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Association between diabetic retinopathy severity and cognitive decline in elderly patients with type 2 Diabetes

Dr. Rajesh Kumar
Department of Neurology National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, Karnataka, India

Abstract
Background: The global aging population has led to a concurrent rise in age-related diseases, including type 2 diabetes mellitus (T2DM), diabetic retinopathy (DR), and cognitive decline. Emerging evidence suggests a potential microvascular link between DR and cognitive impairment, as both conditions share underlying pathophysiological mechanisms such as endothelial dysfunction and chronic inflammation.
Objective: This study aimed to investigate the cross-sectional association between the severity of diabetic retinopathy and cognitive function in elderly patients with T2DM.
Method: A simulated cross-sectional study was conducted using synthesized academic training data of 350 elderly patients (aged ≥65 years) with T2DM. Cognitive function was assessed using the Mini-Mental State Examination (MMSE). DR severity was graded via fundus photography according to the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria. Multivariate logistic regression was used to adjust for potential confounders.
Results: The prevalence of cognitive impairment (MMSE < 24) was 24.3%. A significant inverse correlation was observed between DR severity and MMSE scores ($r = -0.41$, $p < 0.001$). Compared to patients without DR, those with moderate-to-severe non-proliferative DR or proliferative DR had a significantly higher odds of cognitive impairment (Adjusted Odds Ratio [aOR] = 3.45, 95% Confidence Interval [CI] = 1.82–6.54, $p < 0.001$).
Conclusion: In this simulated dataset, increased severity of diabetic retinopathy was independently associated with cognitive decline in elderly T2DM patients. These findings suggest that DR may serve as a potential clinical biomarker for early cognitive screening in this vulnerable population.

Keywords: Diabetic retinopathy, cognitive decline, type 2 diabetes mellitus, microvascular complications

Introduction

The demographic shift toward an older population has precipitated an unprecedented increase in the prevalence of chronic metabolic disorders, with type 2 diabetes mellitus (T2DM) representing one of the most pressing global health challenges. Among the elderly, T2DM is not merely a disease of glycemic dysregulation but a systemic condition that profoundly accelerates aging and promotes multi-organ complications. Two of the most debilitating sequelae in the aging diabetic population are diabetic retinopathy (DR) and cognitive decline, both of which severely impair functional independence, quality of life, and survival rates1.

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Diabetic retinopathy remains the leading cause of preventable blindness in working-age and elderly populations globally. Its pathogenesis is deeply rooted in chronic hyperglycemia-induced microvascular damage, characterized by pericyte loss, basement membrane thickening, endothelial dysfunction, and eventual retinal ischemia2. Concurrently, cognitive decline and dementia in T2DM patients have emerged as critical non-vascular complications. Patients with T2DM exhibit a roughly two-fold increased risk of developing Alzheimer's disease and vascular dementia compared to their non-diabetic peers3. While traditionally viewed as distinct clinical entities affecting separate organ systems, recent pathophysiological insights suggest that DR and cognitive impairment may represent different manifestations of the same underlying systemic microangiopathy4.

The concept of the eye serving as a "window to the brain" has garnered significant academic attention. The retina and the cerebral microvasculature share embryological origins, anatomical similarities, and physiological properties, including a blood-organ barrier and strict autoregulation5. Therefore, the microvascular pathologies observed in the retina such as capillary non-perfusion, microaneurysms, and hemorrhages may parallel subclinical microvascular changes occurring within the cerebral white matter and gray matter. This "common soil" hypothesis posits that systemic inflammation, oxidative stress, and advanced glycation end-products simultaneously degrade the microcirculation of both the retina and the brain6.

Despite the theoretical plausibility of this association, the clinical epidemiology linking DR to cognitive decline remains complex and is characterized by inconsistent findings. Some studies have demonstrated a robust, independent association between DR and reduced cognitive performance, while others suggest that this relationship is entirely mediated by shared macrovascular risk factors such as hypertension, dyslipidemia, and duration of diabetes. Furthermore, the majority of existing literature fails to adequately stratify patients by the specific severity of DR, often relying on a binary presence or absence of DR rather than utilizing standardized grading scales.

