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Original Article

Association Between Serum Vitamin B12 Levels and Glycated Hemoglobin in Diabetic Retinopathy: A Cross-Sectional Study in Type 2 Diabetes Mellitus

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ABSTRACT

Diabetic retinopathy (DR) is a leading cause of preventable blindness and a significant microvascular complication of type 2 diabetes mellitus (T2DM). Emerging evidence suggests that micronutrient deficiencies, particularly vitamin B12 deficiency, may contribute to poor glycemic control and microvascular damage. This hospital-based cross-sectional study was conducted to evaluate the association between serum vitamin B12 levels and glycated hemoglobin (HbA1c) in patients with diabetic retinopathy. A total of 100 patients with T2DM and diagnosed DR were included, while those on metformin therapy and vitamin B12 supplementation were excluded to minimize confounding. Patients underwent detailed clinical evaluation, fundus examination, and laboratory assessment, including serum vitamin B12 and HbA1c levels. Mild non-proliferative diabetic retinopathy (NPDR) was the most common presentation (40%), followed by proliferative diabetic retinopathy (26%). Mean HbA1c levels increased significantly with the severity of retinopathy, from 8.64% in mild NPDR to 9.93% in proliferative diabetic retinopathy (p=0.041), indicating worsening glycemic control. Serum vitamin B12 levels showed a declining trend with increasing severity, ranging from 343.68 pg/ml in mild NPDR to 230.08 pg/ml in proliferative diabetic retinopathy, although categorical analysis was not statistically significant. The study demonstrates that poor glycemic control and lower vitamin B12 levels are associated with increased severity of diabetic retinopathy, suggesting a potential role of vitamin B12 as a modifiable risk factor.

Keywords*: Diabetic retinopathy, Vitamin B12 deficiency, Glycated hemoglobin (HbA1c), Type 2 diabetes mellitus, Microvascular complications.*

INTRODUCTION

Diabetes mellitus, particularly type 2 diabetes mellitus (T2DM), is a major global health challenge and a leading cause of preventable blindness due to its microvascular complications, notably diabetic retinopathy (DR) (1,2). DR is characterized by progressive retinal microvascular damage, including capillary leakage, ischemia, and neovascularization, which may ultimately lead to visual impairment if untreated (2,11).

The pathogenesis of DR is complex and multifactorial. Chronic hyperglycemia plays a central role by activating biochemical pathways such as the formation of advanced glycation end products (AGEs), oxidative stress, and protein kinase C activation (3). These mechanisms result in endothelial dysfunction, pericyte loss, and breakdown of the blood-

retinal barrier. Glycated hemoglobin (HbA1c) is a well-established marker of long-term glycemic control and is strongly associated with the development and progression of diabetic retinopathy (4,5).

However, variability in disease progression despite similar glycemic control suggests the involvement of additional contributing factors. Vitamin B12 (cobalamin), an essential micronutrient involved in DNA synthesis and homocysteine metabolism, has emerged as a potential factor (6). Vitamin B12 deficiency leads to hyperhomocysteinemia, which can cause endothelial dysfunction, oxidative stress, and impaired microcirculation, thereby potentially accelerating retinal damage (7,12).

Vitamin B12 deficiency is relatively common in patients with T2DM, especially in those with long disease duration and vegetarian dietary habits (8). Additionally, long-term metformin therapy is known to reduce vitamin B12 levels (9). Therefore, the present study was undertaken to evaluate the association between serum vitamin B12 levels and glycated hemoglobin (HbA1c), and their relationship with the severity of diabetic retinopathy.

MATERIALS AND METHODS

This hospital-based cross-sectional observational study was conducted at a tertiary care center over a period extending from April 2024 to September 2025. A total of 100 patients diagnosed with type 2 diabetes mellitus (T2DM) and concomitant diabetic retinopathy were enrolled in the study. Patients receiving metformin therapy, those on vitamin B12 supplementation, and individuals with chronic systemic illnesses known to affect vitamin B12 levels were excluded to minimize potential confounding factors.

All participants underwent a detailed clinical evaluation, including comprehensive history taking and ophthalmic examination. Fundus examination was performed in all cases, and diabetic retinopathy was classified according to standard clinical criteria (1). Laboratory investigations included measurement of glycated hemoglobin (HbA1c), serum vitamin B12 levels, fasting plasma glucose (FPG), and oral glucose tolerance test (OGTT), which were carried out using standardized methods.

