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Original Research Article

Diabetes control, dyslipidemia, hsCRP and mild cognitive impairment in non-elderly people with type 2 diabetes mellitus

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ABSTRACT

Background: Mild Cognitive Impairment (MCI) a transitional stage between normal aging and dementia has been observed more in people with diabetes when compared with general population. The risk factors for MCI in type 2 diabetes mellitus (T2DM) have been defined in elderly patients and aging may itself contribute to declining in cognitive functions. As the large number people with T2DM are under 60years, the prevalence of MCI and factors contributing to it are not much studied. So, this study aimed to find out the factors contributing to MCI in non-elderly T2DM patients.
Methods: In this cross-sectional study, 257 patients with T2DM underwent cognitive assessment by Montreal cognitive assessment test and the cognitive levels were correlated with their glycosylated hemoglobin, lipid profile, and highly sensitive C-reactive protein (hsCRP).
Results: The prevalence of mild cognitive impairment (MCI) was 64.2%. MCI significantly correlated with duration of diabetes, socioeconomic status, HbA1c, serum triglycerides, low-density lipoprotein, very low-density lipoprotein and hsCRP levels. The factors that were statistically insignificant were body mass index and high-density lipoprotein levels.
Conclusions: Cognitive impairment is seen even in non-elderly T2DM patients. It should be considered along with the other complications of diabetes and individuals with T2DM should be screened for cognitive impairment to prevent progression to dementia.

Keywords: Dyslipidemia, HbA1c, High sensitivity C-reactive protein, Mild cognitive impairment, Montreal cognitive assessment, Type 2 diabetes mellitus

INTRODUCTION

Mild cognitive impairment (MCI) is a brain function syndrome involving the onset and evolution of cognitive impairments beyond those expected based on the age and education of the individual, but which are not significant enough to interfere with their daily activities.[1] It is often found to be a transitional stage between normal aging and dementia. Diabetes mellitus (DM) patients have changes in brain structure and function, that develops insidiously and are at high risk for cognitive dysfunction referred to as diabetic encephalopathy.[2] Although the exact pathophysiology of cognitive impairment in DM is unclear, hyperglycemia, vascular disease, hypoglycemia, insulin resistance, amyloidosis, inflammation, concomitant hypertension and depression play significant roles.[3-6]

The prevalence of DM is increasing and one-fifth of the total number people with DM are in south-east Asia. In

India, 1 in 12 adults has diabetes. The majority of patients are between 40-80years of age.[7] Most of the studies have focused on elderly diabetics where age may also contribute to the cognitive impairment. So, it is crucial to determine whether the factors described above contribute to cognitive impairment in non-elderly diabetics as well.

This study was planned to investigate the relationship between MCI and diabetes control, dyslipidemia, chronic inflammation in non-elderly type-2 DM (T2DM) patients.

METHODS

This cross-sectional study included young patients with T2DM attending medical outpatient department and those admitted to the hospital from January 2017 to December 2017. All the subjects included in the study were interviewed regarding age, gender, education level, duration, and type of diabetes, history of smoking, history of alcohol abuse, sleep status (sleepless or not), history of hypertension and dyslipidemia using a predesigned and pretested proforma. Medication history regarding the use of lipid-lowering medications, antidiabetic medications, antihypertensive medications, antiplatelet medications or any drug causing cognitive impairment recorded through questionnaires and pill bottle review. Socioeconomic status was classified using BG Prasad scale (updated for 2017).[8,9]

The patients between 15-59years of age, who are either known or recently diagnosed to have T2DM (according to ADA 2017 guidelines) and the patients willing to participate in the study were included.[10]

The exclusion criteria were age ≥60years, T1DM patients with established diagnosis of dementia due to any cause, who were seriously ill, on long-term corticosteroid therapy, thyroid disorder, cerebrovascular accidents, who were either known case of hypertension or recently diagnosed as hypertensive, with spine deformities, pregnant females/lactating females, on drugs like benzodiazepines, opiates, tricyclic antidepressants, corticosteroids and anticonvulsants etc. that may cause cognitive impairment.[11,13] Patients with chronic diseases like chronic liver disease, rheumatological disorders and chronic kidney disease, history of auditory disorders and psychological disturbances, which might interfere with the Montreal Cognitive Assessment (MOCA) test, history of alcohol or any drug abuse and patients who were not co-operative were excluded.

After obtaining informed consent, the data was collected which included age, sex, duration and relevant biochemical tests. For assessment of cognitive functions, MoCA (Hindi version, 7.1) a rapid screening test for mild cognitive dysfunction was used.[13,14] It assesses different cognitive domains like attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation. The total possible score was 30 points, a score of 26 or above is considered normal. The study was carried out in accordance with the declaration of Helsinki (2000) of the World Medical Association and approved by the institutional ethical committee. Informed consent was obtained from all participants.

