



# Cognitive decline in type II diabetes mellitus among post-menopausal women: A cross-sectional study in South India

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## ABSTRACT

This study was contemplated to ascertain the occurrence of cognitive impairment and explore the relationship between cognition and diabetes mellitus type 2 (T2DM) in post-menopausal women. The present cross-sectional study was conducted in the community setting in and around Anaicut Panchayat, Vellore, over 6 months (July 2023 to Dec 2023). Post-menopausal women with T2DM in the age group of above 35 years were included. The Montreal Cognitive Assessment (MoCA) scale was utilized to evaluate the cognitive function. Glycated hemoglobin (HbA1c) was also measured. The acquired data were analyzed using IBM Statistical Package for the Social Sciences (SPSS) software version 23. The inclusion criteria were met by 188 subjects. The diabetic women who were involved in the study have an average age of 57 years. The current study population evinced a mean MoCA score of  $20.91 \pm 3.99$  and a mean HbA1c level of  $9.27 \pm 2.45$  suggesting a strong link between cognitive dysfunction and hyperglycemia. 67% of the study subjects exhibited mild cognitive impairment (MCI). A noticeable inverse relationship was found between MoCA score and duration of T2DM ( $r = -0.744$ ) as well as between MoCA score and HbA1c ( $r = -0.769$ ). This study suggested that the duration of T2DM and the level of HbA1c have an antithetical influence on cognitive function. Due to the higher prevalence exists for MCI in diabetic patients, it is recommended that healthcare professionals should assess cognitive function in diabetic patients in their routine clinical practice to prevent the progression of dementia.

## INTRODUCTION

Cognition and diabetes mellitus are complex and multifaceted conditions in the current scenario that have been subject to extensive research. The prevalence of diabetes mellitus is escalating every year. As per the report of the Indian Council of Medical Research published in 2023, the prevalence of diabetes mellitus is 10.1 crore. It is predicted that by 2045, the prevalence of T2DM in India will increase to 134 million [1]. It devastates many organs of the human

body. Among the diverse complications of diabetes, an underdiagnosed and less addressed complication is cognitive impairment. Various studies conducted in animal models and humans have suggested that there is a strong connection between diabetes and dementia. Learning and memory skills seem to be controlled by insulin and glucose. The abnormal glucose metabolism and impaired insulin function noticed in diabetic patients are intensely connected with cognitive dysfunction. A constant rise or drop in the blood sugar level leads to brain damage and cognitive decline. Throughout the world, over 55 million people were living with dementia in 2020, and it doubles every 20 years; by 2050, it will reach 139 million [2,3]. There are more women with T2DM compared to men. The association between women and T2DM is stronger, especially in overweight, physically inactive women, and women undergoing menopausal transition [4]. The connection between menopause and diabetes remains a query and is

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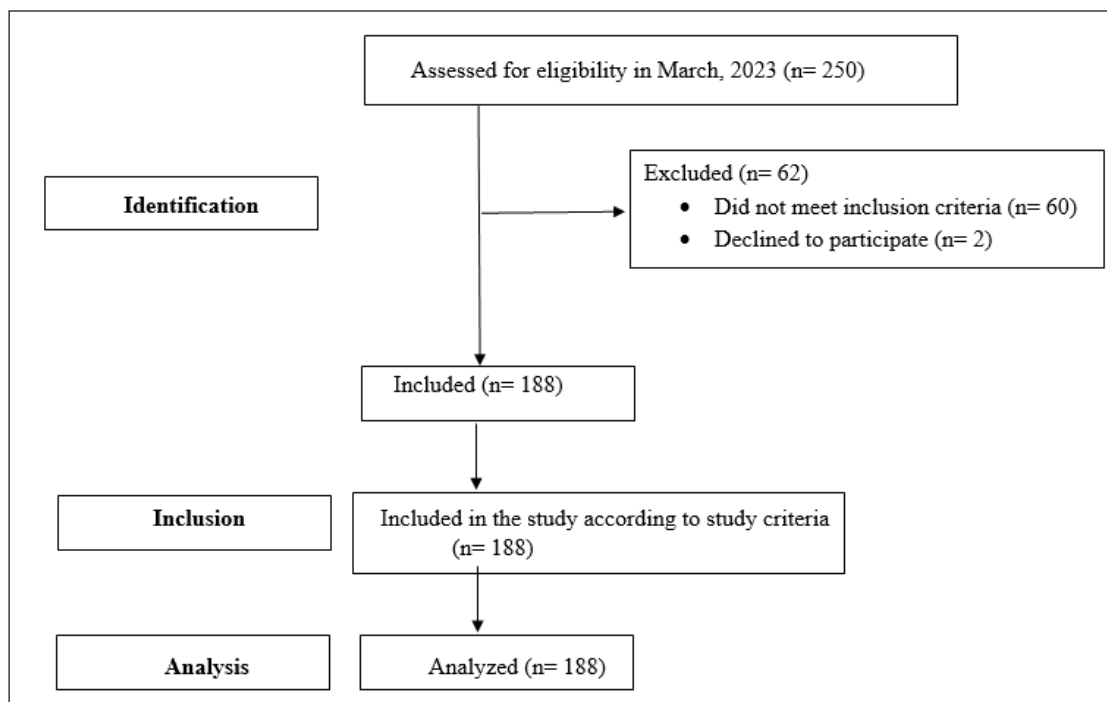


