

Original Article

Impact of treatment with oral calcitriol on glucose indices in type 2 diabetes mellitus patients

Mohammad Hassan Eftekhari PhD, Marzieh Akbarzadeh MSc, Mohammad Hossein Dabbaghmanesh MD, Jafar Hasanzadeh PhD

Nutrition Department, Research Center for Health Sciences, School of Health and Nutrition, Shiraz University of Medical Sciences, Shiraz, I.R. Iran

Introduction: Type 2 diabetes is a major public health problem. Recent epidemiological evidence also points to a potential association of vitamin D insufficiency with adverse metabolic risks, including that for type 2 diabetes. **Subjects and method:** A double-blind randomized placebo-controlled trial was carried out. Seventy subjects with type 2 diabetes, age 30-75 years old, were randomly assigned in a double-blind fashion to two groups. One group received two capsules of calcitriol (0.25 µg 1,25-dihydroxy cholecalciferol per each capsule) per day. The second group received placebo tablets. At the beginning, middle and the end of the 12 week supplementation trial, serum glucose, insulin, calcium and phosphorous, HbA1c and 25(OH) vitamin D were measured. **Results:** There was no significant difference between two groups at baseline. At the end of the study, fasting plasma glucose increased in the control group ($p=0.038$), while it remained unchanged in calcitriol group. Level of insulin and HbA1c increased significantly in both groups ($p=0.013$ and 0.0004 in treatment and control group). Regarding insulin resistance indices, there was a significant change in HOMA-IR and QUICKI in both groups ($p=0.023$ and 0.002 in treatment and 0.001 and <0.001 in control group respectively). Insulin secretion as assessed by HOMA-%β, remained relatively unchanged in the control group, while it increased significantly in the treatment group at the end of study ($p=0.009$). **Conclusion:** Vitamin D supplementation attenuated the increase in glycemia, and increased insulin secretion, but had no effect on insulin resistance.

Key Words: diabetes mellitus, calcitriol, glucose, insulin resistance, hemoglobin A1C

INTRODUCTION

The burden of chronic diseases is rapidly increasing worldwide. Almost half of the total chronic disease deaths are attributed to cardiovascular diseases; obesity and diabetes are also showing worrying trends, not only because they already affect a large proportion of the population, but also because they have started to appear earlier in life.¹

Numerous international expert reviews, including those of WHO,² have identified the close link between certain nutritional factors and risk of diabetes mellitus. Over the last decade, numerous disease associations have been reported with vitamin D deficiency, including type 2 diabetes mellitus.

Now it is clear that vitamin D receptors (VDR) exist in more than thirty different tissues and the number of genes known to be regulated by calcitriol is still growing.³ Recent epidemiological evidence also points to a potential association of vitamin D insufficiency with adverse metabolic risks, including that for type 2 diabetes. A prospective study by Forouhi *et al.*⁴ reported inverse association between serum 25-hydroxy cholecalciferol level and future glycemia and insulin resistance in non-diabetic subjects. There is some evidence that polymorphisms in the VDR gene may be associated with insulin resistance, insulin secretion, and fasting glucose concentrations, sug-

gesting that vitamin D is likely to contribute to glucose metabolism.⁴

Iran has experienced a rapid “nutrition transition” during the 1990s. The implantation of a western life style, along with a lack of sufficient physical activity outdoors and so decrease exposure to sunlight, has resulted in an increasing prevalence of micronutrient deficiency such as that for vitamin D. In a population study, Hashemipour and his co-workers showed that prevalence of vitamin D deficiency among men and women living in Tehran was 81%.⁵ So with respect to the role of vitamin D in glucose metabolism, the aim of the present study was to assess the effects of vitamin D (calcitriol) supplementation on glucose metabolism in diabetic patients.

MATERIALS AND METHODS

Study subjects

A double-blind randomized placebo-controlled trial was

Corresponding Author: Dr Mohammad Hassan Eftekhari, Nutrition Department, Research Center for Health Sciences, School of Health and Nutrition, Shiraz University of Medical Sciences, Shiraz, I.R. Iran.

