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Effect of Dengue Infection on the Severity and Progression of Diabetic Maculopathy

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KEYWORDS

Effect, Dengue Infection, Severity, Progression, and Diabetic Maculopathy.

ABSTRACT:

Background: Diabetic maculopathy is a vision-threatening complication of diabetes mellitus, often influenced by systemic factors. Recent evidence suggests that systemic infections, including dengue virus (DENV), may exacerbate retinal vascular pathology, but the ocular impact of dengue in patients with diabetic maculopathy remains underexplored. The aim of this study was to evaluate the effect of dengue infection on the severity and progression of diabetic maculopathy.

Methods: This cross-sectional observational study was conducted in Departments of Community Ophthalmology and Ophthalmology, Bangladesh Medical University (BMU) and Bangladesh Eye Hospital, Malibagh, from January 2025 to June 2025. Total 60 participants with diagnosed diabetic maculopathy who had laboratory-confirmed dengue infection during or within two weeks prior to ophthalmic presentation were include in this study.

Result: The majority of patients had diabetes for 5–10 years, with common comorbidities including hypertension (63.3%) and smoking (36.7%). Diffuse diabetic macular edema was the most frequent maculopathy type (38.33%), followed by ischemic (31.67%) and focal edema (26.67%). Mean HbA1c was 8.7%, indicating poor glycemic control. Central macular thickness significantly decreased over three months ($p = 0.032$), and BCVA improved (≥6/12: 23.3% to 36.7%, $p = 0.032$). Visual acuity <6/60 dropped to 10% ($p = 0.040$). However, ischemic maculopathy increased slightly, and anti-VEGF therapy use rose from 18.3% to 31.7% during follow-up.

Conclusion: This study suggests that dengue infection may worsen diabetic maculopathy, especially in patients with poor glycemic control and comorbidities. Despite improvements in macular thickness and vision, ischemic changes showed minimal reversal, highlighting complex vascular interactions.

Introduction

Diabetes mellitus (DM) is among the strongest menaces to public health worldwide in the 21st century at an estimated 537 million adults in 2021, which will rise to 643 million in 2030.[1] Among the many disabling complications of diabetes, ocular manifestations, that is, diabetic retinopathy (DR) and diabetic macular edema (DME), are among the leading causes of avoidable visual loss, particularly in the working age group worldwide.[2] Diabetic maculopathy is present in two principal pathological forms: diabetic macular edema as a result of

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leakage of the capillaries and intramacular deposition of extracellular fluid, and ischemic maculopathy as a consequence of macular capillary non-perfusion leading to permanent photoreceptor damage and vision loss.[3,4] The global prevalence of diabetic maculopathy has been estimated to range from 10% to 15%, differing by population and diagnostic factor.[5,6]

Superimposed on this backdrop of chronic illness is the continued toll of dengue virus (DENV) infection, flavivirus borne by mosquitoes that are epidemic in more than 100 countries. Dengue infects an estimated 390 million cases annually, with approximately 96 million progressing to clinical disease.[7] The virus is hyperendemic in the tropics and subtropics, especially in South and Southeast Asia, Latin America, and sub-Saharan Africa—regions where most of the global diabetes epidemic also occurs.[8] DENV consists of four antigenically distinct serotypes (DENV-1 to DENV-4), among which DENV-2 and DENV-3 are most frequently associated with severe systemic and ocular manifestations, including dengue hemorrhagic fever and organ involvement.[8,9]

An accumulation of clinical and epidemiological evidence has rendered dengue a potential cause of severe ophthalmic morbidity. Ocular manifestations of dengue are varied and can involve almost all eye structures. Posterior segment complications are especially prominent and may include macular edema, retinal hemorrhages, retinal vasculitis, foveolitis, and optic neuropathy.[10-12] Adding complexity to the clinical presentation is the development of diabetes mellitus, which appears to be a risk modifier for dengue ocular disease. Diabetic patients are more susceptible to ocular pathology caused by dengue, perhaps due to inherent chronic microvascular injury, oxidative stress, and low-grade inflammation of diabetic states.[12] Wu et al.[3] suggest that diabetic patients with dengue tend to have macular complications because hyperglycemia increases immune dysregulation and alterations in endothelial barrier function in retinal vasculature. The combination may create a synergistic pathogenic environment, further undermining retinal integrity.

