

Association of Cognitive Impairment and Type 2 Diabetes Mellitus: A Case-Control Study

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ABSTRACT

Introduction: Patients with type 2 diabetes mellitus (T2DM) have cognitive deficits that can be attributed to their disease. Mild cognitive impairment (MCI) is a transitional phase between the cognitive decline that is expected due to the normal aging process and the more disconcerting decline of dementia. This case-control study aimed to explore the association between type 2 diabetes mellitus and mild cognitive impairment and compare the prevalence of mild cognitive impairment between non-diabetics and type 2 diabetics.

Material and Methods: 50 patients with T2DM and 50 age and sex matched non-diabetic controls were selected for the study. Demographic data and medical history was collected by face to face interview following which the Mini-Mental state examination (MMSE) and the Montreal Cognitive Assessment (MoCA) were conducted. If either of the screening instruments suggested MCI, the patient was then subjected to an extensive medical examination conducted by qualified medical clinicians blinded to the MMSE and MoCA scores for a more detailed diagnosis of MCI. Chi square test was performed to determine if T2DM was significantly correlated with MCI. Linear regression was performed to determine the strength of years of illness as a predictor of MMSE and MoCA score.

Results: Chi square test revealed a statistically significant correlation between T2DM and MCI. Years of illness was found to predict 5% of the variance in MMSE score and 14% of the variance in MoCA score.

Conclusion: The study established that mild cognitive impairment had a significant statistical association with T2DM.

Key Words: Cognitive Dysfunction; Diabetes Mellitus; Mental Status And Dementia Tests; Case-Control Studies

diabetes (T2DM) also negatively impacts the brain because of its association with obesity, hypertension, dyslipidemia, inflammation and abnormalities in hypothalamic pituitary adrenocortical axis etc.³ There is documented evidence that T2DM amplifies the possibility of mild cognitive impairment and increases risk of developing dementia which includes both Alzheimer's disease and vascular dementia.^{4,5} Though diabetes is regarded as a risk factor for cognitive impairment, the cognitive function of T2DM patients in routine clinical care is rarely evaluated.

Mild cognitive impairment (MCI) is a stage in-between the cognitive decline of caused by normal aging and the more severe decline as that caused by dementia.⁴ It involves deficits with memory, language, learning, intellect etc that are far more pronounced than those caused by age related changes. Since MCI is frequently considered as a transitional stage between cognitive decline caused by aging and Alzheimer's disease, hence identification of the associated risk factors could be useful.⁵ Among the various neuropsychological tests used, the mini-mental state examination (MMSE) and the Montreal Cognitive Assessment (MoCA) are the most widely used tests for screening.

The Mini-Mental State Examination (MMSE) or Folstein test is extensively used to measure or assess MCI during clinical examination or for research purpose.⁶ The MMSE is advantageous as it does not require any specialized equipment or training for its administration, and yet demonstrates validity and reliability in diagnosis and longitudinal assessment of Alzheimer's disease.⁷ The ease of application and the short duration of time required to conduct the examination makes it a popular tool for assessment of cognitive function in the clinician's office or even at bedside.

The Montreal Cognitive Assessment (MoCA) is a well-

INTRODUCTION

About 451 million people have diabetes worldwide, and the number is increasing causing a major public health burden.¹ Diabetes mellitus is a complex metabolic disease manifested in the form of hyperglycemia and glucose intolerance and can have devastating outcomes on various organs in the body. Although the implications of diabetes on the peripheral nervous system have been well established, its effects on the central nervous system are ambiguous. One of the complications of diabetes related to the central nervous system is cognitive dysfunction which isn't well recognized and is sparsely addressed.² Both type 1 and type 2 diabetes mellitus have shown to cause deficiencies in various domains of cognitive function.² Research has shown that Type 2

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validated, reliable, and easily accessible screening tool for the detection of MCI.⁸ The MoCA is a one-page test which assesses 30-points and requires approximately 10 minutes conducting and is also available in 55 languages or dialects. The test is also available in a basic form so that it can be applied to the illiterate subjects or subjects with lower education. As MoCA is a sensitive tool and detects dementia as well as MCI early, it is a good alternative to the MMSE and is also recommended by the Alzheimer's Society as one of the tests that can be used for detection of dementia.⁹ There is scarcity of data that explore the association between MCI and T2DM among the Indian population. Hence this case-control study aimed to explore the association between type 2 diabetes mellitus and mild cognitive impairment and also compare the prevalence of mild cognitive impairment between non-diabetics and type 2 diabetics.

