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Original Research Article

Relationship between Serum Vitamin D Levels and Diabetic Retinopathy

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Abstract

Background: One of the main causes of avoidable blindness is diabetic retinopathy (DR), which is a serious worldwide health hazard associated with type 2 diabetes mellitus. Serum vitamin D levels in Type 2 diabetes patients with and without diabetic retinopathy will be assessed in this study, and the relationship between vitamin D levels and the severity of DR will be examined.

Methods: 200 participants were split into two groups for this analytical cross-sectional study: Group A consisted of diabetic patients with DR, and Group B consisted of diabetic patients without DR. In accordance with ETDRS norms, participants received thorough ocular examinations and DR grading. Other biochemical and clinical indicators were examined in addition to serum vitamin D levels. To compare groups and find correlations, statistical analysis was done.

Results: Group A exhibited significantly lower serum vitamin D levels (17.03 ± 5.11 ng/mL) compared to Group B (27.72 ± 3.81 ng/mL, $p < 0.001$). An inverse relationship was observed between serum vitamin D levels and DR severity, with the lowest levels seen in patients with proliferative DR (15.33 ± 4.4 ng/mL). Additionally, patients with longer diabetes duration, poorer glycemic control, and higher BMI were more likely to develop DR.

Conclusion: In Type 2 diabetes, the presence and severity of diabetic retinopathy are linked to lower serum vitamin D levels. The degree of DR may be predicted by serum vitamin D levels. The possible impact of vitamin D supplementation in halting or slowing the progression of DR requires more research.

Introduction

Diabetes is rapidly reaching epidemic proportions in India, with over 62 million individuals currently affected. [1] According to Wild et al., the global prevalence of diabetes is projected to rise from 171 million in 2000 to 366 million by 2030, with India expected to have the highest burden. Notably, in 2000, India already had a substantial number of individuals diagnosed with diabetes mellitus. [2]

Based on its etiology, diabetes mellitus can be roughly divided into two types: Type 1 and Type 2. The autoimmune loss of the beta cells of the pancreas that produce insulin causes type 1 diabetes mellitus, sometimes referred to as insulin-dependent diabetes mellitus (IDDM). In contrast, insulin resistance, decreased insulin production, and increased glucose production are the three main mechanisms that define Type 2 Diabetes Mellitus. The precise mechanism behind the development of diabetic retinopathy is still unknown, despite the fact that rigorous blood glucose control has been demonstrated to greatly lower the risk of microvascular problems associated with diabetes. [3]

Long-term diabetes and inadequate glycemic management have been identified as major risk factors for diabetic retinopathy (DR). Diabetes can significantly affect one's quality of life, so early detection is essential. Reducing avoidable blindness linked to diabetic retinopathy requires early detection of patients at risk for this condition. Immune system and musculoskeletal functioning are among the many physiological processes in which vitamin D is essential. Furthermore, a number of research point to a link between vitamin D and diabetes. However, studies show that more than half of the world's population suffers from vitamin D deficiency or insufficiency, making it a common health concern. [4]

Vitamin D insufficiency has been linked to an increased risk of cardiovascular disease, cancer, and overall mortality. [5,6] Studies have shown that Vitamin D deficiency is particularly common in

individuals with diabetes mellitus, with a prevalence of 84.2%. Its impact on the immune system, angiogenesis, and anti-inflammatory properties plays a significant role in the pathogenesis of diabetic retinopathy. Furthermore, research using a mouse model of oxygen-induced ischemic retinopathy has demonstrated that calcitriol, an active metabolite of Vitamin D, can inhibit retinal neovascularization. [7,8]

It is still unclear how vitamin D insufficiency and diabetic retinopathy are related in people with type 2 diabetes. Alternatively, some research indicates a link and association between vitamin D insufficiency and diabetic retinopathy. Additionally, there aren't many research on this issue among Indian citizens. Given the prevalence of diabetes mellitus in our area, this study aims to ascertain the prevalence of vitamin D deficiency in individuals with type 2 diabetes who also have diabetic retinopathy and to establish a correlation between vitamin D levels and alterations in retinopathy.

