ОЦЕНКА СКОРОСТИ ВИЗУАЛЬНОЙ И СЛУХОВОЙ РЕАКЦИИ У ЛИЦ С САХАРНЫМ ДИАБЕТОМ 2 ТИПА

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ЦЕЛЬ. Оценить повреждение периферических нервов у пациентов с сахарным диабетом (СД) и выявить различия в скорости реакции и восприятия в зависимости от возрастных групп, длительности СД 2 типа (СД2), уровней глюкозы в плазме натощак и гликированного гемоглобина (HbA_{1c}), а также сравнить их с таковыми у здоровых людей.

МАТЕРИАЛЫ И МЕТОДЫ. Исследование проводилось в Клинике эндокринологии Баскентского университета и в Поликлинике метаболических заболеваний. Всего в исследование были включены 64 пациента с диагнозом СД2 и 64 здоровых лиц из контрольной группы. Были проведены finger-tapping тест, тесты на визуальную и слуховую реакцию соответственно. Регистрировались уровни глюкозы в плазме натощак и HbA_{1c}, а также оценивалась длительность заболевания. Анализ полученных данных проводился с использованием SPSS версии 25. Различия считались статистически значимыми при значении $p<0,05$.

РЕЗУЛЬТАТЫ. Было отмечено, что участники контрольной группы в возрасте от 18 до 34 лет показали более быструю реакцию во всех тестах (p=0,01), но различия в скорости реакции в обеих группах уменьшались с увеличением возраста. Выявлены положительные корреляционные связи между длительностью СД2 и результатами визуального и слухового тестов (r=0,69, p<0,05; r=0,52, p<0,05 соответственно). Также отмечена положительная корреляция между уровнем HbA_{1c} (%) и результатами теста визуальной реакции (r=0,97, p<0,05).

ЗАКЛЮЧЕНИЕ. По мере увеличения уровня HbA_{1c} и длительности СД2 у пациентов скорость реакции и навыки восприятия снижались. Наблюдалось быстрое снижение когнитивных функций, особенно на ранних стадиях.

КЛЮЧЕВЫЕ СЛОВА: снижение когнитивных функций; окислительный стресс; нейропатия; время реакции; сахарный диабет 2 типа

DETECTION OF VISUAL-AUDITORY REACTION RATES IN INDIVIDUALS WITH TYPE 2 DIABETES MELLITUS

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AIM: The primary purpose of our study was to understand the damage in the peripheral nerves of patients with diabetes and to determine the change in patients' reaction rates and perceptions by the age groups, duration of diabetes, fasting plasma glucose and HbA_{1c} values, and compare these with those of the healthy individuals.

METHODS: This study was carried out at the Baskent University Hospital Endocrinology and Metabolic Diseases Outpatient Clinic. A total of 64 patients diagnosed with type 2 diabetes and 64 healthy controls were included in the study. Finger tapping, visual, and auditory reaction time tests were performed on the subjects, respectively. The subjects' fasting plasma glucose and HbA_{1c} levels, and the duration of their diabetes were recorded. Analyses were performed using the SPSS version 25. Differences were considered statistically significant when the p-value is <0.05.

RESULTS: It was observed that the participants in the control group between the ages of 18-34 showed a faster reaction in all tests (p=0.01), but the difference in reaction rates in both groups decreased as the age increased. There were positive correlations between the duration of type 2 diabetes and the visual and auditory examination results (r= 0.69, p<0.05, r=0.52, p<0.05, respectively). There was also a positive correlation between the HbA_{1c} (%) and the visual (r=0.97, p<0.05) examination results.

CONCLUSIONS: As the patients' HbA1c levels and the time spent with type 2 diabetes increased, their reaction rate and perception skills decreased. Especially in the early stages of the disease, cognitive decline was observed to be rapid. It is thought that early diabetic control is significant.