Figure 1. STROBE flow chart.

often reported to be the most common chronic disease among women. The notable decrease in the production of endogenous estradiol after menopause results in a relative increment in androgenic effects and body composition changes, which are believed to influence pancreatic  $\beta$ -cell functioning, hepatic glucose output, and glucose transport [5,6]. The induction of glycolytic enzymes and glycogen synthetase by estrogen has been thought to regulate the capacity of pancreatic islet cells to produce insulin [7]. The estrogen signaling pathway has been demonstrated to be important in regulating glucose homeostasis. Lack of estrogen receptor- $\alpha$  causes both insulin insensitivity and glucose intolerance in mice, rather than estrogen receptor- $\beta$  (Er $\beta$ ) [8].

The occurrence of earlier menopause is found to predispose a woman to develop diabetes, cardiovascular diseases, and osteoporosis. Contrary to the above statement, a delay in menopause elevates the likelihood of developing endometrial and breast cancer [9]. Generally, the incidence of diabetes and glucose intolerance increases after 40 years of age. Women aged 50 years exhibited a lower prevalence of diabetes than women in their 60s and 70s, who had a greater risk of developing the condition [10]. A study conducted in female Japanese individuals without diabetes revealed that hyperglycemia developed independently in postmenopausal women with a significant association, irrespective of demographic, age, and metabolic factors. Menopause and advanced age might have a linear influence on the increased likelihood of dysglycemia in Japanese women [11].

T2DM in elderly women increases the risk of brain atrophy that causes problems with memory, and thinking that eventually lead to vascular dementia. Females diagnosed

with T2DM have a higher likelihood of experiencing rapid cognitive decline than males. The duration of diabetes has a significant effect on the severity of cognitive impairment [12,13]. Cognitive impairment is influenced by both T2DM and the reduction in estrogen levels during perimenopause. Regular physical activity and estrogen replacement therapy seem to possess beneficial hypoglycaemic effects by enhancing the ability of  $\beta$ -cells to secrete insulin [14]. There is a vital demand for propitious health resources centered on dementia related to T2DM. Furthermore, a recent study carried out in Mysuru entrenched that there is a higher prevalence of cognitive impairment among T2DM patients but the association was not concluded due to the inaccessibility of HbA1c data [15]. On this burden, this study has been designed to explore a better understanding of the significant association between cognitive performance and T2DM by measuring HbA1c, especially among post-menopausal women in the community setting.

## MATERIALS AND METHODS

### Study design

The present cross-sectional study was carried out in the community setting in and around Anaicut, Vellore District, for a period of 6 months, from July 2023 to December 2023. The study protocol was approved by the Institutional Ethics Committee of the PM Medical Centre, Vellore, India (Approval No.: EC/2023/01), and the research was carried out in compliance with the Helsinki Declaration. Written informed consent was acquired from the study subjects before they were included in the study. The STROBE guideline has been followed for this study design, and the flow chart is shown in Figure 1.

