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Article

Association of Serum BDNF with Severity of Cognitive Disorders in Patients with Type 2 Diabetes

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Abstract: Background: Cognitive disorders are common in patients with type 2 diabetes mellitus (DM2) and affect the quality of life, work and social adaptation. Diagnosis of cognitive disorders is carried out using various tests, each of which has its own advantages and disadvantages. Aim: To study of the association between serum level of BDNF and the severity of cognitive disorders in patients with DM2. Materials and methods: Included in the study 61 patients with DM2 complicated by central neuropathy with cognitive disorders and 28 clinically healthy volunteers without DM2. The cognitive and depressive disorders were evaluated using the Montreal Cognitive Assessment (MoCA), Frontal Assessment Batter (FAB), Hospital Anxiety and Depression Scale (HADS). The serum level of BDNF was determined via the method of enzyme-linked immunosorbent assay according. Results: Cognitive disorders in patients with DM2 manifests in the form of disorders of spatial orientation, attention and short-term memory. Frontal dysfunction, mainly in the form of impaired conceptualization and grasping reflexes, was recorded in 30% of patients with DM2. The serum level of BDNF in patients with DM2 is significantly lower than in healthy volunteers and is associated with the duration of DM2, the serum level of HbA1c. Conclusion: Serum level of BDNF may by potential biochemical marker of metabolic cognitive disorders in DM2.

Keywords: *diabetes mellitus; adults; cognitive disorders; BDNF; biomarker*

Introduction

Diabetes mellitus type 2 (DM2) belongs to the category of socially significant diseases with epidemically high growth of prevalence [1]. According to the International Diabetes Federation (IDF), the number of DM patients in the world reached 463mil in 2019 and it is expected to grow to 700 million in 2045 [2]. Over the past decade, the increase in the prevalence of DM2 has been registered in Russia as well. The total number of DM patients was 4.8 million (3.23% of the population) in January 2021. Among these, 92.5% of the cases (4.43 million) are DM2.

The relevance of DM2 is also defined by its long-term complications manifesting in different organs and systems. Among these, impairment of the central nervous system (CNS) has been actively studied over the past years [4]. One of the key roles in the pathogenesis of diabetic neuropathy in DM2 patients is played by chronic hyperglycaemia that evokes a multi-stage cascade of metabolic disorders. The main elements of this cascade are considered to be the activation of the polyol pathway of glucose metabolism, suppression of synthesis and activity of Na/K-ATPase, oxidative stress, non-enzymatic glycosylation of proteins, impairment of fatty acid metabolism and neurotrophicity decline conditioned by the change in the synthesis of neurotrophic factors [5]. Apart from that, the role of such endothelial factors as the brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF2), transforming growth

factor beta (TGFb), transcription factor NF-kb, tumour necrosis factor alpha (TNFa), etc. in the pathogenesis of diabetic neuropathy is being actively studied [6].

BDNF belongs to the family of neurotrophic factors – the family of soluble high molecular weight polypeptides that consists of 119 non-glycosylated amino-acid residues. Its mature molecule has a molecular mass of 13 kDa. BDNF is expressed in fibroblasts, astrocytes, neurons of different phenotypes and location, megakaryocytes/thrombocytes, Schwann cells and impairment lesions (**Figure 1**).

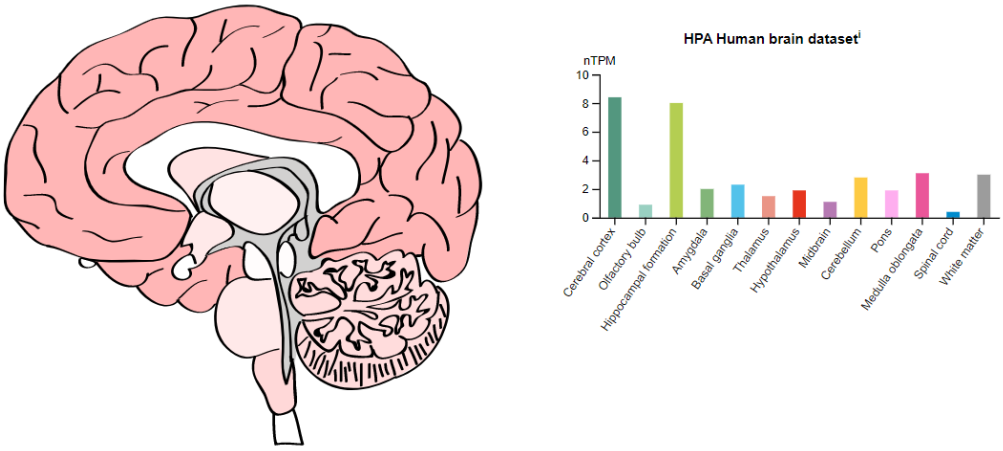

Figure 1. Expression of BDNF in the human brain

BDNF participates in differentiation, neuron maturation and synapse formation during the nervous system development as well as for neuroprotection and synaptic plasticity in the adult organism [7].