Material and Method

This study was conducted in the Outpatient Department of Ophthalmology at the Government Medical College and associated hospitals in Kota, Rajasthan, over 18 months (December 2022 to May 2024) following ethical committee approval. It was designed as an analytical cross-sectional study, involving 200 participants divided equally into two groups. Group A consisted of patients diagnosed with diabetic retinopathy, while Group B included age- and gender-matched diabetic patients without diabetic retinopathy. All participants underwent a detailed medical history review, including symptoms, sun exposure, dietary habits, family history, and use of medications or treatments that could influence Vitamin D metabolism. A comprehensive ocular examination, including visual acuity assessment and dilated fundus examination using indirect ophthalmoscopy, was performed to diagnose and classify diabetic retinopathy according to ETDRS guidelines. Blood samples were collected to measure fasting blood glucose (FBS), postprandial blood sugar, HbA1c, serum Vitamin D, serum cholesterol, serum creatinine, and serum calcium levels. Serum 25-hydroxy Vitamin D, the best indicator of Vitamin D status, was measured using the Cobas e411–Elecsys Vitamin D Total III assay based on electro-chemiluminescent microparticle immunoassay (CLIA) technology. Samples were carefully prepared and analyzed to ensure accuracy. Patients with disorders affecting Vitamin D metabolism, prior Vitamin D supplementation, or other confounding medical or ocular conditions were excluded from the study. Data were analyzed using SPSS version 22, employing statistical methods such as Chi-squared tests, ANOVA, and t-tests, among others, to assess associations and outcomes.

Result

The study compared subjects based on age, age of onset, diabetes duration, sex distribution, BMI, and the severity of diabetic retinopathy, revealing notable differences between cases (patients with diabetic retinopathy) and controls (diabetic patients without retinopathy).

In terms of age, the majority in both groups were aged 61–70 years, with 45 cases and 40 controls. The mean age was significantly higher in cases (64.6 ± 8.8 years) than controls (61.96 ± 10.31 years, p=0.02). For the age of onset of diabetes, cases were predominantly diagnosed before 40 years (64 cases vs. 26 controls), while most controls (72) were diagnosed between 40 and 60 years. The mean age of onset was significantly younger in cases (39.82 ± 3.44 years) compared to controls (43.54 ± 5.2 years, p=0.03). Regarding diabetes duration, more cases had diabetes for over 20 years (71 vs. 53 controls), while fewer had diabetes for less than 10 years (8 vs. 12 controls). The mean duration of diabetes was longer in cases (24.78 ± 8.87 years) than controls (20.97 ± 9.26 years, p=0.04).

Sex distribution showed 64 male and 36 female patients in the case group, compared to 58 males and 42 females in the control group. The p-value for sex distribution was greater than 0.05, indicating no significant difference between the groups.

BMI analysis revealed significant differences between the groups (p=0.01). In the case group, 25 patients had a normal BMI, 42 were obese, 21 were overweight, and 12 were underweight. In the control group, 37 had a normal BMI, 34 were obese, 14 were overweight, and 15 were underweight. The case group had a higher proportion of obese patients and fewer with a normal BMI compared to the control group.

The majority of patients in the case group had advanced stages of diabetic retinopathy, according to the severity of the condition. Of the patients, 38 had the most severe type, Proliferative Diabetic Retinopathy (PDR). 34 individuals had Very Severe Non-Proliferative Diabetic Retinopathy (NPDR), 18 had Severe NPDR, 7 had Moderate NPDR, and only 3 had Mild NPDR.(Fig.1)

Table 1: Comparison of Clinical and Laboratory Parameters Between Cases (Group A) and Controls (Group B)

Parameter	Case (Group A) Mean ± SD	Control (Group B) Mean ± SD	p-value
Fasting Blood Sugar (mg/dl)	216.3 ± 4.61	157.73 ± 12.53	0.00
Post Prandial Blood Sugar (mg/dl)	300.09 ± 7.7	181.88 ± 16.7	0.00
HbA1C (%)	8.63 ± 1.21	7.30 ± 0.59	0.02
Glycemic Control, n %			
- <7.0 (Good)	7	36	0.00
- 7.1-8.0 (Unsatisfactory)	31	51	0.00
- >8.0 (Poor)	62	13	0.00
Serum Vitamin D (ng/ml)	17.03 ± 5.11	27.72 ± 3.81	0.00
Ratio of Male & Female in Serum Vitamin D Levels			
Male	17.46 ± 4.9	27.61 ± 3.7	0.02
Female	16.26 ± 5.4	27.87 ± 3.9	0.02
Serum Calcium (mg/dl)	8.9 ± 0.58	9.56 ± 0.86	0.00
Serum Creatinine (mg/dl)	1.12 ± 0.81	0.71 ± 0.21	0.02
Serum Cholesterol (mg/dl)	167.60 ± 17.14	159.01 ± 100.52	0.03

