectin in cross-sectional studies (5, 7, 21, 24, 25) may be arise from that vitamin D may affect serum adiponectin through increased adiponectin gene expression (5) or renin-angiotensinogen system (11). Given this relationship and since vitamin D status, as well as adiponectin, is inversely associated with insulin resistance and cardiovascular diseases (24-26), it can be suggested a possible role of the adiponectin-dependent vitamin D effect in decreasing insulin resistance and cardiovascular diseases. Thus, it is important to evaluate the effect of vitamin D
supplementation on adiponectin concentration and illustrate whether vitamin D may improve the glycemic indicators through adiponectin. Vitamin D supplementation alone, or in combination with calcium has shown conflicting results in prevention or management of type 2 diabetes (6, 27). These discrepancies may arise from lack of coordination in methodological design, supplementation dosage, duration, baseline body vitamin status and etc.

Since adiponectin is associated with a better glycemic control and other metabolic indicators, identifying the causes of deficiency and its enhancing factors may be useful in the management of diabetes and metabolic syndrome. However, only two interventional studies have been conducted to determine the effects of vitamin D supplementation on serum adiponectin and subsequent blood glucose (10, 28).

2. Objectives

Regarding the high prevalence of diabetes (29) and vitamin D deficiency (30) in Iran and since vitamin D deficiency may increase insulin resistance through low adiponectin levels, the aim of this study was to investigate the effect of therapeutic dose of vitamin D (a single dose of 50000 IU/week for 8 weeks) on serum adiponectin and insulin resistance in vitamin D-insufficient or deficient type 2 diabetic patients.

3. Materials and Methods

This double-blind, randomized, clinical trial was approved by the ethic committee of endocrinology and metabolism research center, Tehran University of Medical Sciences (00220) and was conducted during December-March 2012 at the diabetes and metabolic disease clinic of endocrinology and metabolism research center, Tehran University of Medical Sciences, Tehran, Iran.

3.1. Subjects

Sample size was determined according to variable HOMA-IR of Al-Daghri et al. clinical trial (25) considering \( \alpha = 0.05 \) and \( \beta = 0.02 \), the mean differences for vitamin D and placebo groups were \( 0.04 \pm 0.06 \) and \( 0.01 \pm 0.03 \), respectively. By the possibility of 10% for sample missing, the required sample size per group was determined 44 cases.

Using medical documents, 105 type 2 diabetic patients controlled by oral glucose-lowering agents were invited to participate in the study and 98 patients were selected according to document-based inclusion criteria. Serum 25-hydroxyvitamin D, aspartate transaminase, alanine transaminase, creatinine, blood urea nitrogen and glycated hemoglobin were measured and nine patients were excluded from the study because their vitamin D status was not within the vitamin D range of the study and also two cases were excluded due to HbA1c more than 8%. Overall, 87 patients were recruited the trial and allocated into two groups through sex-stratified randomization (43 receiving vitamin D and 44 receiving placebo) (Figure 1). Inclusion criteria were diagnosed type 2 diabetes mellitus > one year and > 30 years old, aged 31-65, body mass index (BMI) > 25 and < 30 kg/m², serum 25-hydroxyvitamin D 10-30 ng/mL, glycated hemoglobin (HbA1c) < 8%, no alcohol consumption and smoking, insulin therapy, consuming thiazolidinediones, pregnancy or menopause, consuming vitamin D-interfering drugs (corticosteroids, antiepileptics and contraceptives) and also calcium and vitamin D supplementation in last six months, no history of myocardial infarction, angina pectina and stroke in last year or suffering from cardiovascular, liver, kidney, thyroid gland diseases and chronic inflammation. Exclusion criteria were non-regular consumption of supplements (consuming less than 80%), changes in the dietary intake, physical activity level and medications.

Participants were explained in regard to the protocol and the aim of the study and the written informed consent was obtained. A demographic questionnaire was completed for each patient and blood samples were collected for determining the concentrations of serum 25-hydroxyvitamin D. Then, vitamin D-insufficient or deficient diagnosed patients were randomly stratified according to sex into two groups receiving 50000 IU/week vitamin D, or paraffin as placebo.

3.2. Intervention

Current acceptable approaches to treat vitamin D deficiency in infants are 2000 IU/d or a single dose of 50000 IU/week for 6 weeks until the serum 25-hydroxyvitamin D level gets above 30 ng/mL and then 400-1000 IU/d for maintenance. In children 18 years old, treatments are 2000 IU/d at least for 6 weeks or a single dose of 50000 IU/week at least for 6 weeks and the maintenance of 600-1000 IU/d. In all adults the recommended approach is a single dose of 50000IU/week for weeks to reach above 30 ng/mL and the maintenance dose of 1500-2000IU/d. In obesity, malabsorption syndrome or taking drugs affecting vitamin D metabolism, higher doses (6000-10000 IU/d) are recommended and the maintaining dose would be 3000-6000 IU/d(31).

