Chapter 2

Cognitive Impairment in Patients with Diabetes Mellitus

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Abstract

Diabetes mellitus (DM) is a risk factor for the development of cognitive impairment, when unsatisfactory glycemic control is associated with glioma biomarkers and changes in neuronal integrity. Given some limitations in the performance of neuropsychological testing, it is important to indicate specific markers of brain damage.

Keywords: diabetes mellitus, cognitive disorders, neurospecific proteins, magnetic resonance imagining

1. Introduction

One of the most significant in the social aspect of the categories in the population was and still is patients with diabetes mellitus (DM). According to the estimates of the International Diabetes Federation, there are 415 million people with diabetes in the world in 2015, and by 2040, it is projected to grow to 642 million people. In the last decade, it has been proven that diabetes mellitus causes disturbances in the functioning of regulatory systems and the psychological and emotional state has both direct and indirect effects on the development of

complications from the central nervous system, manifested by morphological and functional disorders. The reflection of brain neuroplasticity is the dynamics of cognitive impairment.

According to the latest revision of the international guidelines for the diagnosis of mental disorders, cognitive disorders include a decrease in one or more higher cerebral functions, in comparison with the premorbid level, that provide the processes of perception, preservation, transformation, and transmission of information. The presence of cognitive impairments has an extremely negative effect on the quality of life of the patient and their immediate family and complicates the treatment of concomitant diseases and the conduct of rehabilitation activities. Therefore, timely diagnostics and the earliest possible initiation of therapy for existing cognitive disorders are very important.

Figure 1 shows that the effect of dysglycemia in the debut of type 1 diabetes mellitus, especially in childhood, leads to a statistically more significant pronounced cognitive impairment, as well as structural changes in the brain over time [1].

To date, it is urgent to search for a quick, simple, and well-tried method for diagnosing cognitive impairment, taking into account the minimum costs. One of the promising methods that can be considered is the identification of neurospecific proteins, which are signals of brain damage [2–4]. To diagnose central nervous system diseases, magnetic resonance methods of brain examination are used as additional techniques for detecting morphological changes [5, 6].

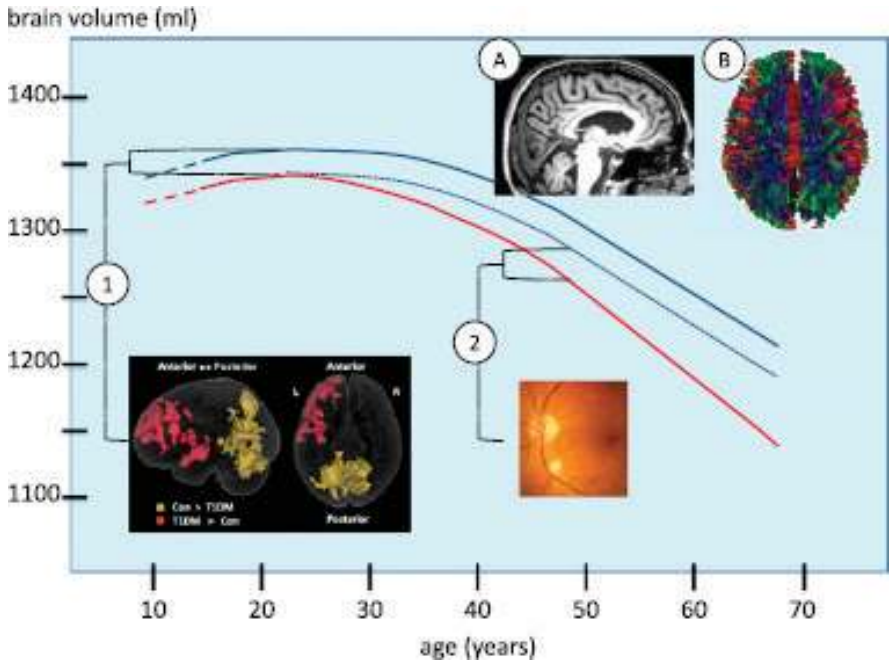

Figure 1. The trajectory of disorders from the brain's magnetic resonance imaging data in patients with type 1 diabetes mellitus is associated with loss of brain volume (blue line, evolution of brain volumes with age in the general population, and red line, estimated trajectories for type 1 diabetes mellitus (A), and brain atrophy is a loss of neuron communication (B)) [1].

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2. Pilot study: identification of cognitive impairment markers (neurospecific proteins, magnetic resonance tomography) in patients with type 1 diabetes mellitus

The study of cognitive dysfunction in patients with type 1 DM was carried out at the clinical bases of the Departments of Endocrinology and Diabetology, Neurology and Neurosurgery of the Siberian State Medical University, and the plan and the study were in full compliance with the principles of Good Clinical Practice (GCP) and Helsinki Declaration (including amendments).

The study included 116 patients with type 1 diabetes mellitus at the age of 22.4 ± 4.6 years, 58 men and 58 women, and the duration of the disease was 6.6 ± 3.9 years. The control group consisted of 29 healthy people, aged 22.4 ± 4.8 years, 14 men and 15 women, without acute and chronic diseases. Inclusion criteria are patients with type 1 diabetes mellitus at the age of 16–30 and signed informed consent of the patient to participate in the study.

Exclusion criteria are hypoglycemic and ketoacidotic coma for 1 year prior to study; presence of hematological, oncological, and serious infectious diseases; condition after severe craniocerebral injuries and surgeries; participation in other clinical trials in the last 30 days; and now refusal to sign an informed consent of the patient to participate in the study.

To detect violations of carbohydrate metabolism, glucose was determined by the glucose oxidase method on the biochemical analyzer "Hitachi 912" (Hoffmann-La Roche Ltd./Roche Diagnostics GmbH, Germany). HbA1c content was analyxed in capillary blood - by liquid chromatography method on DS5 Glycomat analyzer (Drew Scientific, the Netherlands).

