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Cognitive impairment among type-2 diabetic subjects and its relationship with long-term complications

Aim: Studies about relationships between diabetes mellitus, diabetic complications, and cognitive functions have been initiative factors for this study. We evaluated various relations between procedure of the disease, diabetic complications, and cognitive functions among diabetic subjects.

Materials and methods: Type-2 diabetic patients were evaluated for their disease status, complications, and cognitive functions (by Mini Mental State Examination (MMSE) test). We compared MMSE results of the patients with the control group.

Results: We evaluated 75 patients with type-2 diabetes mellitus and 49 control subjects. Orientation ($P = 0.006$), attention and calculation ($P = 0.002$), and total ($P < 0.001$) scores of the control group were significantly greater compared to the diabetic group. We observed negative correlation between the length of disease and cognitive functions within the diabetic group. Recall scores of the diabetic subjects with 6 and less HBAIC levels were significantly greater than those with 6.1 and greater levels ($P = 0.049$). We observed negative relations between registration scores and retinopathy, but not between orientation and total scores and hypertension among diabetic subjects.

Conclusion: Type-2 diabetes mellitus may destroy cognitive function. Length of disease, high serum HBAIC levels, hypertension, and retinopathy are significant additional risk factors. We conclude that cognitive function assessment should be routine procedure in the management of type-2 diabetes mellitus.

Key words: Diabetes Mellitus, cognitive impairment, retinopathy, hypertension

Tip 2 diyabetli kişilerde kognitif bozulma ve uzun süreli komplikasyonlarla ilişkisi

Amaç: Diabetes Mellitusta, diyabetik komplikasyonlar ve kognitif fonksiyonlar arasındaki ilişkileri konu alan çalışmalar çalışmamızın ilham kaynağı olmuştur. Bu çalışmada, Diyabetik hastalarda hastalık sürecinin ve komplikasyonlarının kognitif fonksiyonlar ile olan çeşitli ilişkilerini araştırdık.

Yöntem ve gereçler: Tip 2 diyabetli hastalar, hastalıklarının durumu, diyabetik komplikasyonlar ve kognitif fonksiyonları (Mini Mental Durum İncelemesi ile) yönünden incelendi . Hastaların sonuçları kontrol grubu ile karşılaştırıldı.

Bulgular: Çalışmada, 75 diyabetik hasta ve 49 kontrol vakasını inceledik. Kontrol grubunun "Oryantasyon" ($P = 0,006$), "Dikkat ve Hesaplama" ($P = 0,002$), ve "Toplam" ($P < 0,001$), skorları diyabetik grubunkilerden anlamlı olarak yüksek idi. Diabetik hastalarda "Hastalık süresi" ile çeşitli kognitif fonksiyonlar arasında negative korelasyonlar saptadık. HBAIC düzeyleri 6 ve daha düşük olan diyabetik hastaların "Hatırlama" skorları, HBAIC düzeyleri 6.1 ve daha yüksek olanlarınkinden daha yüksek idi ($P = 0,049$). Diyabetli hastalarda ayrıca "Kayıt" skorları ile Retinopati komplikasyonu arasında, "Oryantasyon" ve "Toplam" skorlar ile hipertansiyon arasında olumsuz ilişkiler gözledik.

Sonuç: Tip 2 Diabetes Mellitus, kognitif fonksiyonları olumsuz yönde etkileyebilir. Hastalığın süresi, yüksek serum HBAIC seviyeleri, hipertansiyon ve retinopati belirgin ek risk faktörleridir. Tip 2 diabetes Mellitusun yönetiminde kognitif fonksiyon incelenmesi rutin bir işlem olmalıdır.

Anahtar sözcükler: Diabetes mellitus, kognitif bozukluk, retinopati, hipertansiyon

Introduction

Relations between mental function impairments and some chronic diseases have been researched previously. Cognitive functions may be influenced by various factors. Diseases or conditions that destroy vascular circulation or brain metabolism may lead to cognitive impairment. In some articles, chronic hypoglycemia has been observed to be responsible for cognitive impairment in type-1 diabetic subjects based on retinopathy (1). Within type-1 diabetic patients, chronic recurrent hypoglycemia may lead to cognitive impairment among subjects with peripheral polyneuropathy (2). However, in another study, chronic recurrent hypoglycemia alone was never found as a risk factor for cognitive impairment (3).