MATERIAL AND METHODS

The study was a case control study which was carried out following approval from the Institutional Ethics Committee. Random sampling was carried out among T2DM outpatients attending the Department of General Medicine and Endocrinology of Vydehi Institute of Medical Sciences and Research Centre, Bangalore, India during the period from March 2017 to June 2017. Patients with T2DM in the age group of ≥ 40 years but ≤ 65 years with duration of T2DM for at least ≥ 5 years were included in the study. Patients with acute medical disorders (Acute respiratory syndrome, acute lymphoid leukemia), any serious physical or mental illness, neurological disorders (Parkinsonism, Alzheimer's), metabolic syndromes (lipodystrophy) and pre-existing systemic illness (Congestive cardiac failure, chronic kidney disease, respiratory failure) were excluded from the study. 50 patients with T2DM and 50 age and sex matched non-diabetic controls were selected for the study. An informed written consent was obtained from all patients prior to the study. All the participants were subjected to a face to face interview during which demographic data (age, sex, education) and medical history (vitals, years of illness, significant comorbidities) were collected. This was followed by conduction of the MMSE and MoCA.

Mini Mental State Examination (MMSE)

MMSE is a 11-question screening measure that systematically assesses the mental status. It tests five areas of cognitive function namely orientation, registration, attention and calculation, recall and language. A maximum score of 30 can be obtained.

Interpretation of MMSE: Severity:

24-30 - No cognitive impairment

18-23 - Mild cognitive impairment

0-17 - Severe cognitive impairment

Montreal Cognitive Assessment (MoCA)

MoCA is a swift screening tool for MCI assessment and it tests various cognitive domains like attention, concentration, memory, language, visuoconstructional skills, calculations and orientation. A maximum score of 30 can be obtained.

Interpretation of MoCA: Severity:

≥ 26 - No cognitive impairment

< 26 - Cognitively impaired

The scores obtained for the MMSE and MoCA were calculated and interpreted to screen for cognitive impairment. The data thus obtained was subjected to statistical analysis. If either of the screening instruments suggested MCI, then the patient was subjected to an extensive medical examination conducted by qualified medical clinicians blinded to the MMSE and MoCA scores for a more detailed diagnosis of MCI and treatment when required.

STATISTICAL ANALYSIS

The power calculation was done prior to initiation of the study. The sample size was estimated using the software GPower v.3.1.9.2. Considering effect size measured (d) at 50%, power of the study at 80% and the margin of error at 5%, the total sample size needed for the study was 88 i.e. 44 subjects per group. The final sample size was rounded off to 100, thereby each study group comprised of 50 subjects.

The data collected was analysed with Statistical Software Package SPSS version 22 (IBM SPSS Statistics for Windows, Version 22.0, Armonk, New York, USA). The frequency distribution for the categorical data was expressed in terms of number and percentage. Chi square test was performed to determine if T2DM was significantly correlated with MCI. Linear regression was performed to determine the strength of years of illness as a predictor of MMSE and MoCA score. The p-value was set at $P < 0.05$.

RESULTS

The demographic characteristics of patients are presented in Figure 1 and 2. The study consisted of 62% males and 32% female participants. 35 participants were in the age group of 45-50 years, 16 were between 50-55 years, 30 were between 55-60 years and 23 were between 60-65 yrs. Intergroup comparison for gender and age did not show any statistical significance.

