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Comparative evaluation of serum vitamin D levels in patients with different types of diabetic retinopathy

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Abstract

Background: Diabetic retinopathy is the most severe ocular complication of diabetes. Despite the known association of low vitamin D level with insulin resistance and diabetes, findings of recent studies on the association of vitamin D deficiency with macrovascular and microvascular complications of diabetes have been somewhat ambiguous and contradictory.

Objectives: To determine the relationship between serum levels of vitamin D and different types of retinopathy in patients with type 2 diabetes.

Methods: This case-control study examined 192 patients with type 2 diabetes who regularly attended the ophthalmologic clinic in 5th AZAR Hospital at Golestan University Medical Center in Gorgan (Iran) from September 25, 2015 to March 15, 2016. Patients were allocated into three matched groups: PDR, NPDR, and control (without retinopathy) (64 participants per group). A questionnaire was used for demographic and general data such as age, gender, height, weight, body mass index, and blood pressure. Fasting venous blood samples were obtained for measuring serum levels of glucose, HbA1c, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, urea, creatinine, and 25-hydroxy vitamin D. A vitreoretinal surgeon performed retinal examination through dilated pupils using slit lamp. The data were analyzed using SPSS v16. Chi-square, ANOVA, Kruskal-Wallis and Logistic Regression were used for data analysis. P-values <0.05 were considered significant.

Results: The mean serum vitamin D level in the PDR, NPDR and control groups were 23.89 (±12.36), 28.18 (±14.99) and 30.24 (±13.85) ng/ml, respectively. According to results of ANOVA, Ln vitamin D differed significantly between the three groups (p=0.007), and pairwise comparisons indicated a significant difference between PDR patients and controls (PP=0.005). The results of logistic regression analysis indicated a 2.4-fold higher risk of vitamin D deficiency in the retinopathy group compared to the control group (OR =2.409, CI (95%): 1.15-5.01).

Conclusion: This study revealed that vitamin D deficiency is significantly associated with the incidence of proliferative retinopathy.

Keywords: Vitamin D, Diabetic Neuropathies, Diabetes Mellitus, Type 2

Abbreviations / Acronyms:
BMI: Body Mass Index; **FBS:** Fasting Blood Sugar; **HDL:** High-Density Lipoprotein; **LDL:** Low-Density Lipoprotein; **PDR:** Proliferative Diabetic Retinopathy; **NPDR**: Non-Proliferative Diabetic Retinopathy

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1. Introduction

Diabetes mellitus is the most common metabolic disorder that affects more than 150 million people worldwide. This number is expected to reach up to 300 million by the year 2025 (1). Diabetic complications are primarily due to vascular damage, leading to increased mortality and morbidity rates in diabetic patients (2). Diabetic retinopathy is the commonest microvascular diabetic complication and the leading cause of blindness in people aged 20-74 years. The risk of blindness in people with diabetes is 25 times more than in non-diabetic individuals (3). Therapeutic advances over the last 40 years have reduced the risk of diabetes-related blindness, but since diabetes is a very common disease, retinopathy remains a major public health problem.

Vitamin D is a fat-soluble vitamin that was discovered in 1930. In fact, vitamin D is a hormone-precursor and its biologically active form is produced in the body. Ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) are some of its metabolites (4). Although 1,25-dihydroxyvitamin D3 [1,25(OH) 2D3] plays an important role in calcium homeostasis, several findings have shown its role in immune function and both type 1 and type 2 diabetes (5). The past studies reported the association of vitamin D deficiency with changes in blood glucose and serum insulin concentrations as well as altered sensitivity of target tissues to insulin (6, 7). Low level of vitamin D increases parathyroid hormone (PTH) level, which in turn increases intracellular concentrations of Ca2+. Increased intracellular concentrations of calcium inhibit insulin receptors in the target tissues and block glucose transporter type 4 (the main glucose transporter found in adipose tissues and striated muscle). On the other hand, insulin secretion from pancreatic β-cells is dependent on the intracellular calcium concentration (8-12). Findings indicate the possible effect of vitamin D on glucose homeostasis (13). Therefore, vitamin D supplementation may be an effective adjunct therapy for diabetes.

