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Cognitive Dysfunction Among Adults With Type 2 Diabetes Mellitus in Karnataka, India

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Background: Type 2 diabetes mellitus is a chronic metabolic disease characterized by hyperglycemia that affects various body systems. Elevated blood glucose levels cause brain malfunction, sorbitol-induced blood vessel damage, and degeneration of the nerves that can lead to dementia or cognitive impairment. Cognitive impairment can result in nonadherence of patients to diabetes treatment, such as diet, medication, and exercise.

Methods: We used a cross-sectional design to individually interview 194 patients with type 2 diabetes in a rural field practice area in India. A questionnaire was used to collect sociodemographic and diabetes disease characteristics; anthropometric measurements were also collected. Cognitive dysfunction was assessed with the Kannada version (local language) of the Montreal Cognitive Assessment (MoCA) tool. Blood pressure was measured for all subjects using a standardized sphygmomanometer on the right arm with the patient in a sitting position.

Results: Among the 194 diabetic subjects interviewed, 98 (50.5%) were cognitively impaired. More than half of the subjects (56.2%) were ≥65 years, and female participants (53.6%) outnumbered males (46.4%). The majority of patients (62.4%) had had diabetes for <10 years. The sociodemographic characteristics age, sex, education, occupation, and socioeconomic status and the anthropometric measurement of waist-to-hip ratio were significantly associated ($P<0.05$) with cognitive impairment. Disease characteristics, religion, and blood pressure showed no significant association with cognitive impairment.

Conclusion: One in two individuals with type 2 diabetes mellitus in our study population had mild cognitive impairment. Older individuals in the low socioeconomic strata and with low levels of education were identified to be at high risk of cognitive impairment. Hence, screening and appropriate care need to be provided.

Keywords: *Cognitive dysfunction, cross-sectional study, diabetes mellitus–type 2, mental status and dementia tests*

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INTRODUCTION

Diabetes mellitus is a chronic metabolic disease characterized by hyperglycemia that affects various body systems. For this progressive, incurable condition, the best scenario after diagnosis is good metabolic control and risk factor management to forestall vascular and neuropathic complications.[1] People with diabetes often develop diverse microvascular, macrovascular, and neuropathic complications that erode quality of life, making diabetes a major concern for much of the developed and developing world.[2,3] The increasing population and increasing sedentary lifestyle worldwide have led to a rise in diabetes, with a 72% increase in the disease projected by 2030.[4]

The impaired insulin metabolism in patients with diabetes results in widespread morbidities involving the retinal, renal, cardiovascular, and peripheral nervous systems[5] and also affects cognition.[6] Elevated blood glucose levels not only cause brain malfunction but also promote the synthesis of sorbitol, which damages blood vessels and causes degeneration of the nerves.[7] Oxidative stress, microvascular vasculopathy, inflammation, and dyslipidemia are other key mediators[8] resulting in neuropathology that can lead to dementia or cognitive impairment.

Patients are said to be cognitively impaired when they have difficulty remembering, learning new things, concentrating, or making decisions that affect everyday life.[9] Cognitive impairment, especially for people with chronic diseases, is likely to be an obstacle to providing appropriate medical treatment, as patients' understanding of the need for treatment, regular follow-up, and self-care can be limited by the cognitive dysfunction.[10] Cognitive functions that enable complex behaviors are particularly important for patients with diabetes. Cognitive impairment might result in nonadherence with diet, medication, and exercise.[11] Older patients with diabetes and concomitant cognitive dysfunction may be unable to follow complicated regimens

(eg, multiple daily insulin injections with or without a sliding scale, multiple oral medications, or a complex dietary regimen).[12] These patients may be at increased risk of treatment complications (eg, omission of meals leading to hypoglycemia or incorrect dose or timing of insulin injections and/or oral medications).[13] Cognitive impairment also increases the risk of major cardiovascular events and all-cause mortality.[14]