With the biochemical methods of research, the content of neurospecific proteins in plasma was determined. To analyze the quantitative content of the S100 protein (S100A1B + S100BB), a kit was used (FujirebioS100 EIA, BioC himMak, Russia). GFAP was determined by enzyme immunoassay using a standard protocol using a reagent kit from the manufacturer (BioVendor Laboratory Medicine, Inc., Germany). The myelin basic protein (MBP) level was studied using the "DSL-10-58,200" kit (BioChimMak, Russia). The complex of mandatory diagnostic methods included magnetic resonance imaging of the brain on the Harmony 1.0 T apparatus (Siemens, Germany) by MDCS-Tomsk Ltd., which was carried out according to the standard procedure in the axial, sagittal, and coronal projections using T2 (TR (time of repetition) 4932 ms, TE (Echotime) 90 ms) and T1 (TR 280 ms, TE 6.1 ms) and using programs with free water signal suppression fluid-attenuated inversion recovery (FLAIR; TR 8000 ms, TE 105 ms, TI (time in version) 2200 ms). Evaluation of gliosis foci of brain substance was carried out according to the size and quantity in the frontal (subcortical, paraventricular), temporal (white matter, hippocampal area), parietal (subcortical, paraventricular), and occipital (subcortical, paraventricular) areas. Taking into account the classification of F. Fazekas, in the modification of NN Yakhno, a quantitative gradation of focal changes in the white matter was carried out [7]. The severity of leukoareosis was assessed in scores proposed by Liu et al. [8]. For the quantitative evaluation of the expansion of perivascular spaces, the estimated scale of MacLullich [9] was used.

Screening for mild and moderate cognitive impairment was performed using the MoCA test, which assesses various cognitive functions: visual–spatial perception (the test of drawing a clock and a cube); executive functions (task of creating an alternating path and testing the ability to abstract thinking); attention, concentration, and operational memory (serial subtraction by 7 and playback of the digital series in forward and reverse order); and speech (naming animals, repetition of two syntactically complex sentences) and the specificity of the method is 90% [10]. Statistical processing of the obtained data was carried out using the application software package R Systems International.

Characteristics of the carbohydrate metabolism parameters showed a difference in the parameters between the main group and the control group. The average level of HbA1c in patients with type 1 diabetes mellitus was 8.8 ± 1.8%, and the average level of fasting glycemia was 11.5 ± 5.0 mmol/l. This indicated an unsatisfactory metabolic control. In addition, differences in the parameters of carbohydrate metabolism were revealed taking into account gender characteristics, so women had better values of fasting and HbA1c glycemia than men.

In the control group, healthy volunteers complained of asthenic syndrome (37.9%), manifestations of which were fatigue (13.3%), dizziness (6.7%), and headache (16.9%). Patients with type 1 diabetes mellitus also had these complaints but in a more pronounced form. The next in frequency recorded cephalic syndrome, occurring in 25.9% of patients. Among the localizations, the most frequent areas were occipital (60%) and temporal (2.6%) areas, with the same frequency; headache was diffuse and was found in the frontal region. The most common cause of headache was overexertion due to stress. In addition, complaints were found from the peripheral nervous system on paresthesia (37.9%), pain (22.4%), numbness (12.1%), and convulsions in the lower extremities (6.9%). Often, patients with type 1 diabetes mellitus complained of memory loss. This was manifested by the difficulty in concentrating, remembering new information, and solving short-term problems. The objective status of patients was characterized by autonomic symptoms, manifested as anxiety. Neurological symptoms of the examined patients were mainly represented by disorders of the autonomic nervous system, namely, distal and diffuse hyperhidrosis (in 43.1% of patients) and persistent red spilled dermographism (in 22.4% of patients) in the face, neck, and décolleté area. The manifestations of lesions of the peripheral nervous system were in the form of diabetic polyneuropathy. Sensory disorders were noted from the lower extremities in 62% of cases and the upper ones in 27.5%. A clinical study of random movements in the limbs with an evaluation of the tone revealed a hypotonia of the upper limbs in 51.7% and lower in 34.5% of cases.

2.1. An analysis of the neuropsychological status in patients with type 1 diabetes mellitus

This study based on the results of a screening MoCA test showed that type 1 diabetes mellitus may manifest cognitive dysfunction in 72.4% of cases. Thus, one-third of patients with type 1 diabetes mellitus had cognitive dysfunction compared to the control group (**Table 1**).

When assessing the individual tasks of the MoCA test, a statistically significant decrease in the parameter of the short-term memory was registered. The exercise included memorizing

Parameters	Type 1 DM (n = 98)	Control group (n = 29)
Alternating Trail Making	3.0 ± 0.4	3.0 ± 0.1
Alternating path (drawing)	3.0 ± 0.8	3.0 ± 0.1
Cube (drawing)	3.0* ± 1.3	5.0 ± 0.2
Clock (drawing)	2.0* ± 0.6	2.0 ± 0.1
Naming	1.0 ± 0.9	1.0 ± 0.1
Memory	2.0* ± 0.8	3.0 ± 0.1
Number series	2.0 ± 0.4	1.8 ± 0.4
Concentration	1.0 ± 0.8	0.8 ± 0.3
Serial subtraction by 7	2.0 ± 0.4	2.0 ± 0.1
Repeat suggestions	6.0 ± 0.2	6.0 ± 0.1
Fluency of speech	25.0* ± 0.8	30* ± 0.4
Abstraction	3.0 ± 0.4	3.0 ± 0.1
Orientation	3.0 ± 0.8	3.0 ± 0.1
Sum of points	3.0* ± 1.3	5.0 ± 0.2

Note: The significance of differences between the control group and patients with type 1 diabetes mellitus at the parameters of MoCA test: *$p < 0.001$, m is the median, and SD is the standard deviation.

Table 1. Characteristics of the MoCA test parameters in patients with type 1 diabetes mellitus and control group.

five words and repeating them after subsequent tasks in about 5 minutes. Patients with type 1 diabetes mellitus had difficulty in reproducing words, were confused, and invented new words. At the same time, this task was performed unsatisfactorily by both men and women. The attention function was evaluated using two tasks. The first task is a numerical series, that is, a repetition of the numbers mentioned. With this task men were worse than women. The second task is the serial subtraction by 7, which was given equally hard.

2.2. Analysis of parameters of neurospecific proteins in patients with type 1 diabetes mellitus

As a result of the analysis, a significant increase in all studied proteins was revealed in patients with type 1 diabetes mellitus, S100, MBP, and GFAP, compared to the control group ($p < 0.001$) (**Table 2**).

The levels of neurospecific proteins, depending on the duration of the disease, had fluctuations. So, the S100 protein was higher in patients with a short duration of the disease (1–4 years) and the smallest with duration of the disease for more than 15 years. While MBP had an equally stable level in patients with different durations of type 1 diabetes mellitus. The fluctuations in the level of GFAP were also insignificant and tended to decrease with increasing duration of the disease. According to our study, in women, the level of GFAP was significantly lower than in men ($U = 643.0$, $z = -2.4$, $p < 0.05$).