Additionally, the elderly diabetic population is uniquely vulnerable due to age-related cognitive changes, polypharmacy, and cumulative metabolic burden, yet they are frequently underrepresented in highly controlled clinical studies9. Understanding whether the anatomical severity of DR can predict cognitive impairment in the elderly has profound clinical implications. If a strong association exists, routine ophthalmologic screening could be leveraged as an opportunistic, non-invasive tool to identify elderly diabetic patients at high risk for cognitive decline, prompting early neurological referral and intervention10. Therefore, this study aimed to systematically evaluate the cross-sectional association between the severity of diabetic retinopathy, graded by ETDRS criteria, and cognitive function, measured by the Mini-Mental State Examination (MMSE), in a simulated cohort of elderly patients with T2DM.

Literature Review The theoretical framework connecting microvascular retinal diseases to cerebral cognitive decline is anchored in the concept of systemic microangiopathy. In T2DM, chronic hyperglycemia triggers a cascade of biochemical aberrations, including the activation of protein kinase C, the accumulation of advanced glycation end-products, and the overproduction of reactive oxygen species11. These pathways collectively induce chronic low-grade inflammation and endothelial dysfunction. In the cerebral microvasculature, endothelial dysfunction compromises the integrity of the blood-brain barrier (BBB), leading to impaired cerebral autoregulation, neuroinflammation, and eventual neuronal injury or death12. This pathology frequently manifests radiologically as white matter hyperintensities, cerebral microbleeds, and cortical atrophy, which are established precursors to vascular cognitive impairment and dementia.

Epidemiological investigations into the retinal-cognitive nexus have yielded compelling, though occasionally contradictory, evidence. Seminal work by Wong *et al*. demonstrated that retinal microvascular abnormalities, including generalized retinal arteriolar narrowing and venular widening, were independently associated with cognitive dysfunction and incident dementia in middle-aged and elderly populations14. Subsequent studies specifically focusing on diabetic cohorts found that the presence of DR was associated with worse performance on neuropsychological tests assessing processing speed, executive function, and memory15. For instance, a prospective analysis by Crosby-Nwaobi *et al*. indicated that patients with T2DM and DR exhibited a steeper rate of cognitive decline over a three-year follow-up period compared to diabetic patients without retinopathy16.

However, a distinct research gap persists regarding the dose-response relationship between the severity of DR and the degree of cognitive impairment. Many previous studies have treated DR as a dichotomous variable (present versus absent), which obscures the potential incremental risk associated with advancing retinal pathology17. The Early Treatment Diabetic Retinopathy Study (ETDRS) grading system provides a highly detailed, validated framework for categorizing DR severity, ranging from mild non-proliferative DR (NPDR) to severe NPDR and proliferative DR (PDR)18. It is biologically plausible that as DR progresses from mild ischemia to proliferative neovascularization, the corresponding cerebral microvascular damage also escalates, leading to a proportional decline in cognitive metrics. Yet, studies explicitly correlating ETDRS severity stages with standardized cognitive scores like the MMSE in the elderly are sparse.

Furthermore, the elderly population presents unique confounding variables that complicate this association. Age-related cognitive decline, co-existing neurodegenerative pathologies (such as Alzheimer's disease), and the high prevalence of sensory impairments (e.g., visual loss from DR itself, which can artificially lower cognitive test scores, thus creating a potential measurement bias19. Addressing this gap is essential to determine whether advanced retinal microvascular pathology can serve as a reliable, accessible biomarker for early cerebral microvascular degeneration in the aging diabetic population.

Methodology

Research Design

This study utilized a simulated cross-sectional research design to examine the association between diabetic retinopathy severity and cognitive function. A cross-sectional approach was selected to efficiently capture the prevalence of cognitive impairment across different spectrums of retinal disease severity at a single point in time.

Data Declaration

It is explicitly stated that this study uses simulated academic training data. No real patients, clinical trials, electronic health records, or published datasets were utilized. The data was synthetically generated using probabilistic algorithms designed to reflect realistic clinical distributions and effect sizes based on established medical literature. The findings are intended strictly for academic writing practice and methodological demonstration and should not be interpreted as actual clinical evidence.

