Journal of Vascular Medicine & Surgery
ISSN: 2329-6925

Gamal et al., Vasc Med Surg 2018, 6:4
DOI: 10.4172/2329-6925.1000369

Research Article Open Access

Study of Cognitive Impairment between Diabetic Foot Patients

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Abstract

Background: Diabetic foot (DF) is one of the most widespread type 2 diabetes mellitus "T2DM" complications, it originates from the conjunction of neuropathy and vascular disease. Some reports suggest that amputees might be prone to cognitive decline.

Aim of the work: To investigate the cognitive function of DF patients and the relations between it and diabetes complications& comorbidities.

Patients and methods: One hundred dementia-free subjects with DF aged >18 were enrolled in the study through the period from March to August 2018 from the Vascular outpatient clinic of Qena University Hospital and only patients whom gave consent have joined the study. The mean age of the study group was 61 years, with 70 males and 30 females, their demographic characters were recorded and medical cognitive tests were applied. Patients have been undergone clinical vascular examination, data on diabetic complications and comorbidities were gathered; (HbA1c) tests were carried out for all patients.

Results: The mean Mini-Mental State Examination "MMSE" score of subjects was 24.6 and 40% had global cognitive dysfunction (MMSE ≤ 24). Between elderly subjects (aged ≥ 65), MMSE impairment was linked to amputation, episodic memory impairment was connected to foot amputation and complications. Elderly subjects with HbA1c >7% had elevated odds of psychomotor slowness and abstract reasoning impairment. However, such findings were not present in adult subjects <65 years.

Conclusion: Diabetic foot is the severest form of T2DM that causes significant impairment in all cognitive domains. The severity of depression is significantly increased with the intensity of amputation.

Keywords: Diabetes; Cognition; Diabetic complications; Diabetic foot; HbA1c

Introduction

Type 2 diabetes mellitus (T2DM) is the most popular form of diabetes and affects about 28 million people worldwide [1]. Chronic elevated glucose levels may cause damage to nerves and vasculatures that can result in diabetic retinopathy, nephropathy, peripheral neuropathy, and vascular diseases [2]. Multiple literatures reported that diabetes is a risk factor for both vascular dementia and Alzheimer's disease [3] and it might speed up advancement from mild cognitive impairment to dementia [4]. T2DM is also correlated to substandard accomplishment in cognitive tasks including attention, executive functions, episodic memory, psychomotor speed, and visual-constructive skills in subjects without dementia [5]. However, findings are inconsistent, and the specific cognitive domains affected by T2DM remain unclear [6].

Despite of many studies have searched the probable impact of diabetic complications on cognition, the cognitive characters of subjects with long term diabetes are not well known [7]. DF comprises skin infection, ulceration, and even devastation of deep tissues that could result in foot amputation. Recently, it has been realized that a foot ulcer is expressive of severe diabetes. Researches realized that patients with diabetic foot ulcers have more intense diabetic complications than others without [8]. DF is the major basis of non-traumatic amputation over the world [8].

Some literatures realized elevated predominance of cognitive impairment between patients with lower limb amputations, which proposes that amputees may be in particular prone to cognitive decline [9]. Our aim is first to estimate the cognitive profile of DF subjects and Second, to investigate the relations between cognitive functioning and diabetic complications and comorbidities considering glycemic control, hypertension, smoking and hyperlipidemia, in mind.

Patients and Methods

The sample size of the study group was 100 cases that were recruited from Vascular outpatient clinic or inpatient wards according to ethical committee of Qena University Hospital, South Valley University through the period from March 2018 to August 2018. Demographic characters of the subjects were recorded. The mean age of the subjects=61, with 70 males and 30 females, all subjects had been undergone peripheral vascular examination to ensure patency of vessels and exclude peripheral vasculopathy and DF patients were classified into 2 groups:

- Group 1: Who underwent debridement
- Group 2: Whom underwent amputation either minor amputation (toes amputation or trans-metatarsal amputation), or major amputation "below knee amputation or above knee amputation.

