The relationship between fatigue severity and mild cognitive impairment in Saudi patients with type 2 diabetes mellitus

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Abstract

Type 2 Diabetes Mellitus (T2DM) is a major health issue in Saudi Arabia, with a prevalence of 23.7% in 2015. Several factors contribute to the occurrence of Mild Cognitive Impairment (MCI) and its progression to Alzheimer's disease in patients with T2DM. This study assesses MCI and fatigue severity and their relationship in patients with T2DM. Out of the 160 Saudi adults interviewed at the King Khalid University Hospital in Riyadh from October 2019 till March 2020, 80 were known cases of T2DM while the rest were non-diabetic individuals. The Montreal Cognitive Assessment (MoCA) test, Mini Mental State Exam (MMSE) and Fatigue Severity Score (FSS) were used to evaluate MCI and fatigue severity, respectively. According to the MoCA scale, 68.7% diabetic individuals as against 42.5% from the non-diabetic group had MCI. While the FSS showed that 40% of the diabetic group vs 26.3% of the non-diabetic were fatigued. In conclusion, patients with T2DM are at a higher risk of developing MCI.

Keywords: Type 2 diabetes mellitus, Mild cognitive impairment, Fatigue, Mini mental state exam, Montreal Cognitive Assessment, Saudi Arabia.

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Introduction

Diabetes mellitus (DM) is a major global health liability, classified as a worldwide health burden. According to the International Diabetes Federation (IDF) estimates, in 2019, the global prevalence of DM was 9.3%, which can be approximated as 463 million diabetic patients worldwide.[1] It attributed to approximately five million deaths around the world, costing an estimated US$850 billion in 2017.[2] T2DM is a major health issue in Saudi Arabia,[3] with a prevalence of 23.7% in 2015 which is considered one of the highest in the world.[2] Besides that, it is accompanied by poor glycaemic control.[3] DM is characterised by persistent hyperglycaemia, either due to insufficient insulin production, which is known as type 1, or defects in secretion and sensitivity, known as type 2.[4] The second type is the most prevalent form, accounting for 90-95% of patients.[4,5]

T2DM is usually asymptomatic or has non-specific symptoms, which leads to delayed diagnosis and treatment. When it is symptomatic, the symptoms are frequent urination, excessive thirst, increased hunger, and fatigue; one life-threatening complication is the hyperglycaemic hyperosmolar state.[4] The problem is that diabetes is related to an increased risk of cardiovascular, renal, ocular, and neuropsychiatric diseases, including fatigue and cognitive dysfunction.[5,6] The presence of these comorbidities can lead to more serious complications, such as heart attack, peripheral vascular disease, foot ulcers, and amputations.[4,5]

MCI is a serious stage, and is considered the transitional stage between the natural deterioration due to aging and the more serious decline in cognitive function which is dementia. And if dementia progresses, it can lead to Alzheimer's disease (AD).[7,8] Patients with diabetes are at the risk of developing normal cognitive ageing up to 50% faster than normal individuals.[9]

Among diabetic patients, several factors contribute to the presence of MCI and its progression to AD, for example, age, education, hypertension, cardiovascular disease, hyperlipidaemia, and traumatic brain injury.[7,10]

It is important to study MCI in our population since it's prevalent. In a study conducted among elderly patients in Saudi Arabia, the prevalence of MCI was 38.6%.[7] Similar articles published in Canada and the USA showed a prevalence of 50% and 36.38%, respectively, among diabetic patients.[11,12] Two large studies done in the Middle East among the elderly population, showed that MCI had a prevalence of 32.1%-38.6% and 41.6%, respectively.[13,10] A systematic review with a meta-analysis study conducted in China revealed that diabetes increases the risk of developing MCI by 21%.[14]

Fatigue is a term used by the public with subjective

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meaning. Terms such as fatigue, sleepiness, tiredness, and exhaustion are used interchangeably. There is a discrepancy among researchers on the definition of fatigue.[15,16] The prevalence of fatigue was 61% at the time of the diagnosis among 1,137 T2DM patients.[5] It was significantly associated with high Fasting Plasma Glucose (FPG) levels, but not with haemoglobin A1c.[5,15]

In patients with T2DM, fatigue is more likely to be related to physiological and psychological aspects of the disease such as abnormal blood glucose levels, depression, or diabetes-related emotional distress. Fatigue may also be related to lifestyle factors, such as sedentary life and obesity, which are common among T2DM patients.[5] Many studies have noted higher fatigue in patients with T2DM as compared to controls.[16] However, the relationship of fatigue severity with cognitive impairment has not been studied in T2DM. An integrated approach encompassing the relationship of fatigue severity and neurocognitive assessment in T2DM needs to be further studied. Therefore, the current study tried to assess the relationship between MCI and fatigue severity among T2DM patients in order to understand what other factors contribute to the presence of fatigue in patients with T2DM.

