Original Article

Quantitative Electroencephalography Findings in Patients With Diabetes Mellitus

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Abstract

Objective. Diabetes mellitus (DM) causes structural central nervous system (CNS) impairment, and this situation can be detected by quantitative electroencephalography (QEEG) findings before cognitive impairment is clinically observed. The main aim of this study is to uncover the effect of DM on brain function. Since QEEG reflects the CNS functioning, particularly in cognitive aspects, we expected electrophysiological clues to be found for prevention and follow-up in DM-related cognitive decline. Since a majority of the psychiatric population have cognitive dysfunction, we have given particular attention to those people. It was stated that a decrease was observed in the posterior cortical alpha power due to the hippocampal atrophy by several previous studies and we hypothesize that decreased alpha power will be observed also in DM. *Methods*. This study included 2094 psychiatric patients, 207 of whom were diagnosed with DM and 1887 of whom were not diagnosed with DM, and QEEG recordings were performed. Eyes-closed electroencephalography data were segmented into consecutive 2 s epochs. Fourier analysis was performed by averaging across 2 s epochs without artifacts. The absolute alpha power in the occipital regions (O1 and O2) of patients with and without DM was compared. *Results*. In the DM group, a decrease in the absolute alpha, alpha 1, and alpha 2 power in O1 and O2 was observed in comparison with the control group. It was determined that the type of psychiatric diagnosis did not affect QEEG findings. *Conclusion*. The decrease in absolute alpha power observed in patients diagnosed with DM may be related to the CNS impairment in DM. QEEG findings in DM can be useful while monitoring the CNS impairment, diagnosing DM-related dementia, in the follow-up of the cognitive process, constructing the protocols for electrophysiological interventions like neurofeedback and transcranial magnetic stimulation and monitoring the response to treatment.

Keywords

diabetes mellitus, quantitative electroencephalography, cognitive impairment

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Introduction

DM is a common disease, in which chronic hyperglycemia is observed and which is known to have adverse effects on all body systems.[1] According to the World Health Organization, at least 171 million people worldwide are diagnosed with DM.[2] Cooccurrence of DM and psychiatric disorder has been established in clinical as well as general population studies.[3]

Chronic hyperglycemia is known to be associated with neuronal damage and dysfunction.[4] Severe peripheral, autonomic, and central neuropathies develop in patients diagnosed with DM in the long term.[2] In comparison with individuals without the disease, a 1.5-time increase in the risk of cognitive impairment and a 1.6-time increase in the risk of dementia were demonstrated in patients diagnosed with DM.[5]

Brain atrophy, especially observed in the hippocampus, is known to be associated with cognitive impairment.[6] It was demonstrated that hippocampal atrophy and neuronal loss occur in DM[7-9] and this hippocampal atrophy occurs before cognitive impairment is clinically observed.[10]

The hippocampus is the main source of the rhythmic activity in electroencephalography (EEG).[11-13] EEG rhythms reflect the underlying brain network activity.[14] In particular, EEG alpha rhythm studies may display the relationship between the structure and function of these brain networks.[15] Alpha rhythms are mainly regulated by thalamocortical and cortico–cortical interactions,[16-18] and their maximal amplitude is on the occipital cortex.[19-22] Previous resting-state EEG studies conducted in DM showed changes in spontaneous brain oscillations.[23]

In QEEG studies conducted in patients diagnosed with DM, while an increase in slow-wave activity (delta and theta) was

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demonstrated in the fronto-central regions, a decrease in high-frequency activity (alpha, beta, and gamma) was detected in the posterior and temporal regions.[24-26] In another study, a linear correlation was detected between the magnitude of alpha 1 oscillations in the occipital, parietal, and temporal regions and the hippocampal volume.[27]

EEG rhythms can be used to assess neuronal degeneration that occurs due to DM.[14,28] These EEG changes can be detected before tissue loss or clinical symptoms emerge. Consequently, QEEG findings can be an early sign of the effects of DM on the CNS.