Studies about the relationship between cognitive impairment and diabetes mellitus are inconclusive because of inconsistent reports. The inconsistency in findings may be attributable to differences in study design, study subjects, duration or severity of diabetes, and the tools used for assessment of cognitive impairment.[15] One such tool, the Montreal Cognitive Assessment (MoCA), was developed to screen for mild cognitive impairment,[16] but few studies[17,18] have reported using the MoCA in community settings. A pilot study from Canada reported the MoCA to be a better screening tool than the Standardized Mini-Mental State Examination for mild cognitive impairment in the diabetic population.[19]

Although diabetes is considered a risk factor for cognitive impairment, the cognitive function of patients with type 2 diabetes is not usually evaluated in routine clinical care. The purpose of this study was to screen for mild cognitive impairment among patients with diabetes in the state of Karnataka in southwestern India.

METHODS

We used a cross-sectional design to interview 194 patients with type 2 diabetes mellitus who resided in the field practice area of the Department of Community Medicine, attached to Kasturba Medical College in the coastal town of Manipal in southwestern India. Institutional ethical committee clearance was obtained before the initiation of the study (IEC 124/2016). The study conformed to the principles of the Declaration of Helsinki. Written informed consent was obtained from all the study subjects.

Study participants were identified with the help of auxiliary nurse midwives in the field practice area. Patients of both sexes who were ≥30 years of age, diagnosed with type 2 diabetes mellitus for at least 2 years, and willing to participate were eligible for inclusion. Patients with type 2 diabetes mellitus who had severe comorbidities such as stroke or documented mental illness, those with speech and hearing disabilities that would interfere with providing answers to the questionnaire, and pregnant females were excluded. Assuming the prevalence of cognitive dysfunction among adults with type 2 diabetic mellitus to be 25% and accounting for an alpha error of 5% at 25% relative precision and a 5% nonresponse rate, the sample size was calculated to be 194 by application of the formula $4pq/d^2$ used for sample size estimation of cross-sectional studies.

Sociodemographic characteristics, details about patients' disease and treatment, and anthropometric measurements were collected during personal interviews according to a predesigned questionnaire. The faculty of the Department of Community Medicine designed the questionnaire and use it routinely for community-based studies. The authors conducted the interviews.

Socioeconomic status was assessed using a modified Udai Pareekh scale[20] that includes the following domains: type of house, ownership, landholding, vehicles, household belongings, livestock, social participation, occupation of the eldest earning member of the household, and family members working abroad. The scores for the domains are summed. A score <40 is considered low socioeconomic status, 40 to 70 is considered middle, and >70 is considered high socioeconomic status.

Cognitive dysfunction was assessed through the administration of the Kannada version (local language) of the MoCA. Permission was obtained to use the MoCA and the translated version. The MoCA assesses 7 cognitive domains: visuospatial/executive (5 points), naming (3 points), memory (5 points for delayed recall), attention (6 points), language (3 points), abstraction (2 points), and orientation (6 points); the upper score limit is 30 points. One point is added if the subject has ≤12 years of education. The cutoff value is 26. A score ≥26 is considered normal.[16]

In addition, blood pressure was measured for all subjects using a standardized mercury sphygmomanometer on the right arm with the patient in a seated position. If the patient's blood pressure was ≥140/90 mm Hg, a repeat blood pressure reading was taken after 5 minutes. The average of the readings was recorded as the blood pressure of the participant. Blood pressure was classified according to Joint National Committee VII criteria.[21]

Anthropometric Variables

All the anthropometric measurements were performed according to World Health Organization (WHO) guidelines, and quality control was maintained during collection of data.[18] Patients wore light clothing when the following measurements were taken: weight, height, waist circumference, and hip circumference.