Tel: 0098-09177088717; Fax: 0098-711-7251008

Email: h_eftkhari@yahoo.com

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carried out. Seventy subjects (35 male and 35 female) with type 2 diabetes, age 30-75 years old, on treatment with oral hypoglycemic drugs were recruited from the outpatient Motahari clinic at Shiraz University of Medical Sciences. No severe fluctuation was seen in their plasma glucose, so there was no need to change their drugs dosage. Criteria for case inclusion were well-controlled fasting plasma glucose, serum calcium <10.5 mg/dL, normal liver and kidney function and no history of kidney stone and hypercalcemia. Exclusion criteria included taking insulin for diabetes control, taking calcium and vitamin D supplements, history of diseases affecting vitamin D status and intestinal malabsorption disease.

At the beginning of the study, subjects were given an oral and written explanation of the study, including its benefits and procedure, and were asked to read and sign an informed consent document.

The study protocol was reviewed and approved by the Human Ethics Committee of Research council of the Dean of Research Affair of Shiraz University of Medical Sciences.

Intervention design

A double-blind randomized placebo-controlled trial was carried out. This 12 weeks clinical trial was conducted between August to November 2009. The patients were randomly allocated into one of the two study groups: treatment and control group. One groups received two capsules of calcitriol (0.25 µg 1,25-dihydroxy cholecalciferol per each capsule) per day. The second group received identical-looking placebo tablets. All calcitriol tablets and their placebo had the same color and shape and were produced by Zahravi Pharmacy Company (Tehran-Iran). Subjects were asked not to take any vitamin or supplements during the trial. Researcher supervised ingestion of supplements each week.

Background characteristics and food consumption assessment

Demographic data were collected by interviews and anthropometric indices were determined for each subject. Anthropometric assessments included measurement of weight and height. Body weight was measured to the nearest 0.1 kg using the Seca 713 scale, while subjects were minimally clothed. Height was determined using measuring tape without shoes and subsequently body mass index was calculated by dividing weight (kg) by squared height (m²).

Food consumption patterns was evaluated by a 24-hour dietary recall questionnaire. Macro- and micronutrient consumptions were calculated by using food processor software NUT-4, modified by incorporating the Iranian food table.

Biochemical assessment

At the beginning, middle and the end of the 12 week supplementation trial, 10 ml fasting venous blood samples were drawn from the arm. Blood was collected for measurement of glucose, insulin, calcium and phosphorous, HbA1C and 25(OH) vitamin D. Glucose was measured using spectrophotometry, insulin was measured by using ELISA, calcium and phosphorous were measured by

spectrophotometry, HbA1c by Nycocard reader and 25(OH) vitamin D was measured by radioimmunoassay (25(OH)cholecalciferol level >30 ng/mL are considered sufficient).^{6,7}

For calculating sensitivity and beta cell function, we used the HOMA method. HOMA-IR (homeostasis model assessment-insulin resistance) was calculated as follows:

$$\text{HOMA-IR} = [\text{fasting glucose (mmol/L)} \times \text{insulin (}\mu\text{IU/mL)}] / 22.5.$$

Beta cell function (homeostasis model assessment- secretion) was calculated as follows:

$$\text{HOMA-\%B} = [\text{fasting plasma insulin (}\mu\text{IU/mL)} \times 20] / [\text{fasting plasma glucose (mmol/L)} - 3.5]$$

We also calculated QUICKI (quantitative insulin sensitivity check index) to assess insulin sensitivity as follows:

$$\text{QUICKI} = 1 / [\log \text{insulin (}\mu\text{IU/mL)} + \log \text{glucose (mg/dl)}]$$

Subjects are considered as insulin resistant when HOMA ≥ 2.6 and QUICKI ≤ 0.33 .^{8,9}

Statistical analysis

The normality of distributions was checked for all variables. Data processing and analysis were done with SPSS version 15.5 for windows (SPSS Inc, Chicago, USA). Normally distributed data were expressed as mean (\pm SD) and were compared by Independent Student's t-test and paired t-test.

General linear model repeated measures analysis was used for comparing triple measurements in each group. Significance was set at $p < 0.05$.

RESULTS

The number of subjects included in this study was 70. There were 35 subjects in the treatment group (received 0.25 mcg of 1,25 (OH)₂ cholecalciferol) and 35 in the control group (received placebo). Two groups were well matched in different variables before intervention. Characteristics of study subjects before intervention are shown in Table 1. There was no significant difference between two groups at baseline.