Neuro-specific proteins	Type 1 DM (n = 98)	Control group (n = 29)
	0.13 ± 0.05*	**0.10 ± 0.036**
Myelin basic protein (MBP) (ng/ml)	0.12 ± 0.04*	0.08 ± 0.033
Glial fibrillary acidic protein (GFAP) (ng/ml)	125.65 ± 66.97*	62.85 ± 19.66
S100 (ng/ml)	0.13 ± 0.05*	0.10 ± 0.036

Note: The significance of differences between the control group and patients with type 1 diabetes mellitus at the level: *$p < 0.01$.

Table 2. Characteristic levels of neurospecific proteins in patients with type 1 diabetes mellitus and the control group.

2.3. Characteristics of magnetic resonance imaging of the brain in patients with type 1 diabetes mellitus and in control group

Analysis of magnetic resonance imaging of the brain revealed indirect signs of atrophy of the gray matter of the frontal and partly parietal lobes. Thus, in patients with type 1 diabetes mellitus, arachnoid changes (93.1%) and expansion of the convective liquor spaces (72.4%) were significantly more frequent. In the control group, changes in thearachnoid changes were detected in 67% (**Table 3**). **Figure 2** in the coronal projection (mode T2) shows the expansion of the convective fluidic spaces.

MRI of the brain showed the presence of gliosis sites in 15.5% of cases and lesions of leukoareosis in 18.3% of cases in patients with type 1 diabetes mellitus, whereas in the control group no changes were revealed (**Table 3**). In **Figure 3**, in the axial projection (FLAIR mode) in the white matter of the frontal and parietal lobes, small foci of a dystrophic character are defined.

In **Figure 4**, coronal lesions are identified in the coronal projection. According to the classification proposed by Lui, the severity of leukoareosis is two points.

Perivascular spaces of Virchow-Robin are a morphological and functional structure of the central nervous system; therefore, various versions of their dilatation can be an indirect reflection of changes in the brain substance and indicate atrophy. In the study, expansion of Virchow-Robin spaces occurred in 80.6% of cases in patients with type 1 diabetes mellitus, which was significantly higher than in the control group, 6.7%, respectively (**Table 3**).

These changes are shown in **Figure 5**, where in the coronal projection in the thalamus region, nonuniformly expanded Virchow-Robin spaces are determined from both sides. Given the classification of MacLullich, they are estimated at 2 points.

Thus, according to MRI, the morphological changes in the brain in patients with type 1 diabetes mellitus are represented by arachnoid changes in the liquor cystic, the expansion of the convective spaces, and the Virchow-Robin spaces of the brain.

2.4. Interrelations of clinical-metabolic, neuropsychological features and markers of cognitive impairment in patients with type 1 diabetes mellitus

When evaluating the results, a negative correlation was found between the fasting glycemia and HbA1c levels with the test parameters responsible for memory and attention (task for

Indicators	Type 1 DM (n = 98)	Control group (n = 29)	χ2
Arachnoidal changes in the cerebrospinal fluid	108 (93.1%)	2 (6.7%)	χ2; p
Expansion of convective fluidic spaces	71 (72.4%)	0 (0%)	$\chi^2 = 63.84$; $p = 0.01$
Expansion of Virchow-Robin spaces	79 (80.6%)	2 (6.7%)	$\chi^2 = 43.4$; $p = 0.01$
Gliosis	15 (15.3%)	0 (0%)	$\chi^2 = 4.32$; $p = 0.01$
Leukoareosis	18 (18.3%)	0 (0%)	$\chi^2 = 5.19$; $p = 0.02$

Note: The significance of the differences between the control group and patients with type 1 diabetes mellitus at the level: $^{*}p < 0.001$.

Table 3. Characterization of the magnetic resonance pattern of the brain of patients with type 1 diabetes mellitus in comparison with the control group.

number series and serial subtraction). That is, the higher the levels of carbohydrate metabolism, the worse the memory and attention are (**Table 4**). On the part of other indicators of the MoCA, the connection was not found.

In assignments for attention, a negative correlation was found only with the protein S100 ($r = -0.3$, $p = 0.02$, $r = -0.3$, $p = 0.004$). We revealed relationship between the decrease in memory functions and the increase in the level was the decrease in memory functions with a simultaneous increase in the level of the studied neurospecific proteins, that is, the presence of a negative correlation with the S100 ($r = -0.4$, $p = 0.001$), GFAP ($r = -0.4$, $p = 0.02$), and MBP ($r = -0.5$, $p = 0.001$) proteins.

To assess the significance for the diagnosis of proteins, sensitivity and specificity were assessed. It was shown that they are highly specific and have a moderate sensitivity (**Table 5**).

Thus, in patients with type 1 diabetes mellitus and identified cognitive dysfunction, an increase in the content of all neurospecific proteins against hyperglycemia is characteristic. Based on the assessment of specificity and sensitivity, a high level of diagnostic significance of neurospecific proteins is shown, which makes it possible to use them in general medical practice.

When evaluating the effect of carbohydrate metabolism parameters on the change in the results of magnetic resonance imaging of the brain in patients with type 1 diabetes mellitus, positive correlation relationships were recorded. Thus, moderate strengths between the expansion of the cerebrospinal fluid and the level of HbA1c ($r = 0.6$, $p = 0.001$) and fasting glycemia ($r = 0.5$, $p = 0.001$) were revealed. In addition, connections have also been found with extensions of the Virchow-Robin spaces ($r = 0.6$, $p = 0.001$, $r = 0.5$, $p = 0.001$) and convective spaces ($r = 0.5$, $p = 0.004$, $r = 0.3$, $p = 0.003$) with the indices of carbohydrate metabolism. Analysis of the effect of cognitive dysfunction on the results of magnetic resonance imaging of the brain showed the presence of a bond. A correlation was found between memory loss in patients with type 1 diabetes mellitus and the expansion of arachnoid ($r = -0.3$, $p = 0.02$) and Virchow-Robin spaces ($r = -0.3$, $p = 0.007$). A link was also found between the decrease in attention and atrophy of gray matter in the brain in patients with type 1 diabetes mellitus. Patients with an expansion of arachnoid ($r = -0.3$, $p = 0.007$), convective spaces

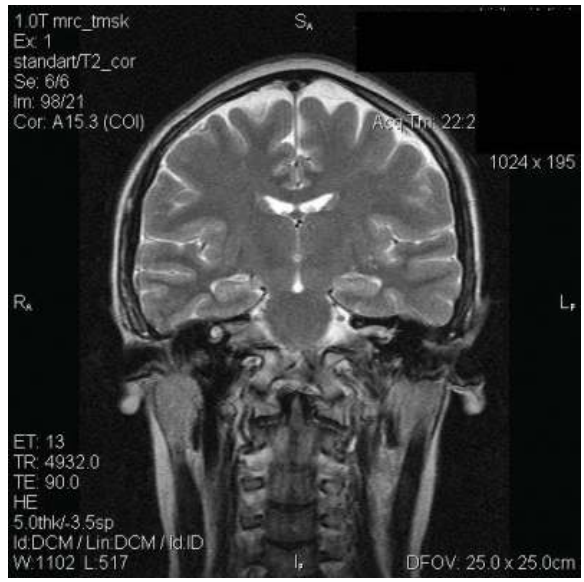

Figure 2. A snapshot of the brain in the coronal projection in T2 mode is determined by the expansion of the convective fluidic spaces (photo by Matveeva, 2015).