It is well known today that vitamin D deficiency is more common than expected even in developed countries (14). Given the importance and high prevalence of diabetes and diabetic retinopathy, several studies have investigated the incidence of retinopathy and factors affecting its progression (15-29). The effect of age, gender, duration of diabetes, body mass index (BMI), fasting blood sugar (FBS), blood lipids and blood pressure on the incidence of diabetic retinopathy were examined by these studies (14). Despite the known association of low vitamin D levels with insulin resistance and diabetes, recent findings regarding the association of vitamin D deficiency with macrovascular (cardiovascular disease and hypertension) and microvascular (retinopathy, nephropathy and neuropathy) complications of diabetes are somewhat ambiguous. Since only a limited number of studies have evaluated the role of vitamin D (independent of HbA1C, duration of diabetes, age and BMI) in diabetic retinopathy (15-17, 19, 22-24, 28), this study aimed to investigate the relationship between serum levels of vitamin D and different types of retinopathy in patients with type 2 diabetes.

2. Material and Methods

2.1. Participants

This case-control study included all patients with type 2 diabetes who were referred to public ophthalmology clinics of 5th Azar Hospital affiliated to Golestan University of Medical Sciences, Iran from September 25, 2015 to March 15, 2016. Overall, 192 subjects (110 males) were enrolled who were divided into three equal groups (64 subjects/group) of patients with proliferative diabetic retinopathy (PDR), patients with non-proliferative diabetic retinopathy (NPDR) and a control group without retinopathy. The groups were matched in terms of age, gender and duration of diabetes.

2.2. Selection criteria

2.2.1. Cases

Inclusion criteria consisted of disease duration of ≥10 years and age 40-70 years with diabetic retinopathy. Exclusion criteria included type 1 diabetes, consumption of calcium and vitamin D supplements within the 6 months prior to study and development of known retinal diseases unrelated to diabetes.

2.2.2. Controls

Inclusion criteria consisted of disease duration of ≥10 years and age 40-70 years without diabetic retinopathy. Exclusion criteria included type 1 diabetes, consumption of calcium and vitamin D supplements within the 6 months prior to study and development of known retinal diseases unrelated to diabetes.

2.3. Clinical characteristics

Demographic data including age, gender, height, weight, BMI and blood pressure were collected. Subjects were weighed in three stages at a fixed time with light clothing and no shoes, using Seca scale (Model 803) with an

accuracy of 0.1 kg. Height of each subject was measured in standing position using a wall-mounted stadiometer (SECA) with 0.1 cm accuracy. Subjects rested supine for 15 minutes and blood pressure was measured in three stages from the right arm of each subject using an upper arm blood pressure monitor (Beurer, Germany).

2.4. Laboratory test

Five milliliters of fasting venous blood samples were collected to measure levels of FBS, HbA1c, triglycerides (TG), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), urea, creatinine, and 25-hydroxy vitamin D1. FBS level was estimated by glucose oxidase method. Cholesterol, TG, HDL and LDL levels were determined by enzymatic method using Pars Azmoon kits, according to the manufacturer's instructions. Serum 25-hydroxyvitamin D levels were measured by ELISA with IDS kits (UK) and HbA1c was measured by NycoCard kits (Norway). Serum 25-hydroxyvitamin D levels less than 20 ng/ml were considered as vitamin D deficiency and values higher than 20 ng/ml were considered as normal. Once eyes of subjects were dilated, a vitreoretinal surgeon performed retinal examination via slit lamp (90D lens) and indirect ophthalmoscopy. Clinical diagnosis of retinopathy and macular edema cases was confirmed by fluorescein angiography and optical coherence tomography, respectively.

2.5. Statistical Analysis

Collected data were analyzed by SPSS (version 16). The data were described by mean, standard deviation (SD) and percentage. Normality of variables was assessed by the Kolmogorov-Smirnov test. Vitamin D was normalized by changing the base of the logarithm to e (Ln VitD). Chi-squared test, analysis of variance (ANOVA), Kruskal-Wallis, and Tukey's tests were used for data analysis. To compare the variables affecting the Ln VitD, the NPDR and PDR groups were merged into a single retinopathy class. Logistic regression analyses (cutoff point for vitamin D=20 ng/ml) and stepwise linear regression were performed with 0.05 and 0.1 significance levels as the entry and exit criteria. P-values less than 0.05 were considered as statistically significant.