In this study, we plan to compare the absolute alpha power in the occipital leads (O1 and O2) of diabetic and nondiabetic patients who applied to the psychiatry clinic. It was stated that a decrease was observed in the posterior cortical alpha power due to the hippocampal atrophy by several previous studies[29] and we hypothesize that decreased alpha power will be observed also in DM. We have chosen only the occipital alpha power in our analysis because the occipital regions have much more artifact-free areas.[30]

The main aim of this study is to uncover the effect of DM on brain function. Since QEEG reflects the CNS functioning, particularly in cognitive aspects, we expected electrophysiological clues to be found for prevention and follow-up in DM-related cognitive decline.[14] Since a majority of the psychiatric population have cognitive dysfunction, we have given particular attention to those people.[31]

Materials and Methods

Participants

Individuals, who applied to the Kemal Arıkan Psychiatry Clinic (a private psychiatric practice) between April 1, 2013 and October 31, 2019 were included in this study. The participants were divided into 2 groups, with (n = 207) and without (n = 1887) DM diagnosis. While 207 of diabetic patients were diagnosed with type 2 DM, 5 of them were diagnosed with type 1 DM. In the psychiatric interview (Structured Clinical Interview for DSM-5) all the participants were diagnosed with psychiatric disorders (bipolar disorder, depression, panic disorder, obsessive–compulsive disorder, schizophrenia, generalized anxiety disorder and borderline personality disorder),[32] the Hamilton Depression Rating Scale (HAM-D) was applied, and QEEG recordings were performed.

EEG Recording

The participants were informed about the procedure prior to EEG recording. In order to reduce anxiety, the participants were allowed to rest in a quiet room for 30 min prior to the procedure. EEG recording was performed in a soundproof, dimly lit, and well-ventilated room. A 19-channel (FP1, F7, T3, T5, F3, C3, P3, O1, FZ, CZ, PZ, F4, C4, P4, O2, FP2, F8, T4, and T6) electro-cap that was compatible with each participant's head measurements was properly fixed to the head of each participant. Electro-gel was used between the electrodes and the scalp to increase conductivity and the signal-to-noise ratio. A sufficient amount of gel was applied to each electrode area using a blunt tip injector. The ground electrode was placed in the FPz position. Reference electrodes were extra electrodes attached with EEG paste to both earlobes, which had first been cleaned with cleansing gel and alcohol.

A vertical electrooculogram (EOG) and horizontal EOG were recorded to determine simultaneous eye movements in EEG imaging; the Ag–AgCl disk electrodes used for this purpose were attached to the relevant area using the EEG paste and fixed to the area with a plaster. Following these procedures, all electrodes were checked for impedance, and additional electro-gel was used, as necessary. EEG recording was initiated when impedances were <5000 Ω. EEG recordings were made using a Neuron-Spectrum-4/P device, and only while the participants were at rest; no activation method was applied. The participants were instructed to sit comfortably, remain awake, and blink as little as possible during EEG recording.

Data Conditioning

Neuron-Spectrum.NET software was used for EEG impedance measurement as follows: notch filter: on; scale: 10 mV mm^{-1} and sweep: 30 mm s^{-1}. As used for standard EEG recording, the high-pass filter was set to 0.5 Hz and the low-pass filter was set to 70 Hz. The EEG range was reinforced using a 0.5 to 70 Hz bandpass filter, with the resistance of the electrodes set at <5000 Ω, and the sampling rate was 250 Hz. All EEG recording data were transferred to a computer hard drive. EEG recordings were made with the participants' eyes open during 2 individual 5 min periods and with their eyes closed during 2 other 5 min periods. Eyes-closed EEG data were segmented into consecutive 2 s epochs. Epochs contaminated by blinking, eye movements, and movement-related artifacts were excluded from analyses by visual inspection performed by an experienced neurologist.[33]

Data Analysis

Fast Fourier transform analysis was performed by averaging across 2 s epochs without artifacts.[33] Spectral analysis is a standard method for EEG quantification[34] that facilitates determination of the distribution of power according to frequency,[35] which provides information about the frequency content of a signal. For O1 and O2 monopolar derivations, absolute (μV2) power were calculated for the alpha (8-13 Hz), alpha 1 (8-10 Hz) and alpha 2 (10.5-13 Hz) frequency bands.[35-37]

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v.24.0 (IBM Corp.). The age and gender

differences between the groups were evaluated by Student's *t*-test and the chi-square test, respectively. The cases differed in terms of age ($P = .000$) and gender ($P = .01$) (Table 1).