**Table 1.** Baseline characteristics.

Variable	Mean $\pm$ SD/ n (%)
Age (years)	57.09 $\pm$ 7.83
	<45
	2 (1)
	46–50
	39 (21)
	51–55
	48 (26)
Age interval (years)	56–60
	46 (24)
	61–65
	31 (16)
	66–70
	10 (5)
	>70
	12 (6)
Age for menarche (years)	13.21 $\pm$ 0.82
Age for menopause (years)	46.56 $\pm$ 3.35
BMI (Kg/ m <sup>2</sup> )	23.96 $\pm$ 4.03
Literacy background	Illiterate
	118 (63)
	Literate
	70 (37)
	Mixed
	164 (87)
Food habit	Vegetarian
	24 (13)
	Betel nut
	63 (34)
Substance abuse	Nil
	125 (66)
	House wife
	0 94 (50)
Occupation	Office
	33 (17)
	Daily wages
	0 31 (25)
	Teacher
	10 (8)
	Osteoporosis
	21 (11)
	Hypertension
	28 (15)
	COPD
	7 (4)
Comorbidity	Asthma
	4 (2)
	Breast cancer
	1 (1)
	Coronary artery disease
	3 (2)
	None
	128 (68)
	Yes
	40 (21)
Family history of DM	No
	148 (79)
HbA1c (%)	9.27 $\pm$ 2.45
Duration of DM (years)	4.67 $\pm$ 1.23

### Study population

This study included post-menopausal women with T2DM above 35 years of age and those who could read and write English or Tamil languages. This study excluded post-menopausal women without T2DM, those who are physically incapable of reading, hearing, or comprehending written or explained instructions properly, or who may have a motor impairment that impairs their writing and drawing skills, and those who are not willing to participate.

### Sample size calculation

The sample size was estimated using the  $n = Z^2P(1-P)/d^2$  formula, resulting in a sample size of 188. Based on a pilot study, the standard normal variate ( $Z$ ) at 5% is 1.96, the estimated population proportion ( $P$ ) is 0.143, and the absolute error ( $d$ ) is 5%.

**Table 2.** Cognitive function using MoCA.

Cognitive function	N	%
Normal	47	25
Mild cognitive impairment	126	67
Moderate cognitive impairment	15	08
Severe cognitive impairment	0	0

### Montreal cognitive assessment (MoCA) scale

A standard and validated MoCA scale has been adapted in English and Tamil languages to assess the cognitive function of the study subjects. The scale was used after obtaining proper permission. It is a highly sensitive tool for discerning mild cognitive impairment (MCI). MoCA examines language, memory, visual thinking, orientation, and reasoning skills. The highest achievable score on the MoCA assessment is 30. A score of 26–30 signifies the absence of cognitive impairment, while a score between 18 and 25 indicates MCI. A score ranging from 10 to 17 suggests moderate cognitive impairment, whereas a score below 10 indicates severe cognitive impairment [16].

### Estimation of HbA1c

A blood sample of 2 ml was obtained from the study subjects by venous puncture and transferred into a vacutainer. After that, the aliquots were transferred into Eppendorf tubes and preserved at a temperature of  $-20^{\circ}\text{C}$  until further analysis. The quantification of HbA1c was performed by the high-performance liquid chromatography method.

### Statistical analysis

Data analysis was done using IBM SPSS version 23. Descriptive statistics were reported as mean (SD) for continuous variables and frequency (percentage) for categorical variables. Pearson's correlation coefficients were employed to evaluate the association between the MoCA score and the duration of T2DM and HbA1c. A statistical significance was indicated by a  $p$ -value of less than 0.05.

