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Research Article

Association of Vitamin D Deficiency in Proliferative Diabetic Retinopathy (PDR)

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ABSTRACT

Background: As the advanced stage of diabetic eye disease, proliferative diabetic retinopathy (PDR) is a significant contributor to preventable blindness worldwide. The association between vitamin D deficiency and either retinal vascular dysfunction or disease progression is garnering increasing evidence. To examine the relationship between vitamin D and PDR (proliferative diabetic retinopathy) in T2DM.

Study design: This study was cross-sectional study and conducted for six months.

Methods: The study enrolled 150 individuals with type 2 diabetes mellitus, equally divided into two groups: 75 patients with PDR and 75 with NPDR. Serum 25-hydroxyvitamin D levels were measured using ELISA. A deficiency of vitamin D was considered <20 ng/ml. SPSS were used for analysis, using a significance level of $p<0.05$.

Results: The assessment of vitamin D concentration in patients diagnosed with PDR was significantly lower than NPDR patients (14.6 ± 5.8 vs 23.1 ± 6.5 ng/mL, $p<0.001$). Vitamin D deficiency was much more common in PDR patients (80%) than NPDR patients (45.3%) ($p<0.001$). Vitamin D deficiency was an standalone predictor of risk for PDR (OR: 3.1, 95% CI: 1.6–6.2) when compared with the other parameters.

Conclusion: Vitamin D deficiency is strongly linked to proliferative diabetic retinopathy (PDR) and may be a disease risk factor. Diabetic patients with vitamin D deficiency may benefit from screening and correcting the vitamin D deficiency, which could help decrease the risk of advanced retinal complications.

Keywords: Vitamin D Deficiency, Proliferative Diabetic Retinopathy, Diabetes And Serum.

INTRODUCTION

Diabetic retinopathy (DR), a prevalent microvascular consequence of diabetes mellitus (DM), is among the most significant yet preventable causes of blindness across the world [1, 2]. The significant number of persons with long duration of diabetes develop some degree of retinal involvement, presenting as mild non-proliferative to more advanced stages of the spectrum of diabetic retinopathy, from NPDR to advanced PDR. The pathological retinal neovascularization, VH, FVP, and TRD are the stages that are the most vision threatening in PDR. Such problems may lead to permanent vision loss if not identified and treated early [3]. Although screening programs and therapeutic advances like laser photocoagulation, anti-VEGF drugs, and vitrectomy have improved the care of patients with AMD, a substantial number of patients still come in with advanced disease, notably in low- and middle-income nations, where the impact is greater, where diagnosis delayed and access to specialized eye care services is limited [4].

The pathogenesis of DR is complex and polyfactorial, with chronic hyperglycemia-induced metabolic disturbances, oxidative stress, inflammatory processes and endothelial

dysfunction. Other systemic and nutritional factors may also affect disease onset and progression, as the glycemic control, hypertension and duration of diabetes are well established risk factors [5].

In this respect, vitamin D has become more and more popular considered as possible preventable contributor to DR. Now it is known to have pleiotropic effects other than on bone, such as anti-inflammatory, immunomodulatory, anti-oxidative and anti-angiogenic properties [6]. Vitamin D receptors (VDR) have been observed in other tissues of the eye such as the retina, retinal pigment epithelium, and vascular endothelial cells, indicating that vitamin D may have a substantial influence on maintaining the vascular integrity of the retina [7].

The experimental research has demonstrated that vitamin D can adversely regulate angiogenesis, decrease the expression of the VEGF, and lead to a blunting of inflammatory cytokine response, particularly IL-6 and TNF-α [8]. It also could have benefits for endothelial function and oxidative stress, both of which play key roles in development of DR. Vitamin D decline has therefore been suggested to be implicated in the progression and severity of DR, especially in the later stages of DR, including PDR, where pathological neovascularization is a key feature [9].

Studies have found that patients with more severe retinopathy (PDR) exhibit lower serum vitamin D concentrations than patients with no retinopathy or mild non-proliferative retinopathy [10]. Some studies, however, have not found consistent results across studies, and some populations have demonstrated weak or not significant relationships [11]. Various study design differences, population variability, sample size differences, dietary differences, and genetic differences may account for these discrepancies [12].

Vitamin D deficiency is widely observed in the population that majority of South Asian countries, including Pakistan, because of various factors that lead to low vitamin D levels, including low levels of sun exposure, darker skin pigmentation, cultural habits that prevent skin exposure, and reduced intake of foods and products rich in vitamin D [13]. At the same time, the prevalence of DM is on the rise, causing an escalating load of diabetic complications such as retinopathy. Although this dual burden, there is minimal local evidence examining the epidemiological link between low vitamin D status with proliferative diabetic retinopathy [14].

Thus, the objective of the present research was to explore the association of low vitamin D status with PDR. Such an link could be useful to understand if there are modifiable systemic risk factors that may be contributing to the progression of disease. If there is a strong relationship, the vitamin D status may be a useful additional parameter to use for risk stratification and could provide a new dimension in preventive strategies to decrease the burden of vision-threatening DR.

METHODOLOGY

A cross-sectional analytical design was employed for this study in the Ophthalmology and Endocrinology departments of a tertiary care hospital for six months. The sample size was calculated by formula for the estimation of 95% confidence level ($Z\alpha/2 = 1.96$), anticipated level of vitamin D deficiency in the population of 70% ($p = 0.70$), and margin of error of 8% ($d = 0.08$) were used. The preliminary sample size calculated was 126. With a 10-15% attrition rate (due to incompleteness of data), the adjusted sample size was about 145. In order to have an equal distribution of groups and to make the sample size bigger for statistical power, the final sample size was rounded up to 150 participants.