The study primarily aimed to evaluate and compare the prevalence of fatigue and MCI among people with and without T2DM. It also sought to explore the correlation between fatigue and MCI among patients with T2DM.

Subjects and Methods

This was an observational cross-sectional comparative hospital-based study carried out at King Khalid University Hospital, Riyadh, from October 2019 till March 2020. We recruited a total of 176 Saudi adults aged 40 and above. As per our inclusion criteria, 160 individuals were enrolled in this study, out of which 80 were diagnosed cases of T2DM, and 80 were non-diabetic individuals. The sample size was computed on two proportion formula with a confidence interval of 95% and 90% power. The value of p1 was 41.6% and the value of p2 was 20% thus the estimated sample size for each group was 82 and a total was 164 but we ended up with 160 patients after following our exclusion criteria. All the participants were enrolled from the outpatient clinics at the King Khalid University Hospital. The investigators did a personal interview with each subject, which included a brief medical history taking and calculating the patient's body mass index (BMI). BMI is a measurement that is used to estimate body fat in people of any age, by providing the person's height and weight. It is calculated by dividing a person's weight, in kilograms, by their height in metres^2 (kg/m^2).[16] The value of BMI 25 to 29.9 is considered overweight, while BMI $\geq$ 30 is considered obesity. There are three classes of obesity: Class I (30 to 34.9), Class II (35 to 39.9), Class 3 is BMI of 40 or higher.[17]

Other parameters were included and recorded on a predesigned proforma like blood pressure and pulse rate. Blood pressure is categorised as normal systolic blood pressure (SBP) <120 mm Hg and diastolic blood pressure (DBP) <80 mm Hg), elevated SBP 120-129 mm Hg and DBP <80 mm Hg, or hypertension. Hypertension is classified into two stages, stage 1 with SBP (130-139 mm Hg) and DBP (80-89 mm Hg) and stage 2 with SBP $\geq$140 mm Hg and DBP $\geq$90 mm Hg.[18]

Patients who had severe physical or mental illnesses, such as dementia, stroke, known depression, recent surgery, major trauma, blindness, etc., or were illiterate, were eliminated from the study. MoCA and MMSE were performed in all subjects to assess their cognition function. FSS was performed to screen the severity of fatigue among the subjects. MMSE is a standard screening tool to detect MCI.[19] A score of 24 or less is the cut-off score to indicate MCI. MoCA test has excellent test reliability and better sensitivity than MMSE, thus it was performed as the second tool to confirm the presence of cognitive impairment and to categorise the participants as having severe cognitive impairment, mild cognitive impairment, or normal cognition state.[19] Both MMSE and MoCA test cognition domains, for example, orientation, attention, calculation, recall, language, and visuospatial function, but only MoCA tests the executive function and abstraction. A score of 26 or less is considered MCI according to MoCA.[19] FSS is a short screening test that investigates the presence of fatigue.[15,16] Arabic versions of MMSE and MoCA, which were already validated and standardised, were used. The size of the sample was analysed using two proportion formula with a confidence interval of 95% and 90% power. The value of P1 is 41.6% and the value of P2 is 20%. The estimated sample size for each group was 80 with a total of 160 participants.

All subjects who participated in this study read and signed the written consent form. All the details related to the study were fully described in this form. No incentives or rewards were given to any participant. Privacy and confidentiality were maintained throughout the study. This study was approved by the institution review board and ethics committee at the King Khalid University Hospital.

Data and statistical analysis: The analysis of statistical data was performed by Statistical Package for the Social Sciences (SPSS) version 22.0 software (SPSS Inc., Chicago,

IL, USA).

The statistical significance and precision of our results were reported as a p-value of ≤ 0.05 and 95% confidence, respectively. Descriptive statistics, for example, frequencies, percentages, standard deviation, and mean were used to describe the categorical and quantitative variables. To compare the mean values of quantitative variables with the categorical outcome variable Student's t-test was used. Pearson correlation coefficient was determined to quantify the relationship between two variables. Lastly, the association and odds ratio between categorical study and outcome variables were analysed and observed by Pearson's Chi-square test.

