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Full Length Research Article

Cognitive Functions Assessment among Type 2 Diabetics with and without Diabetic Foot

[1]Eman M. Alsofyani, [1]Manal F. Alshanbari, [2,*]Khaled A. Alswat and [3]Dhaifallah Almalki

[1]Medical Intern, Taif University School of Medicine, Taif, Saudi Arabia
[2]Assistant Professor of Medicine, Taif University School of Medicine, Taif, Saudi Arabia
[3]Consultant Physician of Family Medicine and Diabetes, Prince Mansour Hospital

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Introduction: Diabetic foot is a one of the most common complications of type 2 diabetes mellitus (T2DM). Saudi Arabia ranked among the top 10 countries in the worlds with the highest prevalence of T2DM.
Methods: A cross-sectional case control study for patients with T2DM divided into two groups; group 1 with diabetic foot and group 2 without diabetic foot.
We evaluated their cognitive function using the Mini Mental State Examination (MMSE) and also we assessed severity of diabetic foot by using Wagner's classification to compare the results between both groups. Our goal is to assess the relation between diabetic foot and cognitive impairment.
Result: Total of 102 patients participated, with mean age of 56.39 years; duration of T2DM is 14.69 years (SD 9.2), and 58.8% were male. 66.7% of the screened patients have normal cognitive function, 15.7% have mild, and 17.6 % have moderate cognitive impairment.
Diabetic foot group were more likely to have moderate cognitive impairment and significantly more likely to use aspirin than non-diabetic foot group. The severity of diabetic foot didn't affect the MMSE score.
Conclusion: T2DM patients with diabetic foot tend to be male, older, and have longer duration of T2DM. There was non-statically significance in regards to the MMSE score between groups. Those with diabetic foot were non-significantly more likely to score lower in the mean total MMSE score and were more likely to have moderate cognitive impairment compared to those without diabetic foot.

Key words: Type 2 Diabetes Mellitus, Diabetic Foot, Cognitive Function, Mini Mental Status Examination (MMSE).

INTRODUCTION

Type 2 diabetes mellitus (T2DM) prevalence is growing rapidly worldwide. In 2011 the global prevalence of T2DM was estimated to be 366 million cases and the prevalence expected to rise in 2030 to 552 million (Whiting *et al*., 2011). According to the International Diabetes Federation (IDF) Saudi Arabia ranked among the top 10 countries in the worlds with the highest prevalence of T2DM with an estimated prevalence of 24% (Whiting *et al*., 2011). T2DM complications can be divided to macro- and microvascular complications. Among the macrovascular complication is the diabetic foot. It's a combination of peripheral vasculopathy, peripheral neuropathy, and it can be associated with an infection, ulcer and destruction of deep tissue. Diabetic foot is an indicative of poorly controlled diabetes and it is accounted for a 25 % of the T2DM hospitalization in Saudi (Al-Maskari and El-Sadig, 2007). Another study showed that 19% of the T2DM patients with diabetic foot had non traumatic amputations (Al-Tawfiq and Johndrow , 2009). Wagner's classification is commonly used to assess the diabetic foot lesion which classified the diabetic foot into six grades depend on the depth of ulcer, the presence of the infection and the gangrene (Amit Kumar *et al*., 2013).

Corresponding author: Khaled A. Alswat,
Assistant Professor of Medicine, Taif University School of Medicine, Taif, Saudi Arabia.

Cognitive impairment refers to changes in memory, mood, perception, reaction times, attention, and concentration (Cranston, 2005). The cognitive function impairment increased about 1.5- 2.5 fold in patient with T2DM (Mark, 2011). The pathophysiology of cognitive impairment in T2DM is not clear but it is multifocal. The poor glycemic control, hypoglycemia, and the macrovascular complications contributed to the most common causes of the impaired cognitive function in T2DM patients (McCrimmon *et al*., 2012). There are many validated tools to assess the cognitive impairment, the Mini Mental State Examination (MMSE) is considered to be the gold stander tool and is the most commonly used in clinical practice primary and specialist care setting (Molloy, 2014). Other tests used to assess cognitive function as 6 -Item Cognitive Impairment Test (6CIT) is brief and takes about 5 min and has good psychometric properties, but it is low in quality of the validation and this improved when combined it with MMSE.