Waist-to-hip ratio was calculated by dividing waist circumference in cm by hip circumference in cm. Body mass index (BMI) was calculated by dividing weight in kg by height in square meters. Overweight and obesity were defined as follows:

- BMI (WHO classification): ≥25.0 kg/m^2 (overweight) and ≥30.0 kg/m^2 (obese)[22]
- BMI (Southeast Asian classification): ≥23.0 kg/m^2 (overweight) and ≥25.0 kg/m^2 (obese)[23]
- Waist-to-hip ratio ≥0.90 for males and ≥0.85 for females (truncal obesity)[24]
- Waist circumference >90 cm in males and >80 cm in females (central/abdominal obesity)[24]

Data Analysis

Data were entered and analyzed using the Statistical Package for Social Sciences (IBM) v.15. The results are summarized as percentages and proportions. Chi-square test was used for univariate analysis. The association between categorical variables and the presence of cognitive dysfunction was assessed by univariate analysis. A P value <0.05 was considered significant.

RESULTS

Among the 194 patients who were interviewed, 98 (50.5%) were cognitively impaired (score ≤25 on the MoCA). The highest mean score was in the domain of orientation (5.53),

Table 1. Association Between Cognitive Dysfunction and Sociodemographic Characteristics of the Study Participants

Variable	All Patients (n=194), n (%)	Cognitive Dysfunction Present (n=98), n (%)	Cognitive Dysfunction Absent (n=96), n (%)	*P* Value
Age, years				
<45	10 (5.2)	5 (5.1)	5 (5.2)	**0.009**
45-54	22 (11.3)	4 (4.1)	18 (18.8)	
55-64	53 (27.3)	26 (26.5)	27 (28.1)	
≥65	109 (56.2)	63 (64.3)	46 (47.9)	
Sex				
Female	104 (53.6)	62 (63.3)	42 (43.8)	**0.006**
Male	90 (46.4)	36 (36.7)	54 (56.2)	
Religion				
Hindu	126 (64.9)	62 (63.3)	64 (66.7)	0.656
Christian	31 (16.0)	18 (18.4)	13 (13.5)	
Muslim	37 (19.1)	18 (18.4)	19 (19.8)	
Education[a]				
Illiterate	16 (8.2)	15 (15.3)	1 (1.0)	**<0.001**
Grade 1-4	34 (17.5)	21 (21.4)	13 (13.5)	
Grade 5-12	112 (57.7)	55 (56.1)	57 (59.4)	
Graduate	32 (16.4)	7 (7.1)	25 (26.0)	
Occupation				
Homemaker	95 (49.0)	59 (60.2)	36 (37.5)	**0.003**
Retired	66 (34.0)	29 (29.6)	37 (38.5)	
Skilled	33 (17.0)	10 (10.2)	23 (24.0)	
Socioeconomic status				
Low	34 (17.5)	25 (25.5)	9 (9.4)	**0.008**
Middle	159 (82.0)	73 (74.5)	86 (89.6)	
High	1 (0.5)	0 (0)	1 (1.0)	

[a]In the US education system, grades 1 to 5 are elementary (primary) school, grades 6 to 8 are junior high or middle school, and grades 9 to 12 are high school. In the Indian education system, grades 1 to 4 are primary, grades 5 to 7 are middle school, and grades 8 to 10 are high school. After high school, students study for 2 years (grades 11 and 12) in pre-university college. On completion of grade 12, they are eligible to enroll in a college to obtain their bachelor's degree. After 3 years of study, they are called graduates with an undergraduate/bachelor's degree.

while the lowest mean score was in the domain of abstraction (1.78).

Among the study participants, 162 (83.5%) were ≥55 years, females (53.6%) outnumbered males (46.4%), 8.2% were illiterate, 49.0% were homemakers, and 82.0% were assessed as middle class (Table 1). Age, sex, education, occupation, and socioeconomic status were associated with cognitive dysfunction.

Among those cognitively impaired, 89 (90.8%) were ≥55 years. A higher proportion of females had cognitive dysfunction compared to males, 62 (63.3%) vs 36 (36.7%), respectively.