Vitamin D supplementation in this study was 50000IU vitamin D3 soft gelatin spherical pearls with clear and transparent shell. Placebo contained paraffin and were as similar as vitamin D pearls in appearance. All supplements were supplied by Zahravi, Iran. Vitamin D and placebo batches were named as A or B by a third person. Each volunteers received eight pearls (vitamin D or placebo) in one batch at the beginning of the study and were asked to take weekly for eight weeks.

All participants were recommended not to change their usual physical activity level and food intakes. Maintaining the medication as before was a criteria for continuing the study. At the end of the study, compliance rate of the patients was evaluated through counting the remaining capsules.
3.3. Anthropometric Measurements and Physical Activity Level

Height was measured with a wall-mounted stadiometer to the nearest 0.1 cm. Weight was determined to the nearest 0.1 kg on the same properly calibrated electronic digital scale, without shoes, with minimal clothing, and after voiding. Two measurements were obtained and averaged; with a third measurement taken if the first two differed by 0.1. Body mass index (BMI) was estimated as the ratio of body weight to height squared and expressed as kg/m$^2$. Physical activity level was assessed by a validated questionnaire in which nine different metabolic equivalent (MET) levels were ranged on a scale from sleep/rest (0.9 METs) to high-intensity physical activities (> 6 METs).

3.4. Dietary Intake

Dietary intake of vitamin D and calcium were ensured through 1-day 24-hour dietary recall at the baseline and end of the eighth week of the study. This dietary information was analyzed with N4 software (Nutritionist: version 4.0; Tinuviel Software, Warrington, United Kingdom).

3.5. Biochemical Data Assessment

Seven ml 12-hour fasting state blood samples were collected from brachial vein at the baseline and end of study. The samples centrifuged immediately at 3000 rpm for 15 minutes and promptly the serum aliquoted into separate tubes. Aliquoted samples were stored at -70°C until analysis. One mL whole blood samples were stored to measure HbA1c.

Serum glucose concentration was measured (Glucose determination kit, Parsazmun, Tehran, Iran) through auto-analyzer instrument (Sleckta II, Dieren, Netherlands) and fluorometric method according glucose oxidase principle. Serum insulin was measured by enzyme-linked immunosorbent assay (ELISA) kit (Monobind, Uppsala, US). Homeostasis model of assessment (HOMA-IR) as an index of insulin resistance was used (32). Glycated hemoglobin was determined in whole blood sample by D55 chromatography method (HbATc Kit, Drew Scientific Limited, Villaricca, United Kingdom). The intra- and inter-assay coefficients of variation (CVs) for glucose, insulin and HbA1c were 4.7%, 5.5%, 5.6% and 4.9%, 5.8%, 5.8%, respectively. The sensitivity of the assays for glucose, in-
sulin and HbA1c were 1 mg/dL, 1 mU/L and 1%, respectively. Serum 25-hydroxyvitamin D was measured using ELISA (IDS, Boldon, UK). The intra- and inter-assay CVs for serum vitamin D were 5.4% and 5.5%, respectively. The sensitivity of the assays was 5 nmol/L. Serum adiponectin were also measured by ELISA kit (Mediagnost, Uppsala, Germany). The intra- and inter-assay CVs for adiponectin were 1.5% and 2%, respectively. The sensitivity of the assays was 0.6 ng/mL.

3.6. Statistical Analysis

Data were analyzed with statistical package software for social sciences, version 16 (SPSS Inc. Chicago, IL, USA). Kolmogrov-Smirinov test was used to show the normality and homogeneity of variances. Paired t-test was used to compare the mean variables before and after the intervention in each group. T-test was used to compare the mean differences of variables before and after the intervention as well as the mean changes between the groups. An alpha level of less than 0.05 was accepted in all tests as statistically significant and with the sample size of 87; a power value of %90 was generated. This study was submitted in Iranian Registry of Clinical Trials as IRCT2013052111421N2.

4. Results

Among 87 patients, two patients receiving placebo and two cases in vitamin D receiving groups were excluded from the study due to the changes in diabetes treatment procedure and one placebo as immigration. At the end, 82 patients completed the study. Baseline characteristics of the patients listed in Table 1. There were no significant differences in baseline characteristics between the groups. A statistical, but not clinical significant difference with higher level in the placebo group was shown in HbA1c (P value = 0.048).

As seen in Table 2, there was no significant difference in baseline serum 25-hydroxyvitamin D concentration between the two groups. After eight-week intervention, serum 25-hydroxyvitamin D increased significantly in the group receiving vitamin D (P value < 0.001). The lowest and highest of achieved 25-hydroxyvitamin D concentration in the intervention group were 29.2 and 88 g/mL, respectively. Comparing difference in changes between the two groups showed that vitamin D increased serum 25-hydroxyvitamin D by about 200 percent (P value < 0.001).