The results of dietary analysis are shown in Table 2. There was no significant difference between the mean intake of energy, carbohydrate, protein, fiber, vitamin D, calcium and phosphorus between the two groups while the mean intake of fat was significantly higher in the control group compared to the treatment group ($p < 0.05$).

Table 1. Baseline characteristics of the treatment and control groups

Variable	Treatment	Control	<i>p</i> -value [‡]
Age (year)	53.8 \pm 8.9 [†]	52.4 \pm 7.8	0.462
Weight (kg)	72.9 \pm 12.7	70.9 \pm 12.5	0.514
Height (cm)	160 \pm 8.9	161 \pm 10.4	0.718
BMI (kg/m ²)	28.3 \pm 4.4	27.0 \pm 3.4	0.164
Education (year)	7.2 \pm 4.5	7.2 \pm 4.8	0.980
Diabetes duration (year)	6.3 \pm 5.3	6.6 \pm 4.8	0.819
Metformin (500 mg/day)	2.9 \pm 1.4	2.4 \pm 1.2	0.110
Glybenclamide (5 mg/day)	3.2 \pm 1.3	2.9 \pm 1.7	0.437

[†]mean \pm SD

[‡] Independent Samples t-test

Table 2. Dietary intake of subjects in the treatment and control groups

Variable	Treatment	Control	<i>p</i> -value [‡]
Energy (kcal)	1728±455 [†]	1664±454	0.560
Carbohydrate (%)	65.6±7.3	63.8±4.3	0.233
Protein (%)	15.3±4.3	14.6±3.3	0.463
Fat (%)	18.8±4.4	21.2±4.3	0.026
Fiber (g)	15.7±5.7	14.1±6.4	0.286
Vitamin D (µg)	3.4±1.8	2.8±1.5	0.160
Calcium (mg)	848±317	815±300	0.660
Phosphorus (mg)	975±313	921±254	0.426

[†] mean±SD

[‡] Independent Samples t-test

Comparison of the mean biochemical variables between the two groups in each time point of the study is shown in Table 3. As shown, there were no significant differences between variables in the two groups at baseline, 1.5 months and 3 months of the intervention.

By using repeated measurement analysis, we compared biochemical variables and insulin sensitivity indices in the two groups at three times points in the study. As shown in table 4, compared to the treatment group, at the end of the study, fasting plasma glucose increased in the control group ($p<0.05$). Level of insulin during the

study increased significantly in two groups ($p<0.05$), however, the rate of increase was higher in the treatment group than in the control group. But like fasting plasma glucose, changes in level of insulin in each point in time of the study were not significantly different between two groups. The directions of changes in HbA1c was similar to that of serum insulin, in that the level of HbA1c in each group at the end of study showed a significant rise ($p<0.05$), although, the rate of increase in the control group was greater than that in the treatment group.

We assessed insulin resistant by using HOMA-IR and QUICK index. As Table 3 shows, concerning these two indices, that there was no significant difference between the two groups, but according to Table 4, there was a significant change in HOMA-IR and QUICKI at the end of study compared to baseline ($p<0.02$ and $p<0.002$ respectively) in treatment group. Changes in these two indices in the control group were significantly higher than that found in the treatment group ($p<0.001$ and $p<0.001$ respectively).

Insulin secretion assessed by using HOMA-%β, remained relatively unchanged in the control group, while it increased significantly in the treatment group at the end of study ($p<0.005$).

At the end of the study, levels of 25(OH) cholecalciferol decreased significantly in both groups ($p<0.01$). The

Table 3. Comparison of the mean biochemical values between the treatment and control groups in each time point of the study §