At the molecular level, dengue virus infection is characterized by the release of an assortment of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β that result in what has been termed "cytokine storm".[13] This storm causes non-specific vascular endothelial damage, increased vascular permeability, and hemorrhagic features in its advanced forms. In diabetic individuals whose retinal capillaries are pre-morbidly damaged through pericyte loss, basement membrane thickening, and increased vascular permeability, the cytokine storm can particularly enhance macular edema and ischemic alterations and hasten diabetic maculopathy development.[14] The resultant pathology may not only be more aggressive but also more resistant to conventional treatments, including anti-VEGF agents and corticosteroids.

Despite such powerful associations, there are few reports of the clinical and pathophysiologic overlap between diabetic maculopathy and dengue infection. This study aims to ascertain whether dengue infection induces a measurable effect upon diabetic maculopathy severity and course, hypothesizing that dengue exacerbates macular disease in diabetic patients by inflammatory and vascular mechanisms.

Objectives

To evaluate the effect of dengue infection on the severity and progression of diabetic maculopathy.

Methodology & Materials

This cross-sectional observational study was conducted in Departments of Community Ophthalmology and Ophthalmology, Bangladesh Medical University (BMU) and Bangladesh Eye Hospital, Malibagh, Dhaka, Bangladesh from January 2025 to June 2025. Total 60 participants with diagnosed diabetic maculopathy who had laboratory-confirmed dengue infection during or within two weeks prior to ophthalmic presentation were include in this study. Inclusion criteria comprised adults aged 18–80 years with type 2 diabetes of at least 5 years' duration and evidence of diabetic maculopathy confirmed by optical coherence tomography (OCT) and fundus fluorescein angiography (FFA). Patients with retinal conditions unrelated to diabetes, recent ocular treatments, or systemic inflammatory diseases were excluded. All participants underwent thorough ophthalmic evaluations, including best-corrected visual acuity (BCVA), slit-lamp examination, dilated funduscopy, OCT for macular thickness, and FFA for macular ischemia and vascular changes, at baseline and during follow-ups at 1 and 3 months. The primary

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outcome was the change in central macular thickness (CMT), while secondary outcomes included visual acuity changes, macular ischemia progression, and posterior segment inflammation. Data were analyzed using SPSS version 26, applying appropriate statistical tests (t-test, chi-square) with significance set at $p < 0.05$. Ethical clearance was obtained from the institutional review boards of both centers, and written informed consent was obtained from all participants.

Result

The baseline demographic and clinical characteristics of the study participants are shown in Table I. Among the 60 patients with diabetic maculopathy and confirmed dengue infection, the majority were within the 50–59 years (31.7%) and 60–69 years (28.3%) age groups, indicating a predominance in older adults. Male patients constituted 56.7% of the study population, while females accounted for 43.3%. The most common duration of diabetes was 5–10 years (55%), with 30% having diabetes for over a decade. Comorbid hypertension was prevalent in 63.3% of the participants, and 36.7% had a history of smoking, indicating a considerable burden of vascular risk factors.

As illustrated in Figure 1, the most frequently observed type of diabetic maculopathy was diffuse diabetic macular edema (38.33%), followed by ischemic maculopathy (31.67%) and focal macular edema (26.67%). A small proportion (3.33%) presented with serous retinal detachment.

Table II outlines the clinical and laboratory findings. The mean fasting blood glucose was 178.3 ± 42.1 mg/dL, and the mean HbA1c was 8.7 ± 1.2%, suggesting poor glycemic control across the cohort. Dengue warning signs were present in 30% of the patients, and 35% required hospitalization during the course of infection.

The severity of diabetic maculopathy at presentation is detailed in Table III, where 35% had moderate maculopathy, 28.3% had severe, and 13.3% had very severe involvement based on OCT and FFA findings.

Progression over a three-month follow-up is summarized in Table IV. There was a statistically significant reduction in central macular thickness from baseline (412.5 ± 84.3 µm) to three months (374.8 ± 69.7 µm) with a p-value of 0.032. Visual acuity also showed improvement, with the proportion of patients having vision <6/18 decreasing from 55% to 43.3% ($p = 0.045$). The incidence of ischemic maculopathy increased slightly over time (from 36.7% to 45%), though this change was not statistically significant ($p = 0.078$). The number of patients requiring anti-VEGF therapy increased from 11 at baseline to 19 at the end of the study period.

