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RESEARCH ARTICLE

# Assessment of memory and cognitive functions in controlled and uncontrolled Type 2 diabetes mellitus patients

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## ABSTRACT

**Background:** In Type 2 diabetes (T2D) mellitus, chronic hyperglycemia and hyperinsulinemia with resultant increased advanced glycosylated end products cause the acceleration of the brain aging in its structure and functions. This complication increases the risk of memory and cognitive dysfunctions. **Aims and Objectives:** This study was aimed to compare the memory and cognitive functions between controlled and uncontrolled T2D mellitus patients. **Materials and Methods:** The study is undertaken in the Department of Physiology, Velammal Medical College Hospital, Madurai. 100 known T2D mellitus patients aged between 30 and 50 years of both sexes are included after obtaining informed written consent. Patients with conditions and factors affecting memory and patients with defective hearing and speech are excluded from the study. Recent hemoglobin A1c (HbA1c), fasting blood sugar (FBS), and postprandial blood sugar (PPBS) values are collected from their hospital records. Cognition and memory assessment is done using Mini-Mental State Examination (MMSE) by 30-point questionnaire. **Results:** The average MMSE score of uncontrolled diabetes mellitus is less than the average MMSE score of controlled diabetes mellitus patients (HbA1c<7). Student's unpaired *t*-test among these two groups for MMSE was statistically significant ($P = 0.02$). The duration of diabetes mellitus, FBS, PPBS, and HbA1c showed negative correlation with MMSE score. **Conclusion:** The above result shows that there is more impairment in memory and cognitive functions in the uncontrolled than the controlled diabetes mellitus patients.

**KEY WORDS:** Type 2 diabetes mellitus; Memory and Cognition; Mini-Mental State Examination, Hemoglobin A1c

## INTRODUCTION

Type 2 diabetes mellitus (T2D) is a worldwide prevalent disease and India places among the top three countries with diabetic population. The well-recognized complications of T2D mellitus are neuropathy, retinopathy, and nephropathy. Insulin resistance and hyperglycemia in T2D increases the oxidative stress, leading to these conditions.

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### Angiopathy in T2D

Heredity, family predisposition, and obesity are the etiological factors for insulin resistance. Hyperglycemia as a result of insulin resistance leads to the production of reactive oxidant species (ROS). ROS activates protein kinase C and also increases the production of the advanced glycosylated end products. Activated protein kinase C causes the production of nuclear factor kappa B ($NF_KB$), angiogenesis, and increased cell growth. The receptors for the inflammatory products and thereby permeability to monocytes and the low-density lipoprotein (LDL) into the intimal layer are enhanced by the $NF_KB$. The monocytes transformed into macrophages engulf the LDL to form foam cells. Liberation of lipids and release of TNFα and IL1 from foam cells induces the production of inflammatory products and smooth muscle proliferation into the intimal layer of the blood vessels. The high level

of metabolic toxins and vascular inflammation causes endothelial dysfunctions ensuing micro- and macro-vascular complications.[1]

### Angiopathy Effects on Brain

Effect of micro- and macro-angiopathy due to hyperinsulinemia and hyperglycemia on brain is quite significant to bring about deterioration in its structure and thereby its functions. Neuroimaging and neuropathological studies have confirmed the role of T2D in degenerative changes in the brain.[2]

Brain, significantly the Hippocampus, goes for the atrophic changes, more and faster in aging among T2D than in normal. The decreased blood flow coupled with the stimulation of thromboxane A2 receptor-induced vasoconstriction aggravates cerebral ischemia.[3]

Thickening of capillary basement membrane,[4] hyperglycemia-induced lactate accumulation, and glutamate brings about the neuronal damage accelerating the aging of the structure and functions of the brain.[5]

In a previous study carried out in diabetic patients, assessed cortical and subcortical infarcts and higher incidence of white matter lesions in their brain.[6]

Another study evaluated the cognitive functions and found that the diabetic patients thought processing and execution were low.[7]

Another important dysfunction is depression seen in T2D patients and its prevalence is twice more common than the controls. Depression that may be associated with the T2D also can be a causative factor for the cognitive dysfunction.[8]

Oxidative stress due to the insulin resistance and with the resultant hyperglycemia contributes to the future development of the Alzheimer's disease by tau hyperphosphorylation,[9] β-amyloid deposition, and mitochondrial dysfunction.[10] Considering the significant effect of T2D on brain structure and functions, cognitive dysfunction is assessed and compared between the controlled and uncontrolled diabetic patients in this study.

### Aim

This study aims to assess and compare the cognitive functions in the controlled and uncontrolled T2D mellitus patients.