2.6. Ethics of research

The proposal for this thesis research was presented to the Research Ethics Committee of Golestan University of Medical Sciences, Gorgan, Iran and approved by the Internal Medicine Department. The Ethics Committee approved the study (Ref: 174791793061912). Patients were informed about the objective and nature of the study. Written informed consent was obtained from all participants after obtaining permission.

3. Results

Clinical and laboratory characteristics of patients are shown in Table 1. In total, 57.3% of patients were male. Gender, age, duration of diabetes and BMI of subjects did not differ significantly between the three groups. The mean (±SD) of SBP were 138 (±25), 134 (±21) and 128 (±19) mmHg in the NPDR, PDR and control groups, respectively. The difference between the three groups were statistically significant (p=0.038), and pairwise comparison indicated a difference between the NPDR and control groups (p=0.013). The mean (±SD) of DBP was 81 (±13), 77 (±11) and 74 (±21) mmHg in the NPDR, PDR and control groups, respectively. The difference between the three groups were statistically significant (p=0.018), and pairwise comparison indicated a difference between the NPDR and control groups (P=0.03). The mean levels of FBS, HbA1c and GFR differed significantly among the three groups (Table 1). The mean (± SD) serum vitamin D level in the NPDR, PDR and control groups was 28.18 (±15), 23.9 (±12.36) and 30.24 (±13.85) (ng/mL), respectively. According to results of ANOVA, Ln vitamin D differed significantly between the three groups (p=0.007), and pairwise comparisons indicated a significant difference between PDR patients and controls (p=0.005) (Figure 1).

Table1. Clinical and biochemical characteristics of diabetic patients with and without retinopathy

Variables	Control (n=64)	NPDR (n=64)	PDR (n=64)	p-value
Gender (male/female)	44/20	33/31	33/31	0.076*
Age(year)	57.2 (8.42)	56.83 (7.42)	56.73 (5.42)	0.975**
Disease duration(year)	14.95 (4.7)	14.85 (5.32)	16.6 (5.5)	0.103**
SBP (mmHg)	128.35 (18.5)	138.2 (24.8)	134.29 (21.4)	0.038**
DBP (mmHg)	73.9 (21.4)	80.07 (13.01)	77.42 (11.12)	0.018**
BMI (Kg/m^2)	27.97 (4.2)	28.58 (4.27)	28.24 (5.84)	0.775**
HbA1c (%)	7.9 (1.3)	8.9 (1.9)	8.6 (1.6)	0.004***
TG (mg/dL)	150.38 (72.9)	168.46 (93.9)	208.85 (154.8)	0.105***
Cholesterol (mg/dL)	161.74 (39.9)	170.83 (45.7)	181.3 (52.02)	0.1***
HDL Cholesterol (mg/dL)	46.75 (9.57)	47.5 (10.28)	45.46 (10.2)	0.472***
LDL Cholesterol (mg/dL)	86.2 (34.7)	90.9 (36.3)	100.48 (47.6)	0.364***
FBS (mg/dL)	148.3 (48.5)	183.06 (87.5)	179.01 (72.5)	0.025***
GFR ($mL/min/m^2$)	83.04 (23.45)	77.9 (26.08)	73.14 (29.5)	0.035***
25(OH)D (ng/mL)	30.24 (13.85)	28.18 (15)	23.9 (12.36)	0.007***
Ln25(OH)D	3.31(0.42)	3.21(0.48)	3.05(0.48)	0.007**

NPDR: non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; FBS: Fasting blood glucose; HbA1C: Glycosylated hemoglobin; LDL: Low density lipoprotein; HDL: High density lipoprotein; 25(OH) D: 25 hydroxy vitamin D; GFR: Glumerolar filtration rate; Ln25 (OH) D: Log 25(OH) D
*Chi square test, **one way analysis of variances, ***Kruskal-Wallis test