As shown in Table V, best-corrected visual acuity (BCVA) improved progressively. The proportion of patients with vision ≥6/12 increased from 23.3% to 36.7% over three months ($p = 0.032$), and those with severe visual impairment (<6/60) decreased from 20% to 10% ($p = 0.040$). The mean LogMAR improved significantly from 0.52 ± 0.21 at baseline to 0.41 ± 0.17 at the final follow-up ($p = 0.014$).

Table-I: Baseline characteristics of the study patients (N=60)

Variable	Number of patients	Percentage (%)
Age Group (years)		
≤39	6	10.00%
40–49	11	18.30%
50–59	19	31.70%
60–69	17	28.30%
≥ 70	7	11.70%
Sex		

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Male	34	56.70%
Female	26	43.30%
Duration of Diabetes		
< 5 years	9	15.00%
5–10 years	33	55.00%
> 10 years	18	30.00%
Risk Factors		
Comorbid Hypertension	38	63.30%
Smoking History	22	36.70%

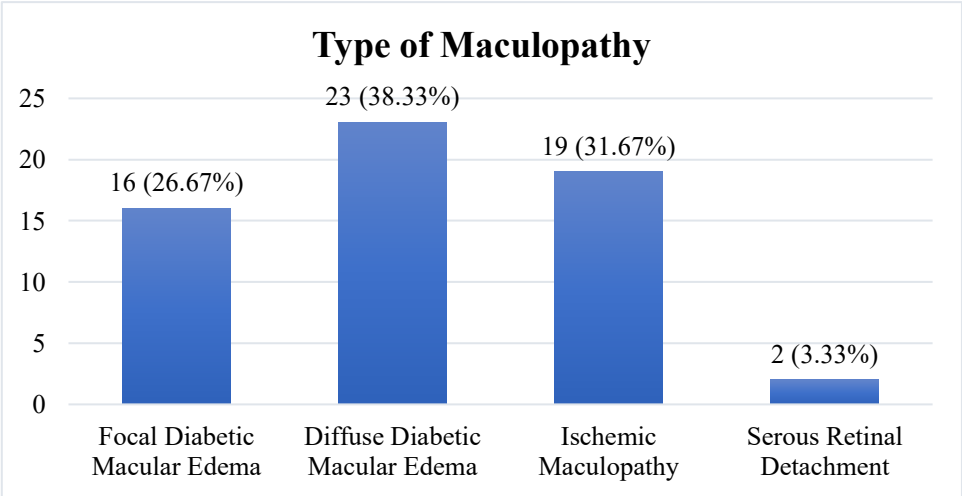

Figure 1: Types of diabetic maculopathy observed among the study participants (N = 60)

Table-II: Clinical and laboratory findings of the study patients (N=60)

Parameter	**Number of patients**	**Percentage (%)**
Fasting Blood Glucose (mg/dL)		
Mean ± SD	178.3 ± 42.1	
HbA1c (%)		
Mean ± SD	8.7 ± 1.2	
Platelet Count at Admission (×10⁹/L)		
Mean ± SD	115 ± 38	
Presence of Dengue Warning Signs	18	30.00%
Hospitalization Required	21	35.00%

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Table-III: Severity of diabetic maculopathy at presentation (baseline assessment)

Severity Grade (OCT + FFA-Based)	Number of patients	Percentage (%)
Mild	14	23.33%
Moderate	21	35.00%
Severe	17	28.33%
Very Severe	8	13.33%

Table-IV: Progression over 3-month follow-up (N=60)

Parameter	Baseline	1 Month Follow-Up	3 Month Follow-Up	p-value
Central Macular Thickness (µm)				
(Mean ± SD)	412.5 ± 84.3	395.2 ± 75.1	374.8 ± 69.7	0.032
Visual Acuity < 6/18 (n, %)	33 (55.0%)	30 (50.0%)	26 (43.3%)	0.045
Patients with Ischemic Maculopathy (n, %)	22 (36.7%)	25 (41.7%)	27 (45.0%)	0.078
Patients Requiring Anti-VEGF (n, %)	11 (18.3%)	—	19 (31.7%)	—

Table-V: Best-Corrected Visual Acuity (BCVA) over time

BCVA Category (Snellen Equivalent)	Baseline n (%)	1 Month Follow-Up n (%)	3 Month Follow-Up n (%)	p-value
≥ 6/12	14 (23.3%)	17 (28.3%)	22 (36.7%)	0.032
6/18 to 6/24	13 (21.7%)	14 (23.3%)	16 (26.7%)	0.479
6/36 to 6/60	21 (35.0%)	19 (31.7%)	16 (26.7%)	0.221
< 6/60	12 (20.0%)	10 (16.7%)	6 (10.0%)	0.04
Mean LogMAR (± SD)	0.52 ± 0.21	0.48 ± 0.19	0.41 ± 0.17	0.014