### Objectives

The objectives of this study were as follows:

- To assess the fasting blood sugar (FBS), postprandial blood sugar (PPBS), and hemoglobin A1c (HbA1c) in T2D patients.
- To assess the cognitive and memory functions using MMSE questionnaire in controlled and uncontrolled T2D patients.
- To compare the blood parameters with cognition in both controlled and uncontrolled T2D patients.

## MATERIALS AND METHODS

Institutional ethical committee clearance was obtained before the start of the study.

This comparative study was done in the Department of Physiology, Velammal Medical College Hospital and Research Institute (VMCHRI), Madurai, Tamil Nadu, India. 50 known T2D mellitus (T2D) patients of both the genders within 30–50 years of age attending the medicine Outpatient Department in VMCHRI are included in this study. The criteria of minimum high school education of the patients are considered for the assessment of cognition by MMSE scale. The informed written consent was obtained from all the participants before the study.

The duration of the study was 3 months. The recent blood parameters such as FBS, PPBS, and HbA1c are collected from their hospital records. HbA1c was done by high-performance liquid chromatography method and FBS and PPBS were done by glucose oxidase-peroxidase method in the hospital biochemistry laboratory.

Cognition and memory assessment was done by the Mini-Mental State Examination (MMSE).[11] MMSE is a 30-point questionnaire which is used extensively in clinical and research settings to measure cognitive impairment.

MMSE can also be used to estimate the severity and progression of cognitive impairment. Administration of this test takes between 5 min and 10 min. The domains of the cognition examined are registration, attention, calculation, recall, language, ability to follow simple commands, and orientation.[12]

This study excluded Type 1 diabetes mellitus patients, diabetes patients with hypertension and T2D <30 years and >50 years of age, those patients with the other ailments that might be causative factors for the decline in learning and memory, and finally, those T2D patients with speech difficulties, learning disorders, and mental disorders.

### Statistical Analysis

Values were tabulated and analyzed in SPSS 20 version.

The following data have been done by:

- Frequency table
- Descriptive statistics: Mean, standard deviation, and Pearson correlation.

## RESULTS

Tables 1-4 depict the distribution of the patients according to gender, diabetes status, drug intake, and treatment compliance, respectively. Controlled and uncontrolled patients highly differed on the basis of cognitive score, as the significance value is <1% level. Controlled patients have more cognitive score compared with uncontrolled patients [Table 5 and Figure 1]. Table 6 and Figure 2 show significant difference in the cognitive score among patients who took regular treatment and patients with irregular treatment. Since the difference is highly significant ($P < 0.01$), i.e., patients, who take regular treatment, did not have the cognitive impairment, while patients, who take irregular treatment, had the marginal level of cognitive impairment.

## DISCUSSION

In the present study, the patients who were having HbA1c levels more than seven were considered to be in the uncontrolled state. From this study, the impact of age and sex of T2D mellitus patients over cognitive functions is not found to be present. High level of blood glucose was observed both in the fasting and postprandial state in the uncontrolled T2D patients. On comparison, MMSE score assessed in uncontrolled is lower than the controlled state T2D patients. The low MMSE score indicates the impairment of the memory and cognitive functions in these patients. 98% of T2D patients in this study are taking oral hypoglycemic drugs. These drugs induce endogenous secretion of insulin which may cause frequent episodes of hypoglycemia in these patients. T2D patients in this study with the regular treatment had good control over their HbA1c level and their MMSE score showed no decline in their cognitive functions, while patients who are irregular in their treatment suffer with marginal level of cognitive dysfunctions.

**Table 1:** Distribution of male and female patients

| Gender | Frequency (%) |
|---|---|
| Male | 24 (48) |
| Female | 26 (52) |

**Table 2:** Distribution of controlled and uncontrolled diabetics

| Diabetes | Frequency (%) |
|---|---|
| Controlled | 8 (16) |
| Uncontrolled | 42 (84) |

**Table 3:** Distribution of drug intake

| Metformin and sulfonylurea intake | Frequency (%) |
|---|---|
| Yes | 49 (98) |
| No | 1 (2) |

These findings of cognitive dysfunction with chronic hyperglycemia as indicated by the raised HbA1c level correlate well with the earlier reports.[13] The effect of prolonged hyperglycemia on cognitive function is attributed to the oxidative stress-induced changes in the structure and the metabolism in the neurons. These changes alter the electrophysiological properties of the neurons, culminating to advanced brain aging in the uncontrolled T2D patients. This finding can be referred with the previous study.[14] Hypoglycemic episodes are again another important risk factor for the neuronal degeneration, leading to subsequent cognitive decline in T2D patients may be correlated with supportive evidence of the earlier studies.[15,16] The effect of regular treatment compared with irregular treatment on cognitive functions correlates with the study of Meilly[17] and a study done by Gradman.[18] A previous study supports the fact that insulin resistance with hyperglycemia in T2D causes oxidative stress to the cerebral vasculature and promotes deposition of senile plaques of beta-amyloid which Christopher T Kodi denotes it as the hallmark of dementia in Alzheimer's disease.[5] All the above said factors have contributed to the cognitive decline in the uncontrolled T2D patients when compared with the patients who have good control over their HbA1c level with the regular treatment.