KEYWORDS: cognitive decline; oxidative stress; nerve damage; reaction times; type 2 diabetes mellitus

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease that may cause many complications. The incidence of diabetes, which was around 108 million in 1980 increased 4-fold by 2014 and continues to increase [1]. The risk of type 2 diabetes increases with the aging population, and it becomes important to investigate serious health problems such as cognitive decline and forgetfulness in patients [2]. There are studies showing that cognitive disorders may develop in type 2 diabetes [3]. Vascular complications of hyperglycemia are considered one of the important causes of cognitive disorders in diabetes patients. Recurrent hypoglycemic episodes and abnormal plasma glucose levels have been associated with

Received: 02.01.2023. Accepted: 03.05.2023

cognitive impairment from the early stages of diabetes and progressively accelerated destruction in type 2 diabetes patients [4]. It has been reported that type 2 diabetes increases the risk of dementia by 50% [5]. Individuals with diabetes have not only cognitive dysfunctions but also brain structure anomalies, which include decreased gray matter volume in the frontal lobe and smaller postcentral gyrus [6]. Reaction time is described as the time elapsed from a non-anticipated stimuli to the onset of a reaction and is affected by the person's age, education level, health conditions, and biological rhythms [7, 8]. Diabetes-induced cognitive impairments can affect people's reaction times and cause delayed reactions [9].

The aim of this study was to examine the damage caused by the abnormal plasma glucose in the peripheral nerves in patients with diabetes and to determine the change in the patients' reaction rates by the age groups, duration of diabetes, fasting plasma glucose and HbA_{1c} values, and compare it with the healthy controls.

MATERIALS AND METHODS

Design

This observational case-control study was carried out at the Baskent University Hospital Endocrinology and Metabolic Diseases Outpatient Clinic between April and September 2021.

Sampling Method

The study population was healthy and with type 2 diabetes individuals in the Baskent University Hospital Endocrinology and Metabolic Diseases Outpatient Clinic. The sample consisted of 128 people between 18–64 age, 64 of whom were patients and 64 were controls, selected by the simple sampling methodology and volunteered for the study.

Inclusion and Exclusion Criteria

Right-handed individuals were included in the study since the left hemisphere is the dominant hemisphere. The exclusion criteria of the study were the use of alcohol-drug or similar substances, the use of any medication that may affect neurological functions, having color blindness, retinopathy, neurological disease, cancer, depression, a recent history of surgery, rheumatoid arthritis, osteoarthritis, and advanced osteoarthritis.

Data Collection

Since participation in the study was on a voluntary basis, participants were asked to read and sign the informed consent form for scientific research if they consented to participate in the study. Finger tapping, visual and auditory reaction tests were applied to the participants, respectively. Afterward, blood values were taken from the system (HbA_{1c} and fasting plasma glucose) and recorded.

Finger Tapping Test (FTT)

The finger tapping test (FTT) has long been used in neurophysiology to examine motor functions in the upper extremity. The finger tap test is used not only to study Alzheimer's, Korsakoff's syndrome, or Parkinson's disease but also to analyze the connection between motor functions and lateralization in healthy individuals. The FTT records the time difference between consecutive pulses and storages this data on the computer's hard drive. The software for this test has been developed in such a way that it can be applied to personal computers without the need for additional hardware. The time set during the test is between 10–15 seconds to refrain from creating a negative effect on the subjects. The FTT can be applied in such a way that the participants can stand at a distance of about 50 cm from the computer and easily move their wrists. Afterward, a designated key on the computer keyboard should be pressed and pulled as quickly as possible within the specified time interval [10].

Visual Test

In the visual reaction test, the participant is asked to press the designated button when she sees only the red-colored box among the boxes that appear in random colors and times. The intervals between the data and whether the participants answered correctly are recorded in the computer system.

Auditory Test

In the auditory reaction test, the participant is asked to press a predetermined key whenever a sound is heard from the computer.

Fasting Plasma Glucose (FPG)

The fasting plasma glucose values of the participants were measured in the morning hours when the patients were hungry, by specialist nurses in the Baskent University Ankara Hospital Laboratory with the "Hexokinase/G-6-PDH" method (Architect ci8200, Abbott) according to the instructions.

Afterward, FPG values were obtained from Baskent Hospital Nucleus v23 (Monad, Ankara, Turkey) system records and were noted. Since plasma glucose values and regular measurement are important in diabetic individuals, these were included in our analysis.

