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Association between Serum Vitamin D Levels and Diabetic Retinopathy: A Cross-Sectional Study

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Abstract

Background: Diabetic retinopathy is a common vascular complication of diabetes. Vitamin D has been found to play a role in the development and progression of diabetic retinopathy. The aim of this study is to investigate the relationship between vitamin D levels and proliferative and non-proliferative retinopathy in diabetic patients.

Methods: The present study is a cross-sectional analytical study. This study was conducted at Hafiz Sabzevar Diabetes Clinic and involved diabetic patients. A total of 80 diabetic patients were categorized into three groups: patients without retinopathy, patients with proliferative diabetic retinopathy, and patients with non-proliferative retinopathy. Patients' information was collected through a demographic questionnaire and a researcher-made checklist. The data were analyzed using SPSS 28, with descriptive statistical tests, Chi-square, ANOVA, and Bonferroni's post hoc test.

Results: The results of the study showed a significant difference in vitamin D and creatinine levels among the three groups ($p<0.001$). The post hoc test was used to accurately determine this significant difference. The data revealed that both retinopathy groups had lower levels of vitamin D and higher creatinine compared to the non-retinopathy group, and this difference was statistically significant ($p<0.001$). However, there was no significant difference between the groups in terms of HDL ($p=0.23$), LDL ($p=0.52$), and total cholesterol ($p=0.95$).

Conclusion: Vitamin D deficiency increases the risk of developing diabetic retinopathy, both proliferative and non-proliferative. Therefore, it is recommended to consider taking vitamin D supplements in diabetic patients to maintain normal vitamin D levels, since it has positive effects in preventing the occurrence of diabetic retinopathy.

Keywords: Creatinine, Diabetic retinopathy, Retinal diseases, Vitamin D, Vitamin D deficiency, Vitamins

Introduction

Diabetes is a growing public health concern in the 21st century, ranking as the fifth cause of death worldwide (1,2). In Iran, the prevalence of diabetes is over 8% according to the World Health Organization (WHO) (3). Uncontrolled diabetes can lead to various long-term complications, including microvascular (blindness, nephropathy, and neuropathy) and macrovascular (cardiovascular and stroke) issues (4). Diabetic Retinopathy (DR) is a common vascular complication of diabetes and a leading cause of blindness globally. Approximately 5% of blindness cases are attributed to DR, affecting nearly all adults with type 1 diabetes and around 75% of adults with type 2 diabetes after about 15 years of disease duration (5,6). Diabetic retinopathy causes retinal vascular abnormalities and severe visual impairment. It is characterized by changes in the structure of retinal endothelial vessels and blockage of retinal blood flow due to hyperglycemia (7).

There are two types of diabetic retinopathy: Proliferative Diabetic Retinopathy (PDR) and Non-Proliferative Diabetic Retinopathy (NPDR). NPDR occurs in the early stage and causes ischemia and blockage of retinal blood vessels, which can progress to PDR. Diabetic retinopathy is responsible for most complications and vision loss associated with diabetes (8). Vitamin D level is one of the factors involved in the development of retinopathy. Vitamin D is a fat-soluble molecule that exists in two forms, vitamin D2 and vitamin D3 (9). Vitamin D deficiency is linked to the pathogenesis and progression of diabetes, as well as obesity, insulin resistance, metabolic syndrome, and cardiovascular diseases (10,11).

Inflammation and vascular endothelial growth factor (VEGF) play significant roles in the development of macular edema and neovascularization in PDR (12). Vitamin D can reduce VEGF levels and inhibit the replication of vascular smooth muscle cells (9). Additionally, vitamin D may protect the retina and Retinal Pigment Epithelium (RPE) against oxidative stress, inflammation, and apoptosis by suppressing pro-inflammatory mediators and enhancing anti-oxidant defense mechanisms (13).

Due to conflicting previous studies and the increasing prevalence of diabetes and its high-risk complications in today's society, it is necessary to investigate the risk factors associated with these diseases. One potential factor to evaluate is the effect of vitamin D deficiency in reducing the progression of vascular complications of diabetes. However, no similar study has been conducted in the population of Sabzevar. Therefore, the present study aims to evaluate the level of vitamin D in diabetic retinopathy patients and investigate its relationship with the severity of retinopathy in the population of diabetic patients referred to Sabzevar Diabetes Clinic.

