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Research Article

ASSOCIATION BETWEEN RISK FACTORS AND COGNITIVE IMPAIRMENT AMONG TYPE II DIABETES MELLITUS PATIENTS

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Abstract: *Diabetes mellitus type II is considered one of the leading causes of illness and mortality over the globe. Diabetic retinopathy, neuropathy, and nephropathy are all effectively screened on a regular basis. Recent research has shown that cognitive deterioration can occur in patients with diabetes and that it can go unnoticed for a long time, implying that routine screening is necessary. An observational cross-sectional study was conducted among 158 patients with a complaint of Type II Diabetes Mellitus aged between 60-79 years of age were found with cognitive impairment on the basis of Mini-mental Score Examination (MMSE) in a tertiary care center. Detailed history along with laboratory and biochemical data were taken from patients after taking written informed consent and approval of the Institutional Ethical committee through the pre-structured questionnaire. Mild cognitive impairment was noted in 88 (55.69%) type II diabetes mellitus patients and Normal cognitive function in 70 (44.30%). Those with Mild Cognitive Impairment had higher HbA1c (6.57 ± 1.27 vs. 6.13 ± 1.22), higher Fasting Blood Sugar (148.34 ± 18.61 vs. 145.25 ± 16.31), Post Prandial Blood Sugar (173.91 ± 42.64 vs. 167.47 ± 38.15) and Tumor Necrosis Factor-α (79.32 ± 8.74 vs. 72.98 ± 6.76), which were statistically significant. The cognitive domains of executive function, naming, attention, language, and memory showed a statistically significant difference between those with Mild cognitive impairment and Normal cognitive function. There were no differences in the mean age, duration of disease, and education level between the groups. The significant prevalence of Mild cognitive impairment in type II diabetes patients emphasizes the value of routine screening of cognitive functions. Further research into the link between cognitive impairment and poor blood glucose control is needed to see if improving blood glucose control can assist in enhancing cognitive functions.*

Keywords: *Cognitive impairment, Type II diabetes mellitus, MMSE, Risk factors, TNF-α*

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1. Introduction

The major risk factors for Type II diabetes mellitus (T2DM), are characterized by relative insulin deficiency and insulin resistance, sedentary lifestyle, and obesity [1]. The prevalence of T2DM is increasing in developing and developed countries because of changes in socioeconomic factors and the increased practice of unhealthy lifestyle habits [2]. T2DM is associated with cognitive impairment and exhibiting worse cognitive ability and more abnormalities on brain imaging than individuals without

diabetes [3,4]. The prevalence is particularly higher for mild cognitive impairment (MCI) in T2DM patients older than 65 years [5]. Multiple long-term epidemiological studies have implicated T2DM as a risk factor for cognitive impairment and dementia in the elderly [6,7].

The causes underlying T2DM patients' cognitive impairment and brain anatomical abnormalities are still unknown. Several risk factors for Mild cognitive impairment in T2DM patients have been identified, including vascular risk factors, macrovascular diseases, microvascular complications, poor glycaemic control, increased insulin level, increased oxidative stress, accumulation of amyloid-beta peptide and tau hyperphosphorylation, and decreased nerve growth factor [3, 7, 8]. However, the significance of such impairment is generally overlooked in favour of other T2DM consequences; there are no specific tools for avoiding or correcting cognitive deficiencies in diabetic patients [9]. Given that early-stage therapies for cognitive impairment are somewhat effective [10], it's crucial to understand the features of MCI in T2DM patients and to discover the most efficient diagnostic indicators for Mild cognitive impairment in these patients.

The aim of the current study was to determine the characteristics of cognitive impairment in T2DM patients in this age range, as well as to identify potential risk factors and biomarkers based on the demographic and clinical parameters of the patients. This knowledge could aid efforts to detecting MCI in T2DM patients early on.