Performing analysis for all EEG bands or on all EEG locations may reveal a statistical fact called *p*-hacking.[38] Studying certain bands and certain areas was suggested to eliminate *p*-hacking. Alpha rhythms are mainly regulated by thalamocortical and cortico-cortical interactions,[16-18] and their maximal amplitude is on the occipital cortex.[19-22] Therefore, we preferred to investigate the occipital alpha power in this study.

Student's *t*-test was performed for the alpha bands in O1 and O2 (O1-alpha, O1-alpha 1, O1-alpha 2, O2-alpha, O2-alpha 1, and O2-alpha 2), provided that DM was a dependent variable ($\alpha = 0.05$) (Table 2). Logistic regression analysis was performed provided that alpha bands, for which a significant difference was determined in Student's *t*-test (O1-alpha, O1-alpha 1, O1-alpha 2, O2-alpha, O2-alpha 1, O2-alpha 2), age, gender, the HAM-D score, and diagnosis were independent variables, and DM was a dependent variable (Table 3).

Measurements with a *P* value of <20% in Student's *t*-test were subjected to logistic regression analysis,[38] and in the logistic regression analysis, O1-alpha 1 and O2-alpha 1 gained significance. In the logistic regression analysis, $\alpha = 0.00416$ (0.05/12) was taken. Since the change in 6 EEG bands, including O1-alpha, O1-alpha 1, O1-alpha 2, O2-alpha, O2-alpha 1, and O2-alpha 2, according to 2 medical conditions of with/without DM was analyzed, the current statistical significance level was divided into 12.

Logarithmic transformation was applied to all measurements because the EEG data contained a high degree of skewness. Since some EEG measurements took values of between 0 and 1, 1 was first added to all measurements, and then they were log-transformed. The mean, standard deviation, and standard error values given in Student's *t*-test were the transformed values. Both Student's *t*-test and logistic regression analysis were performed with the transformed data.

In the graph, EEG values that were subjected to logarithmic transformation were used by performing back-transformation. Since there was transformation, it was not found appropriate to include standard deviations in the graph.

Table 1. Demographic Characteristics of Groups.

	N	Gender		Age
		Female (n)	Male (n)	Mean ± SD
Group 1 (DM)	207	119	88	42.86 ± 15.27
Group 2 (Control)	1887	906	981	33.92 ± 11.69
P value		.010*		.000*

Abbreviations: DM, diabetes mellitus; SD, standard deviation.
*A statistically significant difference was detected between the groups in terms of age ($P = .000$) and gender ($P = .01$).

Table 2. Comparing the Groups in Terms of Log-transformed Absolute Power (log μV2).

EEG band	DM	Control	*P*
O1-alpha	3.23	3.54	.036*
O1-alpha 1	2.46	2.69	.135
O1-alpha 2	2.55	2.92	.015*
O2-alpha	3.24	3.59	.020*
O2-alpha 1	2.52	2.74	.129
O2-alpha 2	2.55	2.95	.006*

Abbreviations: EEG, electroencephalography; O, occipital; DM, diabetes mellitus.
*Student's *t*-test; the difference between the groups was found to be statistically significant.