Variable	Baseline			1.5 months			3 months		
	Control	Treatment	<i>p</i> -value	Control	Treatment	<i>p</i> -value	Control	Treatment	<i>p</i> -value
FBS (mg/dL)	142±48.5 [†]	146±52.1	0.753	154±57.2	148±52.0	0.671	158±60.8	144±51.8	0.310
Insulin (µIU/mL)	8.2±3.8	9.7±5.3	0.180	9.9±4.5	11.2±5.9	0.303	11.3±6.7	13.9±8.1	0.155
Hb.A1C (%)	7.03 ±1.7	7.08±1.6	0.675		NA [‡]		8.59±2.5	7.90±2.1	0.268
HOMA-IR	2.85±1.5	3.55±2.5	0.170	3.59±1.6	4.19±2.6	0.253	4.26±2.4	4.77±2.7	0.413
QUICKI	0.33±0.02	0.33±0.03	0.456	0.32±0.01	0.32±0.03	0.852	0.31±0.02	0.31±0.02	0.427
HOMA-%B	2.87±2.8	3.35±3.0	0.500	3.47±3.5	3.50±2.6	0.965	3.55±4.2	4.78±3.8	0.212
25(OH) vitamin D (ng/mL)	38.5±29.9	43.3±32.1	0.526		N.A		30.9±22.2	34.1±31.5	0.628
Calcium (mg/dL)	9.01±0.6	8.94±0.9	0.741	9.22±0.4	9.33±0.5	0.285	9.14±0.3	9.26±0.5	0.268
Phosphorus (mg/dL)	3.87±0.5	3.87±0.5	0.885	4.19±0.6	4.39±0.8	0.326	4.07±0.5	4.13±0.4	0.600

[†] Mean±SD

[‡] Not Assessed

§ independent samples t- test

Table 4. Biochemical variables and insulin sensitivity indices at baseline and 1.5 and 3 months after intervention

Variable	control				treatment			
	Baseline	1.5 months	3 months	<i>p</i> -value [§]	Baseline	1.5 months	3 months	<i>p</i> -value
FBS (mg/dL)	142±48.5 [†]	154±57.2	158±60.8	0.038	146±52.1	148±52.0	144±51.8	0.712
Insulin (µIU/mL)	8.2±3.8	9.9±4.5	11.3±6.7	0.002	9.7±5.3	11.2±5.9	13.9±8.1	0.002
Hb.A1C (%)	7.03 ±1.7	NA [‡]	8.59±2.5	0.004*	7.08±1.6	NA	7.90±2.1	0.013 *
HOMA-IR	2.85±1.5	3.59±1.6	4.26±2.4	0.001	3.55±2.5	4.19±2.6	4.77±2.7	0.023
QUICKI	0.33±0.02	0.32±0.01	0.31±0.02	<0.001	0.33±0.03	0.32±0.03	0.31±0.02	0.002
HOMA-%B	2.87±2.8	3.47±3.5	3.55±4.2	0.095	3.35±3.0	3.50±2.6	4.78±3.8	0.009
25(OH) vitamin D (ng/mL)	38.5±29.9	N.A	30.9±22.2	0.013*	43.3±32.1	N.A	34.1±31.5	0.017 *
Calcium (mg/dL)	9.01±0.6	9.22±0.4	9.14±0.3	0.272	8.94±0.9	9.33±0.5	9.26±0.5	0.136
Phosphorus (mg/dL)	3.87±0.5	4.19±0.6	4.07±0.5	0.091	3.87±0.5	4.39±0.8	4.13±0.4	0.005

FBS: Fasting Blood Sugar, HOMA-IR: homeostasis model assessment-insulin resistance, QUICKI: quantitative insulin sensitivity check index

[†] Mean±SD

[‡] Not Assessed

§ Repeated measurements analysis

* Paired t-test

level of calcium increased in the two groups but remained within the physiological range. The level of serum phosphorous increased significantly ($p < 0.005$) in the treatment group but not in the control group. On the other hand, with regard to the levels of serum calcium and phosphorous, as table 3 shows, there were no significant differences in each time point of the study between the groups.

DISCUSSION

The present study explored the hypothesis that vitamin D supplementation might improve glucose metabolism, as previously reported in animal and human studies.^{8,10} In our study, supplementation with 0.5 µg calcitriol per day for 3 months increased insulin secretion and prevented further rise in plasma glucose, but did not show any decrease in the HbA1c levels and insulin resistance in subjects with type 2 diabetes.