Relevance of cognitive impairment has increased when APOE epsilon 4 genotype based on type-1 diabetes mellitus (DM) was present (4). Visual functions (visual reaction time) have been destroyed by both hypoglycemia (50 mg/dL) and hyperglycemia (300 mg/dL) in type-1 diabetic subjects (5). Diabetic retinopathy and polyneuropathy both led to the limited cognitive impairment in the Type-1 DM even in the absence of the diabetic encephalopathy (6).

Complications of DM may be micro vascular (retinopathy, nephropathy, and neuropathy) (7) or macro vascular (hypertension) (8), as well. Diabetic retinopathy may be classified as nonproliferative (background) and proliferative. Constitutional vascular changes, retinal hypo perfusion and edema, and intraregional hemorrhages are essential components of nonproliferative (background) retinopathy. Neovascularization is the cornerstone of the proliferative changes.

Mini Mental State Examination (MMSE or Standardized Mini Mental Test) is very effective method frequently used for assessment of cognitive function. MMSE observes 5 departments of cognitive function (orientation, recall, registration, attention and calculation, language) (9, 10) (Figure 1).

In this study we aimed to research cognitive function impairments of Type 2 DM subjects because it is a very frequent disease encountered in daily practice. We also aimed to research the effects of the duration of disease, long-term complications, and glycemic control on these functions. With a comprehensive approach, we may achieve more effective management of DM by determining patients' cognitive functions.

Materials and methods

Subjects

This was an observational, case-control, and analytical study approved by the Ethical Committee of the University. Data were collected from patients in Family Medicine, Neurology an Ophthalmology clinics of Fatih University hospital in Ankara, Turkey. Subjects (older than 40 years) with Type-2 DM were evaluated between 2002 and 2007. We evaluated patients' records consecutively in this time period. A detailed history of all patients (age, gender, educational level (years of schooling), history of diabetic complications (hypertension, nephropathy, neuropathy, etc), medications, confounding diseases (especially neurological), and any condition that may have effects on mental status were recorded. Type of anti-diabetic medication (insulin or oral agents), serum HBAIC levels (mean of multiple HBAIC records were used, if possible) and the length of disease of diabetic patients were recorded. We performed a detailed physical examination, routine biochemistry screening including renal, hepatic function tests. Serum TSH and vitamin B12 levels of the subjects were also determined, if necessary, according to the clinical data.

Inclusion criteria were: age 40 years and older, Type-2 DM with no accompanying disease, and no other condition or medication affecting the mental status. Exclusion criteria were: existence of any other disease or use of any medication that may affect mental functions negatively except diabetic complications (Parkinson's disease, some medications, etc), any condition that may impair cognitive functions (depression, hypothyroidism, vitamin B12 deficiency, electrolyte disturbance, hepatic diseases, etc).

We also formed a control group with subjects in the same age margins without any chronic disease, chronic medication, or chronic hazardous habits.

Evaluation of subjects was performed by family medicine, ophthalmology, and neurology specialists.

Mini Mental State Examination

Maximum Score *Score*

Orientation
5 ------ What is the Year Season Month Date Day
5 ------ Where are we State County Town or City Building Floor

Registration
3 ------- Name three common objects. (Pencil, clock, apple etc) Then ask the patient to repeat all after you have said them
Give one point for each correct answer. (Give 20 seconds)

Attention and Calculation
5 -------Count back from 100 by subtracting 7 for each step. (100, 93, 86 etc). Give one point for each correct calculation.

Recall
3 ---------- Ask for the three objects repeated above. Give one point for each correct answer. (Give 20 seconds)

Language
2 --------- Name two objects you saw (Clock, pen)
1 ---------- Repeat the following: "No ifs, ands or buts."
3 ---------- Follow three command after listening (Give one point for each correct movement)
1 ---------- Read the sentence and follow
1 ---------- Write a meaningful sentence
1 ---------- Copy the following design

Total
30 ---------

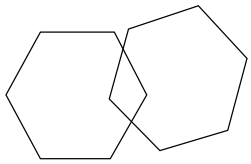

Figure 1. Mini Mental State Examination of Folstein (Modified by Molley and Standish).