Cognitive function and depression degree were assessed. Assessment of cognitive function was done through using Mini-

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Received August 09, 2018; **Accepted** August 24, 2018; **Published** August 31, 2018

Citation: Gamal WM, Abbas MAA, Mohamed AA (2018) Study of Cognitive Impairment between Diabetic Foot Patients. J Vasc Med Surg 6: 369. doi: 10.4172/2329-6925.1000369

Mental State Examination "MMSE" (score 24 till 30 is normal below 24 is considered to have cognitive impairment) [10], Montreal Cognitive Assessment "MOCA" test (score 26 till 30 is normal below 26 is considered to have cognitive impairment) [11], Trail Making Test-A (score more than 78 sec considered to have cognitive impairment) Trail Making Test-B (score more than 273 sec considered to have cognitive impairment) [12], Assessment of depression by using Hamilton depression scale "HDRS also named as the Ham-D" (score more than 7 considered to have depression) [13] throughout the study, diabetic foot was used as a measure of intense DM.

Inclusion criteria

- Presence of T2DM.
- History of DF ulcers or amputation or debridement.
- Age >18 years old.
- No history of disabling stroke or dementia.

Exclusion criteria:

- T1DM "Type 1 diabetes mellitus".
- Age less than 18.
- Disabling stroke or dementia.
- Traumatic amputations.

Statistical Analysis

Statistics were done using the SPSS software (version 24). Data were displayed as means with standard deviation and frequencies depending on the type of data displayed. Independent t-test was performed to compare means between 2 groups. ANOVA was done for comparing means of more than 2 groups. Parison and spearman correlation coefficients were performed to test correlation between variables. P value all over the study was considered significant when it is <0.05 with confidence interval 95%.

Results

Our study group included 100 patients, 46 (46%) were aged below 65 years while 54 patients (54%) were ≥ 65 years, seventy patients (70%) were males while 30 (30%) were females,16 patients (16%) were smokers, while 84 (84%) were non-smokers.

Of all patients in the study, 30 (30%) had diabetic foot that didn't require amputation while 70 (70%) had amputations with different levels. Patients that have been undergone amputation were further divided as following; 38 (38%) had amputated toes, 12 patients (12%) trans-metatarsal amputation, 12 patients (12%) had below knee amputation and 8 patients (8%) had above knee amputation. Distribution of amputation level within the age groups is shown in Table 1.

Comparisons between the study groups

To compare study groups, we used many parameters and significances were calculated. Comparison was done between subjects <65 years and patients ≥ 65, statistical significant differences between both age groups were found in cognitive function "as P value <0.05". Means of scores of MMSE and MOCA were significantly higher in patients <65 years "as P value <0.05", while scores for TMT (A, B) were significantly higher in patients ≥ 65 " as P value <0.05".There is no significant difference regarding depression scores, HbA1C levels or lipid profile between both age groups "as P value<0.05" as shown in Table 2.

We noticed a highly significant difference between group 1 and group 2 patients in HbA1c levels (higher in group 2) as P value <0.006. Regarding cognitive function scores, there is a significant difference between the 2 groups. Scores of MMSE and MOCA were significantly higher in (group 1) patients while scores for TMT (A, B) were significantly higher in (group 2) patients. Scores for depression were significantly higher (p<0.0001) in (group 1) patients. Differences in lipid profile were highly significant between both groups being higher in (group 2) patients, as (P value <0.000) as shown in Table 3.

Regarding sex and smoking, no significant differences could be detected between both of them in all study parameters as (p value >0.05). Analysis of the variance test (one-way ANOVA) was done to compare different amputation levels regarding the study parameters (Table 4). Cognitive function testing showed highly significant differences between group 1 and deferent levels of amputation within group 2 (toes, trans-metatarsal, below knee and above knee) as p value >0.05 in all variables.

Correlations between different study variables were carried out. HbA1c showed significantly positive correlation to the scores of TMT (A, B), while significantly negative correlation to MMSE and MOCA scores (Table 4). Amputation level and cholesterol also showed similar correlations with cognitive function testing (positive to TMT and negative to MMSE and MOCA) as shown in Tables 5-7.

Amputation level showed significantly positive correlation to the scores of depression (as p value is >0.05). No significant correlation could be found between age and depression, (as p value is >0.05) (Table 8).

Discussion

Despite adult DF patients fulfill more sensibly than elderly subjects on examinations of cognitive functioning, both of them display poor cognitive achievement in global cognition and multiple subdomains. Among DF elderly subjects, amputation was correlated with lower MMSE score and episodic memory impairment. Furthermore, micro vascular complications and rigorous glycemic control were associated with substantial odds of reduced accomplishment in episodic memory, processing speed and abstract reasoning in such patients [14].

