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The Effect of Vitamin D Treatment on Advanced Glycation End-Products in Patients with Prediabetes and Type 2 Diabetes Mellitus

ABSTRACT

Objective: The aim of this study was to investigate the role of vitamin D replacement therapy on advanced glycation end-products in prediabetes and type 2 diabetes mellitus patients with vitamin D deficiency.

Methods: One hundred twenty subjects with serum 25-hydroxyl vitamin D levels less than 20 ng/mL were included in the study. Forty type 2 diabetes mellitus patients (type 2 diabetes mellitus group), 40 prediabetes patients (prediabetes group), and 40 non-diabetes controls (non-diabetes group) were given oral vitamin D_3 50 000 units/week for 8 weeks as loading and followed by 1500 U/day as a maintenance dose. We measured serum 25-hydroxyl vitamin D, glycated hemoglobin, carboxymethyl lysine levels, and skin autofluorescence before and on the fourth month of the therapy.

Results: Basal serum carboxymethyl lysine and skin autofluorescence measurement in type 2 diabetes mellitus and prediabetes groups were significantly higher than the non-diabetes group. While no difference was found between glycated hemoglobin and skin autofluorescence, serum carboxymethyl lysine levels were significantly elevated for each group following vitamin D replacement.

Conclusions: Vitamin D loading did not affect skin advanced glycation end-product levels and glycated hemoglobin but was associated with increased serum carboxymethyl lysine levels in all groups.

Keywords: Vitamin D, type 2 diabetes, serum carboxymethyl lysine, skin autofluorescence, AGE

Introduction

In recent years, it has been hypothesized that low blood 25-hydroxyl vitamin D (25(OH)D) has been linked to type 2 diabetes mellitus (T2DM); vitamin D therapy has been shown to lower the risk of diabetes.[1,2] Previous reports have revealed an inverse relationship with low blood 25(OH)D and the risk of developing T2DM, especially in people with prediabetes.[3] However, reports have shown that prediabetes patients given vitamin D_3 ($VitD_3$) supplementation each day did not significantly observe a reduction in diabetes risk.[4] Vitamin D (VitD) deficiency has been linked to metabolic syndrome, insulin resistance (IR), and beta-cell dysfunction.[5] There are conflicting data regarding the glycemic effects of VitD deficiency. A randomized controlled trial in patients with a high risk of T2DM and new diagnosis showed that $VitD_3$ therapy partially normalized insulin dysregulation[6]; however, these findings have been debated.[7]

Hyperglycemia is seminal for vascular impairment through the increases in advanced glycation end-products (AGEs).[8] The AGEs form through glycation, a non-enzymatic reaction occurring with carbohydrates and amino residues on proteins.[9] The rate of AGEs formation in hyperglycemia condition has been directly linked to the glucose concentration and duration of exposure. The AGEs contribute to the formation of macrovascular/microvascular complications involved in T2DM by increasing intracellular oxidative stress, β-cell failure,[10] and IR.[11] Increased circulating AGEs, including N𝜀-carboxymethylated (carboxymethyl lysine (CML)), pentosidine, and serum associated fluorescence (AGE)- associated fluorescence have been associated with arterial disease, renal injury, and mortality in T2DM.[12]

The AGEs can also be measured easily in the dermal tissue as they have fluorescent properties. Skin autofluorescence (SAF) measurement is a non-invasive method, and AGE-specific readers have been used. Studies have shown that AGE levels in skin biopsies are closely related to SAF.[13] The SAF has been linked to chronic cardiovascular issues including death in T2DM.[14,15]

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Reports have shown that the role of VitD replacement on advanced glycosylation is limited. A previous report demonstrated a negative association with VitD and serum or skin AGE-associated fluorescence.[16] In a randomized controlled study, it was reported that diabetic patients receiving 4000 IU of $VitD_3$ supplementation per day in 12 weeks had significantly reduced AGEs serum levels.[17] Cross-sectional studies in healthy and diabetic subjects reported no significant long-term link with serum VitD and SAF.[18,19]

We aimed to test the hypothesis that VitD replacement decreases serum AGE levels as well as glucose levels in diabetic, and prediabetic VitD-deficient patients in the short term. In this prospective case-control study, we evaluated VitD replacement on serum CML and skin AGE levels in T2DM and prediabetic subjects vitamin D deficiency in short term interval.