There is accumulating evidence to suggest that altered calcium and vitamin D homeostasis may play a role in the development of type 2 diabetes.¹¹

Vitamin D exerts its effects through the vitamin D response element (VDR). As VDR and vitamin D binding proteins can be found in the β cell pancreatic tissue, it is possible to hypothesize that the genetic profile of the VDR gene may contribute to the development of T2D.¹²

Several mechanisms are suggested through which vitamin D affects insulin secretion and insulin action. The direct effect of vitamin D on insulin secretion may be mediated by binding of its circulating active form, 1,25(OH)₂D, to the β-cell vitamin D receptor. Alternatively, activation of vitamin D may occur within the β-cell by the 1-α-hydroxylase enzyme, which was recently shown to be expressed in β-cells. The indirect effects of vitamin D may be mediated via its important and well-recognized role in regulating extracellular calcium and calcium flux through the β-cell. Insulin secretion is a calcium-dependent process; therefore, alterations in calcium flux can have adverse effects on β-cell secretory function.¹¹

Vitamin D may also have a beneficial effect on insulin action either directly, by stimulating the expression of insulin receptor and thereby enhancing insulin responsiveness for glucose transport, or indirectly via its role in regulating extracellular calcium and ensuring normal calcium influx through cell membranes and adequate intracellular cytosolic calcium [Ca²⁺]_i pool. Calcium is essential for insulin-mediated intracellular processes in insulin-responsive tissues such as skeletal muscle and adipose tissue. Changes in [Ca²⁺]_i in primary insulin target tissues may contribute to peripheral insulin resistance via impaired insulin signal transduction, leading to decreased glucose transporter-4 activity.¹¹

Several studies of vitamin D treatment have been performed. A similar observation was made by Pittas *et al.*,¹³ who reported that in healthy, older adults, with impaired fasting glucose (IFG), 3 years supplementation with calcium and vitamin D may attenuate increases in glycemia and insulin resistance that occur over time. In a similar study by Jorde *et al.*,¹⁴ supplementation with 40000IU cholecalciferol per week versus placebo for 6 months, did not lower the Hb.A1c level in subjects with type 2 diabetes, nor was there any improvement in parameters of insu-

lin secretion or resistance. The results of a Women's Health Initiative study,¹⁵ revealed that daily supplementation with calcium (1000 mg) plus vitamin D (400IU) versus placebo, in 33951 healthy participants, did not reduce the risk of developing diabetes over 7 years of follow-up. In a study by Tai *et al.*,⁹ correction of vitamin D deficiency in adults without diabetes, had no effect on blood glucose or insulin concentrations or insulin sensitivity. Short term administration of (supra) physiological doses of calcitriol (1.5 µg per day) for 7 days, had no effect on insulin sensitivity in healthy subjects.¹⁶

As reported by Tai *et al.*,¹⁷ and Pittas *et al.*,¹³ vitamin D supplementation had no effect on plasma glucose and insulin resistance in subjects with normal fasting glucose. We can hypothesize that vitamin D has no effect on glucose homeostasis in healthy adults and it only affects glucose homeostasis in patients with impaired glucose homeostasis or insulin resistance. We should note that the subjects of our study had established diabetes mellitus with diabetes mean duration of 6.6 and 6.3 years in the treatment and control groups, respectively. Chronic exposure to hyperglycemia decreases insulin secretion and insulin sensitivity. This effect of hyperglycemia is regarded as glucotoxicity.¹⁶ So in diabetic patients, as duration of diabetes increases, glucotoxicity damages β-cells and worsens the condition. Therefore, it may be the case that the more severe the diabetes, the less effect vitamin D has; and vitamin D may only have positive effects on IFG or newly diagnosed cases of diabetes, and it is recommended that this will be taken into account in future trials.

Moreover, as mentioned above, vitamin D affects insulin secretion and action directly via gene regulation and indirectly via regulation of intracellular calcium homeostasis.¹¹ So, the effects of vitamin D on plasma glucose may be affected by calcium status of the subjects. It is shown in table 1 that the calcium intake was below the RDA in our subjects and this may prevent vitamin D from producing its maximum effect. Although serum calcium levels were within the normal range, we don't have any information on intracellular calcium. There are evidences suggesting that abnormal regulation of intracellular calcium affects both insulin sensitivity and insulin release.¹¹

As we mentioned in our results, significant changes in serum calcium levels were not found, so the changes in insulin secretion and plasma glucose level might have been due to direct effects of vitamin D on tissues or because of normalization of intracellular calcium that we have no data on. It is possible that vitamin D may improve insulin sensitivity only when given with calcium, and future studies in this area should take this into account.