The analysis of clinical and laboratory parameters between patients with diabetic retinopathy (cases) and those without (controls) showed significant differences. The case group had higher fasting blood sugar (216.3 ± 4.61 mg/dl) and post-prandial blood sugar (300.09 ± 7.7 mg/dl) levels compared to the control group (157.73 ± 12.53 mg/dl and 181.88 ± 16.7 mg/dl), with p-values of 0.00. HbA1C levels were also higher in the case group (8.63 ± 1.21%) than in the control group (7.30 ± 0.59%), with a p-value of 0.02. Serum vitamin D levels were significantly lower in the cases (17.03 ± 5.11 ng/ml) compared to the controls (27.72 ± 3.81 ng/ml), with a p-value of 0.00. Moreover, serum calcium and creatinine levels were lower in the control group, while serum cholesterol levels were higher in the case group. These findings suggest that poor glycemic control and lower vitamin D levels are linked to the presence of diabetic retinopathy.(Table1)

Table 2: Distribution of Different variables according to Severity Grading of DR

Grade of Diabetic Retinopathy	Fasting blood sugar (mg/dl) Mean ± SD	Post prandial sugar (mg/dl) Mean ± SD	HbA1C (%) Mean ± SD	Serum vitamin-D (ng/ml) Mean ± SD
Mild NPDR	148.33±8.50	197.3±3.69	6.9± .25	25.36± 2.41
Moderate NPDR	164±10.3	199.4±16.6	7.31±.53	19.34±3.22
Severe NPDR	206.61±35.82	262.94±42.38	7.9±.89	17.76±4.93
Very severe NPDR	247.5 ± .49	371.764±340.0	8.97±1.136	17.33±5.55
PDR	308.4 ±32.1	407.1± 50.25	9.04±1.12	15.33 ±4.4
p-value	0.02	0.01	0.02	0.00

Severity of diabetic retinopathy (DR) increased, fasting blood sugar, post-prandial blood sugar, and HbA1C levels also rose, while serum vitamin D levels decreased. For example, PDR had the highest fasting blood sugar (308.4 ± 32.1 mg/dl), post-prandial blood sugar (407.1 ± 50.25 mg/dl), and HbA1C (9.04 ± 1.12%), but the lowest serum vitamin D levels (15.33 ± 4.4 ng/ml). These differences were statistically significant, indicating a link between more severe DR and poorer glycemic control and lower vitamin D levels.(Table 2)

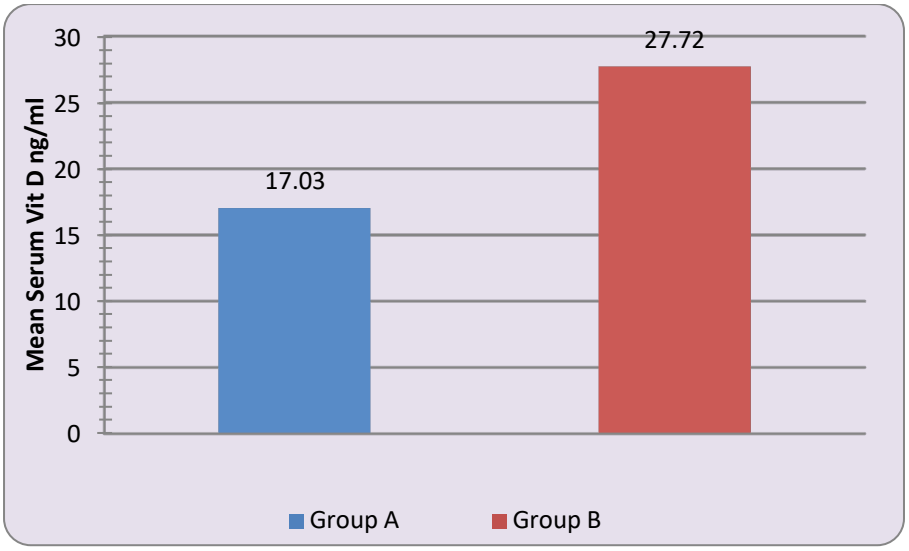

Figure 1: Comparison of Serum Vitamin-D levels in cases (Group A) and Controls (Group B)