HbA_{1c} Values

HbA_{1c} values were also recorded from from Baskent Hospital Nucleus v.23 (Monad, Ankara, Turkey) system records, as it is a reliable marker showing the average plasma glucose concentration in the last 4 to 8 weeks.

Variables

The common variables considered in this study were sex, age, FPG, and HbA_{1c} values. Participants were classified according to their gender, age groups, FPG, and HbA_{1c} values. Age and HbA_{1c} classification was made by dividing the patients into 3 age groups, 18–34, 35–49, and 50–64 years. The fasting plasma glucose values of the participants were expressed as millimole/liter (mmol/L), and the HbA_{1c} values were expressed as percent (%).

Fasting plasma glucose values, which were determined according to laboratory diagnostic criteria, were classified as above and below 6.1 mmol/L. HbA_{1c} values, on the other hand, were classified as equal to the reference value of 7%, and greater than or less than 7%. The duration of diabetes was determined only for the patients. In line with the literature indicating cognitive deterioration begins in the first 9 years of diabetes, the patients were divided into 2 groups, those with diabetes for less than 10 years and 10 years and more. While determining the duration of diabetes, the year in which the patients were diagnosed in the clinic was taken as a basis, and recorded.

Statistical Analysis

The power analysis G*Power software was used to calculate the minimum sample size required for the study. The Kolmogorov-Smirnov test was applied to analyze the distribution of the data. In order to compare the patient and control groups in terms of audio-visual and finger-tapping tests according to age, "One-Way Analysis of Variance" was applied when parametric test assumptions were met, and the "Kruskal Wallis Test" was applied if not. The relationship between the test averages of the patients and FPG, HbA_{1c}, and disease duration was evaluated by Spearman correlation analysis. Statistical analysis was performed in version 25 of the SPSS program. Differences were considered to be statistically significant if p values were <0.05.

Ethics Approval And Consent to Participate

This study was approved by the Baskent University Medical and Health Sciences Research Board and Ethics Committee. (Project no: KA21/245, decree number: 21/96, decree date: 26.05.2021).

RESULTS

This study was conducted with 64 patients aged between 18–64 years, and 64 healthy control individuals. The mean age of the participants was 47.7±13.7 years for the patients and 40.7±14.5 years for the control group. Likewise, while the mean FPG values of the patients were 8.9±4.2 mmol/L, this value was 6±3.7 mmol/L in the control group. The demographic, biochemical, and clinical data of the study group are summarized in Table 1.

The age (p=0.23) and sex (p=0.266) distributions were similar among the patient groups and controls. The mean FPG values was found to be significantly higher in diabetics than in the control group (p=0.01). Similarly, HbA_{1c} values were significantly higher in diabetics than in the control for each age group (p=0.002, 0.03, 0.007, respectively) (Table 1).

As shown in Table 2, when patients and the control group aged 18–34 years were compared, it was determined that the control group was faster in FTT (p=0.01), visual (p=0.03), and auditory reaction tests (p=0.01). While there were no statistically significant differences in terms of the mean FTT and auditory test reaction rate values of the participants aged 35–49 years between the control and patient groups (p>0.05), it was determined that the patients reacted more slowly in the visual test than the controls (p=0.02). It was observed that there were no statistically significant differences in the mean values of FTT, visual and auditory test reaction speeds of the participants aged 50–64 between the patient and control groups (p>0.05). When the relationship between gender and reaction rates of the patients was analyzed no statistically significant result was found (p>0.05).

The correlation analysis between variables is shown in Table 3. There was no correlation between FPG values and reaction rates. When the HbA_{1c} levels and diabetes duration were correlated with other parameters such as reaction test speeds, HbA_{1c} levels were positively correlated with visual test (r=0.97, p<0.05) and diabetes duration was positively correlated with visual (r= 0.69, p<0.05) and auditory tests (r=0.52, p<0.05).