Sampling and Sample Size

The simulated target population consisted of elderly patients aged 65 years and older with a documented diagnosis of T2DM for at least 10 years. Exclusion criteria included a history of diagnosed dementia prior to the diagnosis of diabetes, severe psychiatric disorders, active ocular conditions other than DR (such as glaucoma or age-related macular degeneration) that could independently impair vision, and significant hearing loss that would impede cognitive testing. To detect a moderate effect size (Cohen's $d = 0.35$) in MMSE scores between the severe DR and no DR groups with 80% power and an alpha of 0.05, a minimum sample size of 320 was calculated. The final synthesized dataset comprised 350 patients to account for potential incomplete simulated data points.

Data collection

Baseline demographic and clinical data were simulated, including age, sex, duration of diabetes, glycated hemoglobin (HbA1c), systolic and diastolic blood pressure, body mass index, smoking status, and history of cardiovascular disease.

Ophthalmologic data were simulated to represent bilateral fundus photography results. DR severity was graded according to the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria and categorized into four groups for analysis: (1) No DR, (2) Mild Non-Proliferative DR (NPDR), (3) Moderate-to-Severe NPDR, and (4)

Proliferative DR (PDR). Cognitive function was simulated using the Mini-Mental State Examination (MMSE), a widely validated 30-point questionnaire used to screen for cognitive impairment. A score of 24 or higher was defined as normal cognitive function, while a score below 24 was defined as cognitive impairment.

Statistical software and analysis

Statistical analyses were performed using simulated computations reflective of standard software (e.g., SPSS Version 28.0). Continuous variables were presented as means with standard deviations, and categorical variables as frequencies with percentages. Differences in baseline characteristics across the four DR severity groups were analyzed using one-way analysis of variance (ANOVA) for continuous variables and the Chi-square test for categorical variables. The primary analysis utilized Spearman's rank correlation coefficient to assess the monotonic relationship between DR severity (as an ordinal variable) and MMSE scores. Multivariate logistic regression was performed to calculate the adjusted odds ratios (aOR) and 95% confidence intervals (CI) for cognitive impairment (MMSE < 24), using the "No DR" group as the reference. The regression model was adjusted for age, education level, duration of diabetes, HbA1c, hypertension, and cardiovascular disease. A p-value of <0.05 was considered statistically significant.

Results and discussion

The baseline demographic and clinical characteristics of the 350 simulated patients, stratified by DR severity, are presented in Table 1. The mean age of the cohort was 74.2 years, and 54.3% were female. As DR severity increased, there was a statistically significant trend toward longer duration of diabetes ($p < 0.001$), higher HbA1c levels ($p = 0.002$), and a higher prevalence of hypertension ($p = 0.015$). There were no significant differences in age, sex distribution, or smoking status across the DR severity groups, confirming that these potential confounders were evenly distributed.

Table 1: Baseline Characteristics Stratified by Diabetic Retinopathy Severity

Characteristic	No DR (n=140)	Mild NPDR (n=95)	Mod/Severe NPDR (n=75)	Proliferative DR (n=40)	p-value
Age (years), mean ± SD	73.8 ± 5.4	74.1 ± 5.1	74.9 ± 5.8	74.5 ± 6.2	0.621
Female sex, n (%)	78 (55.7%)	50 (52.6%)	40 (53.3%)	22 (55.0%)	0.948
Duration of T2DM (years)	12.4 ± 3.1	15.2 ± 3.8	18.1 ± 4.2	21.5 ± 4.9	<0.001
HbA1c (%), mean ± SD	7.1 ± 0.6	7.4 ± 0.7	7.8 ± 0.9	8.2 ± 1.1	0.002
Hypertension, n (%)	95 (67.9%)	72 (75.8%)	62 (82.7%)	34 (85.0%)	0.015
Cardiovascular Disease, n (%)	32 (22.9%)	25 (26.3%)	24 (32.0%)	15 (37.5%)	0.184

SD = Standard Deviation; T2DM = Type 2 Diabetes Mellitus; NPDR = Non-Proliferative Diabetic Retinopathy; DR = Diabetic Retinopathy.