Results

Table-1 shows that patients with T2DM had a higher percentage of obesity than the non-diabetics n= 48 (60.0 %) vs n=22 (27.5 %), with ($p \leq 0.0001$). However, a higher percentage of non-diabetics were overweight and of normal weight as compared to the diabetic group n=42 (52.5%) vs n=25 (31.3%) with $p \leq 0.0001$ and n=16 (20.0%) vs n=7 (8.8%) with ($p \leq 0.0001$).

The educational level showed a significant difference between the two groups as the non-diabetic group had a higher prevalence of high educational level (college and bachelor's degrees) than the diabetic group with $p \leq 0.014$.

There was a significant age difference with mean age of 53.87±9.44 years and 58.22±9.56 years with ($p \leq 0.004$) between the non-diabetic and the diabetic groups, respectively; however, gender, physical activities, blood pressure, and pulse rate showed no significant difference between the two groups.

Table-1: Comparison of demographic characteristics between Non-diabetics and patients with T2DM. (data is expressed as Mean ±SD and percentages).

	Non-Diabetic patients (n=80)	Diabetic patients (n=80)	P-value
BMI Classification			
Normal	16 (20.0 %)	7 (8.8 %)	0.0001
Overweight	42 (52.5 %)	25 (31.3 %)	
Obese	22 (27.5 %)	48 (60.0 %)	
Physical activity			
No Exercise	33 (41.3 %)	38 (47.5 %)	0.657
Some Exercise	35 (43.8 %)	33 (41.3 %)	
Regular Exercise	12 (15.0 %)	9 (11.3 %)	
Educational level			
Less than high school	13 (16.3 %)	23 (28.7 %)	0.014
High school graduate	16 (20.0 %)	16 (20.0 %)	
College degree	20 (25.0 %)	6 (7.5 %)	
Bachelor's degree or higher	31 (38.8 %)	35 (43.8 %)	
Age	53.875 ± 9.449	58.225 ± 9.563	0.004
Systolic BP	129.5 ± 17.918	132.238 ± 16.326	0.314
Diastolic BP	80.738 ± 14.703	80.30 ± 14.193	0.848
Mean Arterial BP	96.83 ± 14.474	97.509 ± 13.629	0.76
Pulse	76.575 ± 12.679	76.025 ± 12702	0.784

Table-2: Comparison of prevalence of comorbidities between non-diabetics and patients with T2DM.

	Non-Diabetic patients (n=80)	T2DM patients (n=80)	P-value
Hypertension	10 (12.5 %)	52 (65.0 %)	0.0001
Depression	0 (0 %)	1 (1.3 %)	0.500
Anxiety	2 (2.5 %)	7 (8.8 %)	0.084
Renal dysfunction	2 (2.5 %)	7 (8.8 %)	0.084
Liver dysfunction	2 (2.5 %)	0 (0 %)	0.248
COPD	0 (0 %)	3 (3.8 %)	0.123
Hypothyroidism	3 (3.8 %)	7 (8.8 %)	0.191
Cardiovascular disease	5 (6.3 %)	22 (27.5 %)	0.0001
Cerebrovascular accident	0 (0 %)	0 (0 %)	--
Peripheral vascular accident	0 (0 %)	2 (2.5 %)	0.248
Traumatic brain injury	0 (0 %)	1 (1.3 %)	0.500
Hyperlipidaemia	5 (6.3 %)	22 (27.5 %)	0.0001
Blood disorders	3 (3.8 %)	5 (6.3 %)	0.360

Table-2 gives a comparison between the percentages of comorbidities between the two groups. The patients with T2DM had an increased prevalence of hypertension, cardiovascular disease, and dyslipidaemia with n=52 (65.0%), n=22 (27.5%), and n=22 (27.5%), respectively, as compared to the non-diabetic group which had a prevalence of n=10 (12.5%), n=5 (6.3%), and n=5 (6.3%) of the above-mentioned diseases. Other diseases showed no significant difference between the two groups such as history of depression, anxiety, and chronic obstructive pulmonary disease, etc.

