**Annals of Clinical and Analytical Medicine**
*Original Research*

# Is there a relationship between diabetic retinopathy and vitamin D?



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**Abstract**
Aim: In this study, we aimed to investigate the relationship between vitamin D and diabetic retinopathy by comparing clinical features and serum vitamin D levels of patients with and without diabetic retinopathy.
Material and Methods: The study is retrospective observational, and data were obtained by scanning the data file of patients diagnosed with Type 2 diabetes mellitus and undergoing fundus examination. A p-value < 0.05 was considered significant in all results.
Results: The mean age of patients with diabetic retinopathy (n=40) included in the study was 58.9±7.8 years, and the mean age of patients without diabetic retinopathy (n=40) was 58.5 ±5.2 years. In the diabetic retinopathy group, duration of diabetes ([19.0 ± 7.5] vs. [10.8 ± 7.2], p<0.001), serum glucose level ([218.9 ± 80.9] vs [142.7 ± 44.9], p<0.001), HbA1c level ([10.1 ± 2.1] vs. [7.2 ± 1.4], p<0.001) and total cholesterol level ([203.4 ± 41.2] vs [182.1 ± 37.1], p=0.009) were higher. However, serum 25[OH]D level was lower ([12.8 ± 4.2] vs [19.9 ± 11.2], p=0.011). In univariate regression analyzes, low vitamin D level (OR:0.889, CI[0.802 – 0.987], p=0.027) was determined as a possible independent risk factor for diabetic retinopathy.
Discussion: In our study, we found that low vitamin D levels were associated with an increased risk of diabetic retinopathy. Vitamin D deficiency may be one of the underlying causes of diabetic retinopathy, and we believe that prospective comprehensive studies will shed light on this issue.

**Keywords**
Vitamin D Deficiency, Diabetes Mellitus, Diabetic Retinopathy

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## Introduction

The prevalence of diabetic retinopathy (DRP) has reached approximately 93 million people worldwide and is one of the most important causes of premature visual loss [1]. Factors such as factors the duration of diabetes, hemoglobin A1c (HbA1c) level and hypertension lie in the etiology of DRP and their treatment provides modest improvement in retinopathy [2].

The development of retinal pathology, which includes neovascularization as a result of neural and retinal vascular dysfunction, is thought to be multifaceted. For this reason, various studies involving vitamins and minerals have investigated whether there is a relationship with DRP. 25-hydroxyvitamin D (25[OH]D) deficiency has been shown to be associated not only with DRP but also with other diseases [3,4,5]. In studies investigating the relationship between vitamin D deficiency and DRP, vitamin D receptor (VDR)-dependent calcium-binding proteins have been isolated from the human retina, especially from the photoreceptor layer of the cones [6]. In those expressing VDR in retinoblastoma tissue, Vitamin D supplementation reduced tumor growth and caused apoptosis in retinoblastoma cells [7]. 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) is closely associated with and reversed the regulation of Vascular Endothelial Growth Factor (VEGF) in experimental models, but also hypoxia is hypothesized to be associated with tissue hypoxia [8].

In this study, we aimed to investigate the relationship between vitamin D and diabetic retinopathy by comparing the clinical features and serum vitamin D levels of patients with and without diabetic retinopathy.

## Material and Methods

The study was retrospective, and data were obtained by scanning the files of the patients who were diagnosed with Type 2 diabetes mellitus and had fundus examination. Diabetes mellitus was diagnosed according to the guidelines of the American Diabetes Association (ADA) (fasting blood glucose ≥126 mg/dL, 2-hour plasma glucose level ≥200 mg/dL in oral glucose tolerance test) [9]. Body mass index (BMI) was obtained by dividing kilograms by the square of height (weight, kg/height,m2). Demographic clinical characteristics of the patients were obtained from the hospital data recording environment.