Results

Between April 1, 2013 and October 31, 2019, 2094 people applied to the Kemal Arıkan Psychiatry Clinic. While 207 of these patients were diagnosed with DM, 1887 of them were not diagnosed with DM. Of the diabetic patients, 5 were diagnosed with type 1 DM and 202 were diagnosed with type 2 DM. Patients diagnosed with DM were defined as group 1 and patients without DM were defined as group 2. The participants (1025 women and 1069 men) were evaluated according to the diagnoses, and it was determined that from among the patients with bipolar disorder (n = 208) 25 were diagnosed with DM and 183 were not diagnosed with DM; from among the patients with major depressive disorder (n = 690) 68 were diagnosed with DM and 622 were not diagnosed with DM; from among the patients with panic disorder (n = 245) 24 were diagnosed with DM and 221 were not diagnosed with DM; from among the patients diagnosed with obsessive–compulsive disorder (n = 352) 24 were diagnosed with DM and 328 were not diagnosed with DM; from among the patients with the diagnosis of schizophrenia (n = 115) 5 were diagnosed with DM and 110 were not diagnosed with DM; from among the patients with generalized anxiety disorder (n = 435) 55 were diagnosed with DM and 380 were not diagnosed with DM; and from among the patients with borderline personality disorder (n = 49) 6 were diagnosed with DM and 43 were not diagnosed with DM.

It was detected that the ratio of female patients in group 1 (those diagnosed with DM) was higher compared to group 2, and the mean age was lower in this group. A statistically significant difference was found between the 2 groups in terms of age ($P = .000$) and gender ($P = .010$) (Table 1).

When the absolute alpha power in the occipital region between the 2 groups was compared, the O1-alpha, O1-alpha 1, O1-alpha 2, O2-alpha, O2-alpha 1, and O2-alpha 2 band log-transformed absolute power measurements were found to be lower in group 1 (those diagnosed with DM). A statistically significant difference was

Table 3. Logistic Regression Analysis.

EEG band	*B*	SE	Wald	df	Sig.	Exp(*B*)
Age	0.05	0.01	34.97	1	0.000*	1.05
Gender			1.56	2	0.458	
Female	−0.30	0.24	1.56	1	0.211	0.74
Male	−17.89	40191.44	0.00	1	1.000	0.00
Diagnosis	−0.02	0.03	0.50	1	0.481	0.98
HAM-D	−0.00	0.01	0.11	1	0.735	0.10
Type 1 DM	24.45	18917.48	0.00	1	0.999	41 557 229 804.65
O1-alpha	6.50	2.32	7.87	1	0.005	666.85
O1-alpha 1	−4.01	1.22	10.86	1	0.001*	0.02
O1-alpha 2	−2.32	1.51	2.36	1	0.124	0.10
O2-alpha	−7.48	2.59	8.33	1	0.004	0.00
O2-alpha 1	4.49	1.36	10.95	1	0.001*	89.22
O2-alpha 2	2.79	1.65	2.89	1	0.089	16.35
Constant	3.04	16399.73	0.00	1	1.000	20.94

Abbreviations: EEG, electroencephalography; O, occipital; HAM-D, Hamilton depression rating scale; *B*, beta; SE, standard error; df, degree of freedom; Sig., significance; Exp, exponential; DM, diabetes mellitus.
*A statistically significant correlation was detected, provided that age, O1-alpha 1, and O2-alpha 1 were the independent variables, and DM was the dependent variable.

