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## Original Research

# The Relationship between Polyneuropathy and Cognitive Functions in Type 2 Diabetes Mellitus Patients

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### Abstract

**Objectives:** Type 2 Diabetes Mellitus (DM) is a risk factor for mild cognitive impairment (MCI), Alzheimer's disease and vascular dementia. However, it is not known which pathophysiological mechanisms lead to impairment in cognitive functions in Type 2 DM. This study aims to compare the cognitive functions of diabetic patients with and without polyneuropathy using standardized Mini-Mental Test (MMSE) and the Montreal Cognitive Assessment Scale (MoCA) and to assess whether the presence of polyneuropathy is a predictive factor for the development of cognitive impairment.

**Methods:** Patients with DM who underwent our EMG laboratory for polyneuropathy between January 2014 and January 2015 were included in this study. Patients who underwent electrophysiological examinations were evaluated for polyneuropathy. Patients with polyneuropathy were classified as a patient group and other patients as a control group. In all cases, MMSE and MoCA were administered. The demographic data and educational status of the patients were recorded. Hypertension, coronary artery disease, smoking and alcohol use were questioned. Their complaints, duration of illness and the treatment they were receiving were questioned. Glycosylated hemoglobin (HBA1C) values in the last three months and physical examination findings of patients were recorded. Patients with and without polyneuropathy were compared with statistical methods.

**Results:** Polyneuropathy was detected in 34 (42%) of the 81 patients who participated in our study. The age, disease duration and HBA1C levels were statistically higher in the polyneuropathy group than in the control group ( $p=0.024$ ,  $p=0.000$ ,  $p=0.016$ ). However, there was no statistically significant difference between MMSE and MoCA scores of these groups. In both groups, there were no patients scoring below the MMSE cut-off value of 24. Seventeen of the 34 patients (50%) in the polyneuropathic group and 19 (40,4%) of the 47 patients in the control group had scores below the MoCA cut-off value 21. However, there was no statistically significant difference between the two groups. We also found that the mean MoCA value of all DM patients was 21, which was the MoCA cut-off value. Also, factors affecting cognitive functions in all Type 2 DM patients were evaluated by logistic regression analysis, and it was found that duration of education was an independent factor affecting cognitive impairment ( $OR=8.167$ ;  $p=0.001$ ).

**Conclusion:** In our study, we did not observe significant differences between MMSE and MoCA scores of Type 2 DM patients with and without polyneuropathy. However, the cross-sectional nature of our study makes it impossible to comment on this issue. To clarify whether the presence of polyneuropathy is a predictive factor in the development of cognitive impairment in Type 2 DM, there is a need for a larger sample group and long-term follow-up studies. It has also been shown that patients with Type 2 DM may have low scores according to the MOBID cut-off value even though peripheral neurologic involvement findings are not observed. In the Type 2 DM population, it has also been shown that MoCA may be affected by education level.

**Keywords:** Cognitive functions; cognitive tests; type 2 diabetes mellitus; polyneuropathy.

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**D**iabetes mellitus (DM) is a chronic progressive metabolic disease characterized by hyperglycemia, affecting many systems, especially the cardiovascular and nervous systems. It has been shown in many studies that DM is a risk factor for HBB, Alzheimer's disease and vascular dementia. In developing societies, progressive aging is observed and the frequency of dementia increases. Given that the elderly population with type 2 DM also increases, it is thought that the number of patients with cognitive impairment will increase even more. It is very important to be able to recognize and treat any problem or risk that may cause dementia to resolve the disability of a patient with dementia. Therefore, investigating the cognitive impairment thought to arise from DM is a condition that should be carefully considered.

Studies investigating the relationship between DM and cognitive impairment have concentrated on the presence of apolipoprotein E3 allele, the formation of advanced glycosylation end products, mitochondrial dysfunction, oxidative stress, inflammation, macrovascular mechanisms and insulin resistance.<sup>[1-6]</sup>

The causes for many clinical complications seen in DM are peripheral microvascular pathologies as retinopathy, nephropathy and neuropathy. A limited number of studies has been conducted investigating the relationship between DM and microvascular complications and cognitive disorders.<sup>[7-10]</sup> It has been indicated that diabetic retinopathy and retinal microvascular abnormalities are associated with various cranial magnetic resonance imaging (MRI) findings, such as small white matter hyperintensity and lesions in the brain, which demonstrate microvascular involvement in the brain.<sup>[7]</sup>