Our patients' ages were above 18 years with a mean age of 61. All candidates had diabetic feet with variable degrees, most of our subjects had been undergone amputations (70%) and the larger part were males (70%) as well, this is in harmony with the study of Marseglia et al. who realized that of the 153 participants of his study, 116 (75.8%)

		Amputation level					Total
		Not amputated	Amputated toes	Transmetatarsal	Below Knee	Above Knee	
Age Groups	Below 65	12	22	4	4	4	46
	65 or above	18	16	8	8	4	54
Total		30	38	12	12	8	100

Table 1: Amputation level within age group.

	Age Groups	N	Mean	Std. Deviation	P-value
HbA1c	Below 65	46	7.478	0.79	0.140
	65 or above	54	7.844	0.92	
MMSE	Below 65	46	23.96	2.55	0.002
	65 or above	54	21.63	2.42	
TMT-A	Below 65	46	66.43	24.12	0.000
	65 or above	54	94.67	26.89	
TMT-B	Below 65	46	206.61	91.56	0.006
	65 or above	54	268.74	58.86	
MOCA	Below 65	46	23.13	2.47	0.014
	65 or above	54	21.19	2.86	
Hamilton scale	Below 65	46	9.96	6.53	0.720
	65 or above	54	10.63	6.65	
Triglycerides	Below 65	46	188.13	39.87	0.085
	65 or above	54	196.19	40.76	
LDL	Below 65	46	152.17	23.61	0.095
	65 or above	54	166.96	35.52	
HDL	Below 65	46	49.91	14.87	0.065
	65 or above	54	42.67	12.28	
Cholesterol	Below 65	46	225.04	25.59	0.098
	65 or above	54	241.41	39.99	

Table 2: Comparison between age groups in all study parameters.

MMSE: Mini Mental State Examination; TMT-A: Trail Making Test (A); TMT-B: Trail Making Test (B); MOCA test: Montreal Cognitive Assessment; LDL: Low Density Lipoprotien; HDL: High Density Lipoprotien; p value considered significant <0.05.

	Amputation	N	Mean	Std. Deviation	P-value
HbA1c	Group 1	30	7.173	0.8464	0.006
	Group 2	70	7.891	0.8001	
MMSE	Group 1	30	24.07	2.549	0.018
	Group 2	70	22.11	2.610	
TMT-A	Group 1	30	65.87	29.880	0.010
	Group 2	70	88.46	26.370	
TMT-B	Group 1	30	181.80	91.194	0.004
	Group 2	70	265.17	62.557	
MOCA	Group 1	30	23.60	3.269	0.012
	Group 2	70	21.43	2.392	
Hamilton scale	Group 1	30	5.33	1.759	0.000
	Group 2	70	12.46	6.679	
Triglycerides	Group 1	30	151.07	11.665	0.000
	Group 2	70	210.23	34.433	
LDL	Group 1	30	133.13	12.983	0.000
	Group 2	70	171.74	29.590	
HDL	Group 1	30	59.40	9.833	0.000
	Group 2	70	40.26	11.165	
Cholesterol	Group 1	30	203.93	24.540	0.000
	Group 2	70	246.71	30.519	

Table 3: Comparison between the 2 groups in all study parameters.

MMSE: Mini Mental State Examination; TMT-A: Trail Making Test (A); TMT-B: Trail Making Test (B); MOCA test: Montreal Cognitive Assessment; LDL: Low Density Lipoprotien; HDL: High Density Lipoprotien P value considered significant <0.05.

were men, and 37 (24.2%) were women. The mean age of the patients was 65 years (SD=10.5, ranged=33-90). The mean value of HbA1c was 7.7% (61 mmol/mol) (SD=1.4, range 5%-12.1%), and amputation was performed in 108 subjects (70.6%) [15].

Diabetic foot is the main complaint that pushed our patients to seek medical advice and according we classified our patients into 2 groups: One for non-amputated form of DF that undergone debridement and the other for various degrees of amputated foot either minor or major amputations.