Statistical analysis was performed using appropriate analytical tools. Categorical variables were analyzed using the chi-square test, while continuous variables were compared using one-way analysis of variance (ANOVA). Multivariate logistic regression analysis was employed to identify independent predictors of severe diabetic retinopathy. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 100 patients with type 2 diabetes mellitus and diabetic retinopathy were analyzed. The distribution of retinopathy severity revealed that non-proliferative diabetic retinopathy (NPDR) constituted the majority (74%), while proliferative diabetic retinopathy (PDR) accounted for 26%. Among NPDR cases, mild NPDR was the most prevalent subtype (40%), followed by moderate (19%) and severe NPDR (15%).

A statistically significant progressive increase was observed in age, duration of diabetes, and HbA1c levels with increasing severity of diabetic retinopathy. Conversely, serum vitamin B12 levels demonstrated a declining trend across severity stages.

Table 1: Comprehensive Clinical and Biochemical Profile According to Severity of Diabetic Retinopathy

Variable	Mild NPDR	Moderate NPDR	Severe NPDR	PDR	p-value
Age (years)	51.0 ± 10.96	53.74 ± 9.73	59.2 ± 11.27	58.77 ± 14.21	0.001
Duration (years)	7.6 ± 4.08	8.05 ± 4.96	9.33 ± 4.81	10.31 ± 6.61	0.048
HbA1c (%)	8.64 ± 1.46	9.07 ± 1.48	9.21 ± 1.31	9.93 ± 1.37	0.041
Vitamin B12 (pg/ml)	343.68 ± 173.48	308.84 ± 148.10	266.93 ± 76.74	230.08 ± 27.58	Trend
Gender (M/F)	22/18	10/9	8/7	12/14	0.030
B12 <200 (n)	4	3	3	3	0.41

This analysis shows that age, duration of diabetes, and HbA1c increase significantly with the severity of diabetic retinopathy, reflecting cumulative microvascular damage and worsening glycemic control. Serum vitamin B12 levels decline with increasing severity (though not significant categorically), and gender also shows a significant association, suggesting a possible demographic influence.

Table 2: Multivariate Logistic Regression Analysis for Severe Diabetic Retinopathy

Variable	Adjusted OR	95% CI	p-value
Age	1.04	1.01–1.08	0.012
Duration of DM	1.12	1.01–1.24	0.028

HbA1c	1.35	1.05–1.74	0.019
Vitamin B12	1.28	1.02–1.61	0.032

Multivariate analysis shows that age, duration of diabetes, and HbA1c are strong independent predictors of diabetic retinopathy severity.

Vitamin B12 also emerges as an independent modifiable risk factor, indicating its potential role in disease progression.

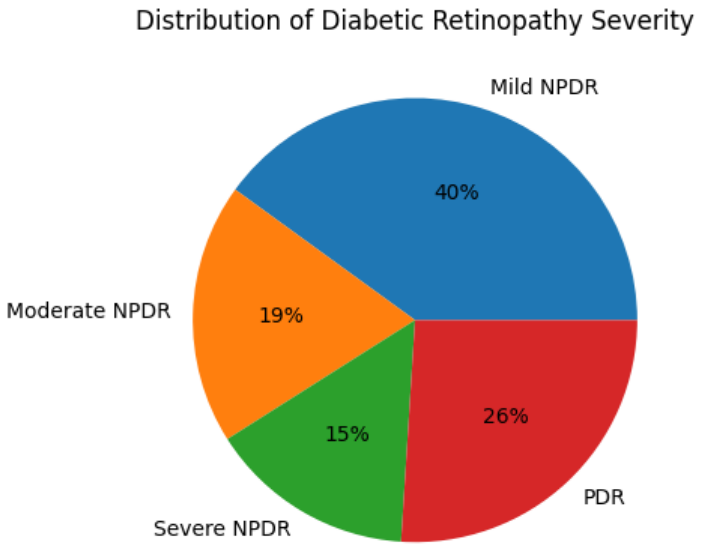

Figure 1: Pie Chart – Distribution of Diabetic Retinopathy Severity

Pie chart demonstrating the proportional distribution of diabetic retinopathy severity, with NPDR forming the majority and mild NPDR being the most common subtype.