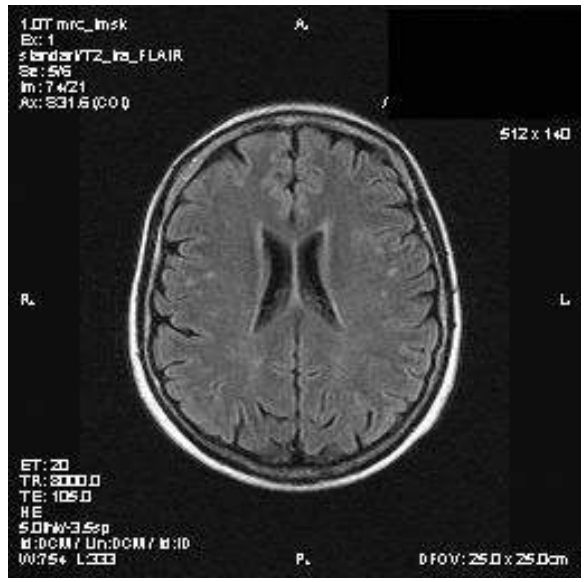

Figure 3. A snapshot of the brain in the axial projection in the FLAIR mode in the white matter of the frontal and parietal lobes is determined by small foci of increased signal on T2 and FLAIR, without signs of perifocal edema, of a dystrophic nature (photo by Matveeva, 2015).

(r = −0.3, p = 0.007), and Virchow -Robin spaces were worse performing the tasks for attention ("numerical series" and "serial subtraction" by 7) (r = −0.3, p = 0.007). To assess the significance of changes reflected in magnetic resonance imaging of the brain in patients with type 1 diabetes

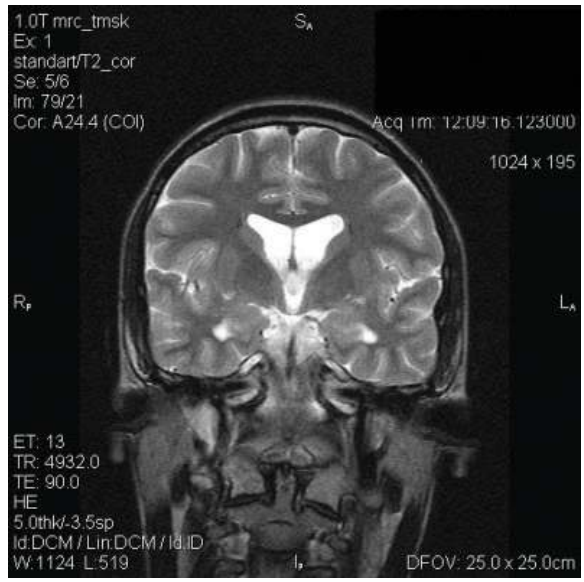

Figure 4. A snapshot of the brain in the coronal projection in T2 mode in the white matter of the frontal and parietal lobes,; the focus of the leukoareosis is determined by the severity of two points [8] (photo by Matveeva, 2015).

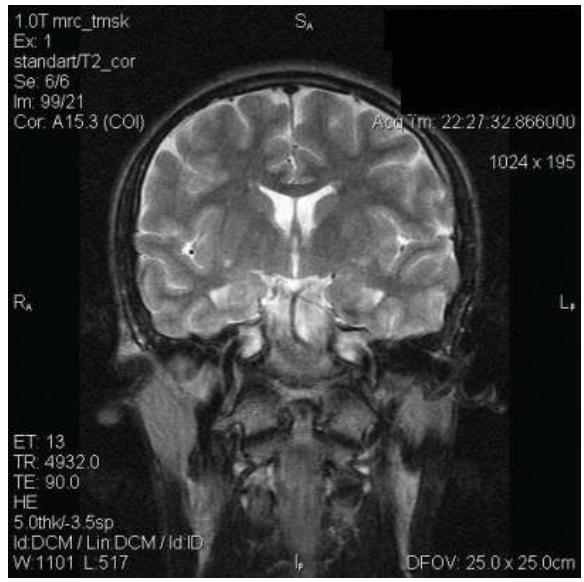

Figure 5. A snapshot of the brain in the coronal projection in the T2 mode in the thalamus region on both sides of unevenly expanded Virchow-Robin spaces is determined (two points according to MacLullich (2003)) (photo by Matveeva, 2015).

mellitus, sensitivity and specificity were assessed. Morphological signs of gray matter atrophy of the brain, namely, arachnoid changes in the liquor cystic nature, widening of the convective spaces, and Virchow-Robin spaces, are highly sensitive, but are not specific (**Table 6**).

	S100	MBP	GFAP
HbA1c	r = −0.69; p = 0.01	r = −0.30; p = 0.01	r = −0.35; p = 0.04
Fast glucose	r = −0.45; p = 0.02	r = −0.36; p = 0.01	r = −0.31; p = 0.01

Note: The significance of the correlation: $^{*}p < 0.05$.

Table 4. Interrelation of the parameters of the MoCA test with HbA1c and fasting glycemia.

Thus, the obtained data showed the relationship of gray matter atrophy of the brain magnetic resonance imaging in patients with type 1 diabetes mellitus with chronic hyperglycemia and cognitive impairment. In addition, nonspecificity of the revealed changes was revealed in patients with type 1 diabetes mellitus in comparison with the control group.