In the studies conducted based on the negative effects of cranial microvascular pathology on cognitive functions, it has been reported that patients with diabetic retinopathy manifest a weaker cognitive skill compared to patients without retinopathy and that because of the presence of microalbuminuria in Type 2 DM patients, which is a vascular dysfunction marker, these patients have weaker cognitive scores.<sup>[8]</sup>

In our study, our aim was to compare Type 2 DM patients with and without polyneuropathy concerning cognitive functions based on the idea that polyneuropathy, a microvascular complication that can be seen in the early stage of diabetes may also correlate with microvascular impairment in the brain and that cognitive functions may be negatively affected in patients with polyneuropathy.

## Methods

Our study was conducted between January and June 2015 with patients diagnosed as Type 2 DM, who were referred

to our electromyography (EMG) laboratory for the investigation of polyneuropathy and nerve conduction examinations were performed. Patients over the age of 40 who were trained for at least five years (primary school-secondary school-high school-university) were included in this study. Before this study, a letter of approval (date: 01.08. 2015 and decision # 828) was obtained from the ethics committee of our hospital.

Patients with a history of cerebrovascular disease, head trauma, cerebral palsy, mental retardation, dementia or neurodegenerative disease (such as epilepsy, multiple sclerosis and Parkinsonism), terminal -stage disease, malignancy, organ failure, psychiatric disease and sleep disorder, those who had acute systemic disease (such as endocrine disorder, fluid-electrolyte imbalance and infection), users of medications (neuroleptic, benzodiazepine and antidepressant) that may cause cognitive impairment, cases with complaints of forgetfulness specified by themselves or their relatives, severe hearing and cases with visual problems, substance, cigarette and alcohol use, diabetic retinopathy and nephropathy, pregnant women and lactating women were excluded from this study. We retrospectively collected the data about results of laboratory tests performed within the past six months involving hemoglobin, ferritin, vitamin B12, folic acid, electrolytes, free T3, free T4, and TSH. Among them, patients whose test results were within normal limits were included in this study. Patients with missing test results or whose laboratory values excluded from this study. Eighty-one enlightened patients who gave their voluntary consent, and met these criteria were examined prospectively.

Demographic data, education levels, complaints of patients (if any), duration of the disease, medications they used, glycosylated hemoglobin (HBA1C) values within the past three months and examination findings were recorded. The patients were questioned as for the presence of hypertension and coronary artery disease. Electrophysiological examinations of patients were carried out according to standard protocols using the Nihon Cohden EMG-EP device, and their data were evaluated. In motor conduction studies, the median, ulnar, peroneal and tibial nerves were stimulated, and compound muscle action potentials (CMAPs), distal latency (DL) and nerve conduction velocities (NCVs) were recorded.

In sensory conduction studies, the median, ulnar and sural nerves were stimulated, and sensory conduction velocities (SCVs), sensory response peak latencies and sensory action potentials (SAPs) were recorded. In cases suggesting polyneuropathy, the presence of polyneuropathy, electrophysiological multiple nerve involvement and pathologi-

cal findings (decrease in SNAP amplitude, slowing in SNCV, lengthening in DL, decrease in CMAP amplitude) evaluated according to the situation. Patients with abnormalities in the nerve conduction study constituted the polyneuropathy group, and patients without abnormalities formed the control group.

### Application of Neurocognitive Tests

After the EMG procedure, SMMT and MOBID were applied to all patients in the same day with a neurologist.

SMMT was published by Folstein et al. for the first time.<sup>[11]</sup> SMMT is a test that can be applied in a polyclinic condition or bedside within a period of 10 minutes. SMMT consists of eleven items collected under five main headings as follows: orientation, recording memory, attention and calculation, recall and language. The maximum scores corresponding to each item are as follows as indicated in parentheses: Time and place orientation (10); recording three words (3); successive backward subtracting or spelling letters from end to beginning (5); recalling words (3); naming (2) points: sentence repetition (1); comprehension (3); reading and reading comprehension (1); writing (1); and copying as 1 point. The lowest score that can be obtained from the scale is 0. The highest score is 30. Based on the study in which Turkish validation was performed, the SMMT cut-off score of <24 points was considered pathological.<sup>[12]</sup>