The aim of this study was the analysis of the association between serum BDNF level and the severity of cognitive impairments in Russian DM2 patients.

Materials and Methods

2.1. Participants

We enrolled 61 (female 35, male 26) adult Russian patients with DM2 complicated by central neuropathy with cognitive impairment (DM2 group). The control group (n = 28; female 18, male 10) included clinically healthy volunteers without DM2 (**Figure 2**).

The median age of the studied participants was 57 [51; 59] years old. The control group included healthy adults aged from 40 to 60 years old, median age - 57 [52,3; 60,0] years old. DM2 group included patients aged from 40 to 60 years old, median age - 57 [51; 59] years old. From these data, it can be noted that there is no significant difference between mean age values in the studied groups ($p > 0.05$).

The median of DM2 duration was 6 [5; 10] years. The median serum level of glycated hemoglobin (HbA1c) was 7.2 [6.8; 7.9] % in the DM2 group.

The median serum level of HbA1c was 7.2 [6.8; 7.9] % in the control group.

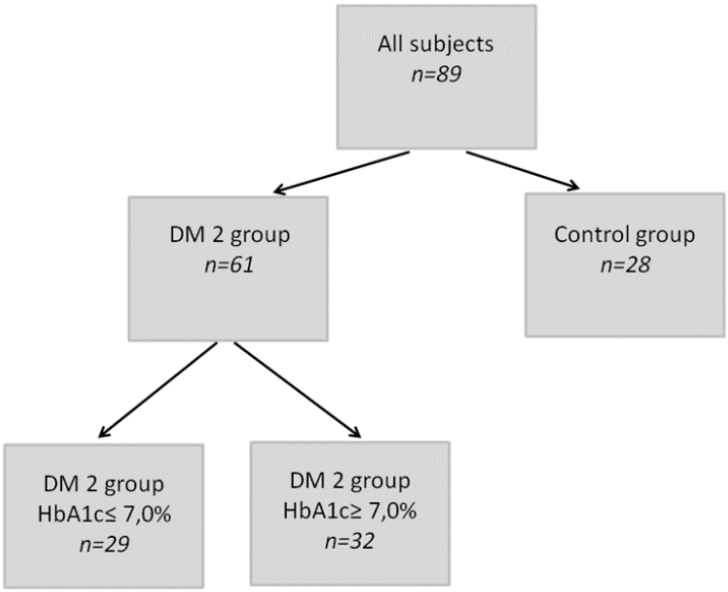

Figure 2. Distribution of patients into groups.

Inclusion criteria in the DM2 and control groups:

- Age—from 40 to 60 years old, including second period middle-aged (males 36–60 years old, females 36–55 years old);
- Medically stable DM2 (the diagnosis was made by an endocrinologist or internist); serum level HbA1c in two separate tests is lower than 7.0%;
- Medically non-stable DM2 (the diagnosis was made by an endocrinologist or internist); serum level HbA1c in two separate tests is above than 7.0%;
- Central neuropathy (diabetic encephalopathy) with cognitive disorders vitrificated by neurocognitive tests (the diagnosis was made by neurologist);
- History of cognitive disorders for over 6 months;

Exclusion criteria in the DM2 and control groups:

- Epilepsy and uncontrolled seizure disorder;
- Severely cognitive disorders (dementia);
- Mental illness;
- Hereditary neuropathy;
- History of stroke, spinal cord injury, traumatic brain injury, multiple sclerosis;
- History of cardiac arrhythmias or hemodynamic instability;
- Cardiac pacemaker or other implanted electronic system.

Voluntary Informed Consent in Research and Clinical Care was signed by all patients with DM2 and all volunteers without DM2. After an explanation of the medical condition, the purpose and benefits of the test, procedure or treatment and description of the proposed test, procedure or treatment were analyzed, including possible complications or adverse events. The study protocol was approved by the local medical ethics committee (protocol № 62/2015, 27.05.2015) of V.F. Voino-Yasenetsky Krasnoyarsk State Medical University. All procedures adhered to the 1984 Declaration of Helsinki and its later amendments. All patients read the abovenamed article in full (including text, figures and Supplementary Material) and agree to its publication.

Participation is not rewarded in this study. The researchers were not rewarded for their work. The study was carried out as part of the research program of the Department of Pharmacology and Clinical Pharmacology of V.F. Voino-Yasenetsky Krasnoyarsk State Medical University (Russia).

2.2. Characteristics of Standard Drug Therapy

All DM2 patients received identical drug therapy with Metformin (median dose - 2000 [1000; 2000] mg in day) during a long time), among them, 30 (49.2 ± 12.5%) patients were additionally treated with Gliclazide (median dose - 60 [30; 60] mg in day).

All participants in the control group did not drug therapy.

2.3. Characteristics of Cognitive and Depressive Disorders

The analysis of complaints among DM2 patients and control group was carried out by means of a survey.