Table-3 presents a comparison between the diabetic and non-diabetic groups regarding the scores of FSS, MMSE, and MoCA tests. There was no statistical significance in fatigue between the two groups (p=0.065). MMSE showed a higher prevalence in diabetics with n=11 (13.8%) as compared to n=2 (2.5%) in non-diabetics ($P \leq 0.009$). The MoCA showed that diabetics had a higher percentage of severe cognitive impairment compared to the non-diabetic group of n=3 (3.8%) vs n=0 (0%) with ($p \leq 0.0001$). Mild cognitive impairment was higher among the diabetic group in comparison to the non-diabetic group with a prevalence of n=55 (68.8%) vs n=34 (42.5%) ($p \leq 0.0001$). However, the non-diabetic group showed a higher percentage of no cognitive impairment compared to diabetic patients n=46 (57.5%) vs n=22 (27.5%) ($p \leq 0.0001$). Pearson's correlation coefficients between the scores of three different tests (FSS, MMSE, and MOCA) among diabetic patients and non-diabetic patients were determined.

For diabetics, a significant positive moderate relationship

Table-3: Comparison between the two groups (diabetic and non-diabetic) with respect to the three total scores (FSS, MMSE, and MOCA).

	Non-diabetics (n = 80)	T2DM (n = 80)	P-value	Odds ratio (95%CI)
Fatigue severity score				
36 and lower (no fatigue)	59 (73.8 %)	48 (60.0 %)	0.065	1.873 (0.959-3.658)
37 and Higher (fatigue)	21 (26.3 %)	32 (40.0 %)		
MMSE				
18 – 23 (mild)	2 (2.5 %)	11 (13.8 %)	0.009	0.161 (0.034-0.751)
24 and Higher (Normal)	78 (97.5 %)	69 (86.3 %)		
MOCA				
< 17 (Severe)	0 (0 %)	3 (3.8 %)	< 0.001	3.091(2.192-4.359)
17 - < 26 (Mild)	34 (42.5 %)	55 (68.8 %)		0.296(0.152-0.574)
26 + (Normal)	46 (57.5 %)	22 (27.5 %)		

between MMSE and MoCA (r = 0.627) with (P ≤ 0.0001) was noticed. No relation between FSS either with MMSE (r = - 0.071) with (P ≤ 0.533), nor MoCA (r = -0.169) with (P ≤ 0.134) was seen.

For non-diabetic, MMSE and MOCA showed a positive moderate correlation with (r = 0.585) (P ≤ 0.0001). No relationship had been shown between FSS and MMSE with (r = 0.163) (P ≤ 0.148), FSS and MOCA and (r = 0.031) (P ≤ 0.785).

Discussion

Many studies have shown that diabetes could be a risk factor for MCI progressing to Alzheimer's disease, however, this topic has been an area of controversy which necessitates more research to support the link between diabetes and MCI. There are several ways to explain why T2DM might increase the risk of MCI and its progression to AD. Firstly, T2DM increases the amyloid concentration in the brain which leads to its accumulation that is known to be the pathophysiology behind AD. Also, indirectly, T2DM contributes to the development of MCI by affecting the cerebral vasculature. The hyperinsulinaemic state, that the patients with T2DM suffer from, could disrupt brain amyloid β clearance through the insulin degrading enzyme.

In this study, patients with T2DM showed a higher prevalence of MCI when compared to patients without diabetes, (68.8% vs 42.5%) with p ≤ 0.0001, which shows a significant difference in favour of the diabetic group which is in congruence with what several studies have previously reported.[11,6,7]

Patients with T2DM were noted to have higher scores in FSS compared to non-diabetics, which was revealed in a study by Lasselin J.[6] However, there was no association between MCI and fatigue severity among these patients. Many associated factors should be taken under consideration that may contribute to the severity of MCI among those patients, for example age, education level, chronic diseases, and BMI, which were all significantly higher in the diabetic group who had MCI compared to the diabetics who did not have MCI.

Our results are inadequate for generalisation, due to the relatively small sample size and because it did not consider other parameters that could contribute to the development of fatigue and MCI, i.e., glycaemic control, sleep quality, and depression.

Conclusions

Our data clearly shows that patients who suffer from T2DM are at greater risk of developing MCI that can progress to dementia as compared to non-diabetics. We believe the higher prevalence of MCI in diabetics emphasises the importance of controlling the disease and implementing preventive measures to protect future generations. We can also consider the duration of the disease and its effect on cognition on a long-term perspective should be investigated separately.

Disclaimer: We declare that this abstract has not been previously presented or published in a conference, Also, was not a part of a research, Ph.D. or thesis project, or any other relevant information.

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Informed Consent: Informed consent was obtained from all individual participants included in the study.

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