The person who performed MMSE was blinded with the respect to the clinical (diabetic) features; ophthalmologist was also blinded with respect to the MMSE test results.

Determination of retinopathy

We performed ophthalmologic examination in the patients and evaluated fundus changes of them in 4 main categories: background, preproliferative, proliferative, and maculopathy. Patients were divided into 2 main groups according to the examination: diabetic with retinopathy and diabetic without any retinopathy.

Determination of peripheral neuropathy

Clinical history and/or electroneurographic examination results, which were performed by a neurologist, were used for records.

Determination of cognitive function

We screened all subjects with the Mini Mental State Examination (MMSE), which is widely used in cognitive function assessment. MMSE scores were evaluated in 5 categories: orientation (10 points), registration (3 points), attention and calculation (5 points), recall (3 points), language (9 points), and total (30 points) (Figure 1).

We also performed further tests (serum vitamin B12 level, TSH, and Hamilton's depression test) and Cranial Computerized Tomography or Magnetic Resonance Imaging to the subjects according to their clinical data whenever we observed that MMSE scores were less than 24.

Statistical analysis

We analyzed the differences in the means of continuous measurements of MMSE by the Mann-

Whitney U test and Student's T test between groups. We performed binary logistic regression between control and diabetic groups to analyze total scores of MMSE. ANCOVA (Factorial ANOVA) was performed for correction of age and educational levels. Multivariate analyses (Pearson correlation) for educational status, duration of disease, and MMSE scores were also performed. A P value of <0.05 was considered to indicate statistical significance; all tests were 2-tailed and in the 95% confidence interval.

Results

Exclusion

In this study, we evaluated 94 patients, 19 of them were excluded for various reasons (5 for depression, 4 for hypothyroidism, 3 for hepatic diseases, 3 for vitamin B12 deficiency, 4 for neurological diseases). We included 75 subjects (35 men and 40 women) into the study. Control group was constituted by 49 subjects.

Patient characteristics

Twenty one patients were treated with insulin & insulin + oral antidiabetic (28%) and 54 received oral antidiabetic (72%). Forty four patients (58.7%) had hypertension and 16 had (21.3%) ischemic heart disease. Other micro vascular and macro vascular features are outlined in Table 1.

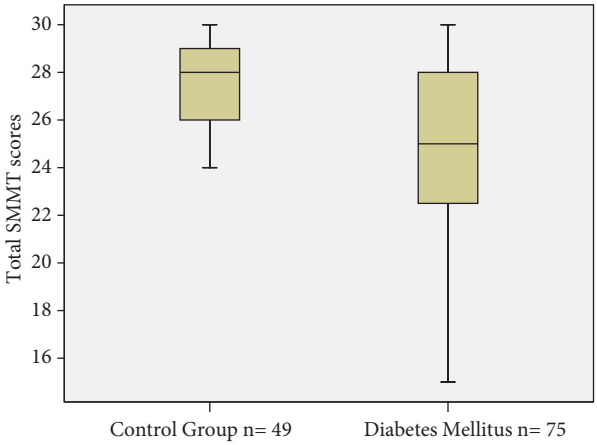

Figure 2. Comparison of total MMSE scores of control group and DM group.

Comparison of the MMSE scores among control group and diabetic subjects generally

Means of the MMSE categories of the control group and diabetic patients are displayed in Table 2. Orientation (P < 0.001), registration (P = 0.026), attention and calculation (P < 0.001), recall (P = 0.030) and total(P < 0.001) scores of the control group

Table.1 Demographic data of the subjects

	Control	DM
Parameter	n (Percent) & mean ± SD	n (Percent) & mean ± SD
Gender		
Men	29 (59.2)	35 (46.7)
Women	20 (40.8)	40 (53.3)
Age	54.7 ± 8.46	57 ± 8.1
Treatment		
OAD		54 (72)
Insulin & Insulin +OAD		21 (28)
Retinopathy		30 (40)
Hypertension		44 (58.7)
Nephropathy		17 (22.7)
Ischaemic Heart d.		16 (21.3)
Peripheral neuropathy		33 (44)
Length of Disease		8.3 ± 5.9

Table 2. Comparison of the Mini Mental State Examination scores of groups generally.