Materials and Methods

The institutional human study review committee of Medical Faculty, Marmara University (Protocol No: 09.2013-0358) approved and the study was carried out at the Department of Endocrinology and Metabolism Diseases, Marmara University. The study was done following the tenets of the Declaration of Helsinki. Informed consent was collected from all subjects before being enrolled in the study.

Patient Selection

A total of 120 subjects (40 T2DM (T2DM group), 40 prediabetes (PD group), and 40 non-diabetes (ND group)) deficient in VitD were included. A deficiency in VitD was classified as circulating 25(OH)D < 20 ng/mL, which is based on the Endocrine Society Clinical Practice Guideline.[20] Diagnosis of diabetes and prediabetes was made according to American Diabetes Association (ADA)criteria.[21]

Type 2 diabetes mellitus patients who had glycated hemoglobin (HbA1c) levels less than 8.5% under oral antidiabetic therapy and prediabetic patients under metformin therapy were included in the study. Patients under insulin treatment, chronic renal, liver, and/or inflammatory diseases as well as cancer were not included in the examination.

Study Protocol

The VitD replacement was performed according to the suggestions of the Endocrine Society guidelines. Vitamin D_3 (Cholecalciferol) (Deva, Türkiye) was given as a loading dose 50 000 units/week p.o. for 8 weeks followed by 1500 units/day as a maintenance dose for 4 weeks.[20] Clinical laboratory parameters were evaluated before loading treatment and at the end of the fourth week of maintenance treatment.

Clinical and Laboratory Assessment

Demographics (age, gender), clinical parameters, medical history, presence of microvascular complications (retinopathy, neuropathy nephropathy), hyperlipidemia, and hypertension were recorded from the patient's files. Body mass index (BMI) was determined using weight (kg) divided by height squared (m). Height (cm) and body weight (kg) were determined with a stadiometer and an electronic scale, respectively.

Biochemical Parameters

Biochemical parameters were studied from fasting serum samples before and after treatment Fasting blood glucose was studied with the spectrophotometric enzymatic (Roche Diagnostics GmbH, Indianapolis, Ind, USA) method in the serum samples. Glycated hemoglobin was analyzed using high-performance liquid chromatography (HPLC).

Serum 25(OH)D was determined using HPLC following the manufacturer's recommendations. The variation coefficients (intra- and inter-) for the VitD concentration range of 21.1-92.7 ng/mL were 0.7%-4.9% and 3.1%-4.7%, respectively. The lowest measurement detection limit for $25(OH)D_3$ was 1.0 ng/mL.

Levels of serum CML were measured from serum samples by ELISA using commercial kits (Bioassay Technology Laboratory, E1413Hu, Shanghai, China). The intra- and interassay coefficients of variation for the concentration range of 20-3000 ng/mL were 8% and 10%, respectively.

Intact parathyroid hormone (iPTH) level was monitored by an immun ochemiluminometric assay. The intra- and interassay coefficients of variation for the concentration range of 21.9-123 pg/mL were 1.1%-2.0% and 2.5%-3.4%, respectively. The levels of calcium and phosphorus from the serum were studied with the spectrophotometric enzymatic (Roche Diagnostics GmbH, Indianapolis, Ind, USA) method in the serum samples.

Skin Autofluorescence (SAF)

The SAF was determined using an autofluorescence reader (DiagnOptics, Netherlands).[22,23] In this method, ~1 cm^2 skin surface was exposed to light for excitation at 300 to 420 nm using a photospectrometer between 300 and 600 nm. To calculate SAF, light emitted at 300-420 nm was divided by the light emitted at 420-600 nm. Arbitrary unit is used to express autofluorescence. All measurements were performed at the lower arm's volar side (10-15 cm from elbow) of the seated patient under room temperature by a diabetes nurse or research assistant. The variation coefficients for repeated autofluorescence measurements were 2.5% and 4.6%, respectively.[22]

Statistical Analysis

Statistical analyses were done using Statistical Package for the Social Sciences software version 21.0 (SPSS Inc Chicago, IL, USA). Continuous and categorical variables were summarized and presented as mean and SD and counts and percentages, respectively. Kolmogorov–Smirnov test was used to assess normality distribution. A non-parametric analysis of variance test was performed to compare 3 groups. The confidential interval was accepted as 95%, and values less than 0.05 were accepted as significant.