The overall prevalence of cognitive impairment (MMSE < 24) in the entire cohort was 24.3% (n=85). Table 2 details the cognitive performance across the different stages of retinopathy. The mean MMSE score demonstrated a progressive, stepwise decline as the severity of DR increased. Patients with no DR had a mean MMSE score of 27.1, which declined to 26.2 in mild NPDR, 24.1 in moderate-to-severe NPDR, and 22.4 in proliferative DR. Spearman's rank correlation analysis confirmed a significant inverse relationship between DR severity and MMSE scores ($r = -0.41$, $p < 0.001$).

Table 2: Cognitive Function (MMSE Scores) by Diabetic Retinopathy Severity

DR Severity Group	n	Mean MMSE Score ± SD	Cognitive Impairment n (%)
No DR	140	27.1 ± 2.2	14 (10.0%)
Mild NPDR	95	26.2 ± 2.5	18 (18.9%)
Moderate/Severe NPDR	75	24.1 ± 3.1	28 (37.3%)
Proliferative DR	40	22.4 ± 3.5	25 (62.5%)

MMSE = Mini-Mental State Examination; SD = Standard Deviation; NPDR = Non-Proliferative Diabetic Retinopathy; DR = Diabetic Retinopathy.

To determine the independent predictive value of DR severity on cognitive impairment, a multivariate logistic regression model was constructed (Table 3). After adjusting for age, education level, duration of diabetes, HbA1c, hypertension, and cardiovascular disease, the association between advanced DR and cognitive impairment remained robust. Compared to patients without DR, those with mild NPDR did not exhibit a statistically significant increase in the odds of cognitive impairment (Adjusted Odds Ratio [aOR] = 1.42, 95% CI: 0.68–2.96, $p = 0.351$). However, patients with moderate-to-severe NPDR had significantly higher odds (aOR = 3.45, 95% CI: 1.82–6.54, $p < 0.001$), and patients with proliferative DR had the highest odds of cognitive impairment (aOR = 5.82, 95% CI: 2.91–11.64, $p < 0.001$).

Table 3: Multivariate Logistic Regression for Cognitive Impairment (MMSE < 24)

DR Severity Group	Adjusted Odds Ratio	95% CI	p-value
No DR (Reference)	1.00	-	-
Mild NPDR	1.42	0.68 - 2.96	0.351
Moderate/Severe NPDR	3.45	1.82 - 6.54	<0.001
Proliferative DR	5.82	2.91 - 11.64	<0.001

CI = Confidence Interval; NPDR = Non-Proliferative Diabetic Retinopathy; DR = Diabetic Retinopathy. Model adjusted for age, education, diabetes duration, HbA1c, hypertension, and cardiovascular disease.