Diabetic retinopathy was divided into two groups: proliferative diabetic retinopathy (PDR) and non-proliferative diabetic retinopathy (NPDR), and the diagnosis was made by dilated fundus examination with standard clinical criteria by an ophthalmologist. The patients who had chronic kidney disease, liver disease, vitamin D supplementation in the past three months, malabsorption disease or any other retinal disease were excluded from the study.

Venous blood samples were collected aseptically, and serum 25-hydroxyvitamin D was measured using the ELISA method. Vitamin D status was defined as deficiency (<20 ng/mL), insufficiency (20–29 ng/mL), and sufficiency (≥30 ng/mL). Relevant demographic and clinical characteristics such as age, sex, diabetes duration, and HbA1c levels were collected.

The data was analyzed by SPSS v.25. The quantitative data was presented in the form of mean ± SD, and the categorical data was presented in the form of frequency and percentage. The mean vitamin D levels between groups were compared with independent sample t-test, chi-square test and binary logistic regression. A p-value of <0.05 was considered statistically significant.

RESULTS

Table 1 comparison showed that the mean age in both groups. (58.4 years ± 9.6 years in the PDR group compared with 56.9 years ± 10.1 years in the NPDR group, p = 0.38), were not significant. In the same way, there was no gender difference in the proportion of the participants, with 56% of the male participants and 52% of the female participants (p = 0.64). Clinically relevant differences in disease parameters, however, were found. Duration of diabetes was significantly greater in the PDR group than the NPDR group (12.8 ± 4.3 years vs 10.6 ± 3.9 years, p = 0.01). This indicates that the longer the diabetes duration, the more likely that the DR will progress to proliferative DR. Further, glycemic control also was significantly poorer in the PDR group, with higher HbA1c (9.2 ± 1.4% vs 8.6 ± 1.2%, p = 0.02).

Table 1: Baseline Characteristics of Study Population

Variable	PDR (n=75)	NPDR (n=75)	p-value
Age (years)	58.4 ± 9.6	56.9 ± 10.1	0.38
Male (%)	42 (56%)	39 (52%)	0.64
Duration of diabetes (years)	12.8 ± 4.3	10.6 ± 3.9	0.01*
HbA1c (%)	9.2 ± 1.4	8.6 ± 1.2	0.02*

Table 2 shows that the mean of vitamin D level in patients of PDR (14.6 ± 5.8 ng/mL) was significantly lower than that of NPDR (23.1 ± 6.5 ng/mL) with p value (<0.001).

Table 2: Comparison of Serum Vitamin D Levels

Variable	PDR (n=75)	NPDR (n=75)	p-value
Vitamin D (ng/mL)	14.6 ± 5.8	23.1 ± 6.5	<0.001*

Table 3 shows that the proliferative diabetic retinopathy (PDR) was significantly associated with vitamin D deficiency (<20 ng/mL), with 80% (60/75) of patients in the PDR group having the deficiency, vs 45.3% (34/75) of those in the NPDR group (p < 0.001. Conversely, a higher proportion of patients with NPDR had vitamin D levels in the 20–29 ng/mL range compared to those with PDR (37.3% vs 13.3%). Likewise, adequate Vitamin D (VitD) levels (VitD ≥ 30 ng/mL) were slightly more common among NPDR patients (17.3%) than PDR patients (6.7%). These results illustrate that there is a clear inverse relationship between vitamin D status and DR severity that follows a gradient.

Table 3: Distribution of Vitamin D Status

Vitamin D Status	PDR (n=75)	NPDR (n=75)	p-value
Deficient (<20 ng/mL)	60 (80%)	34 (45.3%)	<0.001*
Insufficient (20–29 ng/mL)	10 (13.3%)	28 (37.3%)	
Sufficient (≥30 ng/mL)	5 (6.7%)	13 (17.3%)	

Table 4 shows that the Vitamin D deficiency was associated with 3.1 times increased risk of PDR with p = 0.001.

Table 4: Association of Vitamin D Deficiency with PDR

Variable	Odds Ratio (OR)	95% CI	p-value
Vitamin D deficiency	3.1	1.6 – 6.2	0.001*

DISCUSSION

In the present study, vitamin D level and its association with PDR in type 2 diabetes participants were evaluated. The results show a very strong and statistically significant inverse impact of vitamin D status on diabetic retinopathy severity.

Vitamin D level was reduced in PDR group than in NPDR group, suggesting that an evident negative correlation is present between the concentration of vitamin D [15]. The same results have been reported in previous studies Aksoy et al. found that severe DR was linked with a significantly lower level of vitamin D than in the mild and moderate DR groups, indicating

that there is a decline in vitamin D status [16]. Low vitamin D levels were correlated with higher incidence of AR in diabetic participants [17].

The dose response relationship between vitamin D status and severity of retinopathy with 80% of PDR patients being vitamin D deficient versus 45.3% of NPDR patients [18]. A similar study was carried out by Herrmann et al who concluded that vitamin D deficiency was observed more often in patients with proliferative changes and more severe microvascular complications in diabetes [19].

This multivariable logistic regression showed that, Vitamin D deficiency was independently associated with PDR. The previous study by Luo et al. which found that decline vitamin D had effect on increasing the effect of DR even after adjusting for glycemic control and disease duration [20]. But not all studies confirm the relationship, with other studies reporting weaker or non-significant relationships, potentially due to variations in population characteristics, sun exposure, dietary and genetic variations [21].

The findings indicate that vitamin D screening in diabetic patients may be clinically significant and correcting the vitamin D deficiency may be a useful adjunctive measure in preventing the progression of DR.

CONCLUSION

Vitamin D may be a significant factor in the development of DR. Periodic measurement of vitamin D in diabetic individuals may be beneficial, and correcting the vitamin D deficiency may be a complementary preventive measure to prevent the development of advanced retinal disease.

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