The data obtained were tabulated on Microsoft Excel spreadsheet. Categorical data were expressed as rates, ratios, and percentages. Continuous data were expressed as the mean±standard deviation (SD). Pearson's Correlation coefficient (r) was used to assess the correlation between HbA1c, lipid profile, highly sensitive C- reactive protein (hsCRP) and various domains of cognitive impairment. SPSS 17 trial version software was used for analysis.

RESULTS

A total of 257 patients with T2DM participated in the study. MCI was seen in 64.2% patients. Most of the patients in this study were between 40-59years of age (98.1%). The mean age group in patients with MCI was 53.66years and without MCI was 51.35years. Female patients (54.5%) were more in this study and they were represented more in both the groups. Gender didn't have the significant impact on MCI. The prevalence of MCI was more in the patients from the rural area (82.5%) and low socioeconomic (84.3%) group and the observation was significant ($p<0.001$).

About 47.9% diabetics had the disease of fewer than 10years duration and the MCI was observed in 50.4% of diabetics in this group. 25.7% diabetics had the disease of more than 15years duration and 72.7% of the diabetics in this group had MCI. The mean duration of diabetes was also higher in patients with MCI and it was significant ($p<0.001$).

About 39.3% had BMI ≥25kg/m^2 and the prevalence of MCI was 54.45% in this group. Although the BMI was higher in diabetics with MCI, it was not significant because 60.7% diabetics had normal BMI (Table 1).

MCI was observed in 5.8% of the patients with optimal glycemic control (HbA1c <7%) and in 58.4% without optimal glycemic control (HbA1c>7%). This observation was significant ($p=0.036$). 30.2% of the patients with HbA1c>7% had normal cognitive functions. HbA1c values correlated negatively with MoCA score ($r = -0.1$) (Table 2). On correlating the components of MOCA test with HbA1c significant correlations were found with delayed recall/memory ($p<0.001$) and language ($p<0.05$).

The prevalence of dyslipidemia (TG>150mg/dl) was 55.3% and the mean values were higher in patients with MCI. The observation was significant with total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) levels. The significant correlations among the MoCA test were found with all the components but the

orientation, and delayed recall/memory were affected in a highly statistically significant manner (p<0.001). In this study, 81.2% of diabetics with hsCRP levels of more than 1mg/l had MCI, While MCI was found in 10.5% of diabetics with hsCRP levels of less than 1mg/l. It was found that in diabetics with MCI the mean hsCRP levels were higher and the observation was significant (p<0.001). On correlating the hsCRP values with components of MOCA test, significant correlations were found with language (p<0.001), Delayed recall/memory (p<0.001) and naming (p<0.05). Author also found a significant correlation of MCI with ESR. Overall, delayed recall/memory was significantly affected cognitive function affected in this study.

Table 1: Baseline characteristics.

Variable	MCI Present (MOCA score <26)	MCI Absent (MOCA score ≥26)
Age		
Years, mean (SD)	53.66 (5.02)	51.35 (6.93)
Gender		
Male, n (%)	72 (43.6)	45 (48.9)
Female, n (%)	92 (56.4)	47 (51.1)
Residential area**		
Rural, n (%)	104 (63)	22 (23.9)
Urban, n (%)	61 (37)	70 (76.1)
Socioeconomic status**		
Lower, n (%)	74 (44.8)	15 (16.3)
Lower middle, n (%)	61 (37.0)	27 (29.3)
Upper middle, n (%)	30 (18.2)	45 (48.9)
Upper, n (%)	-	5 (5.4)
Duration**		
≤5years, n (%)	23 (13.9)	16 (17.4)
6-10years, n (%)	39 (23.6)	45 (48.9)
11-15years, n (%)	55 (33.3)	13 (14.1)
>15years, n (%)	48 (29.1)	18 (19.6)
Mean (SD)	13.09 (6.34)	9.72 (5.30)
BMI (kg/m^2), Mean (SD)	25.39 (4.29)	25.24 (2.87)
HbA1c (%), Mean (SD)*	9.62 (2.18)	9.09 (1.40)
Lipid profile, Mean (SD),		
TC (mg/dl)*	205.44 (43.90)	189.20 (35.72)
TG (mg/dl)**	203.08 (88.47)	151.26 (47.46)
HDL (mg/dl)	45.72 (17.79)	45.32 (11.51)
LDL (mg/dl)*	126.61 (41.23)	111.84 (31.70)
VLDL (mg/dl)*	37.29 (14.15)	32.04 (10.73)
Hs-CRP (mg/L)**, mean (SD)	4.95 (4.46)	3.13 (2.48)
ESR (mm/h)*, mean (SD)	19.41 (8.47)	16.04 (6.98)

*p<0.05, **p<0.001, SD=standard deviation, BMI=body mass index, TC=total cholesterol, TG=triglycerides, HDL=high density lipoprotein, LDL=low density lipoprotein, VLDL=very low-density lipoprotein, hsCRP=high sensitivity C-reactive protein, ESR=erythrocyte sediment rate, MOCA=Montreal Cognitive Assessment

Table 2: Correlations coefficients of serum values of HbA1c, TG, LDL, VLDL, hsCRP, MOCA score in type 2 diabetics.