	Control		Diabetes Mellitus		
SMMT Category	N	Mean	N	Mean	P
Orientation	49	9.73 ± 0.60	75	8.83 ± 1.6	< 0.001**
Registration	49	2.96 ± 0.2	75	2.77 ± 0.67	0.026*
Attention and Calculation	49	4.35 ± 1.33	75	3.2 ± 1.99	< 0.001**
Recall	49	2.06 ± 0.89	75	1.67 ± 1.08	0.030*
Language	49	8.5 ± 0.65	75	8.2 ± 1.09	0.050
Total	49	27.6 ± 1.09	75	24. 6 ± 3.8	< 0.001**

were statistically higher compared to the DM group (Figure 1). We did not observe any age difference among groups (P > 0.05). However, we observed significant difference regarding educational status (Means; Control: 7.45 ± 4.3 DM: 5.28 ± 4.0, P = 0.005). Therefore, we performed ANCOVA test for correction of the results according to the age and educational status. Then, we observed significant differences regarding orientation (P = 0.006), attention and calculation (P = 0.002), and total (P < 0.001) scores among groups this time.

We categorized the total scores as "24 and less" and "greater than 24" (significant cut-point for dementia) (Table 3). In the logistic regression analysis, the DM group was 7.2 times more relevant than the control group for cut-point of the total score.

Table 3. Comparison of cut-off points of total standardized mental test scores of groups generally.

	Total SMMT points	
Groups	24 and less	greater than 24
DM (n, percent)	33 (44)	42 (56)
Control (n, percent)	4 (8.2)	45 (91.8)

P < 0.001

Table 3A. Logistic Regression output according to the cut-point of Total MMSE scores among Control and DM groups.

	Coefficient	s.e.	Wald	P	OR	95 % CI for OR
DM	1.983	0.581	11.628	0.001 **	7.262	2.324 to 22.698
Age	- 0.017	0.026	0.438	0.508	0.983	0.933 to 1.035
Year of Schooling	0.111	0.057	3.733	0.053	1.117	0.998 to 1.250
Constant	0.671	1.597	0.176	0.675	1.955	

We observed negative correlations between length of disease and orientation scores (Pearson correlation coefficient = -0.250 P=0.032), and between length of disease and total scores (Pearson correlation coefficient = -0.248, P = 0.032) whereas positive correlations were observed between educational status and orientation (Pearson correlation coefficient = 0.378, P = 0.001), and between educational status and total scores (Pearson correlation coefficient = 0.350, P = 0.002) in the DM group (Figure 3).

In the *"Control"* group, we observed negative correlation between age and recall (Pearson correlation coefficient = -0.605 P < 0.001) whereas positive correlations between educational status and orientation (Pearson correlation coefficient = 0.341 P = 0.016), between educational status and language (Pearson correlation coefficient = 0.399 P = 0.005), and between educational status and total scores (Pearson correlation coefficient = 0. 384, P = 0.006).

Comparison of the MMSE scores among DM cases according to the HBAIC levels

We categorized DM cases according to their serum HBAIC levels. We formed 2 groups, namely group 1 (HBAIC levels 6 and less, n=8) and group 2 (HBAIC levels 6.1 and greater, n=67). All scores of the group 2 were lower than those of group 1. However, recall scores of the groups were statistically different (Means = 2.38 ± 0.744, 1.58 ± 1.09, P = 0.049) (Figure 4). We never observed any difference for age, educational status, and length of the disease among groups.

General evaluation of relationships between complications and MMSE scores

We performed ANCOVA test among the DM group to determine the relations between complications and all MMSE scores based on the corrected values of the factors. We observed significant relations between orientation scores and hypertension, between registration scores and retinopathy, between total scores and hypertension (Table 4 A, 4-B, and 4-C).