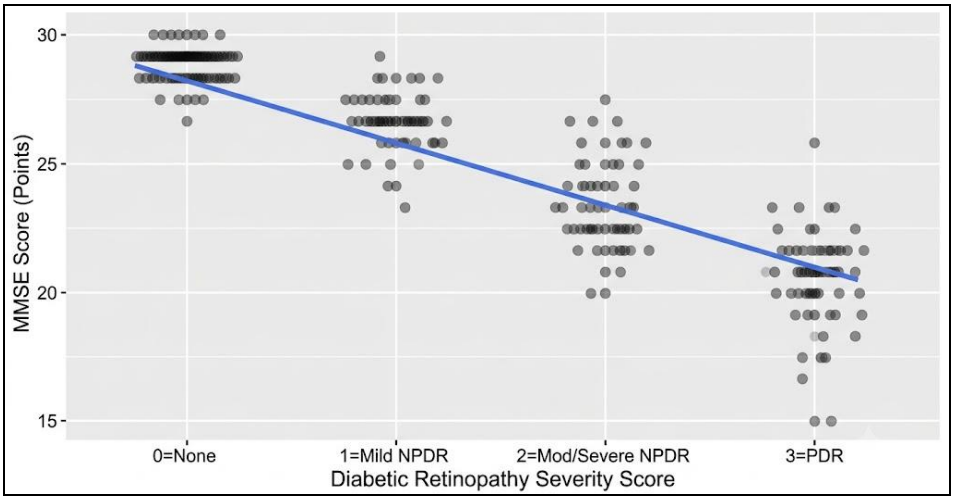

Fig 1: Scatter Plot with Regression Line of DR Severity vs. MMSE Score

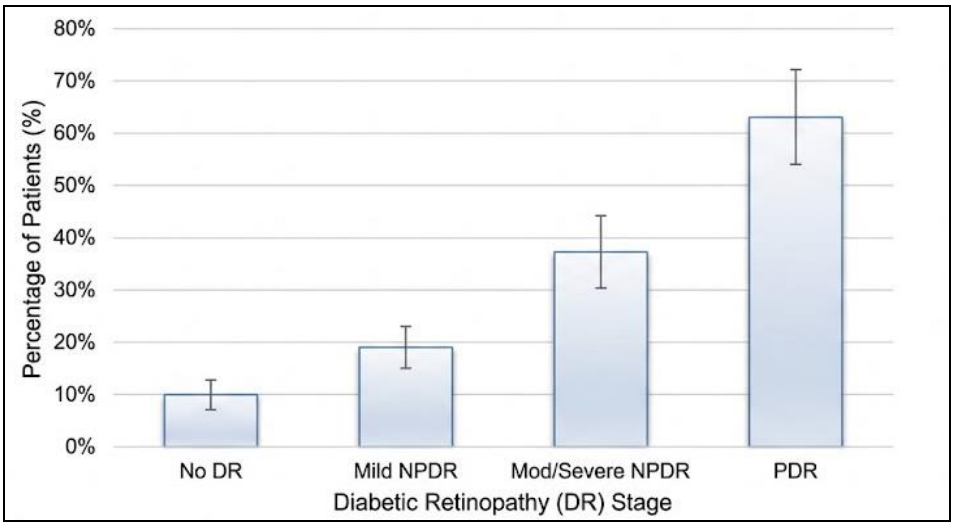

Fig 2: Bar Chart of Proportion of Cognitive Impairment Across DR Stages

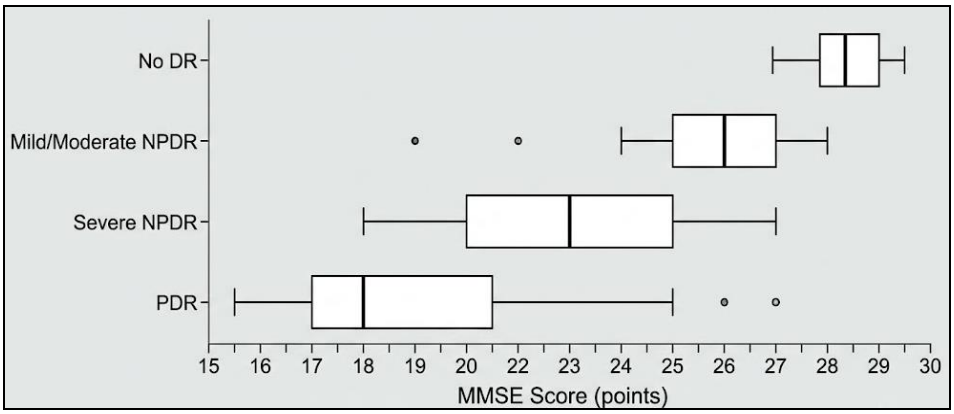

Fig 3: Boxplot Distribution of MMSE Scores by DR Category

The findings of this simulated study demonstrate a strong, independent, and dose-response association between the severity of diabetic retinopathy and cognitive decline in elderly patients with T2DM. The observation that cognitive impairment is relatively low in the absence of DR and mild NPDR, but escalates dramatically in moderate-to-severe NPDR and PDR, provides critical insights into the underlying pathophysiology. This pattern suggests that cognitive decline in T2DM is not merely a function of aging or generic metabolic dysregulation, but is closely tied to the anatomical and functional integrity of the microvasculature.