MoCA is a screening scale developed by Nasreddine et al.<sup>[13]</sup> to evaluate the early stages of cognitive impairment. The application time is about 10 minutes, and it is a short and easy to apply scale consisting of only one page. The scale includes items that evaluate attention and concentration, executive functions, memory, language, visuospatial skills, abstract thinking and computational dimensions. The items of MoCA can be listed as follows: memory tasks, recall from short-term memory, attempts to learn five words (2 points) and delayed recall after five minutes (5 points); tasks that require visuospatial skills, Clock Drawing Test (3 points) and three-dimensional cube copying (1 point); tasks related to executive functions, combining sequential numbers and letter patterns (such as 1-A, 2-B, 3-C) adapted from the Trace Test-B form (1 point), verbal fluency (1 point) and two-item abstract thinking task (2 points); attention, concentration and working memory tasks, successive subtraction (3 points) and forward and backward number space (1 point each); the language-related tasks are naming three relatively less well-known animals (lion, rhino, camel) (3 points), repeating two complex sentences in syntax (2 points), and finally time and place orientation (6 points).

The lowest score that can be obtained from the scale is 0.

The highest score is 30. Based on the study representing the Turkish sample in our country, the MoCA cut-off score of less than 21 points was accepted as cognitive disorders.<sup>[14]</sup> All patients were also evaluated according to MoCA subtests.

### Statistical Analysis

All statistical analyses were performed using SPSS (Statistical Package for Social Sciences) 16.0 package program. In addition to descriptive statistical methods (mean, standard deviation) in the evaluation of the data, chi-square analysis was used to compare the categorical variables in the examined groups; Student's t-test was used for the parameters that fit the normal distribution, and Mann-Whitney U test for the parameters that did not fit. The bivariate correlation method was used for correlation of the parameters within the group, and the Pearson test was used as the correlation coefficient. Independent factors affecting the presence of cognitive dysfunction were evaluated by single and multiple logistic regression analysis.

In single logistic regression analysis, variables with p-value <0.20 (age, education period, gender, DM duration) were taken as independent variables and included in multiple logistic regression analysis. The results were evaluated within the 95% confidence interval, and the significance level was considered as  $p < 0.05$ .

### Results

Polyneuropathy was detected in 34 (42%) of 81 (2%) DM patients, including 45 (55.6%) female and 36 (44.4%) male patients evaluated in our study. Any statistically significant difference was not found between the group with polyneuropathy and the control group as to SMMT and MoCA total score averages ( $p > 0.05$ ). No statistically significant difference was found in the comparison of the MOBID subgroup averages of the two groups ( $p > 0.05$ ). In both groups, any patients with SMMT cut-off score below 24 were not detected, whereas 17 (50%) of 34 patients in the polyneuropathy group and 19 (40.4%) of the 47 patients in the control group scored below the 21 cut-off value of MoCA. However, there was no statistically significant difference between the two groups ( $p > 0.05$ ). While there was no statistically significant difference concerning gender distribution and education level between the two groups, the group with polyneuropathy was found to have a higher average age, a longer average duration of DM, and a higher HBA1C average (respectively;  $p = 0.024$ ,  $p = 0.000$ ,  $p = 0.016$ ). Table 1 shows the detailed comparison of demographic and clinical characteristics of the control groups regarding polyneuropathy and cognitive test results.

After these evaluations, logistic regression analysis was ap-

**Table 1.** Comparison between the patient, and the control groups regarding demographics, clinical characteristics, and cognitive test results