2. Materials and Methods

The present study was conducted among 158 patients with the complaint of T2DM aged between 60-79 years of age who were found with cognitive impairment on the basis of MMSE score in Rajeev Gandhi Centre for Diabetes & Endocrinology and Department of Physiology on patients of Type II Diabetes Mellitus attending Diabetes clinic in Jawaharlal Nehru Medical College hospital, Aligarh Muslim University after approval from Institutional ethical committee dated 17.11.2011. Detailed history along with laboratory and biochemical data were taken from patients after taking written informed consent through the pre-structured questionnaire. The study was extracted by the thesis done for the fulfillment of a Master's Degree (MD) in Physiology after ethical approval of the Institutional Ethical Committee Ethics Committee, Faculty of Medicine, Jawaharlal Nehru Medical College, Aligarh Muslim University dated 17.11.2011.

Tumour Necrosis Factor-alpha (pg/ml) (TNF-α) ELISA in vitro of enzyme-linked immunosorbent assay kit (Gen-Probe Diaclone) was used for the quantitative measurement of human TNF-α in serum of selected study subjects. The test was performed in the departmental laboratory of the Department of Biochemistry, Jawahar Lal Nehru Medical College, Aligarh Muslim University, Aligarh, India.

Only T2DM patients aged 60-79 years were included on the basis of diagnosis of diabetes from revised American Diabetic Association Criteria i.e. fasting plasma glucose >126 mg/dl (> 6.1 mmol/1) and 2 hours postprandial plasma glucose >200 mg/dl (>11.1 mmol/1) along with those given written informed consent were included in the study. Any systemic condition other than T2DM related to neuropathy (malnutrition, alcoholic neuropathy, renal failure), known case of chronic depression, psychiatric illness, neuropathies associated with exogenous toxic agents, metals or drugs, and pregnant women with HRT were excluded from the study.

The data were collected and entered in MS excel 2010. Different statistical analyses will be performed using R software version 4.0.2. The one-sample Kolmogorov – Smirnov test will be employed to determine whether the data sets differed from a normal distribution or not. Normally distributed data were analysed using parametric tests and non-normally distributed data were analysed using non-parametric tests. Descriptive statistics were calculated for qualitative and categorical variables. Graphical representation of the variable was shown to understand the results clearly. An Independent T-test or student t-test was applied to measure the mean difference between the two groups.

The correlation was estimated to measure the strength of the relationship between two or more quantitative variables.

3. Results

Table 1 illustrates the demographic profile of the study subjects. The age of the subjects are categorized into two groups .i.e. 60-67 years and 68-79 years. It is found that subjects are maximum from 60-67 years (53.8%) followed by 68-79 years (46.2%). The BMI of the study subjects are maximum >25 (46.8%) followed by 18.5-24.9 (30.4%) and <18.5 (22.8%). The Mini-Mental Score Examination (MMSE) is maximum in 18-23 (55.7%) followed by 24-30 (44.3%).

Table 1. Distribution of Demographic Profile of study subjects

Variables	Categories	n	%
Age Groups	60-67 years	85	53.8
	68-79 years	73	46.2
Body Mass Index	<18.5	36	22.8
	18.5-24.9	48	30.4
	>25	74	46.8
Mini-Mental Score Examination	18-23	88	55.7
	24-30	70	44.3