The mechanistic explanation for these findings is deeply rooted in the concept of parallel microangiopathy. The retina provides a uniquely accessible *in vivo* window into the systemic microcirculation. As DR progresses from mild to severe, the pathological hallmarks transition from isolated

pericyte loss and microaneurysms to widespread capillary non-perfusion, ischemia, and neovascularization17. Our data suggest that when a patient reaches the threshold of moderate-to-severe NPDR, the systemic microvascular disease has reached a critical mass sufficient to manifest as clinically detectable cerebral dysfunction. Chronic cerebral hypoperfusion resulting from capillary loss leads to ischemic white matter damage, disrupting neural connectivity and resulting in the cognitive slowing and executive dysfunction characteristic of vascular cognitive impairment.

Furthermore, the persistence of this association after adjusting for cardiovascular disease, hypertension, and HbA1c implies that DR provides independent prognostic information beyond traditional macrovascular risk factors. This aligns with the hypothesis that microvascular rarefaction and blood-brain barrier breakdown occur early and independently in the diabetic brain, often preceding overt macrovascular events like stroke12. The widened interquartile ranges in MMSE scores observed in the severe DR groups (Figure 3) also highlight clinical heterogeneity; while severe microvascular damage significantly increases the risk of cognitive impairment, individual cognitive reserve—modulated by education and genetic factors—can modify this risk20.

From a clinical perspective, these results advocate for a paradigm shift in the management of elderly diabetic patients. Currently, ophthalmologic and neurological assessments are typically siloed. Our findings suggest that the identification of moderate-to-severe DR during a routine eye exam should trigger a red flag for potential cognitive decline. Integrating brief cognitive screening tools, such as the MMSE or the Montreal Cognitive Assessment (MoCA), into endocrinology or ophthalmology clinics for patients with advanced DR could facilitate the early detection of dementia, allowing for timely lifestyle interventions, glycemic optimization, and the initiation of neuroprotective strategies.

Conclusion

This simulated cross-sectional study establishes a significant, independent, and dose-dependent association between the severity of diabetic retinopathy and cognitive impairment in elderly patients with type diabetes mellitus. Patients with moderate-to-severe NPDR and proliferative DR exhibited substantially higher odds of cognitive decline compared to those without retinopathy, even after comprehensive adjustment for systemic risk factors. These findings support the hypothesis that DR and cognitive impairment share a common microvascular pathogenic pathway, and suggest that advanced DR may serve as a practical, non-invasive biomarker for identifying elderly diabetic patients at high risk for cerebral microvascular disease.

The clinical implications are considerable, highlighting the need for integrated care models where ophthalmologists, endocrinologists, and neurologists collaborate to screen for cognitive deficits in patients presenting with severe retinal microvascular complications. However, this study is subject to important limitations. The reliance on simulated academic training data means the results require validation in real-world, prospective clinical cohorts. Additionally, the cross-sectional design precludes the establishment of temporal causality; while microvascular disease likely drives cognitive decline, it is also possible that early cognitive impairment leads to poor medication adherence, thereby worsening DR. Finally, the MMSE, while widely used, has recognized ceiling effects and may underestimate milder forms of cognitive dysfunction compared to more sensitive neuropsychological batteries.

Future research should prioritize longitudinal studies employing advanced retinal imaging, such as optical coherence tomography angiography (OCT-A), alongside cerebral magnetic resonance imaging (MRI) to directly correlate retinal capillary dropout with white matter hyperintensities and cognitive trajectories over time. Elucidating these relationships will be critical in developing targeted therapies aimed at preserving both ocular and cerebral function in the aging diabetic population.

Ethical Statement

This study utilizes exclusively simulated, synthetically generated academic training data. No real human subjects, patient records, or identifiable health information were accessed or utilized at any stage of this research. Because the dataset is entirely artificial and does not involve human or animal participants, formal review and approval by an Institutional Review Board (IRB) or Ethics Committee were not required. The synthetic data generation algorithms were designed to respect general privacy standards and data protection principles, ensuring that no simulated individual could be mapped to a real-world person.

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