2.5. Comparison of the results and literature data

As methods for finding markers of cognitive impairments, neurophysiological and biochemical methods with certain limitations are described in the literature. We conducted a comprehensive study that included as a neuropsychological technique a screening MoCA test, an evaluation of neurospecific proteins, and a magnetic resonance imaging data in patients with type 1 diabetes mellitus. In our study, screening for cognitive dysfunction with the MoCA test showed a decrease in only memory function and attention in patients with type 1 diabetes mellitus, while other functions were not impaired. Analysis of the relationship of cognitive dysfunction with sex, age, and duration of the disease did not reveal these. The results confirm the meta-analysis conducted in 2007 by Brands and Bissels, where it was shown that there were moderate cognitive impairments that did not manifest themselves in daily life, but influenced the professional sphere, where high concentration, attention, and memory are required [1]. The question of the metabolic component as the cause of the development of cognitive dysfunction for a long time was debatable. The data obtained in this study on cognitive dysfunction allowed a mathematical analysis of the effect of carbohydrate metabolism on it and the effect of hyperglycemia on the development of cognitive dysfunction in patients with type 1 diabetes mellitus. In patients with type 1 diabetes mellitus, Russian scientists also noted a decrease in memory function, which worsened with chronic hyperglycemia [11]. In the endocrine community, a large-scale study on the control and complications of diabetes (DCCT/EDIC) is considered authoritative [12], which confirmed the absence of the effect of hypoglycemia on the development of cognitive dysfunction. The analysis of additional markers of cognitive dysfunction was carried out with the help of biochemical methods, which made it possible to evaluate neurospecific proteins. In patients with type 1 diabetes mellitus, S100, GFAP, and MBP proteins were elevated, which may indicate microscopic brain damage. One of the proteins studied was S100; as a result, it was found that patients with unsatisfactory control of carbohydrate metabolism had higher levels of S100 protein. So, a positive correlation of S100 protein with the HbA1c level and fasting glycemia was found, which can prove the role of chronic hyperglycemia in the dysmetabolic processes of the brain. A study of this protein in patients with type 1 diabetes mellitus was also conducted by Strachan (2000) [13], but significant changes in groups with

NSP	Value	Sensitivity (%)	Specificity (%)
MBP ng/ml	0.1025	45.7	81
GFAP ng/ml	0.106	41.3	76.2
S100 ng/ml	65.15	58.7	95.2

Table 5. Characteristics of specificity and sensitivity of neurospecific proteins as markers of cognitive dysfunction.

type 1 diabetes have not been found [13]. Comparison of MBP with HbA1c and fasting glucose showed a positive correlation. Most likely, fluctuations in glycemia caused damage to the oligodendrocytes of the brain with the release of more MBP. In the literature, such data were not found. A third, but no less important, protein was the GFAP marker for astrocyte damage. In our study, a positive correlation was found between the parameters of carbohydrate metabolism and the level of GFAP, which indicates the effect of hyperglycemia on the mechanisms of apoptosis of astrocytes. The results obtained are confirmed by the studies of F.E. Saravia and coauthors; they showed the effect of hyperglycemia on higher amounts of GFAP during the manifestation of type 1 diabetes mellitus, when uncompensated hyperglycemia is observed, that is, hyperglycemia has the greatest impact on brain damage [14].

As an additional method for evaluating cognitive dysfunction, magnetic resonance imaging of the brain was proposed; this was performed according to a standard procedure, that is, as screening without additional functional options. As a result of the study, signs of cerebral atrophy were found, namely, arachnoid changes in the liquor cystic and expansion of the convective fluidic spaces, which correlates with the data of the special literature [15]. The data obtained during the study confirm the presence of indirect signs of cerebral atrophy in patients with type 1 diabetes mellitus of a nonspecific type. In addition, the literature addresses the duration of type 1 diabetes mellitus and the possible weighting of morphological changes. In our study, the association with age and duration of the disease was not revealed. However, Trofimova et al. found that the degree of severity of structural changes in the brain substance is associated with the progression of type 1 diabetes mellitus and with an increase in the age of the patients [16]. In the study, an evaluation of the influence of glycemia on the morphological structure of the brain showed the relationship of hyperglycemia with the expansion of fluidic spaces, convective spaces, and Virchow-Robin spaces. In the literature, cases of atrophy of the gray matter of the brain, which was detected predominantly in the frontal lobes and central areas of the parietal lobes [17], is described, both in acute cases of ketoacidosis and prolonged increase in HbA1c. In addition to the relationship with the parameters of carbohydrate metabolism, the analysis revealed the relationship of cognitive impairments to brain atrophy, which was also noted in the publications of Hoogma [18]. In our study, there was a correlation of memory loss in patients with type 1 diabetes mellitus with an expansion of arachnoid and Virchow-Robin spaces ($r = -0.3$, $p = 0.007$). Also, a connection was found between poor performances of tasks for attention (numerical series and serial subtraction by 7) by patients with the expansion of arachnoid, convective spaces, and Virchow-Robin spaces ($r = -0.3$, $p = 0.007$).

Indicators	Sensitivity (%)	Specificity (%)
Arachnoidal changes in the cerebrospinal fluid	92	37
Expansion of convective fluidic spaces	73	26
Expansion of Virchow-Robin spaces	78	34
Gliosis	11	17
Leukoareosis	21	43

Table 6. Characteristics of specificity and sensitivity of signs of magnetic resonance imaging.

3. Pilot study: the role of glycemia variability in development of cognitive disorders in patients with type 1 diabetes mellitus

Design: observational, transverse, and one-stage study. Clinical characteristics of patients is as follows: 30 patients with type 1 diabetes mellitus at the age of 27 (22–31) years and duration of the disease 17 (5–23) years; among them 14 men and 16 women were examined. Patients were divided into two groups: the first group (main)—with the presence of cognitive impairment, and the second group (control)—with normal cognitive functions.

For the diagnosis of fluctuations in the glucose level, continuous monitoring of glycemia was conducted using the iPro2 device (Medtronic, USA) and the CareLink iPro™ software, as well as the Medtronic MiniLink and MMT-700 transmitter, and the Medtronic Diabetes CareLink USB device. Fixation of data on the level of glycemia was carried out at a 5-minute interval for 72 hours using a system of constant monitoring of glycemia. We used the EasyGV calculator (version 9.0), proposed by Hill (2011) [26] (**Figure 6**).

The following glucose variability values were assessed: mean glycemic mean (MEAN), standard deviation (SD), mean amplitude of glycemic fluctuation (MAGE), long-term glycemic index (CONGA), glycemia lability index (LI), hypoglycemia risk index (LBGI), an index of risk of hyperglycemia (HBGI), and average hourly rate of change in glycemia (MAG).