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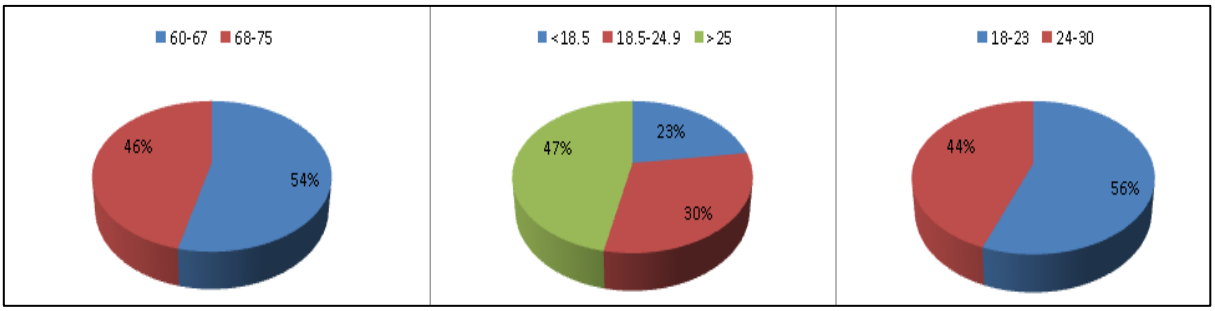

Figure 1. Graphical Representation of Age-groups, Body Mass Index and Mini-Mental State Exam score

Table 2 illustrates the MMSE of the study subjects. The MMSE of the subjects are categorized into five sub-categories .i.e. Orientation, Registration, Attention & Calculation, Recall and Language. It is found that subjects in Orientation were maximum in 8th and 9th score which is 33.5% and 27.2% respectively. In Registration, score is maximum in 2nd (77.8% followed by 3rd score (13.9%). In Attention & calculation, all study subjects is in 3rd score (100%). In Recall, all study subjects is in 1st score (100%). In Language, maximum score is 7 (98.7%) followed by 8th and 9th score in MMSE which was 0.6% in each scores.

Table 2. Distribution of Mini-mental Score Examination (MMSE) scores at different categories among subjects

Variables	Categories	n	%
Orientation	7.0	40	25.3
	8.0	53	33.5
	9.0	43	27.2
	10.0	22	13.9
Registration	1.0	13	8.2
	2.0	123	77.8
	3.0	22	13.9
Attention & Calculation	3	158	100.0
Recall	1	158	100.0
Language	7	156	98.7
	8	1	0.6
	9	1	0.6

Table 3 illustrates the minimum value, maximum value, mean and standard deviation of various socio-demographic variables and clinical parameters. Total 158 study subjects are in this study. The mean age of subjects is 69.48 years with 4.75 standard deviation, the mean weight of subjects is 62.61 kg with 10.34 standard deviation, the mean height of subjects is 1.58m with 0.08m variability, the mean BMI of subjects is 27.16 with 4.59 standard deviation, the mean blood sugar (fasting) of subjects is 156.62 with 17.40 variability, the mean blood sugar (postprandial) of subjects is 243.37 with 30.18 variability, the mean TMF-α of subjects is 62.51 with 13.25 variability, the mean HbsA1C of subjects is 8.44 with 1.25 variability. The mean total score (MMSE) among the study subjects is 23.30 with standard deviation of 2.66 in the study.

Table 3. Description of socio-demographic and clinical parameters

Descriptive Statistics	N	Minimum	Maximum	Mean	S.D.
Age (yrs)	158	61.0	75.0	69.85	4.76
Weight (kg)	158	45.05	84.20	62.62	10.35
Height (m)	158	1.4	1.7	1.58	0.083
Body Mass Index	158	19.03	34.90	27.17	4.59
Blood Sugar (Fasting) (mg/100ml)	158	129.90	187.08	156.62	17.40
Blood Sugar (Post prandial) (mg/100ml)	158	198.78	293.74	243.38	30.19
Tumour Necrosis Factor-alpha (pg/ml)	158	34.71	93.43	62.52	13.26
Hemoglobin A1C (%)	158	7.48	10.95	8.44	1.25
Total Score	158	19.0	29.0	23.30	2.67

Table 4 illustrates the mean difference between the various socio-demographic variables, clinical variables and the Mini-Mental Score Examination (MMSE). It is found that there is statistical significance difference (p-value<0.05) in age, weight, Blood sugar fasting, blood sugar postprandial, tumour necrosis factor-alpha (TNF-α), Haemoglobin A1C (HbsA1C) and Mini-Mental Score Examination **(**MMSE). Furthermore, It is found the statistical insignificant difference (p-value>0.05) between Height, body mass index and Mini-Mental Score Examination (MMSE).