Materials and Methods

The present cross-sectional analytical study received ethical approval from the Ethics Committee of Sabzevar University of Medical Sciences with the code of ethics IR.MEDSAB.REC.1400.002. Full informed consent was obtained from all the participating patients. Ocular involvement was assessed through fundoscopic examination, and fluorescein angiography was performed when necessary, by an experienced ophthalmologist. The patients were categorized into three groups based on the severity of diabetic retinopathy: no retinopathy, proliferative retinopathy, and non-proliferative retinopathy. If retinopathy varied between the eyes, the eye with the higher stage was included. After the client's ophthalmology examination, their vitamin D levels were measured and recorded and then compared. Patients' information, routine tests, and laboratory data were recorded in the Medario System, and the checklist was completed using this system. The criteria for entering the study included patients with type 2 diabetes who visited Hafiz Sabzevar Diabetes Clinic Between September 2020 and March 2021, and the exclusion criteria included patients with type 1 diabetes, using vitamin D supplements, and deficiencies in recorded information. Statistical analysis was performed using SPSS-28 software, including descriptive analysis, ANOVA, chi-square test, and Bonferroni tests.

Descriptive statistics were computed to summarize the characteristics of the study sample. Measures of central tendency (mean, median) and dispersion (standard deviation, range) were calculated for continuous variables, while frequencies and percentages were used for categorical variables. ANOVA (Analysis of Variance) was used to compare

the means of continuous variables (*e.g.*, vitamin D and creatinine levels) across the three groups (NDR, NPDR, PDR). ANOVA was chosen, since it is suitable for comparing more than two groups. The normality of the data was assessed using the Kolmogorov-Smirnov test, and the homogeneity of variances was checked using Levene's test. Post hoc tests (Bonferroni) were conducted to determine which specific groups differed from each other after finding a significant result in ANOVA. The Bonferroni correction was applied to adjust for multiple comparisons. Chi-square test was utilized to evaluate the associations between categorical variables, such as gender distribution and the presence of diabetic retinopathy. The Chi-square test is appropriate for assessing the relationship between two categorical variables.

Results

All the 80 participants completed the study. The average age of the participants was 55.89±10.56, and there were no statistically significant differences in demographic variables between the groups. The individual characteristics of the participants are provided in table 1. As shown in table 1, there is no significant difference in insulin consumption, fasting blood sugar and demographic variables between different groups (NDR, NPDR, PDR). Table 2 displays the average paraclinical data for the NDR, NPDR, and PDR groups. The paraclinical parameters were compared among the three groups. An ANOVA parametric test was used for data analysis, considering the normality of the data (Smirnov's Kolmogorov test) and homogeneity of variances (Levene's test). There were significant differences in Creatinine and Vitamin D variables among the three groups ($p<0.001$). However, there were no statistically significant differences in HDL, LDL, and total cholesterol between the groups (Table 2). Post hoc tests (Bonferroni) were performed to determine the significant difference, showcased in table 3. As revealed in table 3, both the NPDR and PDR groups exhibited a significant difference in Creatinine and Vitamin D variables compared to the NDR group. In other words, regardless of proliferative status, both retinopathy groups (NPDR and PDR) had lower levels of vitamin D and higher creatinine levels compared to the non-retinopathy group, and this difference was statistically significant.

Discussion

The purpose of this cross-sectional study was

Table 1. Comparison of the demographic characteristics of the participants in each group

Variables	Group	NDR No. (%)	NPDR No. (%)	PDR No. (%)	p-value
Age		54.84±10.7	55.24±11.1	57.6±9.9	0.766
Gender	Male	19(42.2%)	13(52%)	4(40%)	0.692
	Female	26(57.7%)	12(48%)	6(60%)	
Taking insulin or oral antidiabetic medication		42(93/3%)	21(84%)	8(80%)	0.320
Fasting blood sugar level		171.6±32.6	186.5±37.2	188.5±36.6	0.146

Table 2. ANNOVA test to compare the paraclinical data between NDR, NPDR and PDR groups

Variables	NDR	NPDR	PDR	p-value
Vitamin D (*ng/dl*)	21.49±5.4	16.44±5.1	13.2±4.4	<0.001
Creatinine	0.91±0.11	1.08±0.11	1.18±0.12	<0.001
HDL (*mg/dl*)	37.49±6.3	36.4±5.9	33.8±6.6	0.234
LDL (*mg/dl*)	103.7±14.7	107.9±14.3	104.5±18.8	0.525
Total cholesterol (*mg/dl*)	165.7±20.7	167.3±22.8	166.9±19.3	0.925

Table 3. Post Hoc Tests

Variables	Bonferroni test		p-value
Vitamin D (*ng/dl*)	NDR *vs*. NPDR	21.49±5.4 *vs*. 16.44±5.1	<0.001
	NDR *vs*. PDR	21.49±5.4 *vs*. 13.2±4.4	<0.001
	PDR *vs*. NPDR	13.2±4.4 *vs*. 16.44±5.1	0.301
Creatinine (*mg/dl*)	NDR *vs*. NPDR	0.91±0.11 *vs*. 1.08±0.11	<0.001
	NDR *vs*. PDR	0.91±0.11 *vs*. 1.18±0.12	<0.001
	PDR *vs*. NPDR	1.18±0.12 *vs*. 1.08±0.11	0.048

to examine the relationship between vitamin D levels and retinopathy in diabetic patients at Hafiz Sabzevar Diabetes Clinic. Overall, the results showed that vitamin D deficiency contributes to the development of retinopathy, both proliferative and non-proliferative. Additionally, the study revealed that creatinine levels have an impact on retinopathy incidence in both groups. However, there was no difference observed in total cholesterol, LDL, and HDL between patients with and without retinopathy. In a 2012 study, it was found that vitamin D inhibits the proliferation of retinal endothelial cells, which is a key contributor to severe retinopathy, and prevents retinopathy by suppressing cell proliferation (14).