The study found that patients with type 1 diabetes mellitus among the main group of cognitive disorders prevailed violation constructive praxis, memory, and attention. The average score in this group was 23.8 ± 0.66, while in the control group, it was 26.4 ± 0.13 points, respectively ($t = 3.6$, $p = 0.001$) (**Table 7**). In the study of HbA1c in plasma, the mean level in the main group was 10.5 ± 1.3%, and in the control group 6.7 ± 0.23% ($t = -2.5$, $p = 0.015$).

The analysis of the GV indicators is presented in **Table 8**. There is a significant difference in MEAN, SD, CONGA, Gindex, LBGI, HBGI, MAGE, Mvalue, and MAG.

Correlation analysis shows that cognitive functions are generally affected by the level of HbA1c ($\chi 2 = -0.450$, $p = 0.014$), as well as the MEAN variability parameters ($\chi 2 = -0.584$, $p = 0.001$), SD ($\chi 2 = 0.022$, $p = 0.022$), CONGA ($\chi 2 = -0.853$, $p = 0.001$), Gindex ($\chi 2 = -0.504$, $p = 0.005$), LBGI ($\chi 2 = -0.451$, $p = 0.014$), HBGI ($\chi 2 = -0.053$, $p = 0.003$), MAGE ($\chi 2 = -0.480$, $p = 0.008$), Mvalue ($\chi 2 = -0.593$, $p = 0.001$), and MAG ($\chi 2 = -0.573$, $p = 0.001$).

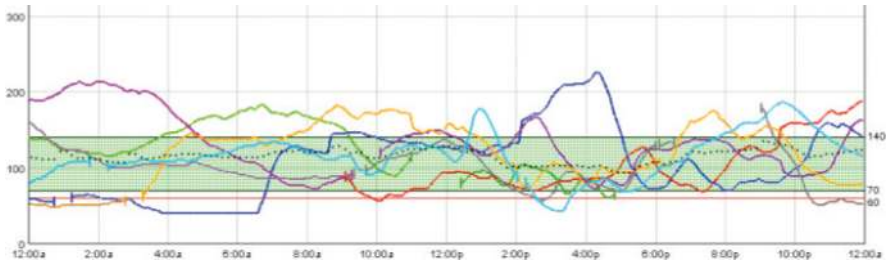

Figure 6. Example of a glycemic profile according to iPro data.

On the constructive praxis in the job, the alternating path is most affected by the CONGA parameter ($\chi 2 = -0.502$, $p = 0.006$) and MAGE ($\chi 2 = -0.555$, $p = 0.002$), and the clock is MEAN ($\chi 2 = -0.379$, $p = 0.043$), LI ($\chi 2 = -0.471$, $p = 0.010$), Gindex ($\chi 2 = -0.497$, $p = 0.006$), LBGI ($\chi 2 = -0.477$, $p = 0.009$), HBGI ($\chi 2 = -0.384$, $p = 0.040$), MAGE ($\chi 2 = -0.386$, $p = 0.038$), Mvalue ($\chi 2 = -0.446$, $p = 0.002$), and MAG ($\chi 2 = -0.505$, $p = 0.005$). To reduce memory, the MEAN indicator is most important ($\chi 2 = -0.455$, $p = 0.013$). Violation of the task of repeating the phrase depends on the level of HbA1c ($\chi 2 = -0.390$, $p = 0.036$), LI ($\chi 2 = -0.463$, $p = 0.011$), LBGI ($\chi 2 = -0.604$, $p = 0.001$), MAGE $\chi 2 = -0.422$, $p = 0.031$), Mvalue ($\chi 2 = -0.483$, $p = 0.008$), and MAG ($\chi 2 = -0.501$, $p = 0.002$). The assignment of MoCA test (repeating speech) depends on the level of HbA1c.

The study showed a decrease in cognitive functions in (constructive praxis, repetition, and memory) in patients with type 1 diabetes mellitus. The currently available markers for the control of glycemia-HbA1c do not always reflect an excursion of hyperglycemia and hypoglycemia [19].

Parameters	The main group	The control group
Alternating path (drawing)	0.26 ± 0.11*	0.92 ± 0.07
Cube (drawing)	1.00 ± 0.00	1.00 ± 0.00
Clock (drawing)	2.60 ± 0.13*	2.14 ± 0.09
Naming	3.00 ± 0.00	3.00 ± 0.00
Memory	2.80 ± 0.32*	3.64 ± 0.24
Number series	1.80 ± 0.10	1.92 ± 0.71
Concentration	1.13 ± 0.13	1.14 ± 0.14
Serial subtraction by 7	2.66 ± 0.18	2.92 ± 0.07
Repeat suggestions	1.46 ± 0.13*	1.07 ± 0.07
Fluency of speech	0.66 ± 0.12	0.92 ± 0.07
Abstraction	1.53 ± 0.19	1.50 ± 0.13
Orientation	0.26 ± 0.11*	0.92 ± 0.07
Sum of points	1.00 ± 0.00	1.00 ± 0.00

Note: *$p \leq 0.05$.

Table 7. Characteristics of parameters of the Montreal scale of cognitive functions in the main and control groups.

Parameters	The main group	The control group	Significance
MEAN	9.17 (8.36–10.00)	7.25 (6.77–7.87)	U = 29, p = 0.001
SD	4.54 (3.86–5.79)	2.95 (2.61–3.47)	U = 26, p = 0.001
CONGA	6.66(5.77–7.81)	4.32 (4.15–4.51)	t = −4.9, p = 0.001
LI	22.35 (20.76–92.99)	27.17(22.84–55.68)	U = 98.5, p = 0.776
Gindex	56.41 (52.00–79.69)	45.50 (36.85–50.76)	U = 43, p = 0.007
LBGI	11.16 (8.24–17.26)	6.77 (4.44–7.53)	U = 53.5, p = 0.023
HBGI	13.19 (11.01–21.25)	8.00 (6.91–10.45)	U = 43, p = 0.006
MAGE	4.86 ± 0.23	2.44 ± 0.13	U = 34, p = 0.002
Mvalue	28.38 (20.46–26.90)	14.43 (11.92–17.04)	U = 124.5, p = 0.001
MAG	59.60 (53.54–88.43)	34.60 (30.83–42.17)	t = −8.5, p = 0.001

Note: Mann-Whitney U test, Student's t-test.

Table 8. Characteristics of VG indicators by groups.