Best-corrected visual acuity (BCVA) was documented using the logMAR scale. All patients underwent detailed fundoscopic examination using stereoscopic slit-lamp biomicroscopy and indirect ophthalmoscopy. All patients underwent digital fundus photography and fluorescein angiography. Diagnosis and classification of patients with diabetic retinopathy were made in accordance with the guidelines of the study group (ETDRS) for the early treatment of diabetic retinopathy in Type-2 DM [10].

Venous blood samples were obtained from the right or left antecubital vein after at least 8 hours of fasting. The level of glycosylated hemoglobin was measured with a standard protocol using an autoanalyzer. Serum 25[OH]D level was measured by the chemiluminescent microparticle immunoassay method (Thermo Scientific, HPLC, Ultimate LPG-3400SD, Thermo Fisher Scientific).

*Exclusion criteria*

Those who had any systemic disease other than diabetes affecting the retina, a history of cardiovascular disease, kidney failure, chronic liver disease, cancer, calcium metabolism disorder, or taking vitamin D therapy for osteoporosis were excluded from the study.

*Ethics Committee Approval*

Ethics Committee Approval was obtained from the local ethics committee of the Faculty of Medicine (Decision number: BAÜN/2021/279, date: 22.12.2021).

*Statistical analyzes*

The obtained data were recorded in the statistical program of SPSS version 20.0 (Statistical Package for Social Sciences, Inc., Chicago, IL, USA). The suitability of data for a normal distribution was evaluated with the Kolmogorov-Smirnov test. Numerical variables with normal distribution were expressed as mean ± standard deviation, and categorical variables were expressed as percent (%). The student's t-test was used to compare normally distributed data between the two groups, and the Chi-square test was used to compare categorical variables. Univariate and multivariate logistic regression analyzes were used to determine independent predictors of diabetic retinopathy. A p-value of $< 0.05$ was considered significant in all results.

## Results

The mean age of patients with diabetic retinopathy (n=40) included in the study was 58.9 ± 7.8 years, and the mean age of patients without diabetic retinopathy (n=40) was 58.5 ± 5.2 years. There was no difference between the two groups in terms of gender, BMI, and frequency of hypertension.

In the diabetic retinopathy group, duration of diabetes ([19.0 ± 7.5] vs. [10.8 ± 7.2] years, p<0.001), serum glucose level ([218.9 ± 80.9] vs [142.7 ± 44.9] mg/dL, p<0.001), HbA1c level ([10.1 ± 2.1] vs. [7.2 ± 1.4], p<0.001) and total cholesterol level ([203.4 ± 41.2] vs [182.1 ± 37.1] mg/dL, p=0.009) were higher. However, serum 25[OH]D level was lower ([12.8 ± 4.2] vs [19.9 ± 11.2] ng/mL, p=0.011), (Table 1, Figure 1).

In univariate regression analyses performed to detect risk

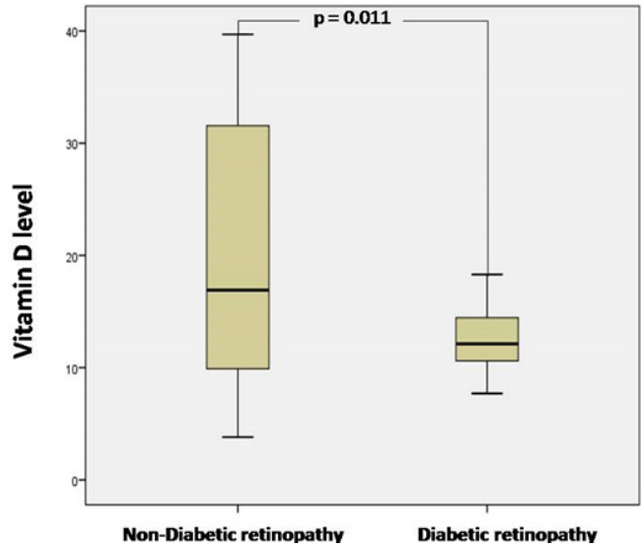


**Figure 1.** Comparison of serum vitamin D levels in patients with and without diabetic retinopathy.

**Table 1.** Comparison of patients with and without diabetic retinopathy in terms of demographic, clinical and laboratory findings.