Comparison of the MMSE scores of DM cases according to the long-term complications

We compared orientation and total scores of DM patients without hypertension (n = 31) and DM patients with hypertension (n = 44) (Means = 9.35 ± 1.14, 8.45 ± 1.77, P = 0.010 and 25.8 ± 2.5, 23.8 ± 4.3, P = 0.013, respectively). We also compared "registration" scores of DM patients without retinopathy (n = 45) and DM patients with retinopathy (n = 30) (Means = 2.96 ± 0.29, 2.5 ± 0.94, P = 0.015, respectively).

We categorized DM cases according to the effective complications status (group 1= Cases without hypertension or retinopathy, n =19; group 2 = Cases with any of these complications, n = 56). We did not observe any significant difference of age or educational status between groups. However, we observed a significant difference regarding the total scores (group 1 = 25.9 ± 2.5, group 2 = 24.2 ± 4.0, P = 0.032). Furthermore, we also compared the control

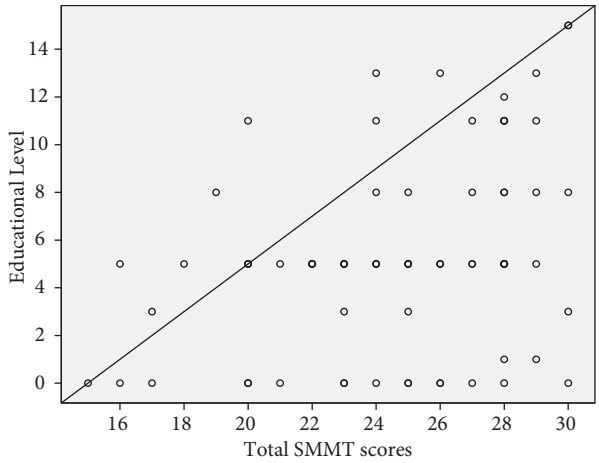

Figure 3. Correlation between Total MMSE scores and educational level among patients with Type-2 DM.

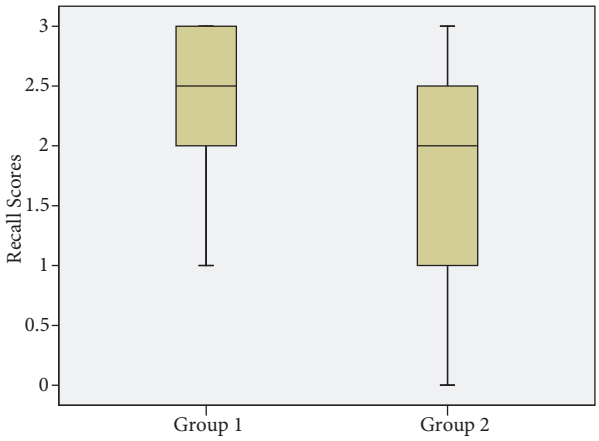

Figure 4. Comparison of recall scores among groups according to HBAIC levels.

Table 4A. Relations between diabetic complications and orientation scores.

Dependent Variable: **Orientation**						
Group	Source	Type III Sum of Squares	df	Mean Square	F	Sig.
DM	Corrected Model	42.83 (a)	7	6.119	2.810	0.013
	Intercept	57.674	1	57.674	26.482	.000
	Retinopathy	2.023	1	2.023	0.929	NS
	Hypertension	11.122	1	11.122	5.107	**0.027**
	Nephropathy	0.045	1	0.045	0.021	NS
	Ischaemic H. Disease	1.319	1	1.319	0.606	NS
	P. Neuropathy	0.244	1	0.244	0.112	NS
	Age	0.134	1	0.134	0.061	NS
	Educational Level	21.993	1	21.993	10.099	**0.002**
	Error	145.916	67	2.178		
	Total	6032.000	75			
	Corrected Total	188.747	74			

(a) R Squared = .227 (Adjusted R Squared = .146)

Table 4B. The relation between diabetic complications and registration scores.

