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ORIGINAL RESEARCH ARTICLE

CORRELATION OF SEVERITY OF DIABETIC RETINOPATHY WITH COGNITIVE IMPAIRMENT IN TYPE 2 DIABETICS

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ABSTRACT

BACKGROUND AND AIM

To assess the severity of diabetic retinopathy and to determine the association between diabetic retinopathy and cognitive impairment in type 2 diabetes mellitus patients.

METHODS

A cross-sectional analytical study was conducted on 215 diabetic patients for a period of 6 months of which 83 had no DR while 132 had DR; the Montreal Cognitive Assessment -B (MOCA-B) test was administered and evaluated for cognitive impairment.

RESULTS

Out of 215 patients, 111(51.62%) individuals were aged <60 years and 104 (48.37%) were above 60 years of age. The study involved 119 males (55.34%) and 96 (44.65%) females of which 83(38.60%) of them had no DR and associated hypertension and 132 (61.39%) had DR associated with hypertension. 90 (41.86%) had NPDR and 42(19.53%) had PDR. It was found that males had a higher preponderance towards PDR while females had a slightly higher preponderance towards NPDR. 18 individuals (8.37%) had associated hypertension among the NPDR group and 42(19.53%) patients had hypertension in PDR group.

Patients, after administering the Montreal cognitive assessment scale were evaluated for cognitive impairment and was found that CI was more in >60 years age group (59.44%) and in males. Duration of diabetes and its association with presence of diabetic retinopathy and cognitive impairment was found to be of significance (9.66±6.16, P=0.0004) 109(76.22%) patients with cognitive impairment had hypertension. 37(25.87%) patients with PDR had cognitive impairment (P=0.001)

CONCLUSION

Older age and progressive DR is associated with development of cognitive impairment especially in the abstraction and delayed recall domains in diabetic retinopathy patients. Hence heightened cognitive impairment prevalence in diabetics with retinopathy is a warning sign of cerebral abnormalities.

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KEY WORDS
Diabetes Mellitus, Diabetic Retinopathy, Cognitive Impairment, MOCA-B

INTRODUCTION

Diabetes Mellitus (type 2) is associated with a spectrum of complications such as diabetic retinopathy.[1,2] DR having a prevalence of 34.6% worldwide is the most common microvascular complication leading to blindness.[1-3] Its prevalence is expected to escalate due to the anticipated exponential increase in global diabetes prevalence in the forthcoming decades.[2,3]

Some cross-sectional studies have shown that in the elderly with diseases of retinal vasculature, there is an association between the severity of the eye disease and cognitive function as cerebral and retinal microvasculature share many similarities with respect to embryological origin, vessel wall structure, and physiological characteristics.

Cognition refers to the mental processes involved in acquiring, processing, understanding, and storing information.[4] Evidence from recent studies suggests that there is a strong correlation between the retinal and cerebral microvascular changes in diabetics with equivocal rise in diabetic retinopathy and CI.[4-7] Inflammatory processes are common in the pathogenesis of both diabetic retinopathy and cognitive impairment.[6,7] In the retina, chronic low-grade inflammation mediated by pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α), leads to retinal endothelial dysfunction, breakdown of the blood-retinal barrier, and neurodegeneration. Similarly, neuroinflammation in the brain, characterized by glial activation and cytokine release, disrupts synaptic function, promotes neuronal apoptosis, and impairs neuroplasticity, thereby exacerbating cognitive impairment.[8] In a study conducted previously, it was demonstrated that patients with cognitive impairment exhibited enlarged FAZ(foveal avascular zone) areas, and decreased microvascular density of superficial and deep choroidal plexus with choroidal thinning. Retinal nerve fibre layer thickness is linked with cognitive performance and therefore may have the potential to detect cognitive impairment in older adults.[8,9] Cerebral vascular lesions reported to occur in diabetes are predominantly capillary basement membrane thickening and increased tortuosity of capillaries. There is no pericyte loss in the vessels of the cerebral cortex while retinal vessels were found to have the same.[10]

Blessed Orientation-Memory-Concentration test (BOMC), Clock Drawing Test (CDT), Mini-Cog, Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Short Portable Mental Status Questionnaire (SPMSQ) are some of the assessment tools available for cognitive impairment in elderly.[11] The temporal relationship between DR and cognitive decline is unclear, with only one study showing no association among selected patients from a clinical trial. The inconsistent results and lack of extensive literature on this subject, particularly in the south Indian population, prompted our study to explore the potential avenues.

Objectives

- To assess the severity of diabetic retinopathy and cognitive impairment in type 2 diabetes mellitus patients.
- To determine the association between diabetic retinopathy and cognitive impairment in type 2 diabetes mellitus patients.