	DM patients with polyneuropathy n (%)	Control group n (%)	p
	34	47	
Female	17 (50)	28 (59.5)	0.392
Male	17 (50)	19 (40.5)	0.392
5 years (primary education)	30 (63.8)	25 (73.5)	0.356
>5 years (more than primary education)	17 (36.2)	9 (26.5)	0.356
OAD	8 (23)	31 (65.9)	0.000*
Insulin±OAD	26 (77)	16 (34.1)	0.000*
HT (-)	10 (29.4)	21 (44.6)	0.163
HT (+)	24 (70.6)	26 (55.4)	0.163
CAD (-)	28 (82.3)	46 (97.8)	0.038*
CAD (+)	6 (17.7)	1 (2.2)	0.038*
MoCA <21	17 (50)	19 (40.4)	0.392
Mean±SD † ≥21	17 (50)	28 (59.6)	0.392
	<b>Mean±SS † (min-max)</b>	<b>Mean±SS † (min-max)</b>	<b>P*</b>
Age	60.73±10.3 (30-80)	55.34±10.6 (40-75)	0.024*
Duration of disease (years)	14.55±8.73 (1-35)	7.68±7.03 (1-40)	0.000*
HBA1C	8.34±2.10 (5.4-14.1)	7.54±2.08 (5.3-14.4)	0.016*
SMMT	28.11±1.87 (22-30)	28.40±1.61 (24-30)	0.582
MoCA Total Score	20.70±4.37 (12-29)	21.17±3.15 (13-26)	0.529
<b>MoCA Subscores</b>	<b>Mean±SD † (min-max)</b>	<b>Mean±SD † † (min-max)</b>	<b>P*</b>
Memory	2.20±0.25	2.40±0.17	0.638
Visuospatial	3.08±0.19	3.06±0.12	0.455
Executive Tasks	2.05±0.21	2.17±0.15	0.593
Attention	4.67±0.24	4.93±0.19	0.345
Language	2.85±0.15	2.70±0.11	0.481
Orientation	5.85±0.74	5.95±0.29	0.198

\*p<0.05; † mean±standard deviation (minimum-maximum); SMMT: Standardized Mini Mental Test; MoCA-Montreal: Montreal Cognitive Assessment Scale; OAD: Oral antidiabetics; DM: Diabetes Mellitus; HT: Hypertension; CAD: Coronary Artery Disease.

plied to determine the variables that may affect cognitive impairment in Type 2 DM patients.

In single logistic regression analysis, variables with p-value <0.20 (age, education period, gender, DM duration) were included in the multiple logistic regression analysis. Other confounding factors are not included in multiple logistic

regression analysis since they did not show significance in single logistic regression analysis. When all Type 2 DM patients were analyzed, it was found that after confounding factors were corrected with this analysis, the duration of training was an independent factor affecting cognitive impairment (OR=8.167; p=0.001) (Table 2).

**Table 2.** Logistic regression analysis performed for factors affecting cognitive impairment in patients with Type 2 DM

	P	OR	95% CI	
			Minimum	Maximum
Age (years)	0.473	1.020	0.966	1.076
Duration of education (years)	0.001*	8.167	2.385	27.967
Gender	0.374	1.578	0.578	4.310
Duration of DM (years)	0.924	1.004	0.929	1.084

\*p<0.05; CI: Confidence interval; OR: Odds ratio; DM: Diabetes Mellitus.

## Discussion

In our study, any statistically significant difference was not found between SMMT and MoCA total score averages of type 2 DM patients with and without polyneuropathy. There is a limited number of studies investigating the relationship between polyneuropathy and cognitive functions in type 2 DM patients in the literature.<sup>[8-10]</sup> In the study of Lorraine Ba-Tin et al.,<sup>[9]</sup> it was stated that there was no significant difference between the Cambridge Neuropsychological Test scores of type 2 DM patients who did not have any microvascular complications (neuropathy-retinopathy-nephropathy) and at least one microvascular complication. In the study conducted by Tekin et al.,<sup>[10]</sup> it was shown that there was no difference in SMMT scores between patients with type 2 DM with and without neuropathy, and lower SMMT scores were obtained in the group without hypertension and retinopathy.

In a study conducted by Jeroen de Bresser et al.<sup>[8]</sup> investigating the possible relationship between microvascular complications and cognitive impairment and brain volume changes, more severe deterioration in cognitive impairment was detected in patients with baseline albuminuria at the end of four years, and an association between other microvascular complications and cognitive impairment and brain volume change was not observed. In support of our study, any relationship between diabetic polyneuropathy and cognitive impairment has not been demonstrated in the literature.

To our knowledge, apart from our study in the literature, none of the studies cited in the literature have investigated the relationship between diabetic polyneuropathy and cognitive impairment using MoCA criteria. Only one study in the literature investigated the presence of cognitive impairment in all type 2 DM patients using MoCA criteria.