Approximately 70% of participants were diagnosed with diabetes after age 50 years (Table 2), so a small percentage (15.5%) had had the disease for ≥20 years. More than 90% of the study subjects were on regular treatment, with the majority (82.0%) exclusively on oral antidiabetic medications. Most patients had regular blood sugar monitoring, 46.9% at a frequency of ≤1 month and 41.8% at 2 to 3 months. None of the disease characteristics or treatment variables was associated with cognitive dysfunction.

The number of patients classified as obese differed according to the definition applied. Based on waist circumference, 158 (81.4%) study participants were obese. However, waist-to-hip ratio identified 174 (89.7%) obese patients. In a comparison of the Southeast Asian BMI classification vs the WHO BMI classification, more patients were obese according to the Southeast Asian criteria: 52.1% with a BMI ≥25.0 kg/m^2 vs 14.9% with a BMI ≥30.0 kg/m^2, respectively.

Among the patients with cognitive dysfunction, 81.6% had central/abdominal obesity based on waist circumference, and 84.7% had truncal obesity based on waist-to-hip ratio.

Table 2. Association Between Cognitive Dysfunction and Disease Characteristics/Treatment of the Study Participants

Variable	All Patients (n=194), n (%)	Cognitive Dysfunction Present (n=98), n (%)	Cognitive Dysfunction Absent (n=96), n (%)	*P* Value
Age at diagnosis, years				0.443
<40	22 (11.3)	9 (9.2)	13 (13.5)	
40-49	37 (19.1)	16 (16.3)	21 (21.9)	
50-59	70 (36.1)	36 (36.7)	34 (35.4)	
≥60	65 (33.5)	37 (37.8)	28 (29.2)	
Duration of disease, years				0.381
<10	121 (62.4)	56 (57.1)	65 (67.7)	
10-19	43 (22.2)	23 (23.5)	20 (20.8)	
20-29	20 (10.3)	13 (13.3)	7 (7.3)	
≥30	10 (5.2)	6 (6.1)	4 (4.2)	
Duration of treatment, years				0.457
<10	122 (62.9)	55 (58.2)	65 (67.7)	
10-19	43 (22.2)	23 (23.5)	20 (20.8)	
20-29	20 (10.3)	13 (13.3)	7 (7.3)	
≥30	9 (4.6)	5 (5.1)	4 (4.2)	
Type of treatment				0.607
Antidiabetic medications	159 (82.0)	81 (82.7)	78 (81.3)	
Insulin	9 (4.6)	5 (5.1)	4 (4.2)	
Both insulin and oral medicines	13 (6.7)	8 (8.2)	5 (5.2)	
Ayurveda	3 (1.5)	1 (1.0)	2 (2.1)	
No treatment	6 (3.1)	1 (1.0)	5 (5.2)	
Lifestyle modification	4 (2.1)	2 (2.0)	2 (2.1)	
Regular treatment				0.396
Yes	179 (92.3)	92 (93.9)	87 (90.6)	
No	15 (7.7)	6 (6.1)	9 (9.4)	
Place of treatment				0.761
Rural health center	12 (6.2)	5 (5.1)	7 (7.3)	
Government hospital	38 (19.6)	17 (17.3)	21 (21.9)	
Private hospital	76 (39.2)	42 (42.9)	34 (35.4)	
Secondary care hospital	33 (17.0)	16 (16.3)	17 (17.7)	
Tertiary care hospital	35 (18.0)	18 (18.4)	17 (17.7)	
Frequency of blood sugar monitoring				0.569
Never	3 (1.5)	0 (0)	3 (3.1)	
<1 month	91 (46.9)	50 (51.0)	41 (42.7)	
2-3 months	81 (41.8)	39 (39.8)	42 (43.8)	
>6 months	19 (9.8)	9 (9.2)	10 (10.4)	

However, 54.1% (53 of 98 patients with cognitive dysfunction) had a BMI <25.0 kg/m^2.