In our patients MMSE was positive in group 2 and higher than group 1 and it means that significant association was found between cognitive decline and amputation. This is in agreement with the study of Coffey et al. whom in 2012 realized an elevated predominance of cognitive decline between lower limb amputation subjects than in the general population [16]. We used MMSE, TMT-A, B and MOCA for testing the cognitive profile of different cognitive domains [17].

Control of DM was assessed using HbA1c level [18]. Severity of depression was measured using the Hamilton scale [19]. Lipid profile was also performed for dyslipidemia [20].

Variables	P-value	Variables	P-value
Age	0.747	Hamilton scale	0.000
HbA1c	0.009	Triglycerides	0.000
MMSE	0.004	LDL	0.000
TMT-A	0.004	HDL	0.000
TMT-B	0.001	Cholesterol	0.000
MOCA	0.035		

Table 4: One-way ANOVA to compare different levels of amputation regarding the study parameters.

MMSE: Mini Mental State Examination; TMT-A: Trail Making Test (A); TMT-B: Trail Making Test (B); MOCA test: Montreal Cognitive Assessment; LDL: Low Density Lipoprotien; HDL: High Density Lipoprotien P value considered significant <0.05.

		MMSE	TMT-A	TMT-B	MOCA
HbA1c	Correlation coefficient	- 0.499	0.529	0.523	- 0.605
	P-value	0.000	0.000	0.000	0.000
	N	100	100	100	100

Table 5: Correlation between glycemic control and cognitive functions.

		MMSE	TMT-A	TMT-B	MOCA
Amputation level	Correlation coefficient	- 0.520	0.558	0.599	- 0.498
	P-value	0.000	0.000	0.000	0.000
	N	100	100	100	100

Table 6: Correlation between amputation level and cognitive functions.

		MMSE	TMT-A	TMT-B	MOCA
Cholesterol	Correlation coefficient	- 0.387	0.430	0.447	- 0.415
	P-value	0.005	0.002	0.001	0.003
	N	100	100	100	100

Table 7: Correlation between cholesterol control and the cognitive function.

		Hamilton scale
Amputation level	Correlation coefficient	0.693
	P-value	0.000
	N	100
Age	Correlation coefficient	0.130
	P- value	0.367
	N	100

Table 8: Correlation between age and amputation level to the depression severity.

Through our work, we carried out a comparison between patients' ages <65 years and others who ≥ 65 years. Significant differences between both age groups were realized in cognitive function, means of scores of MMSE and MOCA were significantly higher in patients less <65 years while scores for TMT (A, B) were significantly higher in patients aged 65 or more in harmony with Gorelick et al. who had the same age group and the same results concerning cognitive assessment tools and results [21].

During our study we compare both groups regarding amputation and glycemic control. Significant difference was found in HbA1c levels (higher in group 1) and this is in conformity with the study of Thomas et al. who found that higher variability in glycemic control might result in development of microvascular complications in diabetic subjects. Hyperglycemia might be able to excite the oxidative stress chain and elevates the manufacture of reactive oxygen forms that in accordingly could result in apoptosis of visceral epithelial cells in the kidney and neuronal cells in the brain [22].

The effect of glucose level in hastening cognitive impairement and beginning of dementia in subjects with long lasting DM requires further work. In our patients, a level of HBA1c>7% was correlated with elevated odds of psychomotor delay and abstract reasoning deterioration [22].

Cognitive function scores also indicated significant differences between both groups. Scores of MMSE and MOCA were significantly higher in (group 1) patients while scores for TMT (A, B) were significantly higher in (group 2) patients. Scores for depression were significantly higher in group 2. Differences in lipid profile were highly significant between both groups and this is matching the findings of Coffey et al. who found that DM subjects who had an amputation as a result of peripheral vascular disease had reduced cognitive functioning, particularly regarding memory and executive function [16].

Through our study we realized that there is no effect of gender on any of study parameters and this is in conformity with the findings of Marseglia et al. who showed that there is no significant difference between both sexes in cognitive function [15].

As regarding Smoking, there were no significant differences between smokers and non-smokers in any of the tests used as P value is above 0.05 in all our study parameters and this is matching the results of Marseglia et al. who showed that there is no difference between smokers and non-smoker regarding cognitive function [15].