Dependent variable: **registration**						
Group	Source	Type III Sum of Squares	df	Mean Square	F	Sig.
DM	Corrected Model	6.665(a)	7	0.952	2.409	0.029
	Intercept	10.792	1	10.792	27.304	.000
	Retinopathy	3.211	1	3.211	8.124	**0.006**
	Hypertension	0.039	1	0.039	0.098	NS
	Nephropathy	1.722	1	1.722	4.357	NS
	Ischaemic H. Disease	0.007	1	0.007	0.017	NS
	P. Neuropathy	0.572	1	0.572	1.448	NS
	Age	0.387	1	0.387	0.978	NS
	Educational Level	0.252	1	0.252	0.638	NS
	Error	26.482	67	.395		
	Total	610.000	75			
	Corrected Total	33.147	74			

(a) R Squared = .201 (Adjusted R Squared = .118)

Table 4C. Relations between diabetic complications and total mmse scores.

Dependent variable: **total**						
Group	Source	Type III Sum of Squares	df	Mean Square	F	Sig.
DM	Corrected Model	250.726(a)	7	35.818	2.945	0.009
	Intercept	719.985	1	719.985	59.202	.000
	Retinopathy	3.239	1	3.239	0.266	NS
	Hypertension	52.201	1	52.201	4.292	**0.042**
	Nephropathy	12.341	1	12.341	1.015	NS
	Ischaemic H. Disease	0.530	1	0.530	0.044	NS
	P. Neuropathy	33.035	1	33.035	2.716	NS
	Age	14.792	1	14.792	1.216	NS
	Educational Level	73.147	1	73.147	6.015	**0.017**
	Error	814.821	67	12.162		
	Total	46551.000	75			
	Corrected Total	1065.547	74			

(a) R Squared = .235 (Adjusted R Squared = .155)

group (n = 49) and group 1 (n = 19) , and we observed significant differences for attention and calculation scores (Means = 4.35 ± 1.3, 3.47 ± 1.8, P = 0.026) and total scores between groups (Means = 27.6 ± 1.9, 25.9 ± 2.5, P = 0.012).

Discussion

Comparison with previous findings

Studies about relationship between Type-1 DM and cognitive function impairment were interesting. In a previous study, frequent hypoglycemic attacks have been displayed to destroy the attention and recall functions based on background retinopathy (1). In another study, retinopathy and peripheral neuropathy have been displayed to affect the cognitive function limitedly (6). In our study, cognitive functions (orientation, attention and calculation, total) are influenced in the Type-2 diabetic patients; however, these impairments were more severe in the existence of some long-term complications, such as retinopathy and hypertension.

In another study, recurrent hypoglycemia has been displayed to effect cognitive function in the existence of distal symmetric neuropathy (2). However, in our study we did not observe any difference for cognitive functions among cases with or without neuropathy. For this reason, we believe that peripheral neuropathy is never an additional risk for cognitive impairment in Type-2 DM.

In one study, effects of long-term glycemic control on cognitive function has been observed and negative effects of excessive glycemic changes on visual functions of the brain have been observed (5). In our study, cut-off point of HBAIC (Reflecting long-term glycemic control) for significant effect on cognitive function (recall) was 6.1 (Figure 3). Here, negative relation between the length of disease and cognitive function (orientation and total) was an interesting point that may show the hazardous effect of long-time hyperglycemic blood levels on cognitive functions.

Clinical implications

It was obvious that Type-2 diabetic patients were under serious risk for cognitive impairment. Especially, poor glycemic control, retinopathy, hypertension, and longer disease periods are significant additional risk factors.

It would be useful observing cognitive functions as well as obtaining good glycemic control and

observing micro-macro vascular complications in the management of diabetes mellitus. Any cognitive decline may be detected by periodical mental examinations and further investigations may be performed. We believe that diabetic patients with retinopathy, hypertension, and longer disease period or with serum levels of HBAIC greater than 6.1 should be examined much more frequently.

Treatment of detected cognitive decline and preventive studies should be planned by more ample studies in the future. Results of our recent study may address risks easily and cost-effectively for cognitive declining among Type-2 diabetic patients.

Conclusions and recommendations

Type-2 diabetic patients are under great risk for cognitive decline. This risk is more relevant in the existence of retinopathy, hypertension, long disease period, and high HBAIC levels. Frequent assessment of cognitive functions in diabetic subjects, especially in the mentioned situations above, preventive approach, and treatment studies should be performed. We conclude that cognitive function evaluation should be a routine procedure in the management of Type-2 DM.

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