High blood pressure was detected among 109 (56.2%) of the study participants. No association was found between blood pressure and cognitive dysfunction: 58.2% of patients with cognitive dysfunction had elevated blood pressure compared to 54.2% of patients without cognitive impairment.

DISCUSSION

Type 2 diabetes mellitus is associated with accelerated cognitive decline,[25] and poor glycemic control is implicated

Table 3. Association Between Cognitive Dysfunction and Anthropometric Measurements/Blood Pressure of the Study Participants

Variable	All Patients (n=194), n (%)	Cognitive Dysfunction Present (n=98), n (%)	Cognitive Dysfunction Absent (n=96), n (%)	*P* Value
Waist circumference, cm				0.945
Normal	36 (18.6)	18 (18.4)	18 (18.8)	
Obese (>90 for males, >80 for females)	158 (81.4)	80 (81.6)	78 (81.3)	
Waist to hip ratio				**0.021**
Normal	20 (10.3)	15 (15.3)	5 (5.2)	
Obese (>0.90 for males, >0.85 for females)	174 (89.7)	83 (84.7)	91 (94.8)	
BMI-Southeast Asian classification, kg/m^2				0.353
Underweight (<18.5)	3 (1.5)	2 (2.0)	1 (1.0)	
Normal (18.5-22.9)	46 (23.7)	27 (27.6)	19 (19.8)	
Overweight (≥23.0)	44 (22.7)	24 (24.5)	20 (20.8)	
Obese (≥25.0)	101 (52.1)	45 (45.9)	56 (58.3)	
BMI-WHO classification, kg/m^2				0.345
Underweight (<18.5)	3 (1.5)	2 (2.0)	1 (1.0)	
Normal (18.5-24.9)	90 (46.4)	51 (52.0)	39 (40.6)	
Overweight (≥25.0)	72 (37.1)	31 (31.6)	41 (42.7)	
Obese (≥30.0)	29 (14.9)	14 (14.3)	15 (15.6)	
Blood pressure, mmHg				0.575
Normal	85 (43.8)	41 (41.8)	44 (45.8)	
>140/90	109 (56.2)	57 (58.2)	52 (54.2)	

BMI, body mass index; WHO, World Health Organization.

in the development of cognitive dysfunction.[26] However, the direct cerebral effects of diabetes, leading to neuropathology and cognitive abnormalities, have not been clearly elucidated. In general, depression is known to complicate the impact of mild neurocognitive decline in patients.[12] Cognitive impairment could therefore be a result of either depression or diabetes, and the coexistence of both conditions might possibly accelerate neurocognitive decline.

Various hypotheses have been proposed about the pathophysiology of cognitive dysfunction. Proposed pathogenic mechanisms of cognitive dysfunction in diabetes include chronic hypoglycemia, vascular disease, the cumulative effect of hypoglycemic events, and possible direct effects of insulin on the brain.[27] Hypoglycemic effects may result in increased inflammation; oxidative stress; advanced glycation end products; and decreased neuronal repair and neurogenesis that may lead to direct neuronal injury, may manifest as brain atrophy, and may provide a structural basis for cognitive impairment.[13] However, whether these factors individually or in combination mediate the pathogenesis of cognitive dysfunction is unclear.