The means and standard deviation of fasting serum glucose, insulin and HOMA-IR at the beginning and end of the study and their changes in each group were presented in Table 3. In patients taking vitamin, fasting glucose concentration decreased significantly in comparison to the beginning (P value = 0.045) and also to placebo (P value = 0.014). Fasting serum insulin was decreased significantly in the intervention group (P value = 0.028). Comparison of the mean changes of serum insulin in the two groups showed a significant change in the group receiving vitamin D (P value = 0.048). Vitamin D significantly decreased insulin resistance (P value = 0.007) and the mean decrease in insulin resistance in patients receiving vitamin D was significantly higher than those who received placebo (P value = 0.006).

The means and standard deviation of serum adiponectin and its change in each group at the beginning and end of study were presented in Table 3. At the end of the study, no significant changes were seen in adiponectin concentrations in neither vitamin D nor placebo groups.
groups (P value = 0.186 and 0.60, respectively). Also, the mean changes were not significantly different between the groups (P value = 0.831).

5. Discussion
In this study, eight weeks of 50000 IU/week vitamin D administration increased serum 25-hydroxyvitamin D and decreased fasting serum glucose, insulin and also insulin resistance with no changes in serum adiponectin. At the end of the study, the lowest concentration of 25-hydroxyvitamin D in the intervention group was 29.2 ng/mL, which was close to the defined normal range (31-40 ng/mL). Also, the highest achieved level was 88 ng/mL compared to the toxicity level of 150 ng/mL. These showed the effectiveness and safety of therapeutic dose of vitamin D in improving vitamin D status.

A significant association have been reported between serum 25-hydroxyvitamin D and glycemic control in cross-sectional studies (5, 33, 34), while interventional studies reported contradictory results on glycemia or other glycemic indicators, which may be as a result of disparities in study design, supplementation dosage and possibly baseline concentration of 25-hydroxyvitamin D (6, 35, 36). In almost all studies reported to date on vitamin D- insufficient or deficient subjects, vitamin D supplementation increased serum 25-hydroxyvitamin D to the normal range and subsequently decreased insulin resistance (6, 25, 37-40). But, some other studies did not show any effects on glycemia (10, 28, 35, 41). Witham et al. (41) did not show any significant improvement in insulin resistance after 16 months of receiving a single dose (100000 and 200000 IU) of vitamin D. Although, a significant decrease in insulin resistance was reported after eight-week 2000000 IU vitamin D supplementation, this effect was less following a decrease in serum 25-hydroxyvitamin D. Moreover, Jorde et al. did not report any beneficial effect of six-month 4000 IU/week supplementation on glycemic indicators in diabetic patients; however, baseline vitamin D status of the participants was higher than 20 ng/mL (35). Breslavsky et al. also failed to bring serum 25-hydroxyvitamin D to the normal levels despite 12-month 1000 IU/day vitamin supplementation; which was justified by the progressive nature of diabetes (10). Patel et al. also failed to achieve normal vitamin D status and reveal any benefits for vitamin D supplementation on glycemic control. Their study was not a placebo-controlled (28).

Nagpal et al. reported an improvement in oral glucose insulin sensitivity (OGIS) in individuals with abdominal obesity along with no achievement of normal serum vitamin D or improvement in other insulin sensitivity indicators or HOMA-IR (36). HOMA-IR is according to fasting plasma glucose and insulin concentration and is an indicator of measuring liver resistance against insulin in producing and releasing glucose, while OGIS measures the ability of insulin in stimulating muscles to uptake 2-hour postprandial blood glucose (36). Neglecting OGIS may be considered as a limitation of our study; because both HOMA-IR and OGIS calculation may be essential to
determine the exact effects of vitamin D supplementation on insulin sensitivity and glycemia. It is possible that a single high dose injection of vitamin D, not only has no beneficial effects on insulin resistance, but also may have adverse effects on glycemic indicators (38). Taylor and colleagues reported increasing in insulin resistance and worsening glycemia in three type 2 diabetic patients with vitamin D deficiency three months following the injection of 300000IU vitamin D; however, significant increases were shown in serum 25-hydroxy vitamin D, but none of three-mentioned patients achieved normal levels (42). Furthermore, Heshmat et al. conducted a similar study and failed to show any improvement of glycemic indicators. Even a non-significant incensement was seen in subjects taking vitamin D (3.1 ± 2.3 to 3.4 ± 1.9) (30). It seems that an injection of vitamin D (a single dose) increased serum 25-hydroxyvitamin D for a short-term; so, measuring the glycermic indicators three months after injection could be affected by other confounders. Furthermore, baseline status (46.92 ± 34.7 ng/ml) was in normal range. Totally, it appears that vitamin D supplementation improves glycemia in vitamin D-insufficient or deficient patients providing improvement of vitamin status.