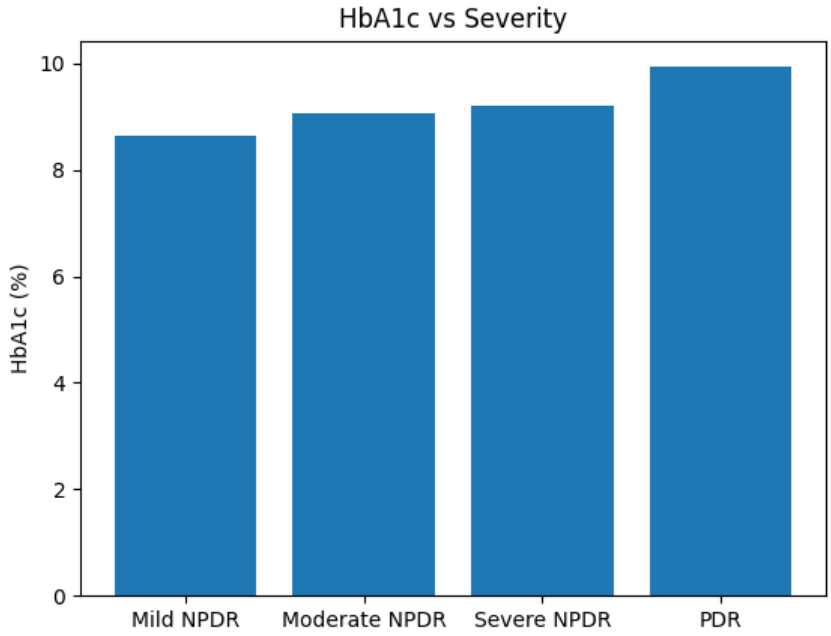

Figure 2: Bar Chart – HbA1c vs Severity of Diabetic Retinopathy

Bar diagram showing a statistically significant rise in HbA1c levels with increasing severity of diabetic retinopathy, indicating worsening glycemic control.

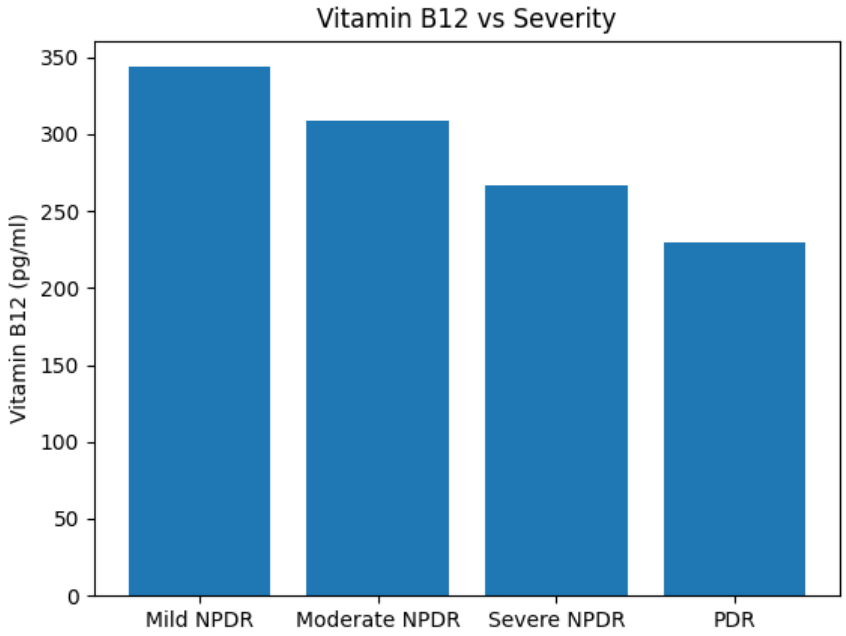

Figure 3: Bar Chart – Vitamin B12 vs Severity of Diabetic Retinopathy

Bar diagram demonstrating decreasing serum vitamin B12 levels with increasing severity of diabetic retinopathy, suggesting a potential contributory role.