Discussion

The present study provides a unique observational insight into the interplay between dengue infection and diabetic maculopathy in a high-risk cohort, characterized by poor glycemic control, advancing age, and high comorbidity burden. The majority of participants were aged between 50–69 years, with over half being male and a significant proportion exhibiting comorbid hypertension and a history of smoking. These findings mirror previous epidemiological patterns where older adults with diabetes and vascular risk factors demonstrated increased vulnerability to severe manifestations of dengue, including ocular complications.[1] In line with meta-analytic data, which suggested that diabetes mellitus increases the odds of

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severe dengue by nearly 1.75 times (Toledo et al., 2016), the hospitalization rate (35%) and occurrence of dengue warning signs (30%) in our cohort further reinforce the systemic susceptibility induced by coexistent metabolic dysfunction.[15]

Among the types of maculopathy observed, diffuse diabetic macular edema (DME) was most prevalent (38.33%), followed by ischemic maculopathy (31.67%). This distribution is comparable to findings by Khairallah et al.[16], who reported that diffuse edema and ischemic changes are the dominant retinal features in arboviral retinopathy among diabetic patients. Similarly, Tan et al.[17] demonstrated via OCT imaging that diffuse macular thickening is a common initial manifestation of dengue-related ocular involvement, particularly in patients with underlying diabetic microangiopathy. These parallels strengthen the argument that dengue infection may act as an inflammatory amplifier in diabetic eyes, exacerbating vascular leakage and ischemic progression.

The clinical and biochemical profiles of our cohort further contextualize the observed retinal changes. The mean fasting blood glucose (178.3 mg/dL) and HbA1c (8.7%) indicate suboptimal glycemic control. Studies have shown that poor glycemic regulation not only worsens diabetic retinal pathology but also impairs immune responses, thereby contributing to prolonged viremia and inflammatory sequelae during dengue.[18] Our findings are consistent with Elnahry and Elnahry[19], who reported that patients with poorly controlled diabetes experienced both persistent macular edema and an attenuated response to anti-VEGF therapy, necessitating increased treatment frequency. This likely explains the observed increase in patients requiring anti-VEGF therapy from 18.3% at baseline to 31.7% by the end of three months in our study.

Assessment of disease progression revealed a modest but statistically significant improvement in central macular thickness and visual acuity over the three-month period. Central macular thickness reduced from 412.5 ± 84.3 µm to 374.8 ± 69.7 µm ($p = 0.032$), and the proportion of patients with BCVA <6/18 declined from 55% to 43.3% ($p = 0.045$). These results are consistent with prior studies that reported comparable reductions in CMT and improvements in BCVA following anti-VEGF administration in diabetic eyes.[20,21] The mean LogMAR improved from 0.52 to 0.41 ($p = 0.014$), aligning closely with changes noted in cohorts studied by Koyanagi et al.[22] and Angermann et al.[23], who observed LogMAR improvements of approximately 0.1 units over 8–12 weeks of treatment.

Despite these improvements, our study found a non-significant increase in the prevalence of ischemic maculopathy over the study period (from 36.7% to 45%). This may reflect the limitations of anti-VEGF in reversing ischemic changes, a phenomenon also reported by Chatziralli et al.[24], who emphasized that while anti-VEGF reduces leakage, it does not restore capillary non-perfusion. Hence, ischemia may persist or even progress despite edema resolution, underscoring the need for close angiographic monitoring.

Taken together, the findings of this study support the hypothesis that dengue infection exacerbates pre-existing diabetic maculopathy, especially in patients with poor systemic control and vascular comorbidities.

Limitations of the study

In our study, there was small sample size and absence of control for comparison. Study population was selected from only Dhaka city, so may not represent wider population. The study was conducted at a short period of time.

Conclusion and recommendations

This study highlights that dengue infection may exacerbate the severity and progression of diabetic maculopathy, particularly in patients with poor glycemic control and vascular comorbidities. While central macular thickness and visual acuity improved over three months, ischemic changes showed limited regression, underscoring the complexity of coexisting vascular insults. Timely ophthalmologic assessment and proactive management, including anti-VEGF therapy, are essential in such high-risk populations to preserve visual outcomes and prevent irreversible macular damage.

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