| Variables | Non-Diabetic Retinopathy (n=40) | Diabetic Retinopathy (n=40) | p-value |
|---|---|---|---|
| Age (years) | 58.9±7.8 | 58.5±5.2 | 0.767 |
| Gender (male,%) | 15 (36.6) | 16 (40.0) | 0.513 |
| BMI (kg/m2) | 25.7±3.6 | 25.7±3.4 | 0.135 |
| Hypertension (%) | 24 (58.5) | 38 (62.5) | 0.407 |
| Diabetes duration (years) | 10.8±7.2 | 19.0±7.5 | <0.001 |
| Glucose level (mg/dL) | 142.7±44.9 | 218.9±80.9 | <0.001 |
| HbA1c level (%) | 7.2±1.4 | 10.1±2.1 | <0.001 |
| Creatinine (mg/dL) | 0.98±0.46 | 0.88±0.25 | 0.167 |
| Calcium (mg/dL) | 8.9±0.5 | 8.8±0.6 | 0.265 |
| Total cholesterol (mg/dL) | 182.1±37.1 | 203.4±41.2 | 0.009 |
| LDL (mg/dL) | 99.4±35.7 | 112.6±37.1 | 0.075 |
| HDL (mg/dL) | 53.6±18.7 | 54.5±17.1 | 0.809 |
| Triglyceride (mg/dL) | 148.3±70.9 | 191.6±128.6 | 0.051 |
| TSH (mIU/L) | 1.67±0.7 | 1.63±0.9 | 0.857 |
| Vitamin D (ng/mL) | 19.9±11.2 | 12.8±4.2 | 0.011 |
| Vitamin B12 (pg/mL) | 336.3±163.7 | 392.6±203.9 | 0.143 |
| WBC (x103/uL) | 7.6±2.3 | 7.7±1.8 | 0.824 |
| Hemoglobin (g/dL) | 13.4±1.3 | 13.3±1.4 | 0.755 |

Abbreviations: BMI: Body Mass Index, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TSH: Thyroid-stimulating hormone, WBC: White Blood Count

**Table 2.** Evaluation of possible independent predictors of diabetic retinopathy by regression analysis.

| Variables | Univariate analyzes | | Multivariate analyses | |
|---|---|---|---|---|
| | OR (95% CI) | p-value | OR (95% CI) | p-value |
| Diabetes duration | 1.167 (1.089 – 1.251) | <0.001 | 1.131 (0.954 – 1.340) | 0.158 |
| Glucose level | 1.020 (1.011 – 1.030) | <0.001 | 0.984 (0.950 – 1. 019) | 0.369 |
| HbA1c level | 2.452 (1.728 – 3.480) | <0.001 | 8.840 (0.963 – 81.135) | 0.054 |
| Total cholesterol level | 1.014 (1.003 – 1.025) | 0.011 | 1.002 (0.968 – 1.038) | 0.890 |
| Triglyceride level | 0.889 (0.802 – 0.987) | 0.027 | 0.970 (0.825 – 1.140) | 0.970 |
| Vitamin D level | 0.889 (0.802 – 0.987) | 0.027 | 0.824 (0.805 – 0.916) | 0.876 |

factors associated with diabetic retinopathy, duration of diabetes (Odds ratio [OR]: 1.167, 95% Confidence interval [CI] [1.089 – 1.251], p<0.001), serum glucose level (OR:1.020) , 95% CI [1.011 – 1.030], p<0.001), HbA1c level (OR:2.452, 95% CI [1.728 – 3.480], p<0.001), total cholesterol (OR:1.014, 95% CI [1.003 – 1.025) ], p=0.011) and vitamin D level (OR:0.889, [0.802 – 0.987], p=0.027) were found to be possible independent risk factors. There is no significant difference was observed between these parameters in multivariate analysis (Table 2).