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MATERIAL AND METHODS

A cross-sectional analytical study was conducted on 215 patients in a Tertiary care teaching institute in Kolar for a period of 6 months for all diabetic patients seeking treatment at ophthalmology outpatient services of the hospital. All Type 2 diabetics, new or old, with or without diabetic retinopathy and those who received treatment were included. All patients with chronic renal failure, hemo dialysis, previously diagnosed case of dementia/ cognitive impairment and head injury were excluded.

Methodology and Data Collection

Type 2 diabetes patients were recruited and subjected to standard DR screening tests and investigations. They were categorized into no DR and NPDR and PDR with different stages according to the ETDRS (Early Treatment Diabetic Retinopathy Study) classification of diabetic retinopathy after dilated fundoscopy. Patients were comprehensively assessed with detailed history regarding the duration of DM, medication history and glycaemic control followed by a thorough physical examination. Ocular examination involved visual acuity with Snellen's chart, anterior segment assessment by slit lamp biomicroscopy, IOP measurement by Goldman's applanation tonometer, gonioscopy by 3-mirror gonio lens, lacrimal sac syringing, dilated fundus examination with indirect ophthalmoscope and fundus photographs were taken.[12] MoCA-B test was administered to the participants, assessing multiple cognitive domains.

Study Tool

The Montreal Cognitive Assessment scale (MoCA test) is a 30-item scale and is a widely used screening tool for detecting mild cognitive impairment (MCI) and assessing cognitive function. The maximum score is 30 points, with impairment suspected in subjects whose score is 25 or lower. Validated and widely used tool, especially in evaluating age-related cognitive decline. The Montreal Cognitive Assessment takes approximately 10 minutes to administer and was designed to detect mild cognitive impairment in elders scoring in the normal range on the MMSE. MoCA-B evaluates various cognitive domains, including attention, memory, naming, language, visuospatial abilities/ executive function, abstraction, delayed recall and orientation. The test consists of a brief assessment sheet administered in approximately 10 to 15 minutes and is suitable for use in any clinical setting. It has been translated into numerous languages and adapted for different cultural contexts. The MoCA has demonstrated sensitivity in detecting early cognitive decline, making it valuable for identifying individuals at risk for neurodegenerative disorders. It is also useful for tracking cognitive changes over time and assessing response to interventions. Cognitive impairment is a common, underdiagnosed complication of diabetes that can interfere with the ability to perform required daily self-care management.

Data Analysis

Data were entered into Microsoft Excel 2019 and analyzed using Epi Info version 7.2.5. CDC, Atlanta. Descriptive analyses were analysed using mean, SD, and proportions. Inferential analyses was done using t-test & Chi-square analysis $p<0.05$ was considered statistically significant.

RESULTS

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This study was conducted on a total of 215 patients in the department of Ophthalmology after obtaining Institutional Ethical Committee clearance prior to the study.

Out of 215 patients, 111(51.62%) individuals were aged <60 years and 104 (48.37%) were above 60 years of age. The study involved 119 males (55.34%) and 96 (44.65%) females of which 83(38.60%) of them had no DR and associated hypertension and 132 (61.39%) had DR associated with hypertension. Among all the domains of MOCA administered, abstraction and delayed recall were domains with significantly less score.

Parameter		Patients without DR	Patients with DR	Test of Significance
Age in Years		59.28 ± 9.78	62.40 ± 10.26	t-test; **P=0.0265**
Age in Years	<60	36 (43.57%)	75 (56.82%)	Chi-square 3.68
	>60	47 (56.00%)	57 (43.18%)	**P=0.050**
Gender	Male	41 (49.40%)	78 (59%)	Chi-square 1.93
	Female	42 (50.60%)	54 (40.94%)	P=0.164
Duration of DM in years		5.49 ± 4.79	10.71± 5.79	t-test **P=<0.0001**
Hypertension	Yes	21 (25.3%)	33 (25%)	Chi-square 0.0025
	No	62 (74.7%)	99 (75%)	P=0.96

Table 1: Diabetic Retinopathy (DR) with demographic and clinical variables (DR- diabetic retinopathy)

Our study also found that 83 (38.60%) had no diabetic retinopathic changes among the given sample. However, 90 (41.86%) had NPDR and 42(19.53%) had PDR. It was found that males had a higher preponderance towards PDR while females had a slightly higher preponderance towards NPDR.