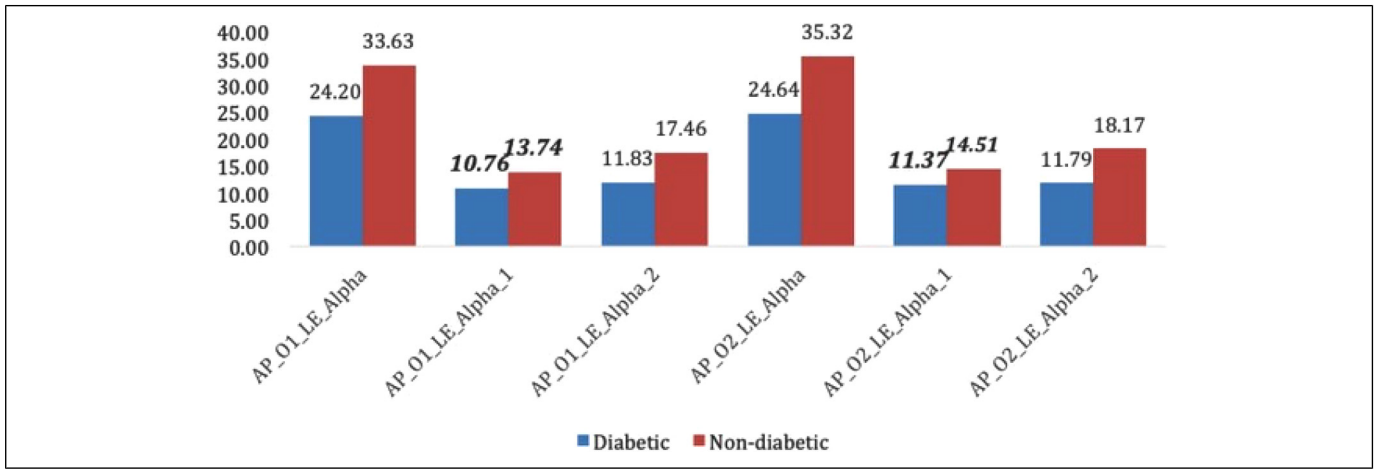

Figure 1. Absolute power according to group (μV2).

determined between the two groups in the O1-alpha ($P = .0360$), O1-alpha 2 ($P = .0154$), O2-alpha ($P = .0201$), and O2-alpha 2 ($P = .0069$) bands (Table 2).

In the logistic regression analysis, it was found that the O1-alpha 1 ($P = .001$), O2-alpha 1 ($P = .001$) band power, and age ($P = .000$) variables were effective on DM; in other words, these bands/channels were affected by DM, and the gender, HAM-D score, and diagnostic variables were observed to be not related to DM diagnosis. In this regard, we observe that especially age is higher in those with DM. In logistic regression analysis, although age included a significant difference as expected, this significance did not affect the significance of O1-alpha 1 and O2-alpha 1. Type 1 DM patients did not affect the statistical data (Table 3) (Figure 1).

Discussion

In this study, QEEG differences were investigated in terms of resting-state occipital alpha power between patients diagnosed with DM (group 1) and without DM (group 2). Six EEG band power values (O1-alpha, O1-alpha 1, O1-alpha 2, O2-alpha, O2-alpha 1, and O2-alpha 2) were found to be lower in patients diagnosed with DM (group 1) than patients without DM (group 2). DM is a disease that increases cognitive impairment risk in individuals.[23] Especially brain atrophy observed in the hippocampus, which is more sensitive to glycemic control than other brain regions,[39,40] is known to be associated with cognitive impairment.[6] It was demonstrated that there was hippocampal atrophy and neuronal loss in DM[7-9] and occipital alpha power decreased in relation to hippocampal atrophy.[29]

The decreased alpha power is most evident in the occipital region.[41] Occipital region is mostly an artifact-free area in EEG recordings.[30] In our study, decreased alpha power was not attributed to any psychiatric disorder; in other words, it was independent of diagnosis. The results suggest that occipital alpha power may decrease as a result of hippocampal atrophy developing in DM.

Our results are consistent with previous QEEG studies in terms of decreased alpha power in DM.[23-26,42]

There are several investigations showing that DM is closely related to cognitive decline. Brismar demonstrated that alpha and beta power decreased in the posterior temporal regions and slow-wave components increased in the frontal regions in type 1 DM.[26] In type 2 DM patients to whom intensified glycemic control was applied, Cooray et al[23] observed an increase in the alpha band power in the central and lateral regions, along with the improvement in visuospatial ability and semantic memory performance, in comparison with patients whose regular DM treatment was maintained.