Results

The demographics are shown in Table 1. The ND group age (38.5 ± 9) was significantly lower than the PD (47.3 ± 8.9) and T2DM (52 ± 7.7) groups.

The BMI, laboratory data, and SAF measurements before and after $VitD_3$ replacement are shown in Table 2. The BMI values were in the

MAIN POINTS

- The aim of this prospective study was to evaluate effects of vitamin D replacement therapy on advanced glycation end-products (AGEs) in prediabetes and type 2 diabetes mellitus (T2DM) patients with vitamin D deficiency.
- Skin autofluorescence measurements were higher in the type 2 diabetes and predşabetes group compared to normoglycemic group.
- Vitamin D replacement did not affect skin AGE levels and glycated hemoglobin levels in 3 months of treatment.

Table 1. Demographic Parameters of Groups

	Nondiabetic (n = 40)	Prediabetic (n = 40)	T2DM (n = 40)
Age (year)	38.5 ± 9	47.3 ± 8.9	52 ± 7.7
Gender (female/male)	37/3	34/6	28/12
Duration of diabetes	-	1.1 ± 0.3	6 ± 3.9
Hypertension (+/−)	4/36	6/34	17/23
Hyperlipidemia(+/−)	2/38	2/38	13/27
Retinopathy (+/−)	-	-	1/39
Nephropathy (+/−)	-	-	7/33
Peripheral neuropathy (+/−)	-	-	3/37
Metformin (+/−)	-	40	40
Sulfonylurea derivate (+/−)	-	-	19
API (+/−)	-	-	9
DPP4 (+/−)	-	-	16

API, alpha glucosidase inhibitor; DPP4-I, dipeptidyl peptidase 4 inhibitor; T2DM, type 2 diabetes mellitus.

overweight range in the ND group, while in the obesity range for PD and T2DM groups. The BMI in ND was lower than PD ($P < .05$) in advance of treatment. Following $VitD_3$, serum 25(OH)D was increased in all groups ($P < .0001$). The average 25(OH)D level reached 35.7 ng/dL in all subjects at 12th-week mark of the treatment initiation. No subject had signs and symptoms of VitD toxicity. After $VitD_3$ administration, iPTH was significantly decreased in all groups ($P < .0001$).

After treatment, ND, PD, and T2DM groups had gained weight. The mean weight gains in ND, PD, and T2DM groups were 0.47 ± 2.4, 0.10 ± 1.4, and 0.10 ± 2.4, respectively. It was not statistically significant compared to the baseline. The largest increase in weight was in ND, but it was not significant ($P > .05$).

Fasting glucose levels were not different following $VitD_3$ in all groups. Glycated hemoglobin levels were not changed following $VitD_3$ in PD and T2DM groups. However, HbA1c levels significantly increased after $VitD_3$ in ND ($P = .001$). The largest weight increase was in ND, but it was not significant ($P > .05$).

Baseline serum CML levels were significantly higher in ND group compared to PD and T2DM groups ($P = .0025$). Post-vitamin treatment levels of serum CML were increased in all groups (ND, PD, and T2DM; $P = .001$, $P = .008$, and $P = .0004$, respectively).

The SAF was higher in T2DM in comparison to the non-diabetics at baseline ($P < .01$) (Table 2). The SAF measurements were similar with basal and post-treatment in all groups.

A direct association was observed with serum HbA1c and FBG ($r = 0.74$, $P < .001$). The serum HbA1c levels were directly associated with the SAF ($r = 0.032$, $P < .0001$) and CML ($r = 0.12$, $P = .04$). No relationship was observed in serum HbA1c and 25(OH)D levels ($r = 0.03$, $P = .53$). A direct association was found for serum CML and 25(OH)D ($r = 0.28$, $P < .0001$).

Multiple logistic regression results are shown in Table 3. When CML was taken as a dependent variable, multiple logistic regression analysis (İncluding.BMI, waist circumference, SAF, HbA1c, fasting blood glucose, 25(OH)D) was associated with 25(OH)D ($P = .001$) ($R^2 = 5.99\%$, $P = .043$).