In our work we realized that, cognitive function testing indicated significant differences within the two study groups. There were also significant differences regarding diabetic control, depression scores and lipid profile. This is in consistent with Marseglia et al. [15] who found that limb absence has a major influence on natural, psychosomatic and public aspects of daily life. A review research 2012 realized an elevated prevalence of cognitive decline between subjects with lower limb amputation than in the general population [16].

Cognitive functioning is a definitive foreteller of the prosperity of rehabilitation approaches after amputation [23]. Poor mental condition is negatively correlated with functional movement ability, obligation to medicine courses, prosthetic fit, use of prostheses, falls or multiple falls, and continuation of pre-operative independent condition after amputation [24].

We realized that amputation was correlated with elevated odds of global cognitive decline and episodic memory impairment in older DF subjects. Overall, our findings indicate that cognitive impairment after lower limb amputation due to diabetic foot is common but underdiagnosed. This is of special interest given that, as observed up, fully-functioning cognition is a substantial foreteller of effective post-amputation rehabilitation. A cognitive estimation before amputation and constant prosecutions postoperative could assist in the preference of the rehabilitation goal (e.g., a prosthetic tool or wheelchair rehabilitation) and in settling suitable and practical objectives [16,24].

HbA1c level showed significantly positive correlation to the scores of TMT (A, B), while significantly negative correlation to MMSE and MOCA scores and this in conformity with the study of Marseglia et al. who found that, the ratio of subjects with declined global cognition, executive task (shifting and mental flexibility), episodic memory (particularly short-term memory), processing velocity, and abstract dialectics was statistically higher between elderly than adult subjects. Elderly patients' mean values were beneath the cut-offs in the MMSE, RAVLT immediate recall "Rey Auditory Verbal Learning Test", and TMT-A and B tests [15].

Amputation level and cholesterol also showed similar correlations with cognitive function testing (positive to TMT and negative to MMSE and MOCA), our findings are in conformity with the findings of Marselgia et al. who found that elevated cholesterol level showed positive correlation with cognitive impairment [15].

Regarding amputation level there are significantly positive correlation to the results of depression. This is in consistent with the findings of Sansam, and his colleagues [25] who found that several mechanisms may be involved in the association among depression and diabetic microvascular complications. Depression might stimulate the hypothalamic pituitary adrenal axis which could catalyze the sympathetic nervous system and elevate inflammatory and platelet accumulation responses, these consequences might result in deficient diabetic control Moreover, depression might show unfavorable consequences on attitudes such as regimen, exercise, blood glucose test and hypoglycemic treatment [24].

The HAM-D24 scores in our subjects with diabetic nephropathy, retinopathy, peripheral neuropathy and DF were significantly elevated than those in subjects with no diabetic microvascular complications. Interestingly, the HAM-D24 values in DF were recorded as the highest value between all levels of amputation.

Our results were consistent with previous studies focusing on the depression level of DF patients and in conformity with the study of Vedhara et al. who realized that there is positive association among depression and DF severity. The cause might be that diabetic foot ordinarily happens as a result of the collective consequences of neuropathy and vascular insufficiency, the presentations like intense foot ache and motion hardness could be intolerable, the concerted results of poorer self-attention and poorer consequences would either result in intense depression in such patients [26].

Depression in T2DM was determined two times the rate of a 1st DF ulcer through a 4 year follow-up duration and elevated rates of amputation which would in the other hand lead to additional intense depression in this population [27].

In our subjects we realized that hyperlipidemia also showed significant correlations with cognitive function testing (positive to TMT, MMSE and MOCA), this is in consistent with Maresiglia et al. who found that hyperlipidemia has positive correlation with cognitive impairment [15]. The EURODIAB study investigated 1172 subjects with diabetes, and reported that episodic neuropathy hazard was elevated by both bad glycemic control and other vascular comorbidities comprising hypertriglyceridemia, hypertension and obesity. Within 28,700 diabetic subjects, serum triglyceride magnitude was an independent gradually increasing risk factor for lower limb amputation [28].

Conclusion

Diabetic foot is the severest form of T2 DM that causes significant impairment in all cognitive domains. Bad glycemic monitoring and hyperlipidemia are significant hazard factors for cognitive decline. The intensity of depression is significantly increased with the amputation's level. Further researches are required for best understanding of the relation between diabetic complications and cognitive decline.

Conflict of Interest

The authors certify that there is no conflict of interest, no sources of funding and nothing to disclose.

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