Variable	Diabetics	Non-diabetics
MCI	22	12
No MCI	28	39

Table-1: Association between the presence of T2DM and MCI

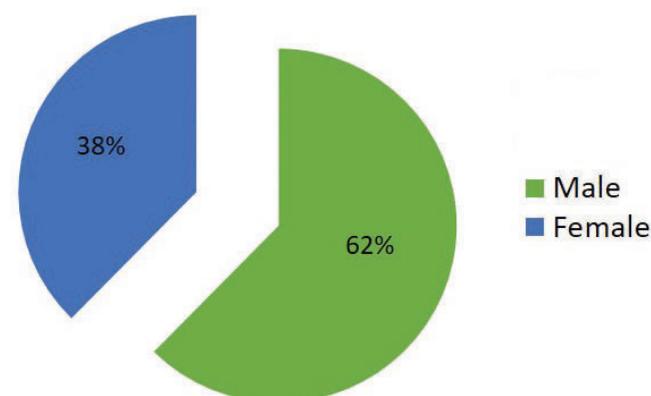


Figure-1: Demographic characteristics: Sex distribution

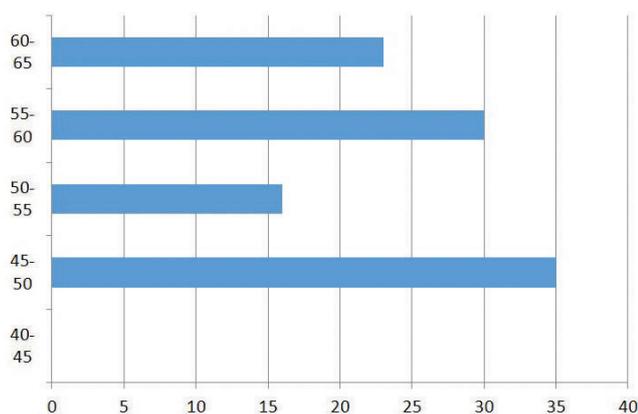


Figure-2: Demographic characteristics: Age distribution

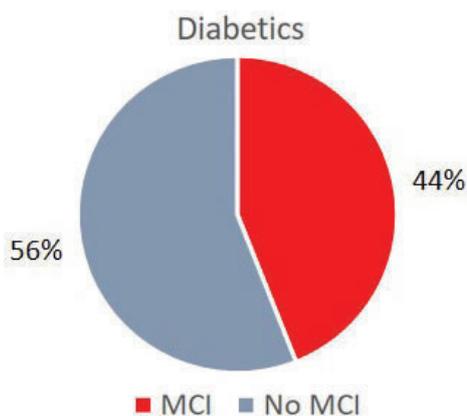


Figure-3: Presence and absence of MCI in diabetics

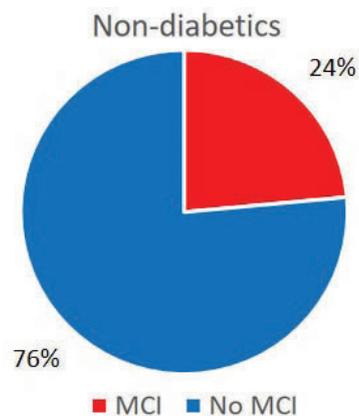


Figure-4: Presence and absence of MCI in non-diabetics

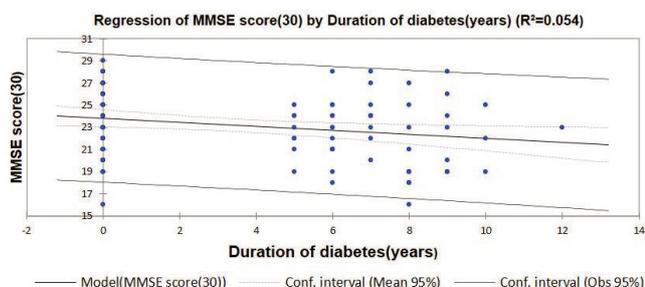


Figure-5: Regression of MMSE scores by duration of diabetes

Table 1, Figure 3 and 4 shows the association between the presence of T2DM and MCI done using Chi square test. 44% of diabetics had MCI while 56% of diabetics had no

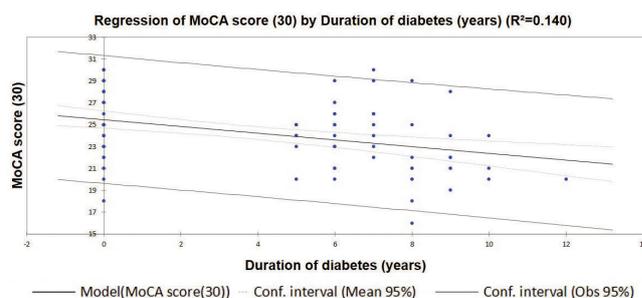


Figure-6: Regression of MoCA scores by duration of diabetes

MCI. 24% of Non-diabetics had MCI while 76% of Non-diabetics did not have MCI. The test revealed that there was a statistically significant relation between the presence of T2DM and MCI with a P value < 0.05 .

Figure 5 shows linear regression analysis performed to determine the strength of years of illness as a predictor of MMSE score. The years of illness was found to predict 5% of the variance in MMSE score with a P value < 0.05 .

Figure 6 shows linear regression analysis performed to determine the strength of years of illness as a predictor of MoCA score. Years of illness was found to predict 14% of the variance in MoCA score with a P value < 0.05 .