## Discussion

In our study, while the duration of diabetes, serum glucose level, HbA1c level and total cholesterol level were high in patients with diabetic retinopathy, vitamin D level was found to be quite low, and low vitamin D was found to be a possible independent risk factor for diabetic retinopathy.

Vitamin D is a multifunctional hormone with the active metabolite 1,25-dihydroxyvitamin D3. Insulin hormone synthesis and secretion are impaired at low vitamin D levels [11]. Vitamin D also has anti-inflammatory and anti-angiogenic properties [12]. In the presence of high glucose levels, inflammation, oxidative stress increases VEGF and ICAM release [12]. Angiogenesis begins to increase in retinal endothelial cells and the ground is prepared for DRP [12]. Vitamin D plays an important role in diabetic retinopathy due to its angiogenesis and anti-inflammatory properties. In in vivo and in vitro animal studies, it has been shown that vitamin D inhibits VEGF, induces endothelial cell apoptosis, and inhibits signalling pathways required for angiogenesis in patients with retinopathy [13,14].

Nadri et al. divided 72 diabetic patients into 3 groups. They found that mean vitamin D levels were 23.3 ng/mL in those without retinopathy, 18.10 ng/mL in those without proliferative diabetic retinopathy, and 14.1 ng/mL in those with proliferative diabetic retinopathy also, they found that statistically, serum vitamin D level was lower in patients with proliferative diabetic retinopathy and it was closely related to the severity of retinopathy [15].

According to Yuan et al. in their meta-analysis, they found that the risk of DRP increased by up to 60% in those with vitamin D deficiency compared to those without it [16]. In this study, they found that vitamin D deficiency was an important risk factor for proliferative diabetic retinopathy, even after necessary adjustments for age, gender, duration of diabetes, and HbA1c level [16].

Patrick et al. in their study, which included 1790 patients, found that as the severity of diabetic retinopathy increased, the rate of vitamin D deficiency increased. However, in the regression analyses, they could not reveal this relationship statistically [17].

Afarid et al. found that serum vitamin D levels of 30 diabetic retinopathy patients and 60 diabetic patients without diabetic retinopathy were generally low (25(OH)D <20 ng/mL) [18]. However, vitamin D levels were found to be quite low in patients with retinopathy compared to those without retinopathy [18].

In our study, in accordance with the literature, vitamin D levels were found to be lower in patients with diabetic retinopathy than in patients without retinopathy (mean 12.8 ng/mL). Unlike in our study, diabetes duration, HbA1c, serum glucose and total cholesterol levels were also found to be higher in patients with diabetic retinopathy. In addition, in the regression analyses, it was seen that the high of these parameters and the low level of vitamin D were significantly associated with diabetic retinopathy.

Although the number of publications showing the relationship between vitamin D deficiency and diabetic retinopathy is considerable, some publications do not find a relationship between these two conditions, and the issue is open to discussion. In the study of Alam et al. in which 657 diabetic patients were recruited, they found similar vitamin D levels in comparison between groups with and without diabetic retinopathy. In this study, similar to our study, diabetes year, glycemic control and lipid levels were found to be associated with diabetic retinopathy [19].

### *Limitation*

Our study was a single-center study and the number of patients was limited. Since it was a retrospective study, patients were

not followed up for adverse events. Determining the relationship between diabetic retinopathy and poor in-hospital and long-term outcomes would have contributed to our study.

### *Conclusion*

In our study, we found that low vitamin D levels were associated with an increased risk of diabetic retinopathy. We found that diabetic retinopathy was also associated with high glucose and lipid values. Vitamin D deficiency may be one of the underlying causes of diabetic retinopathy, and we think that it would be appropriate to measure vitamin D levels as much as possible in these patients. We believe that prospective studies with a larger number of patients will contribute to this issue.

***Scientific Responsibility Statement***

*The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.*

***Animal and human rights statement***

*All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.*

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***Conflict of interest***

*None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.*

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