The finding that the patients with regular treatment and good control with HbA1c levels have better cognition when compared to the patients having uncontrolled HbA1c level with irregular treatment, is well established from their laboratory reports, and cognitive assessment is the strength of this study. Limitation of the study is the inclusion of patients who are over the age of 40 years may also have decline in cognitive functions due to aging.

**Table 4:** Distribution of treatment compliance

| Treatment | Frequency (%) |
|---|---|
| Regular | 32 (64) |
| Irregular | 18 (36) |

**Table 5:** Difference in the MMSE scores among controlled and uncontrolled T2D patients

| T2D patients | MMSE score Mean±SD |
|---|---|
| Controlled | 25.25± 4.17 |
| Uncontrolled | 21.26±3.28 |

*$P$ value=0.004

**Table 6:** Difference in the cognitive score between T2D patients with regular treatment and irregular treatment

| Treatment | MMSE score (Mean±SD) | *P*-value |
|---|---|---|
| Regular | 23.13±2.45 | 0.007** |
| Irregular | 19.72±4.55 | |

**$P$<0.01, T2D: Type 2 diabetes mellitus, MMSE: Mini-Mental State Examination

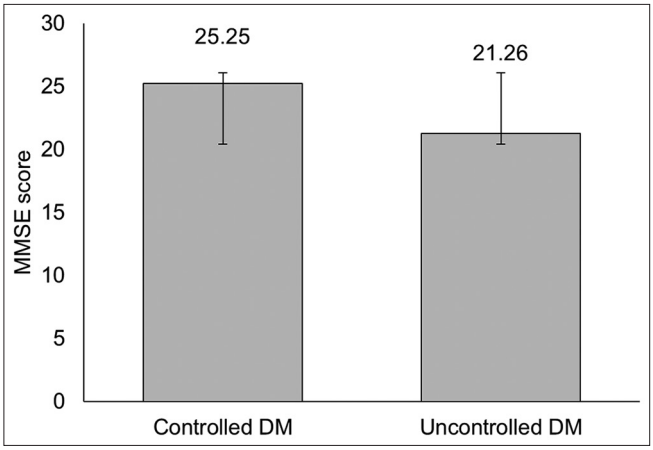


**Figure 1:** Mini-Mental State Examination scores for controlled and uncontrolled diabetes mellitus

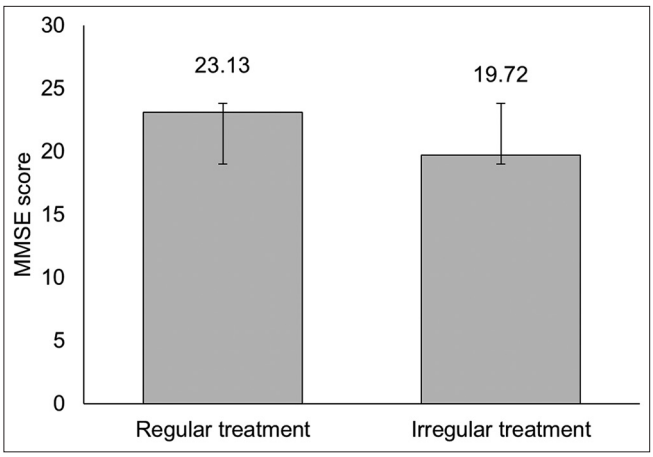


**Figure 2:** Mini-Mental State Examination scores for patients with regular and irregular treatment

## CONCLUSION

T2D mellitus being a common prevailing disorder present globally, cognitive decline becomes a major health and social issue in these patients. Considering T2D is a risk factor to memory impairment and cognitive dysfunction, figuring out the ways to ward off effectively the complications of this disease becomes an important step to prevent this hazard. T2D patients on intensive blood glucose management with insulin and sulphonylureas must be closely monitored for hypoglycemic episodes which are a risk factor for further development of neurophysiological complications. A study states that hypoglycemia-induced neuronal damage may be prevented by the administration of the N-methyl-D-aspartate antagonists.[19] Another study indicates, minocycline prevents hypoglycemia-induced neuronal death.[20] Early management of blood glucose level, effective control of the HbA1c level, appropriate management of the diet with regular exercise, and treatment might help to alleviate the future cognitive decline and subsequent development of dementia in the T2D patients.

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