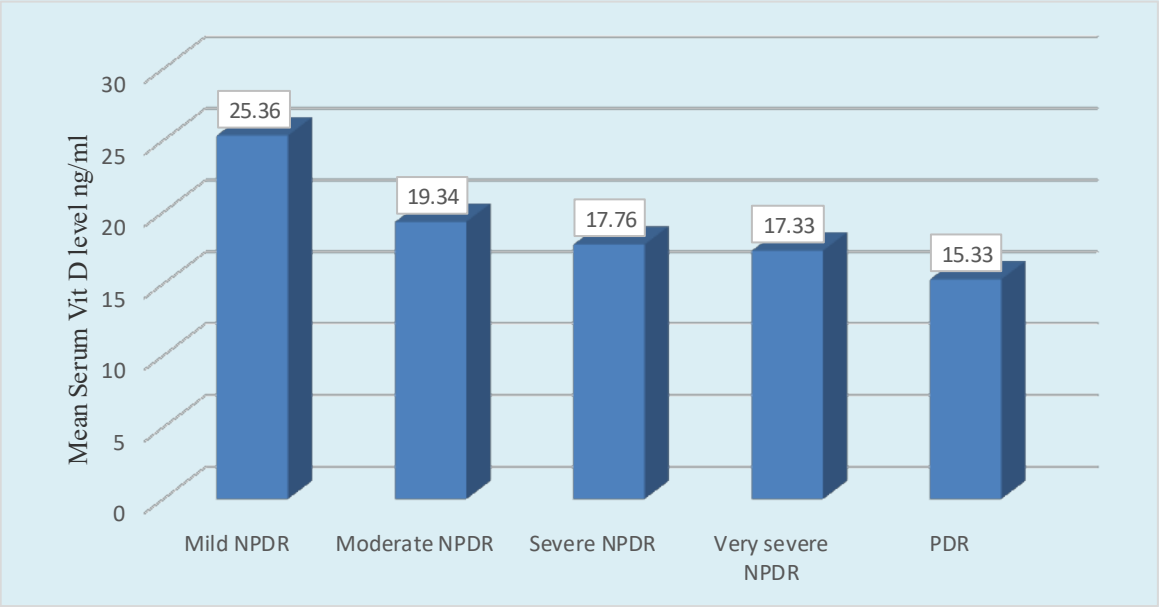

Figure 2: Distribution of Serum Vitamin D levels according to Severity Grading of DR

Discussion

Individuals having a diagnosis of diabetic retinopathy made up Group A in our study, while diabetic individuals without the condition who were matched for age and gender made up Group B. We found that the two groups' demographics differed significantly. With a statistically significant difference (p=0.02), the mean age of Group A (case group) was 64.6 years, marginally older than the mean age of Group B (control group), which was 61.96 years. Although there were more elderly patients in Group A, most of the patients in both groups were between the ages of 61 and 70. Additionally, patients in Group A experienced diabetes for a longer period of time and with an earlier start than those in Group B; this difference was statistically significant ($p<0.05$). A higher proportion of people in the case group had had diabetes for more than 20 years, indicating that having diabetes for a longer period of time is a major risk factor for developing diabetic retinopathy.

With 64 men and 36 women in Group A and 58 men and 42 women in Group B, the gender distribution was comparable in both groups. These results suggest a clear correlation between an elevated incidence of diabetic retinopathy and both advanced age and long-term diabetes.