18 (8.37%) had associated hypertension among NPDR group and 42(19.53%) patients had hypertension in PDR group. (Table 2)

Patients after administering the Montreal cognitive assessment scale were evaluated for cognitive impairment and was found that CI was more in above 60 years age group (59.44%) and in males. (Table 3) Duration of diabetes and its association with presence of diabetic retinopathy and cognitive impairment was found to be of significance (9.66±6.16, P=0.0004) 109(76.22%) patients with cognitive impairment had hypertension. 37(25.87%) patients with PDR had cognitive impairment (P=0.001)

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Parameter		No DR	NPDR	PDR
Age in years	<60 years	36 (43.37%)	11 (61.11%)	25 (59.52%)
	>60 years	47 (56.63%)	7 (38.89%)	17 (40.00%)
Sex	Male	41 (49.4%)	8 (44.4%)	29 (69.05%)
	Female	42 (50.60%)	10 (55.6%)	13 (30.95%)
Hypertension	Yes	21 (25.3%)	4 (22.22%)	9 (21.43%)
	No	62 (74.7%)	14 (77.28%)	33 (78.57%)

Table 2: Comparison of demographic parameters and co-morbidities between patients with different grades of DR (Chi-square test P>0.05)

Parameter		No Cognitive Impairment	Cognitive Impairment	Test of Significance
Age in Years		56 ± 9.21	62.75 ± 9.74	t-test ;**P=<0.0001**
Age	<60 years	53 (73.61%)	58 (40.56%)	Chi-square 20.94
	>60 years	19 (26.39%)	85 (59.44%)	**P=0.000**
Gender	Male	34 (47.22%)	85 (59.44%)	Chi-square 2.89
	Female	38 (52.7%)	58 (40.56%)	P=0.089
Duration of DM		6.76±5.14	9.66±6.16	t-test **P=0.0004**
Hypertension	Yes	20 (27.78%)	34 (23.78%)	Chi-square 0.407
	No	52 (72.77%)	109 (76.22%)	P=0.523

Table 3: Comparison of demographic parameters, duration of diabetes, and Co-morbidity between patients with and without cognitive impairment

(DR- diabetic retinopathy, NPDR- non-proliferative diabetic retinopathy, PDR- proliferative diabetic retinopathy)

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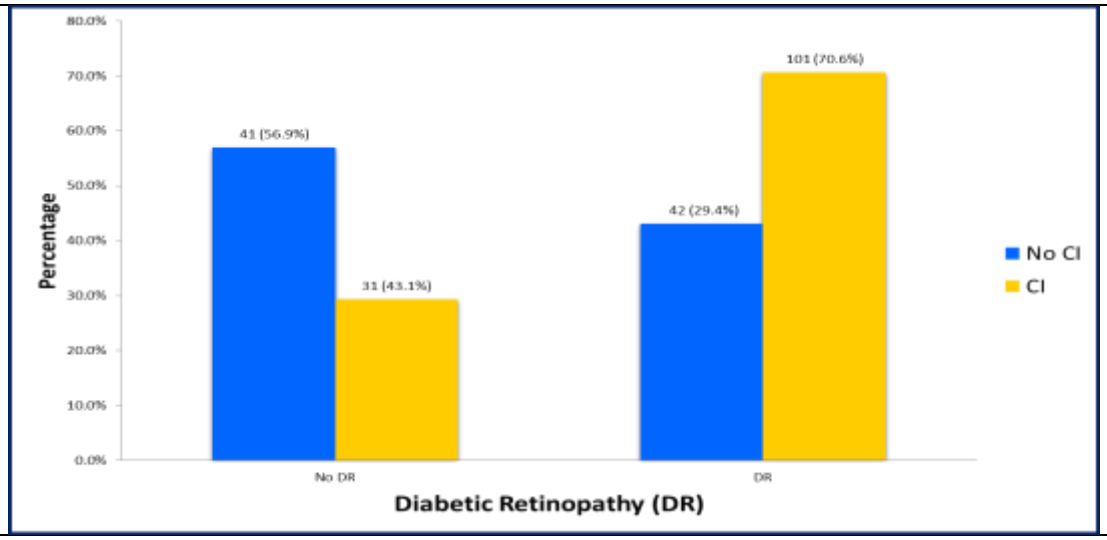

Graph 1: Comparison of Diabetic Retinopathy (DR) and Cognitive Impairment (CI)

Parameter	No CI	CI	Test
No DR	41 (56.9%)	42 (29.37%)	Chi-square 19.39 **P=0.001**
Mild NPDR	6 (8.33%)	18 (12.59%)	
Moderate NPDR	14 (19.44%)	34 (23.78%)	
Severe NPDR	6 (8.33%)	12 (8.39%)	
PDR	5 (6.94%)	37 (25.87%)	

Table 4: Comparison of different grades of Diabetic Retinopathy (DR) and the presence or absence of Cognitive Impairment (CI)

(CI- Cognitive Impairment)

DISCUSSION

The prevalence of type 2 diabetes and cognitive impairment has increased over the past 2 decades.[13] Longer duration of diabetes and poorer glycaemic control are highly associated with diabetic retinopathy and cognitive impairment. [14] Dealing with diabetes mellitus as a chronic condition becomes particularly daunting when cognitive impairment is present, making daily decisions about self-discipline and antihyperglycemic therapy challenging. Identifying the disease process that correlates with diabetic microvascular changes and cognitive impairment could be useful for the development of preventive measures in people with diabetes. The present study examined the prevalence of cognitive impairment in patients with diabetic retinopathy in a tertiary care centre in South India.