Table 2. BMI, Laboratory Data, and SAF Measurements Before and After Vitamin Replacement

	Nondiabetic (n = 40)			Prediabetic (n = 40)			T2DM (n = 40)		
Variables	Pre-Treatment	Post-Treatment	*P*	Pre-Treatment	Post-Treatment	*P*	Pre-Treatment	Post-Treatment	*P*
BMI	29 ± 6.6	29.2 ± 6.4	.21	35.3 ± 7.5	35.4 ± 7.3	.65	31.9 ± 5.6	31.8 ± 5.7	.53
25(OH)D (ng/mL)	8.01 ± 0.6	35.9 ± 6.7	**<.0001**	8.6 ± 4	34.2 ± 6.1	**<.0001**	10.5 ± 5.2	37.1 ± 6.9	**<.0001**
HbA1c (%)	4.7 ± 0.34	4.9 ± 0.4	**.001**	5.87 ± 0.3	5.86 ± 0.4	.2	6.7 ± 0.7	6.73 ± 0.9	.75
FBG (mg/dL)	**87.7** ± 9.2	87.7 ± 9	.98	105.2 ± 14.4	103.4 ± 13.3	.19	132.5 ± 31	129.4 ± 32	.56
CML (ng/mL)	504 ± 285	738 ± 479	**.001**	657 ± 500	903 ± 571	**.008**	726 ± 598	930 ± 579	**.0004**
SAF (AU)	1.86 ± 0.41	1.86 ± 0.3	.99	1.93 ± 0.3	1.98 ± 0.31	.97	2.13 ± 0.4	2.13 ± 0.2	1
Ca (mg/dL)	9.4 ± 0.36	9.7 ± 0.37	.0002	9.6 ± 0.4	9.5 ± 0.5	.13	9.6 ± 1	9.7 ± 0.4	.63
P (mg/dL)	3.09 ± 0.3	3.3 ± 0.4	.0002	3.3 ± 0.5	3.2 ± 0.4	.09	3.24 ± 0.5	3.14 ± 0.4	.26
iPTH (pg/mL)	55.2 ± 23	40.5 ± 14.8	<.0001	64.9 ± 29.6	49.4 ± 17.9	<.0001	59.6 ± 26.7	41.9 ± 13.2	<.0001

25(OH)D, 25-hydroxyl vitamin D; AU, arbitrary unit; BMI, body mass index; Ca, calcium; CML, carboxymethyl lysine; FBG, fasting blood glucose; HbA1c, glycated hemoglobin A1c; iPTH, intact parathyroid hormone; P, phosphorus;, SAF, skin autofluorescence; T2DM, type 2 diabetes mellitus.

Table 3. Multiple Regression Analyses

Variable	Dependent Variable	Independent Variable	R^2	*P*
1	Serum CML levels	BMI, waist circumference, SAF, HbA1c, FBG, serum 25(OH) D ($P = .001$)	5.99%	.043
2	Skin autofluorescence	BMI, waist circumference, serum 25(OH)D, serum CML, FBG, HbA1c ($P = .007$)	11.09%	.0004
3	Serum 25(OH)D	BMI ($P = .035$), waist circumference, SAF, CML ($P = .0018$), and HbA1c, FBG	8.50%	.0048

25(OH)D, 25-hydroxyl vitamin D; AU, arbitrary unit; BMI, body mass index; Ca, calcium; CML, carboxymethyl lysine; FBG, fasting blood glucose; HbA1c, glycated hemoglobin A1c; iPTH, intact parathyroid hormone; P, phosphorus;, SAF, skin autofluorescence.

When SAF was taken as a dependent variable, multiple logistic regression analysis (including BMI, 25(OH)D, CML, FBG, waist circumference, and HbA1c levels) was significantly associated ($R^2 = 11.09\%$, $P = .0004$). When 25(OH)D was taken as a dependent variable, multiple logistic regression analysis (including BMI, waist circumference, SAF, CML, HbA1c, and FBG) was significantly associated with BMI (0.035) and CML (0.0018) ($R^2 = 8.50\%$. $P = .0048$).

Discussion

Serum CML and SAF were found to be higher in the T2DM group with VitD deficiency than PD and ND groups. Immediately after $VitD_3$ loading, serum CML levels were found high in PD, T2DM, and ND groups. However, glycemic levels did not change compared to baseline. High serum AGE and SAF levels in the T2DM group are findings consistent with the literature.[24,25] In a study conducted by Meerwaldt et al.[13] SAF was found to be elevated in T2DM subjects in comparison to non-diabetics. However, SAF was correlated with skin AGE levels. Cross-sectional studies in healthy and diabetes groups showed that SAF levels in diabetics are elevated compared to controls,[19] and no significant change was found for CML in diabetics and controls.