Table 4. Comparison of sociodemographic and clinical parameters with MMSE score

Variables Name	Mini-Mental Score Examination	n	Mean	S.D.	95% CI (LL-UL)		p
Age	18-23	88	66.10	4.76	-3.17	-.19	.027*
	24-30	70	67.78	4.61			
Weight (kg)	18-23	88	64.16	10.0	0.26	6.73	.034
	24-30	70	60.66	10.51			
Height (m)	18-23	88	1.58	0.08	-0.02	.02	.837
	24-30	70	1.58	0.08			
Body Mass Index	18-23	88	24.42	4.38	-0.88	2.02	.437
	24-30	70	23.85	4.85			
Blood Sugar (Fasting) (mg/100ml)	18-23	88	148.34	18.61	-8.59	2.41	.026*
	24-30	70	145.25	16.31			
Blood Sugar (Postprandial) (mg/100ml)	18-23	88	173.91	42.64	-18.28	7.15	.038*
	24-30	70	167.47	38.15			
Tumour Necrosis Factor-alpha (pg/ml)	18-23	88	79.32	8.74	2.24	7.35	.003**
	24-30	70	72.98	6.76			
Hemoglobin A1C (%)	18-23	88	6.57	1.27	-0.64	.148	.032*
	24-30	70	6.13	1.22			

*:p<0.05; **:p<0.01

Table 5 shows the strength of relationship between the various socio-demographic variables, clinical parameters and the Mini-Mental Score Examination (MMSE). It is found that there is weak positive correlation between age, body mass index, blood sugar (postprandial) and MMSE. Moreover, there is negative correlation between the blood sugar fasting and the MMSE. Furthermore, there is positive correlation between TNF-α, HbsA1C and the MMSE.

Table: 5. Correlation of socio-demographic and clinical parameters with total MMSE score

Variables	Statistics	Total Score
Age (yrs)	r	.115
	p	.152
Body Mass Index	r	.055
	p	.023*
Blood Sugar (Fasting) (mg/100ml)	r	-.138
	p	.044*
Blood Sugar (Postprandial) (mg/100ml)	r	.342
	p	.026*
Tumour Necrosis Factor-alpha (pg/ml)	r	.576
	p	.001**
Hemoglobin A1C (%)	r	.638
	p	.023*

r: correlation value; *:p<0.05; **:p<0.01

158 participants having type II DM were included in this study. Eighty eight (55.70%) type II diabetes mellitus patients had Mild cognitive impairment (MMSE score ≤ 23) and 70 (44.30%) type II diabetes mellitus patients had normal cognitive function (MMSE score ≥24). The HbA1c, FBS, PPBS, and TNF-α levels were significantly higher in patients with Mild cognitive impairment [Table 4]. There were statistically significant differences in mean age, weight, blood sugar (fasting), blood sugar (postprandial), TNF-α, and HbA1C between the groups. HbA1c, PPBS, and TNF-α levels showed a positive correlation with the MMSE scores, while FBS showed a negative correlation with MMSE score [Table 5]. Of the domains tested, orientation, registration, attention &calculation, recall, and Language showed a statistically significant difference between those with Normal cognitive function and Mild cognitive impairment [Table 4].

Only 2.6% of those with abnormal results in the Mild cognitive impairment group could name all five terms used for memory tests correctly, whereas 25% of those with normal scores could. Only 10.5% of those with Mild cognitive impairment were able to repeat both of the administered questions, but 53.1% of those with Normal cognitive function were able to do so. The difference in orientation ratings between the groups was just marginally significant. The difference in abstraction scores between the two groups was not statistically significant.