DISCUSSION

Diabetes mellitus not only increases the risk of MCI but also multiplies the risk of such an impairment progressing to dementia.^{4,5} The early prediction of conversion of such impairment to dementia has important clinical considerations.¹⁰ The mild neurocognitive dysfunction caused by diabetes not only complicates the daily activities of patients with diabetes but also doubles the likelihood of such patients developing depression which will further negatively impact the cognitive function and daily activities.¹¹ Patients with T2DM also have a higher incidence of Alzheimer's disease and increased occurrence of vascular dementia.^{4,5} Diabetes accelerates cognitive decline and conversion to dementia through a number of potential mechanisms. Several theories have been proposed for the etiopathogenesis of MCI which include insulin resistance syndrome, hyperglycemia, vascular disease, hypoglycaemia, amyloid deposition or the generation of the advanced glycosylation products etc.^{2,3} Many studies have implicated that the primary complication of MCI is progression to Alzheimer's disease possibly due to hyperlipidemia (seen in T2DM) which augments the risk of vascular dysfunction.^{5,10,12} Although some research has been done with regard to cognitive dysfunction in patients with diabetes, more insightful research is needed to understand the mechanisms and natural course of such a complication in order to better develop strategies for its prevention and treatment.

Over the years newer modalities like neurocognitive testing, evoked response potentials and also magnetic resonance imaging are being used to investigate the effect of diabetes on the brain.² Among the neuropsychological tests, the MMSE is one of the most commonly used screening tests.⁶ The test differentiates patients having non-specified organic

brain syndrome and depression from normal subjects. It is also helpful in estimating the cognitive impairment severity and serially documenting cognitive changes.¹³ Sinclair et al in their study found that subjects who had MMSE scores less than 23 had more difficulty in performing self-care and activities of daily living.¹⁴ These subjects also showed an increased requirement for personal care and elevated rates of hospitalization as compared to controls. Another study showed that there was decreased cognition in 63.33% of diabetics as assessed by their MMSE and based on the Modified Mini-Mental State Examination (3MS), 70% of diabetics had a decreased cognition. Hence they concluded that even MCI can be detected by early implementation of MMSE.¹⁵ The early implementation of mini-mental, which is a simple method of execution, can be done to detect the early stages of dementia. This test could be an important tool for assessing the ability of the patients in understanding their disease and treatment.¹³ The MoCA is a measure of global cognitive function and was initially developed to detect MCI but is now commonly used as a screening tool for dementias.^{9,16} As compared to the MMSE, the MoCA is a more detailed testing of executive function and may help in identifying individuals requiring specialist assessment and treatment for dementia.⁸ A recent Cochrane Database of Systematic Review was done to determine the diagnostic accuracy of MoCA at various thresholds for dementia and its subtypes. The review showed that MoCA was effective in dementia detection when a recognised cut-off score of less than 26 was used and that the studies that used this cut-off, the test correctly detected in all settings over 94% of people with dementia.⁸ With this background in the present case-control study we aimed to explore the association and prevalence between T2DM and MCI between non-diabetics and type 2 diabetics.

This study reveals a statistically significant correlation between T2DM and the presence of MCI independent of hypertension. The results of the present study are in agreement to studies by Alencar RC et al and Alagiakrishnan K et al.^{13,17} The results of the present study also suggests that the risk of developing MCI (and hence Alzheimer's disease) increases with duration of disease. The results of our study are consistent with studies conducted by Li W et al and Albai O et al.^{4,5} This association may be partly independent of efficacy of glycemic control. In addition, we did not find the effect of the duration of T2DM and hypoglycemic agents on cognitive function. However, studies have shown that there was a negative correlation between cognitive function and of duration T2DM. Hsu et al reported that both sulfonylureas and metformin independently decrease risk of dementia, and that a combined use of the two drugs decreased the risk of dementia by 35% in patients T2DM for >8 years.¹⁸ These results indicated that this association exists among the Indian population as well.

Thus, results of the present showed significant association between T2DM and MCI. However studies with larger sample size along with assessment of Glycemic status of the patient and detailed data on patient's medication would

probably throw more light on the association.

CONCLUSION

This study established that type 2 diabetes mellitus has a significant statistical association with mild cognitive impairment. This study aims to create an awareness regarding the early neurological manifestations of this rampant disease with the use of sensitive screening tools.

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