These findings align with the results of our study, indicating that vitamin D helps prevent diabetic retinopathy. Similarly, a 2020 study by Robredo *et al* demonstrated that vitamin D prevents retinopathy by suppressing pro-inflammatory mediators and enhancing antioxidant defense in the retina (13). Consistent with other studies, this research suggested that vitamin D deficiency increases the risk of retinopathy. Furthermore, the present study indicated that the deficiency of this vitamin is associated with both proliferative and non-proliferative retinopathy, with proliferative cases having more severe deficiencies. The results reveal that the prevalence of retinopathy, regardless of type, is higher in diabetic patients with vitamin D deficiency compared to those without deficiency. These findings suggest that vitamin D supplementation in diabetic patients can help maintain normal vitamin D levels. Diabetic patients with normal levels of vitamin D have better controlled blood pressure. The reason for this is that vitamin D plays a role in the development of conditions such as hypertension, kidney disease, and diabetes by regulating the Renin-Angiotensin System (RAS). RAS hyperactivity is involved in the development of hypertension, chronic kidney disease, decreased insulin secretion, and insulin resistance. Animal studies support the reduction of renin expression and activity through vitamin D interaction with the vitamin D receptor. Additionally, vitamin D metabolites in animals have been shown to reduce blood pressure, proteinuria, kidney damage, and improve β-cell function (15). The results of this study were consistent with the previously mentioned study. In patients with vitamin D deficiency, their creatinine levels were higher and they experienced a greater extent of diabetic retinopathy. Other studies have also shown that patients with vitamin D deficiency have lower levels of glucose control and higher levels of HBA1C. This is because vitamin D supplementation reduces AGE levels and the expression of RAGE in patients with type 2 diabetes. This reduction increases IL-6 and NFκB-p65 DNA binding activity, both of which contribute to better blood glucose control (16). These findings align with our study, suggesting that vitamin D not only directly prevents retinopathy, but also improves endothelial dysfunction and strengthens vascular regeneration through the activation of diabetic retinopathy. This, in turn, regulates the expression of genes involved in cardiovascular function (17). Vitamin D is also indirectly involved in preventing all types of retinopathy by helping to better control blood pressure and blood glucose. However, the current study had some limitations, including a small sample size and potential laboratory errors. In conclusion, it can be stated that taking vitamin D supplements in diabetic patients to maintain normal

levels of this vitamin can play a significant role in preventing the occurrence of retinopathy.

The findings of this cross-sectional study show a significant relationship between the low levels of serum vitamin D and the intensity of diabetic retinopathy. Both NPDR and PDR groups had significantly lower vitamin D levels than the NDR group, indicating that vitamin D deficiency may be involved in DR pathogenesis. However, it is important to admit that cross-sectional design limits our ability to infer causation. Therefore, the observed relationship does not mean that vitamin D deficiency causes diabetic retinopathy. Longitudinal future studies are essential to investigating the relationship between the potential cause and preventive effects of vitamin D supplementation on DR progress.

In addition, diabetes control, which is not considered in this study, can potentially affect serum vitamin D and blood sugar levels, thereby affecting the observed relationship. Future research should include diabetes control criteria, such as HBA1C levels to better understand this interaction.

In addition, comparing the treated and ignored PDR groups can provide insights about different levels of VEGF, since treatment, especially anti-VEGF treatment, may change VEGF expression and affect the severity of retinopathy. This distinction helps to better understand the relationship between vitamin D, VEGF, and DR.

Conclusion

The present study showed a significant relationship between lower levels of serum vitamin D and increased intensity of diabetic retinopathy in patients in Sabzevar Diabetes Clinic. While the cross-sectional nature restricts the study of causal inferences, the findings show the potential role of vitamin D in DR pathogenesis. Future longitudinal studies are essential for causality and discovery of vitamin D supplementation therapeutic potential. In addition, considering the status of diabetes control and comparing PDR groups treated with ignored groups in future research, provides a more comprehensive understanding of the factors affecting DR intensity and progress.

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Conflict of Interest

The authors hereby declare that there is no conflict of interest regarding the present study.

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