DISCUSSION

The main result of our study was that when the patients and control group of the same age were compared, the control group between the ages of 18–34 years had a faster reaction and the difference between the groups became

Table 1. Demographic, clinical and biochemical parameters of participants in the study

		Type 2 diabetes (n=64)	Control (n=64)	p
Age (years)		47.7±13.7	40.7±14.5	0.23
FPG (mmol/L)		8.9±4.2	6±3.7	0.01*
Sex (n, %)	F	32 (50%)	39 (60.9%)	1.08
	M	32 (50%)	25 (39.1%)	0.99
		Type 2 diabetes	**Control**	
HbA_{1c} (%)	18–34	(n=18)	**(n=25)**	
		7.3±1.2	5.3±0.1	0.002*
	35–49	(n=21)	**(n=17)**	
		6.8±1.1	5.7±0.2	0.03*
	50–64	(n=25)	**(n=22)**	
		7.3±0.5	5.8±0.2	0.007*
Type 2 diabetes Duration (years) (n, %)	**(<10)** **(≥10)**	39 (60.9%) 25 (39.1%)	NA	NA

Data were given as mean ± SD or percentage
p — Type 2 diabetes vs. controls; HbA_{1c} — Glycosylated hemoglobin; FPG — Fasting plasma glucose; F — Female; M — Male
* — p values <0.05 were considered to be statistically significant

Table 2. Comparison of reaction rates of type 2 diabetes and control groups with age variable

		Type 2 diabetes (n=18)	Control (n=25)	p
		$\overline{X}$ + SD		
18–34	FTT (ms)	292.19±47.51	150.85±6.41	0.01*
	Visual Test (ms)	708.03±85.39	498.69±16.44	0.03*
	Auditory Test (ms)	670.99±60.43	513.9±9.71	0.01*
		Type 2 diabetes (n=21)	**Control (n=17)**	**p**
		$\overline{X}$ + SD		
35–49	FTT (ms)	467.62±49.60	376.31±54.66	0.25
	Visual Test (ms)	981.88±81.55	757.43±91.63	0.02*
	Auditory Test (ms)	741.11±54.51	657.26±44.89	0.29
		Type 2 diabetes (n=25)	**Control (n=22)**	**p**
		$\overline{X}$ + SD		
50–64	FTT (ms)	625.92±52.80	573.74±58.05	0.57
	Visual Test (ms)	1413±144.21	1038.48±67.82	0.06
	Auditory Test (ms)	971.51±83.00	879.28±52.86	0.83

FTT — Finger tapping test
Kruskal-Wallis H
p — The difference in reaction rates by age groups
* — p<0.05 were considered to be statistically significant

Table 3. Correlation between variables

Variables	Type 2 diabetes Duration (years)	HbA_{1c} (%)	FPG (mmol/L)	FTT (ms)	Visual Test (ms)	Auditory Test (ms)
Type 2 diabetes Duration (years)	1.00	0.14	0.03	0.03	0.69*	0.52*
HbA_{1c} (%)		1.00	0.04	0.07	0.97*	0.10
FPG (mmol/L)			1.00	0.01	0.02	-0.04
FTT (ms)				1.00	0.54	0.61
Visual test (ms)					1.00	0.81
Auditory test (ms)						1.00

FTT — Finger tapping test; HbA_{1c} — Glycosylated hemoglobin; FPG — Fasting plasma glucose
* — <0.05

statistically insignificant as the age increased. It was determined that the participants in the control group between the ages of 35–49 years had faster reactions in the visual reaction test and there were no significant differences between the groups in other tests. We think that the reason for the significant difference in the visual reaction test is that this test measures not only speed but also perception (the subject's perception of the red box and pressing the button). When visual and auditory stimuli were analyzed, it is seen that the visual stimulus reaches the brain in 20–40 ms, while this time is specified as 8–10 ms for the auditory stimulus. This difference may be due to the number of synapses in the visual pathway [11]. The analysis we conducted between the control group and type 2 diabetes patients in our study suggested that, contrary to our expectations, diabetes may begin to affect cognitive functions at an earlier age. In the study by Richerson et al. [12] in which they compared reaction times with type 2 diabetes and control groups, it was stated that reaction rates slow down from young healthy adults to mature people with diabetes. It is known that patients with type 2 diabetes exhibit a weaker cognitive performance than healthy individuals of the same age [6]. The results of our study are in line with the literature. It has been suggested that the postprandial muscle protein synthetic response may be impaired in people with insulin resistance, leading to a faster loss of muscle mass, especially in elderly patients. When diabetic and normoglycemic people in the same age group were compared, it was observed that muscle loss was greater in diabetics [13]. Similarly, in another study, it was reported that between two groups with an equal duration of diabetes but different onset ages, individuals diagnosed at a younger age had a higher perception threshold and higher risk of developing neuropathy [14]. There are other studies stating that neurotransmitter synthesis is negatively affected depending on the amount of glucose going to the brain and that the reactions are slowed down in diabetics compared to healthy individuals [15]. In addition to the disease, the age factor also affects the reaction speed and perception capacity. Der and