The Mini-Cog is another useful test that combines of words, clock drawing, and memory but it is less sensitive than MMSE. Memory impairment screen test (MIS) depends on 4 items but sensitivity only 80 % to detect dementia. There are a lot of tests to assess the cognitive function but the MMSE the most widely used in clinical practice as it can be used by non-specialist and easy to do (Latha Velayudhan *et al*., 2014). One study used MMSE showed that T2DM patients with diabetic foot, poorly controlled diabetes, or those with microvascular

complications were more likely to have cognitive impairment (Marseglia *et al*., 2014). Other study used MMSE as a screening tool, found a correlation between the cognitive impairment and diabetes and its related complications after excluding hypothyroidism, vitamin B12 deficiency, and hepatic disease which can affects cognitive function (Oğuz *et al*., 2009). On the other hand, a preliminary published study that was focused on 2 T2DM groups with the 1st one been with foot ulcers or Charcot foot arthropathy and the 2nd group with a lower extremity amputation and they used the Short Form 36 (SF-36) health survey tool in addition to two cognitive function tests (MMSE and the Clock Drawing Test) to assess the cognition and they found a decrease in quality of life in the health survey test in both groups but no evidence of cognitive impairment (Willrich *et al*., 2005). Since there is limited national and local data about the potential relationship between diabetic foot and cognitive impairment, we designed this study to evaluate the relationship between them using the MMSE as a tool to evaluate the patient's cognitive function.

MATERIALS AND METHODS

A cross-sectional case control study that included a total of 102 female and male patients with T2DM divided into 2 groups. Group 1, included 51 T2DM patients with diabetic foot and Group 2, included 51 T2DM patients without diabetic foot. Patients were selected randomly from Diabetic Center department in Prince Mansour Hospital in Taif city, Saudi Arabia between May-October 2015. The inclusion criteria included T2DM Patients with or without Diabetic foot ulcer. Patient were excluded if they have uncontrolled hypothyroidism, type I diabetes, gestational diabetes, liver cirrhosis, cerebral vascular accident, and multiple sclerosis. Personal and diabetes related data were collected from patients during their follow up clinic visit through a personal interview with the researchers after obtaining their consents.

The data included age, sex, duration of T2DM; types of medications and history of hypertension were collected. We also inquired about the regular calcium and vitamin B12 intake. At the time of the follow up visit; the vital signs, weight, and height were measured then we calculated the body mass index (BMI). Recent laboratory data that includes HbA1c, total cholesterol, triglyceride, LDH, HDL, urine microalbuimin and Vitamin D (Vit D) were collected from the electronic medical record of the participated patients. To screen for the cognitive function, we used the Mini-Mental Stat Examination Test (MMSE). The MMSE test composed of 11 questions that assess different areas of cognitive function. Every one of those questions has points, orientation questions 10 points, registration 3 points , attention and calculation 5 points , recall 3 points, and language 9 points . We scored the MMSE according to the sum of the total score of the correctly answered questions.

The maximum score of MMSE is 30 and we considered any patients who scored 24 or less to have cognitive impairment. In case of physical disabilities, language difficulties, speech problems, or low education we adjusted the score by using this validated formula: total score of test multiply by 30, divided by maximum obtainable score (Molloy, 2014). To determine the stage and the severity of the diabetic foot we used the Wagner's classification. Wagner's classification is a validated tool that is consistent of 6 stages as following; stage (0) intact skin, stage (1) superficial ulcer of skin or subcutaneous tissue, stage (2) deep ulcer includes tendon or bone, stage (3) deep ulcer with abscesses or osteomyelitis, stage (4) gangrene of toes or forefoot, stage (5) gangrene of mid-foot , hind-foot or leg. The primary goal of the study is to determine the prevalence of the cognitive impairment among the diabetics with and without diabetic foot. We also correlated the MMSE score with the Wagner classification to evaluate the role of the diabetic foot severity on the score obtained from those with diabetic foot. Data were collected and analyzed using the SPSS software. The Chi squared test was used to study the relationship between variables and the independent T-test was used to compare between means.