## RESULTS

### Socio-demographic and clinical details

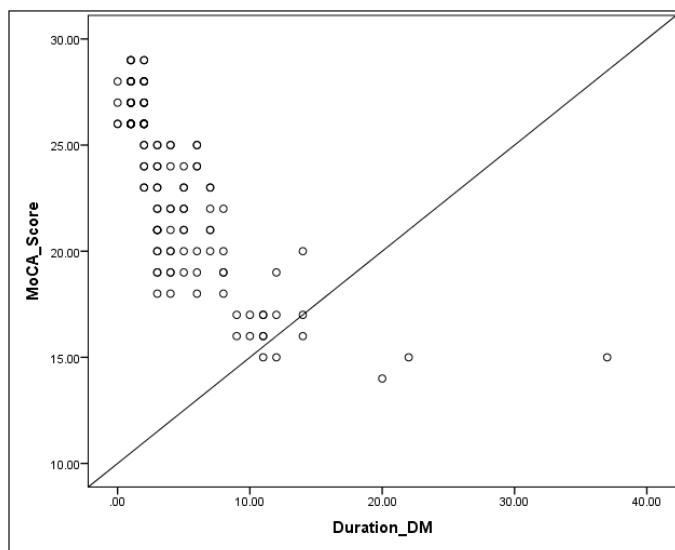
After screening, 188 subjects were included in this study. A significant proportion of the study subjects were in the age bracket of 51–55 years, accounting for 26% of the population. Subsequently, the age range of 56–60 years constituted 24% of the study population. The most common comorbidities observed in this study subjects were hypertension (28%) and osteoporosis (21%). Only 1% of the subjects had breast cancer as shown in Table 1.

### Assessment of cognitive function

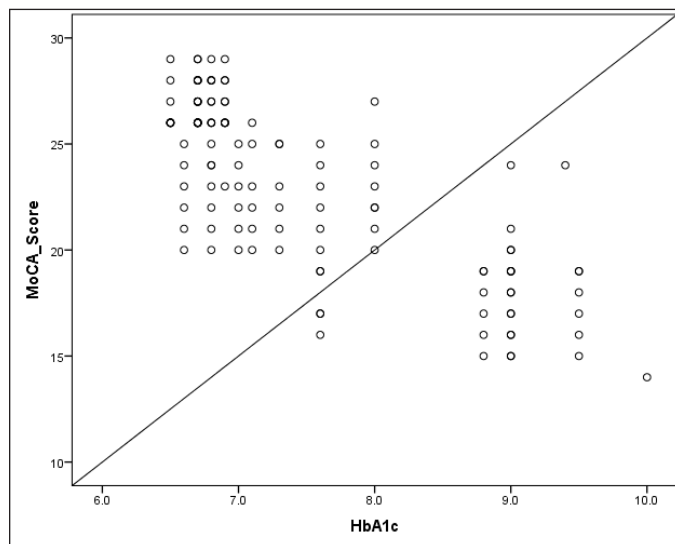
The cognitive function of post-menopausal women was assessed using the MoCA scale as shown in Table 2. The majority of the women were with MCI (67%) followed by normal cognitive function (25%). The mean and SD of the MoCA score and duration of T2DM were  $20.91 \pm 3.99$  and 4.67

**Table 3.** Mean of subdomain and total MoCA score.

Cognitive domain	Maximum score	Mean $\pm$ SD
Visuospatial/Executive function	5	1.92 $\pm$ 0.16
Naming	3	2.49 $\pm$ 0.08
Attention	6	3.64 $\pm$ 0.13
Language	3	1.78 $\pm$ 0.09
Abstraction	2	1.03 $\pm$ 0.11
Delayed recall	5	1.10 $\pm$ 0.17
Orientation	6	5.82 $\pm$ 0.12
Total score	30	20.91 $\pm$ 3.99



$$r = -0.744, p = 0.0004$$

**Figure 2.** Correlation of MoCA score with duration of T2DM.

$$r = -0.769, p = 0.0002$$

**Figure 3.** Correlation of MoCA score with HbA1c.

$\pm 1.23$ . The performance score in each cognitive subdomain and the total MoCA score are outlined in [Table 3](#).

### Correlation of MoCA with duration of DM and HbA1c

An association between the MoCA score and duration of T2DM as well as between the MoCA score and HbA1c was established to correlate the influence of hyperglycemia on cognitive impairment as depicted in [Figures 2 and 3](#).

### DISCUSSION

The current study was designed to discern the connection between cognitive function and T2DM in postmenopausal women. Women with T2DM have a higher chance of developing diabetes-associated complications than males. The majority of the study population lies within an age range of 51–55 years (26%), and the average age was 57 years. This study depicted the average age for menarche and menopause to be 13 years and 46 years, respectively. With advancing age, cognitive function tends to decline naturally. This decline is worsened and accelerated in individuals with diabetes when compared to those without diabetes. In a study performed by Bjelland *et al.* [17] the average age for menarche was 13 years, whereas menopause was in the range of 49–54 years. The average age of menopause seems to vary depending on geographic and racial differences.