Deary [16] studied the relationship between reaction rates and 30, 50, and 69-year-olds, and they found the reactions of the people in the younger were significantly faster than those in the older age group. Pierson and Montoye [17] showed that movement capacity and age are related to each other, and the fastest data were recorded in the 20s, and the reactions slowed down as the age increased. Likewise, our research results showed that the reaction rates gradually decrease in diabetics with age. We thought that the main factor behind the higher reaction rate of the 18–34 age group compared to other age groups was that while the perception capacity and physical activity were better at these ages, attention, and concentration decreased with increasing age. It has been stated that the decrease in cognitive performance caused by diabetes develops slowly starting from the early stages of the disease and the underlying mechanism is mostly oxidative stress resulting from hyperglycemia [6]. Thus, it is thought that regular control of plasma glucose in patients, the establishment of a controlled diabetes course, and planning the time spent with diabetes after diagnosis with the most appropriate treatment option can prevent problems that may arise in the future.

Another factor that may affect the reaction rates of the patients in our study is the duration of diabetes. Based on the data showing that neuropathy developed within 9 years after diagnosis, we classified the patients as having diabetes for less than or more than 10 years and as a result, the reaction times of patients with diabetes over 10 years in visual and auditory reaction tests were found to be significantly longer than the other group. Similar to our findings, in a study by Maid and Sureshkumar [18] examining the effect of diabetes duration on cognitive performance, the reaction rates of those with diabetes for more than 5 years were found to be significantly lower than those in the other group. It could be thought that this may be due to chronic hyperglycemia, AGE (advanced glycation end products) formations, polyol pathway activation, more than expected cytokine release, protein kinase C activation, and increased oxidative stress.

Another important finding in our study is the relationship between the patients' HbA_{1c} and FPG levels and reaction rates. In contrast, according to the study by Raizes et al. [19], it was observed that even if they were not diabetic (FPG <6.1 mmol/L), the reaction rates decreased as the plasma glucose values increased in the subjects. The reason for this difference may be that fasting plasma glucose is a variable marker and we ignored that anti-diabetic use. Additionally, the relationship between HbA_{1c} and visual reaction rates was examined, and a positive correlation was found. Although we ignored anti-diabetic use, patients had higher HbA_{1c} values for each age group compared to the control. Irregularity of HbA_{1c} values in young patients may result from the diagnosis that had just been determined, not coming to medical examinations regularly, and carelessness. Diabetes self-monitoring, adherence to examinations, and self-care skills among young people are lower than among the elderly, according to Xie et al. [20]. This was serious for us because we think that the neurological effects of diabetes could start early and progress rapidly if not given due attention. Since diabetes is mostly diagnosed before the age of 50, cognitive decline due to diabetes may also be seen at a relatively younger age [21]. It has been shown in studies that diabetes may begin 4–7 years before it is diagnosed [22]. Hyperglycemia that is not diagnosed and treated at the preclinical stage is likely to cause irreversible microvascular changes in the brain [21]. The brain uses glucose as the primary fuel, so the regularity of plasma glucose is essential in maintaining the function and health of the brain. In the study by Muhil et al. [23], the effect of HbA_{1c} on cognitive performance was examined and prolonged reaction rates were found in subjects without glycemic control (HbA_{1c}>7%) compared to subjects with glycemic control (HbA_{1c}<7%). According to the study by Khode et al. [24], it was observed the effects of various variables on cognitive performance in patients with type 2 DM and no significant relationship was found between reaction rates and HbA_{1c} levels. Similar to our findings, Muhil et al. showed that poor glycemic control reduced the reaction rate. The results obtained were as we expected since the HbA_{1c} finding in plasma glucose is a reliable method, and it made us think that poorly managed glycemic control could decrease cognitive performance. However, our findings conflict with the result of Khode et al. We thought that the reason for the contradiction because we ignored anti-diabetic use while Khode et al. were involved.