RESULTS

A cross-sectional case control study included 102 patients with T2DM. The mean age was 56.39 years (SD 11.12), they were predominantly male with the mean duration of diabetes of 14.69 year (SD 9.2), nearly more than half of the included patients have hypertension with a mean duration of 9.73 years (SD 8.3) (Table 1). The mean BMI of patients was within the class 1 obesity and the mean HbA1c of 8.59 (SD 2.1). About half of the patients were on combination of oral hypoglycemic agents and insulin; third of them were on oral hypoglycemic agent only and the rest of them on insulin only.

Table 1. Baseline characteristics for the whole cohort

Baseline characteristics	
Mean age (yrs)	56.39 (SD 11.12)
Male (%)	58.8
Female (%)	41.2
Duration of Diabetes (years)	14.69 (SD 9.2)
Hypertension (%)	58.8
Duration of Hypertension (years)	9.73 (SD 8.3)
Mean BMI (Kg/m^2)	33.74 (SD 6.99)
Mean heart rate (bpm)	85.63 (SD 13.3)
Mean systolic blood pressure (mmHg)	131.02 (SD 25.3)
Mean diastolic blood pressure (mmHg)	75.4 (SD 11.01)
Medications	
Oral hypoglycemic agents only (%)	31.7
Insulin only (%)	15.8
Oral agents and Insulin (%)	52.5
Anti-hypertensive medications (%)	90
Metformin (%)	70.7
Sulfonylurea (%)	29.3
DPP-4 Inhibitors (%)	22.2
Statin (%)	72.5
ACEi/ARB (%)	42
Aspirin (%)	73
Calcium tablets (%)	17.8
Vitamin B12 supplementation (%)	38.2
Laboratory result	
HbA1c	8.59 (SD 2.1)
Total Cholesterol (mmol/L)	4.7 (SD 1.01)
LDL (mmol/L)	2.91 (SD 0.91)
Triglyceride (mmol/L)	1.71 (SD 1.0)
HDL (mmol/L)	0.98 (SD 0.22)
Urine microalbuminuria	24.28 (SD 66.4)
Vitamin D (ng/dl)	17.73 (SD 9.24)

All patients were evaluated for cognitive function by using the MMSE test and the mean Total Score was 25.4 (SD 4.01), around two-third of participated patients scored above 25 and were considered to have normal cognitive function (Table 2). The mild and moderate cognitive dysfunction was about 15.7% and 17.6% according to the MMSE score respectively; none of patients have severe cognitive impairment. We classified patients into two groups; T2DM without diabetic foot and T2DM with diabetic foot (Table 3).

Compared to T2DM without diabetic foot, those with diabetic foot significantly were more likely to be male, with longer duration of T2DM, and non-significantly older and have higher HbA1c than those without diabetic foot.

Table 2. Evaluation of Cognitive function using the MMSE

Mini-Mental Status Examination (MMSE)	
Total score	25.4 (SD 4.01)
Orientation	9.24 (SD 1.31)
Registration	2.97 (SD 0.29)
Attention and Calculation	2.97 (SD 2.01)
Recall	2.36 (SD 0.87)
Language	7.61 (SD 1.5)
Categories according to the MMSE	
Normal Cognitive function (MMSE score 25-30)	66.7 %
Mild Cognitive Impairment (MMSE score 21-24)	15.7 %
Moderate Cognitive Impairment (MMSE score 10-20)	17.6 %
Sever Cognitive Impairment (MMSE score < 10)	0 %

The prevalence of hypertension and the BMI were non-statically significant different between groups. Those with diabetic foot were non-statically significant more likely to be on insulin only and less likely to be on the different oral hypoglycemic agents, more likely to be on ACEi/ARB, statin and Vitamin B12. The diabetic foot groups were significantly more likely to use aspirin than non-diabetic foot group (p 0.046).