1,25(OH)₂D₃ deficiency is a common complication in patients on dialysis and may contribute to the pathogenesis of insulin abnormalities in uremia.¹⁰ So in these patients, supplementation with calcitriol makes obvious effects on plasma glucose and insulin sensitivity. In a study by Bonakdarian *et al.*,⁸ treatment with oral calcitriol (0.5 µg per day) in hemodialysis patients for 2 months significantly reduced Hb.A1c and insulin resistance. In another study by Mak *et al.*,¹⁰ injection of 1.8±0.3 µg calcitriol versus dihydrotachysterol (DHT) for 1

month in 16 patients on hemodialysis, reduced blood glucose and increased serum insulin and insulin sensitivity. These observations are compatible with the notion that the effect of calcitriol on insulin sensitivity is present only in uremic 1,25(OH)₂D-depleted patients.¹⁶

With regard to the mean concentration of 25(OH)D in our patients, we can explain the difference in our results and the results of uremic patients. The lack of any calcitriol effect on insulin sensitivity in diabetic patients is different from that seen in uremic patients,¹⁰ and we cannot extrapolate the results of vitamin D supplementation in uremic patients to the diabetic population. Disturbance in vitamin D metabolism in uremic patients may be related to disturbances in glucose metabolism. Regarding 25(OH)D levels, our subjects had normal vitamin D status. Since there is no evidence on 1,25(OH)₂D deficiency in diabetics, we assume that their 1,25(OH)₂D level would have been within the normal range and 1,25(OH)₂D was doing its physiological roles properly before our intervention.

The strength of our study included its randomized, placebo controlled design and a drawback to our study is that we evaluated the insulin sensitivity and secretion based on fasting levels only, which is not as accurate as the glucose clamp method. We should also note that in our study, calcitriol demonstrated its acute biological actions, ie, an increase in plasma phosphorus level in the treatment group.

In conclusion, in our diabetic patients, vitamin D supplementation attenuated the increase in glycemia, and increased insulin secretion but it had no effect on insulin resistance.

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AUTHOR DISCLOSURES

The authors have no conflicts of interest.

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Original Article

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Mohammad Hassan Eftekhari PhD, Marzieh Akbarzadeh MSc, Mohammad Hossein Dabbaghmanesh MD, Jafar Hasanzadeh PhD

Nutrition Department, Research Center for Health Sciences, School of Health and Nutrition, Shiraz University of Medical Sciences, Shiraz, I.R. Iran

第 2 型糖尿病患者口服鈣三醇對血糖指數的影響

前言：糖尿病是公共衛生的一大問題。近來流行病學證據也指出，維生素 D 缺乏與不良的代謝性風險有潛在相關。對象與方法：本研究是一個雙盲隨機分派控制組使用安慰劑試驗。70 位第 2 型糖尿病患者，年齡在 30-75 歲之間，雙盲隨機分派成 2 組。一組每天服用 2 顆鈣三醇膠囊(每一顆膠囊含 0.25 μg 1,25-雙羥膽骨化醇，維生素 D-3)；第二組則是服用安慰劑錠。在為期 12 週試驗的開始、中間及結束時分別檢測受試者的血清糖、胰島素、鈣、磷、糖化血色素及 25(OH)維生素 D 值。結果：兩組在基線時並沒有顯著差異，在研究結束時，控制組的空腹血糖有顯著上升($p=0.038$)，實驗組則沒有太大變化。兩組的胰島素和糖化血色素值均有顯著增加(實驗組 $p=0.013$ 、控制組 $p=0.0004$)。在胰島素抗性指數，兩組的 HOMA-IR 和 QUICKI 值均有顯著改變(實驗組 $p=0.023$ 和 0.002 ；控制組 $p=0.001$ 和 <0.001)。以 HOMA-% β 評估胰島素的分泌，結果控制組並沒有太大改變，但實驗組在研究結束時有顯著增加。結論：服用維生素 D 補充劑，會降低血糖上升的程度並增加胰島素分泌，但對於胰島素抗性沒有影響。

關鍵字：糖尿病、鈣三醇、葡萄糖、胰島素抗性、糖化血色素