4. Discussion

The current study examined the prevalence of Mild cognitive impairment in type II diabetes patients in North India. Mild cognitive impairment was shown to be prevalent in 54.3% of the people in our study. This is higher than earlier Indian research, which showed a range of 19.5% to 48.0% [11,13]. Earlier studies using the MMSE, trail-making tests, modified MMSE, and other neuropsychological tests such as the digit span test, digit symbol substitution test, and others were found to be less sensitive in detecting Mild cognitive impairment when compared to the current study using the MMSE score test for cognitive functions evaluation.

Patients with cognitive impairment had significantly higher FBS, PPBS, HbA1c, and TNF-α, all of which were negatively associated with MMSE scores in our study. Cognitive impairment was detected in 11.6% of patients with good glycemic management (HbA1c under 7%) and 30.2% of patients with HbA1c 7% or higher in a prior study by Roy et al. [11]. Subjects with glucose levels >125 mg/dl had 1.73 times increased chance of developing neurocognitive impairment, according to Khullar et al. [12,13]. The ACCORD MIND experiment, which included 2977 type II diabetes patients, discovered a statistically significant age-adjusted link between HbA1c level and four cognitive test scores [14]. The HbA1c level has been shown to be inversely related to both the clock in a box and the clock drawing test [15]. As a result, our findings are consistent with previous research suggesting that poor glycemic management in type II diabetes is linked to cognitive deterioration.

While there is a considerable body of evidence relating abnormal blood glucose levels to cognitive impairment, it is unclear whether bettering glycemic control leads to improved cognition. Enhanced HbA1c was linked to improved cognition in non-amnestic areas in the diabetes control and complications study in type 1 diabetes [16]. Improving HbA1c levels in an aged population over a 5-year period was linked to a slower rate of global cognitive deterioration, according to Luchsinger et al. [17].

In previous research, being a woman and having diabetes for a longer period of time were found to be independent risk factors [12]. Our research found no evidence of a gender difference or a link between diabetes duration and gender.

Executive function, name, attention, language, and memory indicated a statistically significant difference between those with Normal cognitive function and those with mild cognitive impairment in the current study. Attention, language, orientation, visual perception, visual movement organisation, and

logical questioning were all found to improve with effective cognitive training in individuals with mild cognitive impairment in a prior study [18]. The relevance of early identification of mild cognitive impairment was highlighted in a study on the outcome of a cognitive training programme in adults with mild cognitive impairment [19].

We used the Oxford Medical Education version of MMSE score, which is relatively easy and quick to perform. The level of education among subjects in both groups was similar.

In conclusion, our research reveals a high prevalence of undiagnosed mild cognitive impairment in type II diabetes patients who visit an outpatient clinic. All glycaemic control indicators and MMSE scores, which represent cognitive function, had a strong negative connection. These findings support the use of a sensitive measure like the MMSE in routine screening of type II diabetes mellitus patients to detect mild cognitive impairment. In the future, studies on the effects of better glycaemic control on cognitive function will be needed to better appreciate the implications of our findings in the long-term management of these patients.

Authors' Contributions:

All authors mentioned in the paper must have significantly contributed to the research. The level of their contribution also must be defined as follows:

Author Name	Conceptualization	Data Collection	Methodology	Analysis & Interpretation	Drafting Manuscript	%
Mir Abdul Munif	√	√	√		√	65%
Laxman Verma			√		√	20%
Malik Faizan Ahmad	√				√	20%
Anas Ahmad Khan			√	√	√	30%
Ankit Singh	√		√	√	√	35%

Ethical statement

The study was extracted by the thesis done for the fulfillment of a Master's Degree (MD) in Physiology after ethical approval of the Institutional Ethical Committee Ethics Committee, Faculty of Medicine, Jawaharlal Nehru Medical College, Aligarh Muslim University dated 17.11.2011.

Conflicts of interest

The authors declare no potential conflicts of interest related to the research, authorship, and publication of this article.

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