Compared to the diabetics without diabetic foot, those with diabetic foot tends to have lower mean of total cholesterol, LDL, and HDL but tends to have higher mean triglyceride, HDL, and urine microalbuminuria but comparable Vitamin D level. The cognitive function showed non-statically significant difference between both groups when using the MMSE (Table 4). Although, those with diabetic foot tends to have lower mean of the MMSE total score, more likely to have moderate cognitive impairment, and scored lower in the registration, attention and calculation, recall and language section of the MMSE compared to those without diabetic foot.

27 patients out of the 51 diabetics with diabetic foot had Wagner's classifications done at the time of the cognitive function assessment. There was no statically significant difference in the MMSE total score achieved when groups were divided according to the severity of the diabetics foot. Those with advance stage defined as Wagner's classification $\geq$3 scored 24.4 in the MMSE compared to MMSE score 25.6 for those with Wagner's classification of <3 (P value 0.504). Partial correlation adjusting for age, BMI, HTN. and T2DM duration, Statins, Metformin, Vit.B12 intake, HbA1c, SBP, DBP, LDL, and TC level showed non-significant negative correlation between Wagner's classification and MMSE total score (r -.265, p 0.334).

Table 3. Comparison between the Diabetics with Diabetic foot and Diabetics without diabetic foot

	Diabetic Foot	Non-Diabetic foot	P value
Baseline characteristics			
Mean age (yrs)	59.1 (SD 9.4)	53.6 (SD 12.2)	0.13
Male (%)	74.51	43.14	0.001*
Duration of Diabetes (years)	17.5 (SD 9.8)	11.9 (SD 7.64)	0.002*
Hypertension (%)	64.7	52.94	0.157
Duration of Hypertension (years)	9.31 (SD 8.6)	10.2 (SD 8.1)	0.678
Mean BMI (Kg/m^2)	30.47 (SD 5.7)	34.63 (SD 7.1)	0.067
Mean heart rate (bpm)	86.7 (SD 14.0)	85.42 (SD 13.3)	0.801
Mean systolic blood pressure (mmHg)	130.1 (SD 21.4)	131.2 (SD 26.3)	0.901
Mean diastolic blood pressure (mmHg)	73.6 (SD 9.7)	75.76 (SD 11.3)	0.55
Medications			
Insulin only (%)	19.61	11.76	0.479
Oral agents and Insulin (%)	47.1	56.86	0.595
Anti-hypertensive medications (%)	56.9	49.01	0.437
Metformin (%)	60.78	76.47	0.141
Sulfonylurea (%)	21.57	35.29	0.129
DPP-4 Inhibitors (%)	13.73	29.41	0.062
Statin (%)	74.51	70.59	0.412
ACEi/ARB (%)	43.14	39.22	0.355
Aspirin (%)	78.43	64.71	0.046*
Calcium tablets (%)	13.73	21.57	0.232
Vitamin B12 supplementation (%)	43.14	33.3	0.208
Laboratory Result			
HbA1c	8.86 (SD 2.34)	8.31 (SD 1.81)	0.221
Total Cholesterol (mmol/L)	4.58 (SD 1.1)	4.77 (SD 0.91)	0.43
LDL (mmol/L)	2.8 (SD 1.0)	3.02 (SD 0.81)	0.29
Triglyceride (mmol/L)	1.8 (SD 1.15)	1.6 (SD 0.85)	0.38
HDL (mmol/L)	0.94 (SD 0.23)	1.01 (SD 0.12)	0.128
Urine microalbuminuria	30.21 (SD 67.3)	18.3 (SD 66.1)	0.493
Vitamin D (ng/dl)	18.37 (SD 9.6)	17.3 (SD 9.2)	0.695