Parameter	HbA1c	TG	LDL	VLDL	HsCRP	MOCA score
HbA1c	1	0.017	0.111	0.003	0.220	-0.100
TG	0.017	1	-0.025	0.520	0.229	-0.178
LDL	0.111	-0.025	1	-0.076	0.329	-0.202
VLDL	0.003	0.520	-0.076	1	0.078	-0.114
HsCRP	0.220	0.229	0.329	0.078	1	-0.144
MOCA score	-0.100	-0.178	-0.202	-0.114	-0.144	1

TG=Triglycerides, LDL=Low Density Lipoprotein, VLDL=Very Low-Density Lipoprotein, hsCRP=high sensitivity C-reactive protein, MoCA=Montreal Cognitive Assessment.

DISCUSSION

DM is a complex metabolic disease that can have devastating effects on multiple organs in the body. A less addressed and not well-recognized complication in young diabetics is cognitive dysfunction, which can be explained by the high prevalence of MCI in this study. The prevalence of MCI was more in patients from the rural area and low socioeconomic status. This can be explained by the level of education, awareness of the disease, access to health care, regular follow up and frequent assessment of complications may be better in the patients from the urban area and high socioeconomic status. This finding was significant even after removing the confounding factor of education by employing MOCA test in this study.

Gender has no impact on cognitive impairment, whereas in a study by Ryan CM et al, female patients performed better.[15] The duration of DM has shown to influence the cognitive decline in T2DM.[16,17] The studies in elderly diabetics have shown that longer duration of disease is associated with cerebral microvascular disease, cerebral infarctions, and subclinical infarctions that may impair cognitive function.[18,19] The mean HbA1c was higher in patients with MCI and it had a weakly negative correlation with MOCA scores. Similar observations were also made in a study involving non-elderly diabetics.[17]

The mechanisms of hyperglycemia leading to MCI can be explained by oxidative stress and glycation of important functional and structural proteins, which can have a direct detrimental effect on brain cells and the microcirculation.[20] Altered synthesis or reuptake of monoamine neurotransmitters as a result of altered precursor or changes in insulin availability to the brain are other possible explanations.[21,22] Studies involving elderly T2DM patients have shown a strong negative correlation between cognitive impairment and diabetic control.[1,5,6,23] This may be due to combined effects of vascular insults, age-related changes and hyperglycemia on cognitive decline.

BMI didn't correlate with cognitive impairment in this study. In Framingham study, obesity was independently associated with cognitive impairment.[24] On comparing the components of lipid profile with cognitive functions, diabetics with dyslipidemia had the significant decline in cognitive functions. TG, VLDL and LDL levels had a weak negative correlation with MOCA scores. Previous studies have also shown the significant impact of dyslipidemia on cognitive impairment.[25,26] Dyslipidemia may contribute to cognitive impairment by causing denaturation of neurons responsible for cognitive functions and accelerating the progression of atherosclerosis.[25]

The mean serum level of hsCRP was higher in diabetics with MCI and had a negative correlation with MOCA score (r = -0.144). The subclinical inflammatory reaction has a role in the pathogenesis of MCI in DM by inducing oxidative stress and promoting insulin resistance.[27] The combination of hyperglycemia and increased oxidative stress results in enhanced LDL modification. Oxidized LDL activates T cells, leading to enhanced inflammation through the release of macrophage-activating mediators causing endothelial dysfunction and accelerating the development of atherosclerosis.[28] So, the combined effect of oxidative stress on neurons and vascular disease of the brain leads to impairment of cognitive functions in people with DM. The Edinburg type 2 diabetes study and the GDMD study showed a significant association between CRP and MCI in elderly T2DM patients.[29,30] In a study done by Gorska-Ciebiada M et al, the elderly T2DM patients with MCI had higher levels of leptin and IL-1 β and lower levels of adiponectin.[31] Cai R et al, showed elevated plasma levels of lipoprotein-associated phospholipase A2 and hsCRP were found to be associated with the increased risk of MCI among T2DM patients.[32]

On comparing the different components of MOCA test delayed recall/memory was significantly affected and had a negative correlation with HbA1c, dyslipidemia and hsCRP levels. It has been observed that T2DM patients with higher TG and VLDL levels performed poor in short-term memory tasks.[26,33] In Edinburg study, it was found that the general intelligence factor was significantly less in patients with raised levels of IL-6 and TNF-α.[29]

There were few limitations in this study. It was conducted on small sample size, which may not be a true representative of the whole population. Baseline cognitive functions were not available. All the participants were from the same health center and a selection bias could not be excluded.

CONCLUSION

Cognitive impairment is seen in early stages of T2DM. Poor glycemic control and associated metabolic derangements with T2DM are associated with cognitive impairment. Individuals with T2DM should be screened for cognitive impairment along with other known macro and microvascular complications of diabetes. Early detection of cognitive impairment in DM and correction of the contributing factors may prevent the development of dementia.

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