In studies investigating the QEEG findings associated with cognitive impairment, it was demonstrated that the alpha power decreased in those with mild cognitive impairment (MCI),[27,43-50] and that there was a decrease in parieto-occipital alpha 1 power in Alzheimer's disease patients.[6,51]

The hippocampus is one of the brain regions affected a lot by DM,[52] and it was demonstrated that there was hippocampal neuronal loss in rats due to diabetic encephalopathy.[9] Hippocampal atrophy is associated with DM-related cognitive dysfunction.[53,54] However, hippocampal atrophy occurs before cognitive decline becomes visible.[10] Hagar et al[14] detected hippocampal atrophy at a rate of 37.5% in DM patients with MCI and at a rate of 12.5% in DM patients without cognitive impairment, and they did not observe hippocampal atrophy in the healthy controls. In 2 other studies conducted on similar patient groups, a significant difference was found between DM patients with cognitive impairment and the control group in terms of the hippocampal volume.[55,56]

The strengths of our study are that the number of cases is high, and the decreased alpha power is not attributed to any psychiatric diagnosis and replicability of the data, which were obtained from the artifact-free regions of occipital leads.

There are many studies that demonstrate the presence of hippocampal atrophy in DM and are consistent with each other.[7-9,53-63] However, still, the biggest limitation of our study is that the volume of the hippocampus was not examined.

Of the diabetic patients included in our study, 5 were of type 1 DM and 202 were of type 2 DM. The rate of type 1 DM among diabetic patients was found to be 10% in epidemiological studies.[64] According to epidemiological data, our data can be considered within normal limits in terms of the incidence of type 1 and type 2 DM. However, type 1 DM and type 2 DM have distinct pathophysiological effects on the CNS.[65] Therefore, we showed that type 1 DM patients in our study had no effect on statistical data.

Neurocognitive tests were not applied to our patients. However, it is known that hippocampal atrophy occurs before cognitive impairment is clinically observed[10] and that QEEG findings emerge before neuropsychiatric tests deteriorate.[66]

The fasting blood glucose and HbA1c levels of our patients were not evaluated. In a study conducted on the elderly population, high serum HbA1c levels were demonstrated not to be associated with hippocampal volume loss.[67] Another study found that the temporal alpha power decrease was not associated with poor metabolic control or hypoglycemia.[25] Soltesz and Acsadi[68] determined that the degree of metabolic control did not affect EEG findings. However, in another study that followed up DM patients for 2 months by dividing them into 2 groups in which intensified glycemic control and the regular treatment were maintained, the alpha power in the central and lateral regions was observed to increase in the intensified glycemic control group at the end of 2 months.[23] In another study conducted on adolescents diagnosed with type 1 DM, the decreased relative alpha power was found in patients with high HbA1c levels.[69]

Lack of information about the duration of the illness is another limitation of this study. Our groups do not match in terms of age and gender. It is known that alpha power decreases with age.[70] There are contradictory results in the studies that compare genders in terms of alpha power. While some researchers did not find a difference in terms of gender,[71] there were also studies that found higher alpha power in men[72,73] and higher alpha power in women.[74]

Although we preferred reducing the alpha level for logistic regression some other statistical maneuvers can be taken into account like Bonferroni correction, which may be considered as a limitation of this study.

In conclusion, our results demonstrate that there was a decrease in the occipital alpha power in patients diagnosed with DM in comparison with the nondiabetic control group. This situation may be due to hippocampal atrophy. These results show that QEEG findings can be useful while monitoring the CNS impairment, diagnosing DM-related dementia, in the follow-up of the cognitive process, constructing the protocols for electrophysiological interventions like neurofeedback and transcranial magnetic stimulation and monitoring the response to treatment in DM. However, further QEEG studies that support hippocampal atrophy in DM patients with objective measurements are needed.

Author Contributions

ÖÖ contributed to the conception and design and the acquisition and interpretation, drafted the manuscript, critically revised the manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. GG contributed to the analysis, drafted the manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. MKA contributed to the conception, critically revised the manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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