Several vitamin D and diabetes linking mechanisms have been suggested including the effects of vitamin D on insulin secretion, peripheral insulin resistance and inflammation. 1,25-dihydroxyvitamin D bind to nuclear receptors and up-regulate insulin cell-membrane receptors, increases the receptor synthesis resulting more presence of insulin-dependent glucose transporter (GLUT4) in cell membrane (43). Vitamin D also up-regulates peroxisome proliferator-activated receptors, which improve fatty acid metabolism and insulin sensitivity (44). It was also reported that vitamin D regulates renin-angiotensin system through down-regulating renin and inhibiting angiotensin-I receptors, which their activity involves in insulin resistance, inflammation and hypertension (45). Another suggested mechanism is an increasing of parathyroid hormone and subsequently lipogenesis, obesity and insulin resistance due to vitamin deficiency (46).

Despite the reported associations between vitamin D status and serum adiponectin as a cause of insulin resistance in individuals (7, 11, 25), in the present study, vitamin D therapeutic dose had no effect on improving serum adiponectin. This finding is similar to the study by Breslavsky (1000 IU/day vitamin D for 12 months) (10) and Patel et al. (400 IU and 1200 IU/day for 4 months) (28). However, in the first study, normal serum vitamin D levels did not achieve (10) and in the second, low sample size and absence of control group was prompted less power (28).

Several mechanisms have been suggested to express the potential effects of vitamin D on adiponectin. Vitamin D may affect adiponectin through renin-angiotensinogen system. Increased activity of renin-angiotensinogen system is associated with an increased angiotensin production, which leads to the production of dysfunctional adipocytes and finally, decreased adiponectin production. Vitamin D may involve in increasing serum adiponectin by down-regulating and decreasing angiotensin production (11, 21). Insulin resistance and glucose intolerance are inflammatory conditions that are associated with decreased production of adiponectin and increased activity of inflammatory cytokines as well as TNF-α and interleukin-1. TNF-α reduces adiponectin synthesis and vitamin D may be associated with increased serum adiponectin through decreasing gene expression (5). With vitamin D receptors on adipocytes, direct involvement of vitamin D in adiponectin gene expression is considered (5). Vitamin D and calcium may play a role in the regulation adipocytokine gene expression in visceral adipose tissue. Another mechanism explaining the association between vitamin D and adiponectin is osteocalcin. Vitamin D is associated with the up-regulating of osteocalcin, which its carboxylated form plays a role in energy and glucose homeostasis (7). Adding osteocalcin into adipocyte cell cultures increased an adiponectin gene expression (7). Despite aforementioned mechanisms, in the present study, although serum vitamin D reached to normal levels and led to improvement in insulin resistance, no statistical significant changes were shown in serum adiponectin concentration. It should be noted that two forms of circulating adiponectin are found; low-molecular weight (LMW) and high-molecular weight (HMW) adiponectin. The second is active form and the ratio of HMW adiponectin to total is more accurate in assessment of the association between insulin resistance and adiponectin (47). So, the measurement of only total adiponectin level could be a big limitation of our study. Indeed, further studies recommended to investigate the effects of vitamin D on different forms of serum adiponectin. Another weakness of this study was the biochemical assessments immediately at the end of the study. It appears likely there was not enough time for revealing the positive effects of vitamin D on adiponectin gene expression or other possible mechanisms. So, it could not be definitely assigned vitamin D as no effect on adiponectin. The strong point of this study was the inclusion of vitamin D-insufficient or deficient type 2 diabetic patients with a narrow range of 25-hydroxyvitamin D concentrations that may be the most predictive value in interpreting of the results but has been ignored in previews studies.

In summary, therapeutic dose of vitamin D (50000 IU/week) for 8 weeks in vitamin D-insufficient or deficient type 2 diabetic patients improves the low levels of vitamin D status and glycemia, with no positive effect on serum adiponectin. A routine control of vitamin D status in type 2 diabetic patients and treatment of deficiency is suggested in vitamin D-insufficient patients to achieve a better control of glycemia.

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Authors’ Contributions

Nima Baziar conceived of the study, carried out the design of the article, coordinated the implementation, drafted the manuscript, and performed the statistical analysis. Kurosh Jafarian participated in the design of the study and revised the manuscript. Zhaleh Shadman conceived of the study, carried out the design, coordinated the implementation, drafted the manuscript, and performed the statistical analysis. Mostafa Qorbani participated in the implementation, drafted the manuscript, and performed the statistical analysis. Mohammad Khoshnian participated in the design of the study and revised the manuscript. Mahshid Abd Mishani participated in acquisition of data and revised the manuscript. The authors thank all who participated in or collaborated with the present study.

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