Table 4. Mini Mental Status Examination results according to presence and absence of the Diabetic foot

Mini Mental Status Examination (MMSE)	Diabetic Foot	Non-Diabetic foot	P value
Mean MMSE total score	24.96 (SD 4.3)	25.78 (SD 3.7)	0.302
Normal Cognitive (%)	64.7	68.6	0.55
Mild Cognitive Impairment (%)	13.73	17.65	0.54
Moderate Cognitive Impairment (%)	21.57	13.73	0.44
Mean Orientation score	9.29 (SD 1.2)	9.18 (SD 1.42)	0.652
Mean Registration score	2.94 (SD 0.42)	3.0 (SD 0.00)	0.322
Mean Attention and Calculation score	2.88 (SD 2.03)	3.06 (SD 2.01)	0.66
Mean Recall score	2.27 (SD 0.89)	2.45 (SD 0.83)	0.305
Mean Language score	7.43 (SD 1.55)	7.78 (SD 1.33)	0.221

DISCUSSION

Our study showed that T2DM patients with diabetic foot were more likely to be male with longer duration of T2DM. In our evaluation of cognitive function using the MMSE score we found that there was no statically significant difference between both groups.

T2DM with diabetic foot tends to have moderate cognitive impairment and lower in mean total score of MMSE than T2DM without diabetic foot but was non-significant. When we assessed severity of diabetic foot we did not observe significant difference in MMSE total score according to Wagner's classification. The prevalence of cognitive impairment increased about 1.5 - 2.5 fold in patients with T2DM (Mark, 2011).

Few studies reported that T2DM associated with cognitive function impairment (McCrimmon *et al*., 2012; Oğuz *et al*., 2009). Recent study has shown that patients with T2DM more likely to have mild cognitive impairment 92% (MMSE score ≥ 21) and 8% with moderate cognitive impairment (MMSE 10-20 score) in the age of 50 -59 years, also they observed the duration of DM non-statistically significant on MMSE score (Mirela Tache *et al*., 2014). In our study the patients were predominantly male with similar mean age but with 66.7% of the screened patients considered to have normal cognitive impairment, 15.7% have mild, and 17.6 % have moderate cognitive impairment.

Another cross sectional study showed that mild cognitive impairment in about 64.86% in T2DM patients and severe cognitive impairment MMSE score ≤ 21 was seen mainly in the elderly patients, they also observed high significant difference in cognitive function in patient with longer duration of diabetes (Kataria *et al*., 2013). Previous study reported that patients with diabetic foot have cognitive impairment with mean score of MMSE was 24.6 and it domains among elder patients ≥65 years. Similar to our study where we found that the patients with diabetic foot have mean 24.96 (SD 4.3) MMSE score and more likely to have moderate cognitive impairment but with younger age group.

In our study we observed patients with diabetic foot more likely to use aspirin than patients without diabetic foot. Studies showed that patients who use low dose of aspirin in long duration more likely to have protective effect on cognitive function especially memory in elder patient in age of 75 years (Jonker *et al*., 2003). Recent study suggested worse cognitive function associated with those who used metformin who have vitamin B12 deficiency while cognitive improved and alleviate with who metformin when used along with calcium supplement and vitamin B 12 (Moore *et al*., 2013).

Also another study showed patients who use Statin less likely to have cognitive impairment (Cramer *et al*., 2008). We didn't observe in our study any significant effect of metformin, vitamin B12, calcium and statin on cognitive performance. Our study strengths included a case control study, using MMSE which considered as an effective screening tool to assess cognitive function; we used Wagner's classification to assess the diabetic foot severity, and data about the significant related comorbidities and medications.

Our weakness included small sample size, single center, and difference in age at baseline.

Conclusion

T2DM patients with diabetic foot tend to be male, older, and have longer duration of T2DM. There was non-statically significance in regards to the MMSE score and categories between groups. Although, those with diabetic foot tend to score lower in the mean total MMSE score and were more likely to have moderate cognitive impairment compared to those without diabetic foot.

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