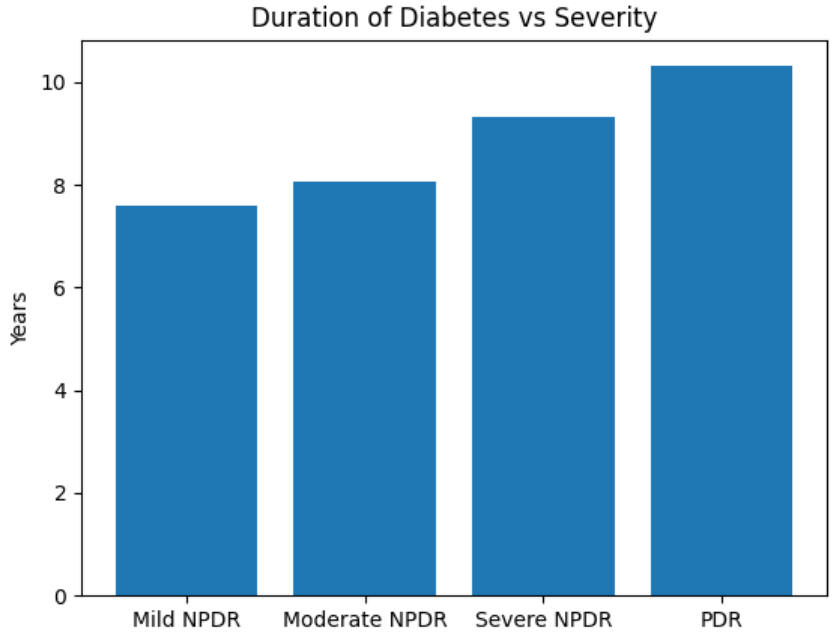

Figure 4: Bar Chart – Duration of Diabetes vs Severity

Bar chart illustrating increasing duration of diabetes with advancing severity, supporting cumulative microvascular damage.

DISCUSSION

The present study evaluated the association between serum vitamin B12 levels, glycemic control, and the severity of diabetic retinopathy (DR) in patients with type 2 diabetes mellitus. The majority of patients in this study had non-proliferative diabetic retinopathy (NPDR), with mild NPDR being the most common subtype, while a considerable

proportion had progressed to proliferative diabetic retinopathy (PDR). This distribution aligns with previously reported epidemiological patterns (10,11) and reflects delayed detection and suboptimal glycemic control in many patients. Furthermore, increasing age and longer duration of diabetes were significantly associated with greater severity of DR, reinforcing the concept of cumulative microvascular damage over time.

Glycemic control, as assessed by glycated hemoglobin (HbA1c), demonstrated a statistically significant positive correlation with the severity of diabetic retinopathy. Patients with more advanced stages of DR exhibited higher HbA1c levels, consistent with findings from landmark studies such as the UK Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT), which established hyperglycemia as a key driver of microvascular complications (4,5). These findings underscore the critical importance of strict glycemic control in preventing the progression of diabetic retinopathy and reducing the burden of visual morbidity.

A notable finding of this study was the inverse relationship between serum vitamin B12 levels and the severity of diabetic retinopathy. Although categorical analysis did not reach statistical significance, a clear declining trend in vitamin B12 levels was observed with increasing severity of DR. This may be explained by the role of vitamin B12 in homocysteine metabolism, where deficiency leads to hyperhomocysteinemia, resulting in endothelial dysfunction, oxidative stress, and impaired retinal microcirculation (6,7,12). Multivariate analysis further identified vitamin B12 as an independent predictor of severe DR, suggesting its potential role as a modifiable risk factor. These findings highlight the need for routine assessment of vitamin B12 levels in patients with diabetes and warrant further large-scale prospective studies to establish causality and explore therapeutic implications.

CONCLUSION

The present study demonstrates that poor glycemic control and lower serum vitamin B12 levels are associated with increased severity of diabetic retinopathy in patients with type 2 diabetes mellitus. While HbA1c remains a key predictor, vitamin B12 deficiency may also contribute to retinal microvascular damage.

Routine assessment of vitamin B12 levels, particularly in high-risk populations, may aid in early identification and management. Further large-scale prospective studies are required to establish causality and evaluate the therapeutic role of vitamin B12 supplementation.

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