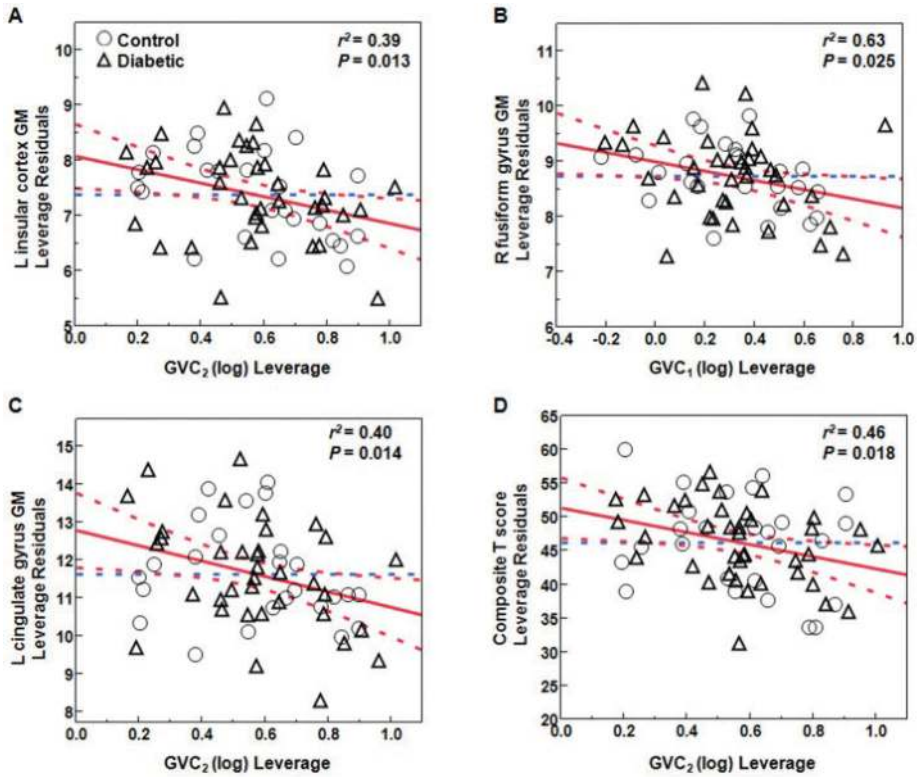

Figure 7. Examples of models with the smallest squares indicating a negative relationship between a multi-scale SH, the volumes of regions of the brain, as well as cognitive functions: (A) the ratio between GVC2 and volume of GM in the left island cortex, (B) the ratio between GVC1 and GM volume in the right spindle-shaped gyrus, (C) the ratio between GVC2 and GM volume in the left cingulate gyrus, and (D) the ratio between GVC2 and total cognitive performance (composite T) (SD, triangles; control, circles).

Patients with similar levels of HbA1c and average glucose values may have a significantly different daily variability in glycemia. In his study, Rizzo et al. showed that MAGE was associated with impaired cognitive functioning, regardless of the level of HbA1c among patients with diabetes ($R = 0.83$, $p < 0.001$) [20]. Although the mechanisms by which the variability of glycemia affects cognitive function are not clear, they can also be associated with oxidative stress. In this context, daily glucose fluctuations, such as peaks and falls, affect the development of oxidative stress more than chronic hyperglycemia. The work of Abbatecola et al. also demonstrated that an increase in postprandial glucose variability is associated with attention impairment [21] (**Figure 7**).

Thus, the present study demonstrated a link between high HbA1c, glycemic variability, and cognitive function in patients with type 1 diabetes mellitus. Since dysglycemia is a risk factor for both mild to moderate cognitive impairment and dementia, the present data provide opportunities for interventional studies to stabilize glycemia, not only by reducing HbA1c but also leveling out acute glucose fluctuations.

4. Pilot study: magnetic resonance spectrometry as a method of estimation of brain metabolism in type 1 diabetes mellitus

The proton magnetic resonance multilocular spectroscopy of the brain was carried out on a MAGNETOM Symphony 1.5 T (Siemens) device with the relaxation time TE = 135, and the voxel volume was 1.5 cm3; the main spectra of choline (Cho), creatine/phosphocreatine (Cr, Cr2), and N-acetylaspartate (NAA) were analyzed [22]. With the help of the regional approach, the data of metabolites Cho (choline), creatine), Cr2 (phosphocreatine), NAA (N-acetylaspartate), localized in the hippocampal region on the left and right.

The study revealed that the average age of patients with type 1 diabetes mellitus was 26 ± 4.8 years, and the control group was 30 ± 6.4 years. When comparing patients with type 1 diabetes mellitus (30 people) and control group (18 people) in metabolites Cho (choline), Cr (creatine), Cr2 (phosphocreatine), NAA and (N-acetylaspartate), distributed by the method of linear grouping and regional approach, no statistically significant differences were found.

When comparing the values obtained for the Cho metabolite, a statistically significant difference in the Cho12 index was found: in patients with type 1 diabetes mellitus, 0.82 (0.75–0.84), compared with a higher value in the control group, 0.87 (0.81–2.02).

When comparing the tables for the Cr metabolite, statistically significant differences in the indices were found: Cr5, Cr10, Cr25, Cr26, Cr28, Cr31, and Cr36.

In the study of the metabolite NAA, no significant differences in voxels were found. The study revealed changes in the ratio of metabolites Cho, Cr, Cr2, and NAA.

Thus, the main differences in patients with type 1 diabetes mellitus and in the control group were found by the metabolites Cr and Cr2. At the same time, these parameters are energy metabolism markers in their function and promote glycolysis [23, 24]. In addition, it was reported that in the voxel assessment there are significant differences in Cr and Cr2 in the

hippocampus region. This is due to the presence of a concentration gradient of these metabolites between the anterior and posterior parts of the hippocampus in the main group.

5. Conclusion

The central nervous system is one of the key targets for diabetes mellitus, and the disruption of which is manifested by cognitive impairment [25]. More recently, it has been shown that in patients with diabetes not only the risk of developing dementia is increased but also the likelihood of progression from a mild cognitive disorder to Alzheimer's disease [21]. Chronic hyperglycemia and also glucose variability are risk factors for the development of cognitive dysfunction, which confirms the need for more severe compensation of the disease. A complex diagnosis of cognitive impairment by studying the neuropsychological status of patients is suggested. The markers of cognitive dysfunction-neurospecific proteins and structural changes in the magnetic resonance imaging of the brain are studied. The test markers were associated with unsatisfactory metabolic control. In addition, the effect of cognitive impairment on QoL of patients with type 1 diabetes mellitus has been shown, especially in cases of impaired memory and attention functions. In addition, modern metabolism of the brain was studied with the help of the modern MRS method in type 1 diabetes mellitus, and changes in the parameters of Cr and Cr2 in the hippocampal region responsible for cognitive changes were detected. That confirms the fact of functional changes in the brain in diabetes and in the early stages of the disease and can be corrected with the help of rehabilitation measures in the form of cognitive training and/or therapeutic physical training.