In our study, earlier onset and duration of diabetes are related to a higher prevalence of Diabetic retinopathy in contrast to a study by Parvathy et al.[2] Also, duration and elderly age are more affected by cognitive impairment in relation to DR. Hypertension was found to be an

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associated co-morbidity with DR however this was contradicted in a study by Vuyyuru et al[13] suggesting there was no significant association between hypertension and DR.

In our study, MoCA-B was used to correlate the cognitive function with grades of diabetic retinopathy. MoCA-B being more sensitive than other cognitive assessment tests such as Mini-cog and MMSE, gave better results as it is education-adjusted with easy pictorial depiction and non-time-consuming.[15] The maximum score for MoCA-B and MMSE is 30. In MoCA-B, a score lesser than 26 is considered to have cognition impairment. In this study patients scored less in the delayed recall and abstraction domains when compared to the study by Parvathy et al[2] patients with DR scored lower than those without DR in most domains of cognitive functions, except for the "naming" domain. Males with a mean age of 62.75+/- 9.74 years had cognitive impairment which was statistically significant (p=0.0001). However, it was observed that patients with DR and hypertension did not have significant cognitive impairment.

It was observed that participants with diabetic retinopathy experienced a greater incidence of cognitive impairment compared with no DR (70.63%). We did not observe any gender differences in contrast to male preponderance reported by Ding and associates. [16] Mild to moderate grades of NPDR are associated with a higher incidence of cognitive impairment, consistent with the findings of a study by Ong et al [17] & Mathupriya et al [18] and in contrast to study by Crosby-Nwaobi et al [3,5] where patients with minimal DR demonstrated more cognitive impairment than those with advanced DR. In a study conducted by Stuler et al [19] diabetes without DR was linked to lower Alzheimer's and the presence of DR was associated with a 34% higher risk of AD.

Strengths

- This study stands out given the limited data on DR and CI in India and this sociocultural setting.
- We screened all diabetic patients systematically for DR.

Limitations

- Due to the small number of PDR and Severe /Moderate NPDR merging, the data may have diluted the findings
- These findings are independent of key risk factors of CI, such as HbA1c, education and socioeconomic status, refractive error, CVD, and visual acuity.
- Longitudinal population-based cohort studies are more accurate to ascertain association and progression.

CONCLUSION

Early onset and longer duration of diabetes mellitus is a significant predictor of diabetic retinopathy with slightly higher male preponderance. [20-23]

The above analysis showed that participants with no retinopathy had less cognitive impairment than those with mild retinopathy because glucotoxicity causes neurological damage to cerebral tissue with raised metabolic stress. Progressive diabetic retinopathy (higher grades) and severity has had a higher risk of developing cognitive impairment which has been established in various studies conducted. [24-28} Older age is a significant risk factor for the development of Cognitive impairment in diabetic retinopathy patients. Furthermore, we have discussed the implications of cognitive impairment in individuals with T2DM, emphasizing the importance of early detection and intervention to mitigate the progression of cognitive decline. Collectively, our results suggest that strategies focusing on DR screening and

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preventing the development or progression of DR may reduce the risk of onset of Cognitive Impairment in people with diabetes.

Enhancing quality of life with lifestyle modifications, including diet and exercise and formulating effective treatment plans are essential in managing T2DM and potentially reducing the risk of cognitive decline.[20,30]

Educating patients and their families about the significance of routine eye examinations, maintaining optimal sugar levels and HbA1c, and screening for cognitive impairment is mandatory. Continued research efforts are warranted to further elucidate the complex interplay between T2DM and cognitive impairment, paving the way for innovative therapeutic strategies and improved clinical management paradigms.

Summary

This cross-sectional study investigated the association between diabetic retinopathy (DR) and cognitive impairment (CI) in 215 type 2 diabetes mellitus (T2DM) patients at a tertiary care institute in Kolar, India. Results showed that 61.39% of patients with DR also had hypertension, and CI was significantly more prevalent in older adults and males, particularly affecting those with proliferative diabetic retinopathy (PDR). Using the Montreal Cognitive Assessment (MoCA) test, the study found that cognitive impairment was more common in patients with DR, highlighting the importance of early detection and management of both conditions to improve patient outcomes. The study underscores the need for further longitudinal research to confirm these associations and explore preventive measures.

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