In our study, it was determined that the mean total score of MOBID in all DM patients was within the cut-off value of 21, and there were no patients who scored below the cut-off value of SMMT. When patients were divided into two groups as MOBID cut-off values below 21 and above 21, no statistically significant difference was found in the comparison of the two groups concerning age, gender, DM duration, HBA1C, DM treatment they received, HT, polyneuropathy and presence of coronary artery disease. In the study of Alagiakrishnan et al.<sup>[15]</sup> comparing the availability of SMMT and MOBID in detecting HBB in the type 2 DM population, the average of MOBID was 25.6 in the group diagnosed with HBB and 27.3 in the group without HBB. Alagiakrishnan and et al.<sup>[15]</sup> also supported our study, and there was no difference between the group with and without HBB concerning age, gender, education level, duration

of DM, and treatment they received.

It was observed that the MOBID total score average of the DM population in our study was quite low compared to the MOBID total score average of the DM population participating in the study of Alagiakrishnan et al.<sup>[15]</sup> This difference is higher in the mean DM duration in our study, lower education level, higher number of patients, cultural (such as away from older people from cognitive exercise and occupations, daily life activities provided by young family members) and/or educational (lifelong). It is thought that the understanding of education is not settled, there are no habits such as reading/hobby).

Selekler et al.,<sup>[14]</sup> in the study in which Turkish validation of MOBID was performed between Alzheimer's patients, patients diagnosed with HBB and the control group in 2010, the cut-off score was found to be 21. MOBID is not affected by variables, such as age and education level, it can be seen as an advantage, but it may be because the level of education is divided into two groups (above eight years or more) in their research, and the detailed study of the effects of education level on MOBID results. It was stated that it would be positive concerning reliability of the test.<sup>[14]</sup> Our study supports that MOBID can be used for screening cognitive functions in type 2 DM patients. However, in our study, on the patient population with DM, it was observed that only 11.1% of the patients with a MOBID average of 21 were below, and 48.9% of the patients with a MOBID average of 21 and above had a level of education above five years and also in the logistics model created. Training time in type 2 DM patients was found to be an independent risk factor affecting cognitive dysfunction. Thus, besides the negative effects of DM, we think that 67.9% of all patients are individuals with only five years of education; thus, we think that the education level variable may also be effective in the MOBID results obtained in Type 2 DM patients in our study. We believe that in the rapidly increasing Type 2 DM population, MOBID may be affected by the level of education, MOBID cut-off score may differ in this population. Thus, a separate study is needed in which the MOBID will be evaluated in screening the cognitive impairment in the DM patient population.

The shortcomings of our study are the low sample size, the majority of the study population consisted of individuals of low-education level, the limited number of tests performed for neurocognitive functions. The patients who had a history of depression and antidepressant use were not included in this study, and patients could not be evaluated for possible depression. Still, blood glucose levels were not determined before the application of neuropsychological tests and cranial imaging was not performed. In addi-

tion, although patients with known malignancy were not included in our study and any systemic clinical manifestations suggesting malignancy were not detected, cancer markers were not determined, and cancer screening tests were not performed.

## Conclusion

Our study is important because it is one of the limited numbers of studies evaluating the relationship between polyneuropathy and cognitive functions in type 2 DM patients. In our study, no statistically significant difference was found between the cognitive test scores evaluated with SMMT and MoCA in Type 2 DM patients with and without polyneuropathy. However, given that our study is cross-sectional prevents us from commenting on this issue. To clarify whether the presence of polyneuropathy will be the predictive factor in the development of cognitive impairment in Type 2 DM, long-term follow-up studies with a larger sample group should be conducted.

In addition, although the findings of peripheral neurological involvement are not observed, it has been shown that patients with Type 2 DM may have low scores according to MoCA cut-off value and that MoCA may be affected by the level of education in these patients. In this population, it is thought that a comprehensive study is needed to evaluate MoCA for the purpose of screening cognitive impairment.

## Disclosures

**Ethics Committee Approval:** This study was approved by the local Ethics Committee of Sisli Etfal Training and Research Hospital (01.08.2015/828).

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – S.M.T., M.C.G.; Design – M.C.G.; Supervision – M.C.G.; Materials – S.M.T., E.T., N.P.Y.; Data collection &/or processing – S.M.T., E.T.; Analysis and/or interpretation – S.M.T., E.T.; Literature search – E.T., N.P.Y.; Writing – S.M.T., E.T.; Critical review – M.C.G.

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