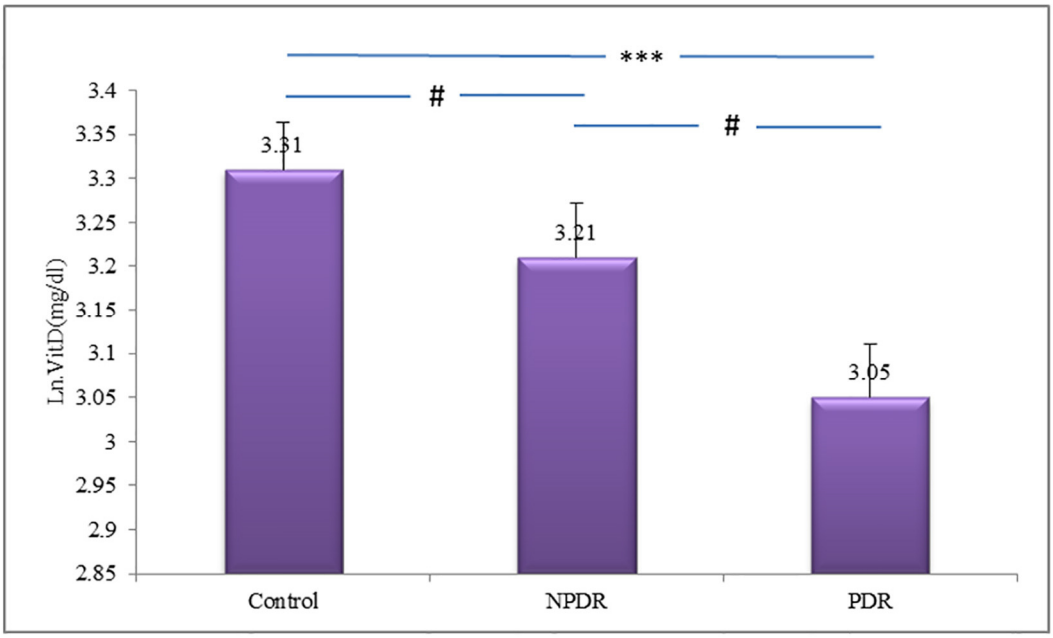

Figure1. Mean ± SD of Ln vitamin D among the three groups. # not significant, ***statistically significant

The results also showed that vitamin D levels were unfavorable in 36.5, 50 and 23.4% of the participants in the NPDR, PDR and control groups, respectively (p=0.008) (Table 2). Results of the multivariate analysis showed that there was a significant association of retinopathy and 25(OH)D, even when considering other variables associated with this variable. These results were consistent when analyzing by linear and logistic regression. On the other hand, both the logarithm of vitamin D and the presence of vitamin D deficiency, as defined by a 25(OH)D < 20 ng/ml (p=0.011 and p=0.019, respectively) (Table 3). The results of logistic regression analysis indicated a 2.4-fold higher risk of vitamin D deficiency in the retinopathy group compared to the control group (OR =2.409, CI (95%): 1.15-5.01) (Table 3).

Table 2. Comparison of vitamin D levels in the three groups

Vitamin D	Control	NPDR	PDR	p-value
25(OH)D ≥ 20 ng/mL (Favorable)	76.6	63.5	50	0.008
25(OH)D <20 ng/mL (Unfavorable)	23.4	36.5	50	

Table 3. Multivariate regression analysis with vitamin D cutoff of 20 ng/ml

Variables	Linear Model; 25(OH)D Concentration		Logistic model deficiency; (25(OH)<20mg/ml)		Exp (B)	95.0% C.I for Exp (B)	
	B (SE)	p-value	B (SE)	p-value		Lower	Upper
Retinopathy	-0.197 (0.077)	0.011	0.879 (0.374)	0.019	2.409	1.157	5.014
Age	0.008 (0.006)	0.932	-0.021 (0.023)	0.353	0.979	0.936	1.024
Gender (male/female)	0.182 (0.083)	0.038	0.089 (0.362)	0.806	1.093	0.538	2.222
Diabetes duration	-0.126 (0.007)	0.115	0.049 (0.034)	0.145	1.050	0.983	1.122
BMI	-0.059 (0.009)	0.501	0.006 (0.038)	0.871	1.006	0.933	1.085
SBP	0.045 (0.002)	0.655	-0.013 (0.011)	0.242	0.988	0.967	1.008
DBP	-0.140 (0.004)	0.134	0.023 (0.018)	0.198	1.023	0.988	1.060
HbA1c	0.112 (0.022)	0.152	-0.172 (0.099)	0.082	0.842	0.693	1.022
TG	-0.108 (0.000)	0.178	0.002 (0.002)	0.130	1.002	0.999	1.005
HDL	-0.138 (0.004)	0.092	-0.005 (0.017)	0.794	0.995	0.962	1.030
LDL	-0.054 (0.001)	0.494	0.002 (0.004)	0.715	1.002	0.993	1.010
GFR	-0.073 (0.002)	0.460	0.001 (0.008)	0.917	1.001	0.985	1.017