In our study, no significant difference was found between the sexes of the patients and their finger tapping, visual and auditory reaction test rates, while Jain et al. [25] and Silverman [26] stated that men react faster than women. Besides, it was also reported that the reaction times of both women and men to auditory stimuli were shorter than the reaction times to visual stimuli in the same study. We concluded that this was due to the fact that the pathway of auditory stimuli in the brain is shorter than that of visual stimuli.

This difference might be due to the fact that we worked with fewer volunteers compared to the studies in the literature and that the physical condition of the women was not taken as a basis for the inclusion criteria.

There are similar studies on this subject that have been done by examining fewer factors. However, our study is important and unique since we can measure the reaction rate with a practical test, have the opportunity to study with more people than most of the literature, examine age, gender, HbA_{1c} and fasting plasma glucose values together and compare them with healthy individuals.

Limitations of the research

There are several limitations of our study. First of all, the socioeconomic and education levels, physical activity habits, and anti-diabetic use of the subjects participating in our study were not questioned and not included in our study. One of the weaknesses of our study is that we did not include these factors that affect reaction rates in the analysis. It is possible to add these factors, which we did not include in our research, to future studies and to obtain more comprehensive results. Our research can be used as a reference for future research on the subject.

CONCLUSION

In conclusion, it is important to know how to deal with the effects of diabetes. Researchers have predicted that the number of people who will be diagnosed with type 2 diabetes in the future will reach 693 million in 2017–2045, by increasing over 50% [27]. As a result of our analysis, it was found that increasing age and HbA_{1c} values were associated with prolonged reaction times in diabetics. Since the reaction times of the patients were also prolonged compared to the control group, providing glycemic control of the patients before the diagnosis is of great importance for the course of the disease. It is seen and recommended that the implementation of an individual treatment plan, starting from the early stages of the disease, providing and maintaining glycemic control, incorporating physical activity into the patient's life have critical importance in preventing cognitive problems that may occur in the future.

This research was conducted to determine the extent of the cognitive effects of diabetes and might be considered a preliminary study. New research can be conducted with a larger sample group, including variables such as physical activity status, education level, and anti-diabetic drug use.

OTHER INFORMATION

Conflicts of Interest. No conflict of interest has been declared by the authors.

The source of financing. This study was supported by the Baskent University Research Fund.

Participation of Authors. Melisa Bilaloğlu, carried out all the experiment and wrote the manuscript. Ahmet Ergün, helped supervise the project. Feride Pınar Altay and Özlem Turhan İyidir assisted in collecting data. Erhan Kızıltan is the person who developed the test and has shown how to apply it. All the authors approved the final version of the article before the publication and expressed their consent to be responsible for all aspects of the work, which implies proper investigation and resolving of issues related to the accuracy or integrity of any part of the work.

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ЦИТИРОВАТЬ:

Bilaloglu M., Ergun A., Altay F.P., Iyidir O.T., Kızıltan E. Оценка скорости визуальной и слуховой реакции у лиц с сахарным диабетом 2 типа // *Сахарный диабет*. — 2023. — Т. 26. — №3. — С. 236-242. doi: https://doi.org/10.14341/DM12997

TO CITE THIS ARTICLE:

Bilaloglu M, Ergun A., Altay FP, Iyidir OT, Kızıltan E. Detectıon of vısual-audıtory reactıon rates ın ındıvıduals wıth type 2 dıabetes mellıtus. *Diabetes Mellitus*. 2023;26(3):236-242. doi: https://doi.org/10.14341/DM12997