The mean BMI of subjects was found to be 23.96, which falls under the normal BMI category. Some studies have shown that women with higher BMI are related to impaired glucose tolerance independent of menopause, and changes in adiposity in postmenopausal women with higher BMI predispose to elevated fasting blood glucose levels [18]. Women with early menopausal age have a higher likelihood of being affected by hypertension, chronic obstructive pulmonary disease, osteoporosis, asthma, peptic ulcer, and breast cancer which abides with our study as shown in [Table 1](#). The common comorbidities noticed in our study were hypertension and osteoporosis [19,20].

Cognitive function was assessed using the MoCA scale, which is a comprehensively accepted tool with high sensitivity and specificity. In addition, we measured the level of HbA1c to evaluate its association with cognitive function. The current study population evinced a mean MoCA score of  $20.91 \pm 3.99$  and a mean HbA1c level of  $9.27 \pm 2.45$ . The range of cognitive impairment can vary from mild to severe dementia. Early recognition of cognitive decline could improve the management of the condition. In this study, 67% of women had MCI, and 8% had moderate cognitive impairment. Only 25% of the women had normal cognitive function as shown in [Table 2](#). These outcomes are in line with the previous study performed by Lalithambika *et al.* [21]. The performance score of the diabetic population in each cognitive subdomain was assessed. The diminished score was seen in domains including delayed recall, attention, and visuospatial/executive function. However, modest scores in the domains including naming, language, abstraction, and orientation were observed as exhibited in [Table 3](#). These results are congruent with the earlier investigation conducted by Kinattungal *et al.* [15].

The complex nature of diabetes, specifically oxidative stress, vascular changes, and chronic inflammation, makes hyperglycemia a vulnerable component for developing Alzheimer's disease and vascular dementia [22]. A noticeable inverse relationship was found between the MoCA score and duration of T2DM ( $r = -0.744$ ), the MoCA score and HbA1c ( $r = -0.769$ ), suggesting a strong link between cognitive dysfunction and hyperglycemia, as shown in Figures 2 and 3. High blood sugar changes cerebral structure and function. The occurrence of cognitive impairment and dementia is 1.5 times greater in individuals with hyperglycemia when compared to healthy individuals. The longer duration of DM has also been shown to be one of the risk factors for cognitive dysfunction [23]. Besides that, estrogen exerts neurocognitive effects through its action on brain regions such as the hippocampus and prefrontal cortex. Estrogen counteracts the negative influence of cortisol on cognitive function. A noticeable surge in follicle-stimulating hormone and a simultaneous decline in estradiol are noticed in the menopausal transition [24]. Hence, a fall in estrogen levels in addition to T2DM affects the cognitive function of post-menopausal women. However, estrogen level was not measured in our study. Hence, further research is imperative to establish a correlation between cognitive function and T2DM among post-menopausal women by considering the estrogen level and other reproductive factors along with the HbA1c level which may act as independent factors in developing cognitive dysfunction.

Our study highlights that the escalation of HbA1c diminishes the cognition of hyperglycemic patients. This would be the first community-based study in South India to enlighten the association between cognition and T2DM in post-menopausal women based on real-world data. The limitations of the study were a single-center study and a smaller sample size.

## CONCLUSION

Our study emphasizes the significance of a strong correlation between cognitive function and T2DM. Three-fourths of the present study population had mildly declined cognitive function. This study will be the first step to shed light on the impact of diabetes-associated cognitive dysfunction among post-menopausal women in South India. On the basis of this obtained evidence, this study drags attention to healthcare professionals in demonstrating effective prevention strategies to mandate the importance of screening cognitive performance routinely and early. This study also opens new avenues of future research to probe into the depth of knowledge on cognition and diabetes among post-menopausal women.

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## AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and

interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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## CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

## ETHICAL APPROVALS

The study protocol was approved by the Institutional Ethics Committee of the PM Medical Centre, Vellore, India (Approval No.: EC/2023/01), and the research was carried out in compliance with the Helsinki Declaration. Written informed consent was acquired from the study subjects before they were included in the study. The STROBE guideline has been followed for this study.

## DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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## USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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