Cognitive domains that have been studied in type 2 diabetes include memory, psychomotor speed, visuospatial functions, frontal executive functions, processing speed, verbal fluency, attention, and complex motor functions.[28] In a review of literature on the association between impaired glucose tolerance, type 2 diabetes, and cognitive function, the authors concluded that the most consistently reported measures were impairment in verbal memory and processing speed, with preservation of functions in other areas including visuospatial function, attention, semantic memory, and language.[29]

Our finding that 64.3% of study subjects with cognitive impairment were ≥65 years is similar to the study by Salthouse showing that age-related cognitive impairment is most commonly reported after 60 years of age.[30] Langa and Levine[31] and Harada et al[32] reported that healthy individuals >65 years have mild cognitive impairment. Nooyens et al reported that middle-aged individuals with type 2 diabetes mellitus showed a greater decline in cognitive function than middle-aged individuals without diabetes.[33]

More than 60% of females had cognitive impairment in the present study. This finding is also supported by the Salthouse study.[30] Similarly, Ferris et al[34] showed cognitive decline to be more prevalent among females. In our population, education was significantly associated with cognitive impairment. Evidence for this association conflicts. Prakash et al[35] and Brayne and Calloway[36] showed that higher educational attainment is associated

with reduced chance of cognitive impairment. On the other hand, studies by Andel et al[37] and Stern et al[38] showed that education attainment was associated with accelerated cognitive decline in patients with Alzheimer disease.

Disease characteristics were not significantly associated with cognitive dysfunction, similar to a study by Manschot et al.[39] Ruis et al reported that modest cognitive decrements were identifiable at the early stage of type 2 diabetes.[25] They also postulated that diabetes duration seemed to be linked to the effect sizes of the studies: the longer the duration of diabetes, the higher the noted effect size. Reitz et al proposed that hypertension may cause cognitive impairment through cerebrovascular disease,[40] but our study did not identify any association between blood pressure levels and cognitive impairment, correlating the findings of Kuo et al.[41] However, van Swieten et al reported impaired cognition in the hypertensive group.[42]

Among the anthropometric measurements assessed in the current study, only waist-to-hip ratio was significantly associated with cognitive impairment. However, a study by Kerwin et al among postmenopausal women showed that increased BMI was associated with poorer cognitive function in women with smaller waist-to-hip ratio, and increased waist-to-hip ratio was associated with higher cognitive abilities.[43] The authors recommended further research to clarify the mechanism for this association.

In our study, the factors associated with cognitive dysfunction were older age group, female sex, lower educational qualification, low socioeconomic status, occupation, and high waist-to-hip ratio, a finding supported by Wright et al who reported that greater adiposity is an independent risk factor for cognitive decrements among African Americans.[44]

A strength of this study is the uniformity in data collection by investigators trained in community-based data collection and conduct of the interviews. A limitation is that a language barrier was perceived during some interviews, but this shortcoming was largely circumvented through the help of the auxiliary nurse midwives, especially for rapport building. Because of the cross-sectional nature of the study, only referrals could be provided to the subjects identified with mild cognitive impairment. Subjects with poor glycemic control or high blood pressure were also referred to the health centers. Follow-up could not be done, but the patients residing within the field practice area have easy and affordable access to healthcare facilities, and the best possible recommendations were provided. The small sample size, single-center assessment, unequal distribution of participants across social classes, and a predominance of subjects with a nonsevere disease condition (indicated by the low frequency of insulin usage) are other limitations of the study.

Early identification and regular follow-up of patients with mild cognitive impairment could initiate early psychosocial interventions and minimization of triggers to prevent further cognitive decline. As obesity was identified as a risk factor, promotion of regular physical activity could be recommended for patients with diabetes, not only to achieve better glycemic control but also to slow the process of cognitive impairment.

Assessing the baseline prevalence is the first step in designing programs to address any health issue. Health education pertaining to cognitive decline, early identification, and management can be effective only if patients and their caregivers are aware of the importance of cognition and its decline and are accepting of treatment.

CONCLUSION

More than half of the individuals with type 2 diabetes mellitus interviewed for this study had mild cognitive impairment. Potential predictors for cognitive impairment identified in the study were older age group, female sex, lower educational qualification, occupation, low socioeconomic status, and truncal obesity. Hence, screening and care need to be provided for older individuals with low literacy status who belong to the lower socioeconomic strata, as they were identified to be at high risk of cognitive impairment.

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