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References

[1] Brands AM, Biessels GJ, Kappelle LJ, et al. Cognitive functioning and brain MRI in patients with type 1 and type 2 diabetes mellitus: A comparative study. Dementia and Geriatric Cognitive Disorders. 2007;**23**(5):343-350

[2] Sahin K, Tuzcu M, Orhan C, Ali S, Sahin N, Gencoglu H, et al. Chromium modulates expressions of neuronal plasticity markers and glial fibrillary acidic proteins in hypoglycemia-induced brain injury. Life Sciences. 2013;**93**(25-26):1039-1048. DOI: 10.1016/j.lfs.2013.10.009

[3] Pesaresi M, Giatti S, Calabrese D, Maschi O, Caruso D, Melcangi RC. Dihydroprogesterone increases the gene expression of myelin basic protein in spinal cord of diabetic rats. Journal of Molecular Neuroscience. 2010;**42**(2):135-139 (48)

[4] McIntyre EA, Perros P. Serum S-100beta protein as a biochemical marker for cerebral oedema complicating severe diabetic ketoacidosis. Diabetic Medicine. 2001;**18**(12):1008R

[5] Wessels AM, Simsek S, Remijnse PL, et al. Voxel based morphometry demonstrates reduced grey matter density on brain MRI in patients with diabetic retinopathy. Diabetologia. 2006;**49**:2474-2480

[6] Frokjaer JB, Brock C, Sifteland E, et al. Macrostructural brain changes in patients with longstanding type 1 diabetes mellitus – A cortical thickness analysis study. Experimental and Clinical Endocrinology & Diabetes. 2013;**121**(6):354-360

[7] Fazekas F, Chawluk JB, Alavi A, et al. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. American Journal of Roentgenology. 1987;**149**:351-356

[8] Liu C, Miller B. A quantitative study of vascular dementia. Neurology. 1992;**42**:138-143

[9] MacLullich AMJ, Wardlaw JM, Ferguson KJ, et al. Enlarged perivascular spaces are associated with cognitive function in healthy elderly men. Journal of Neurology, Neurosurgery, and Psychiatry. 2004;**75**:1519-1523

[10] MoCA test [Electronic resource]. Available from: http://www.mocatest.org/default.asp

[11] Zakharov VV. Neuropsychological tests. Necessity and possibility of application. Consilium Medicum. 2012;**13**(2):82-90

[12] Jacobson AM, Musen G, Ryan CM, et al., For the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Long-term effect of diabetes and its treatment on cognitive function. New England Journal of Medicine. 2007;**356**(18):1842-1852

[13] Strachan MW, Abraha HD, Sherwood RA, Lammie GA, Deary IJ, Ewing FM, Perros P, Frier BM. Evaluation of serum markers of neuronal damage following severe hypoglycaemia in adults with insulin-treated diabetes mellitus. Diabetes/metabolism Research and Reviews. 1999;**15**(1):5-12

[14] Saravia FE, Revsin Y, Gonzalez Deniselle MC, et al. Increased astrocyte reactivity in the hippocampus of murine models of type 1 diabetes: The nonobese diabetic (NOD) and streptozotocin-treated mice. Brain Research. 2002;**57**(2):345-353

[15] Biessels GJ, Reijmer YD. Brain MRI in children with type 1 diabetes: Snapshot or road map of development changes? Diabetes. 2014;**63**:62-64

[16] Trofimova AV, Gaikova ON, Anan'eva NI, et al. Perivascular spaces: Morphology, neuroimaging, atypical variants. Radiation Diagnostics and Therapy. 2011;**2**(2):37-44

[17] Ho MS, Weller NJ, Ives FJ, et al. Prevalence of structural central nervous system abnormalities in early-onset type 1 diabetes mellitus. The Journal of Pediatrics. 2008;**153**(3):385-390

[18] Hoogma RP, Moll AC, Snock FJ, Stain CJ, Diamant M. Functional brain connectivity and neurocognitive functioning in patients with longstanding type 1 diabetes with and without microvascular complications. Diabetes. 2009;**58**:2335-2343

[19] Perantie DC, Koller JM, Weaver PM, Lugar HM, Black KJ, White NH, Hershey T. Prospectively determined impact of type 1 diabetes on brain volume during development. Diabetes. 2011;**60**:3006-3014. DOI: 10.2337/db11-0589

[20] Rizzo MR, Marfella R, Barbieri M, et al. Relationships between daily acute glucose fluctuations and cognitive performance among aged type 2 diabetic patients. Diabetes Care. 2010;**33**:2169-2174. DOI: 10.2337/dc12-0199

[21] Zhong Y, Zhang XY,Miao Y, Zhu JH, Yan H, Wang BY, Jin J, Hu TJ, Jia WP. The relationship between glucose excursion and cognitive function in aged type 2 diabetes patients. Biomedical and Environmental Sciences. 2012;**25**(1):1-7. DOI: 10.3967/0895-3988.2012.01.001

[22] Abbatecola AM, Rizzo MR, Barbieri M, et al. Postprandial plasma glucose excursions and cognitive functioning in aged type 2 diabetics. Neurology. 2006;**67**:235-240. DOI: 10.1212/01.wnl.0000224760.22802.e8

[23] Bogdan AA, Khomenko Yu G, Kataeva GV, et al. Principles of grouping data in the evaluation of the results of multivocaval spectroscopic examination of the brain. Radiation Diagnostics and Therapy. 2016;**4**(7):15-19

[24] Castillo M, Kwock L, Mukherji SK. Clinical applications of proton MR spectroscopy. American Journal of Neuroradiology. 1996;**17**:1-15

[25] Maheshwari SR, Fatterpekar GM, Castillo M, et al. Proton MR spectroscopy of the brain. Seminars in Ultrasound, CT, and MR. 2000;**21**:434-451

[26] Hill NR, Nick SO, Choudhary P et al. Normal Reference Range for Mean Tissue Glucose and Glycemic Variability Derived from Continuous Glucose Monitoring for Subjects Without Diabetes in Different Ethnic Groups Diabetes. Technology & Therapeutics. 2011;**13**(9):921-928. https://doi.org/10.1089/dia.2010.0247