B: Standardize coefficient (Beta), SE: Standard error of mean, Exp (B): Odds ratio، BMI: Body mass index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, HbA1C: Glycosylated hemoglobin, TG: Triglycerides, LDL: Low density lipoprotein, HDL: High density lipoprotein, GFR: Glomerular filtration rate

4. Discussion

The present study demonstrated an association between vitamin D deficiency and diabetic retinopathy. Patients with retinopathy had lower serum vitamin D levels, and there was a higher prevalence of vitamin D deficiency in patients with retinopathy compared to the diabetics without retinopathy. This difference was significant between patients with PDR and controls. Moreover, this difference remained significant after considering the simultaneous influence of different variables including age, gender, duration of the disease, DBP, SBP, HbA1c, TG, HDL, LDL, and GFR. Several studies during the past 10 years have investigated the relationship between vitamin D deficiency and microvascular complications of diabetes such as retinopathy. However, the results of these studies often had some inconsistencies. The results of the present study were consistent with the results of Alcubierre et al. in Spain (15), Zoppini et al. in Italy (19), Ahmadieh et al. in Lebanon (23) and Kaur et al. in Australia (28). However, the results of the present study were not in agreement with findings of Bhanuprakash Reddy et al. in India (16). To the best of our knowledge, this is the first study in Iran that reports the association of vitamin D deficiency and diabetic retinopathy. A study by Bonakdaran et al. in Mashhad (17) found no difference between vitamin D levels in diabetic patients with and without retinopathy, and reported no relationship between vitamin D levels and severity of retinopathy. There was not a significant linear correlation between levels of FBS, HbA1c, BMI, SBP, DBP, TG, cholesterol, HDL, LDL, and GFR with mean serum levels of vitamin D, which is not consistent with findings of some previous studies (21, 23, 26, 29). This difference could be because the present study did not primarily aim to investigate the aforementioned relationships, thus the methodology and sample size had not been determined accordingly.

Vitamin D receptors in pancreatic β-cells are essential for insulin secretion and glucose tolerance. Insulin secretion decreases in hypovitaminosis D that could be normalized by vitamin D supplementation (24). In addition to its osteocalcic effect, vitamin D has immunomodulatory, anti-inflammatory, anti-oxidative, anti-angiogenesis and anti-proliferative functions in various cells. These functions are carried out through vitamin D receptors, which exist widely in the retina (24). Animal studies have shown that vitamin D inhibits neovascularization (17, 24), while this vitamin inhibits endothelial cell proliferation via reduction of vascular endothelial growth factor and advance glycation end products in vitro (24). Moreover, anti-cancer effect of vitamin D in some cancers such as retinoblastoma has been demonstrated (24). Furthermore, vitamin D deficiency is associated with an increase in PTH. The increased PTH in the subretinal fluid of the human eye impairs glucose tolerance and elevates inflammatory cytokines (24). In addition to vascular changes, the early stages of retinopathy include neurodegenerative changes such as loss of ganglion cells and reduction in thickness of retinal nerve fiber layer.

Study of Gungor et al. has recently reported the association of vitamin D deficiency with reduction in thickness of retinal nerve fiber layer (18).

5. Conclusions

This study revealed that vitamin D deficiency is significantly associated with the incidence of proliferative retinopathy. Since this is a case-control study, the reliability of the findings could be further validated via prospective interventional studies. Further studies are required to determine whether vitamin D supplementation can prevent the risk of developing diabetic retinopathy and affect its clinical course.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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