The increase in CML levels after $VitD_3$ replacement in T2DM, ND, and PD groups was the first finding in the literature. However, we found serum CML and 25(OH)D to be directly correlated. The BMI was high for the ND group, while in the obesity range for PD and T2DM groups. Although after treatment, all of the groups had gained weight, it was not statistically significant. The reason for it might be the weight gain in all groups due to VitD treatment with high liquid oil content (15 cc liquid sunflower oil in a bottle). Another reason might be the appetizing effect of VitD. The CML is a widely accepted marker for AGEs. The CML has also produced lipid peroxidation of polyunsaturated fatty ascites without non-enzymatic glycation and oxidation reactions of protein.[26,27] A previous report showed that lipid peroxidation is a more important source for CML formation than glycoxidation reactions.[26] A cross-sectional trial demonstrated that mean serum CML was directly correlated with BMI and waist circumference.[28] The reason for the increase of CML levels in our study might be the polyunsaturated fatty ascites in VitD preparations and increased lipid peroxidation, fatty acid levels, and oxidative stress in the participant's adipose tissue with weight gain.

$VitD_3$ treatment did not affect the SAF in all groups. Similarly, 50 000 IU VitD supplementation per month did not affect skin AGE levels following 6 months in mild VitD-deficient subjects.[29] However, a previous report showed no relationship with VitD and SAF or AGE-AF in diabetic subjects.[19] Stürmer et al[18] did not find an association with VitD and SAF, plasma AGE-AF, or CML in healthy and hypertensive subjects. On the other hand, evaluating serum 25(OH)D in a healthy population was reported to be inversely proportional to SAF measured after 11.5 years.[16] Skin AGEs may have a half-life of about 10-15 years; therefore, treatment time may be too short to see the relevant outcomes.[30]

After $VitD_3$ replacement, we could not obtain a significant change in HbA1c and FBG levels in PD and T2DM groups. However, HbA1c levels significantly increased after $VitD_3$ treatment in ND subjects. The higher amounts in the ND group were most likely due to weight gain; the highest weight gain was in the ND group. The association between VitD replacement and glycemic control has been debatable. Zhang et al[31] analyzed results from 8 randomized controlled trials in prediabetics and showed that VitD replacement decreased diabetes risk by 11% compared to placebo. On the other hand, another study of 511 prediabetics given 20,000 IU/week $VitD_3$ (or placebo) showed a lower risk of diabetes following VitD; however, it was not significant.[32] Similarly, in the VitD and T2DM (D2d) study , 2423 patients with prediabetes were randomized to take $VitD_3$ 4000 IU daily or placebo. In this study, VitD3 replacement was not shown to reduce the risk of T2DM. . The median duration of these studies is 4 and 2.5 years, respectively. However, subgroup analyses of the D2d trial showed a reduced level of diabetic risk following $VitD_3$ higher than 100 nmol/L (40.1 ng/mL).[33] A meta-analysis investigating the glycemic effect of oral VitD replacement T2DM subjects showed that 25(OH)D vitamin replacement did not affect HbA1c and FBG in this study, and short-term 3- and 6-month studies were examined.[34] Our results are consistent with the reports showing $VitD_3$ administration does not affect glycemic indices. In studies conducted previously, differences in glycemic results after VitD treatment may result from initial VitD status, dose, and duration, study design, ethnic difference, BMI, and individual differences.

Parathyroid hormone (PTH) is a hormone secreted in response to low VitD concentration in the blood. The relationship between hyperglycemia and significantly attenuated PTH responsiveness to VitD deficiency has been established recently.[35] In our study, the high level of PTH due to deficiency in VitD decreased following $VitD_3$ replacement treatment as expected.

Our study's main limitation is the short duration of $VitD_3$ replacement therapy and no placebo group. Another limitation is the limited number of the study population. This study should be repeated using high-dose VitD in a larger population, including a placebo group.

In summary, our work shows that $VitD_3$ replacement for 3 months did not reduce FBG, HbA1c, and SAF levels. However, serum CML levels increased in all groups after $VitD_3$ replacement therapy, and this result was the first finding in the literature and can not be explained with present study parameters, more randomized controlled long-term studies that focus on VitD therapy use in skin and the relationship with plasma AGE are needed.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Marmara University (Date: September 3, 2013, Decision No: 0358)

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

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