Additionally, our results align with previous studies which also emphasized the importance of early age onset and long disease duration as significant risk factors for diabetic retinopathy. [9,10]

The mean serum vitamin D level in patients with diabetic retinopathy is 17.03 ng/mL, with a standard deviation of 5.11 ng/mL. On the other hand, the mean serum vitamin D level in patients without diabetic retinopathy is 27.72 ng/mL, with a standard deviation of 3.81 ng/mL. According to earlier research, individuals with type 2 diabetes who have lower serum vitamin D levels are far more likely to develop diabetic retinopathy. Similarly, studies have found that people with diabetic retinopathy frequently have vitamin D insufficiency, and that the severity of the illness is correlated with lower vitamin D levels. [11,12]

In the case group, males with diabetic retinopathy had a mean serum vitamin D level of 17.46 ng/mL (SD 4.9), and females had 16.26 ng/mL (SD 5.4). In contrast, the control group without retinopathy showed higher levels, with males at 27.61 ng/mL (SD 3.7) and females at 27.87 ng/mL (SD 3.9 indicating statistical significant difference. Researchers also found that found that vitamin D deficiency is more prevalent among individuals with diabetic retinopathy, and this deficiency is significant in both males and females. [13]

Our study also highlighted that lower vitamin D levels are correlated with more severe forms of DR. For mild non-proliferative diabetic retinopathy (NPDR), the mean serum vitamin D level is 25.36 ng/mL (SD: 2.41 ng/mL). Patients with moderate NPDR have a mean serum vitamin D level of 19.34 ng/mL (SD: 3.22 ng/mL). Those with severe NPDR show an even lower mean level of 17.76 ng/mL (SD: 4.93 ng/mL). Patients with very severe NPDR have a mean serum vitamin D level of 17.33 ng/mL (SD: 5.55 ng/mL), while those with proliferative diabetic retinopathy (PDR) have the lowest mean level of 15.33 ng/mL (SD: 4.4 ng/mL). The p-value of <0.05 indicates a statistically significant difference in serum vitamin D levels among the different grades of diabetic retinopathy, suggesting that lower serum vitamin D levels are associated with more severe forms of DR and it shows that serum vitamin D levels have an inverse relationship with severity grading of Diabetic Retinopathy. Studies have demonstrated a significant association between low vitamin D levels and the severity of diabetic retinopathy, suggesting that vitamin D deficiency may be a risk factor for its progression. Research also indicates that patients with lower serum vitamin D levels are more likely to have severe diabetic retinopathy, proposing a potential protective role of vitamin D in maintaining retinal vasculature health. [12,14]

Studies have demonstrated an inverse relationship between serum vitamin D levels and the severity of diabetic retinopathy (DR). Patients with proliferative diabetic retinopathy (PDR) tend to have the lowest serum vitamin D levels, suggesting that retinal neovascularization may contribute to this deficiency. Research comparing diabetic patients to non-diabetics found significantly lower vitamin D levels in diabetics, with the lowest levels observed in those with PDR. These findings indicate that measuring serum vitamin D levels may help predict the severity of DR.

Further studies in various populations, including those in Japan, Lebanon, and China, support this association. For instance, patients with sight-threatening retinopathy often have serum vitamin D levels below 15.57 ng/mL, and this deficiency is linked to a two-fold increase in the risk of severe retinopathy. Observations also reveal that vitamin D deficiency is prevalent among diabetics with microvascular complications and is associated with factors like HbA1c, age, and serum albumin levels. Additionally, vitamin D deficiency may contribute to retinal nerve fiber layer (RNFL) thinning, suggesting a neuroprotective role for vitamin D in the early stages of DR, which feature both vascular changes and neuro degeneration. [8,15,14,12,16,17]

Conclusion

Our study demonstrated that diabetic patients with diabetic retinopathy (Group A) had significantly lower serum vitamin D levels compared to those without diabetic retinopathy (Group B) (17.03±5.11 ng/mL vs. 27.72±3.81 ng/mL, $p < 0.001$). An inverse relationship between serum vitamin D levels and the severity of diabetic retinopathy was observed, with lower vitamin D levels associated with higher retinopathy grades. These findings suggest that serum vitamin D levels could serve as a predictor of diabetic retinopathy severity. Despite advancements in glycemic control, blood pressure management, and lipid stabilization, many individuals worldwide continue to develop sight-threatening diabetic retinopathy, leading to significant visual impairment. Further research is needed to evaluate whether vitamin D supplementation could play a role in the prevention or treatment of diabetic retinopathy.

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