In the control group, volunteers complained of fatigue in 10 (35.7 ± 17.3%), headache in 13 (46.4 ± 18.5%) and mild memory impairment in 9 (32.1 ± 17.3%). Volunteers had no subjective complaints of decreased mood.

DM2 patients complained about memory impairment (36 pers.; 59.0 ± 10.6%), mild general fatigue (31 pers.; 50.8 ± 12.5%), headache (18 pers.; 29.5 ± 11.4%), ataxia (5 pers.; 8.2 ± 6.9%). All DM2 patients had no subjective symptoms of depressive disorders.

2.4. Characteristics of Cognitive and Depressive Disorders Assessment Tools

Montreal Cognitive Assessment (MoCA): cognitive disorders were evaluated using the MoCa. The questionnaire consists of questions and tasks grouped in 7 categories making it possible to examine the visuoconstructive skills (the clock drawing test and the cube copy), memory (memorisation and delayed repetition of words), attention (a series of numbers forward and then backward), abstraction, orientation (the date, the time, the place) and speech function (animal naming). The maximum score is 30 points, a result of 26 points or higher is considered normal. The score of 25 points or less points attests to the presence of cognitive disorders.

Frontal Assessment Batter (FAB): the FAB was used for diagnosis of cognitive disorders with predominant impairment of the frontal lobes of the brain. The survey assesses conceptualisation (similarities between objects), lexical fluency, dynamic praxis, simple and complicated choice reactions, grasp reflex. The maximum score is 18 points, the result of 16 points is considered normal, 12-15 points attest to moderate frontal dysfunction, while the score of below 12 points reflects pronounced frontal dysfunction.

Hospital Anxiety and Depression Scale (HADS): the scale consists of two subscales: the first subscale is for assessment of the anxiety level, the second one is for assessment of the depression level. The scale contains 14 questions. Every question offers 4 answer variants that reflect the gradation of the symptom severity and coding the increment of the symptom severity from 0 (absence) to 4 points (maximally manifested). The questionnaire is filled in by the patient with no assistance. The sum of 0-7 points is considered as the absence of reliably manifested symptoms of anxiety/depression, 8-10 points: subclinical anxiety/depression, 11 points and more: clinical anxiety/depression.

2.5. BDNF Serum Level Study

The serum level of BDNF was determined via the method of enzyme-linked immunosorbent assay according to the standard protocol with the Human BDNF Quantikine ELISA Kit (DBD00) and the Thermo Scientific Multiskan FC spectrophotometer (ThermoFisher Scientific Inc., Finland). Measurement range: 62.5 – 4000 pg/ml (0.0625 – 4.0 ng/ml). Sensitivity: 20.0 pg/ml (0.02 ng/ml).

The sample preparation protocol: 1 ml of the serum used was obtained through sedimentation of venous blood (5 ml) in a glass tube without filler (Improvacuter, Guangzhou Improve Medical Instruments Co., China) for 30 minutes in room temperature. The serum was then centrifuged for 15 min at the speed of 1000 xg. The serum was withdrawn into a cryotube and stored at the temperature of (-) 20° C without repeated freezet haw cycles before the enzyme-linked immunosorbent assay (**Figure 3**).

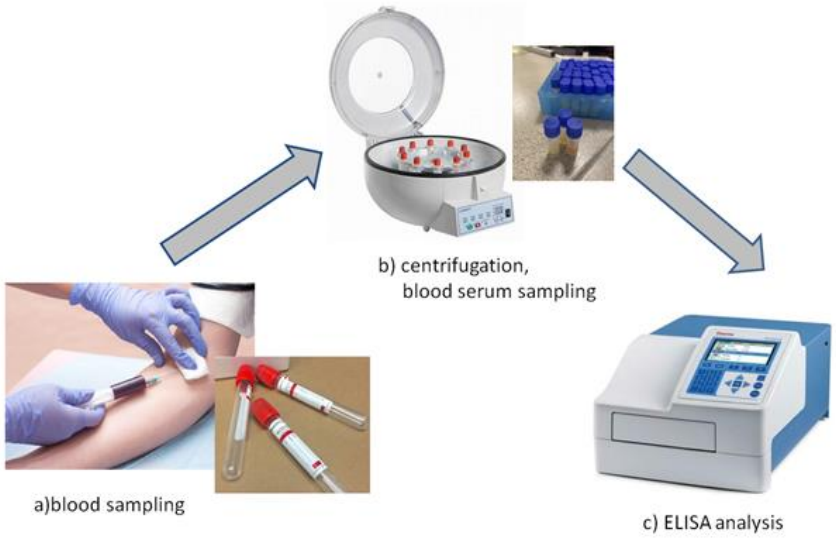

Figure 3. BDNF serum level study.

2.6. Statistical Analysis

Collected data were computed and analyzed using SPSS software for Windows, version 20 (IBM, Armonk, NY, USA).

The Shapiro–Wilk test was used to test the normality of the distribution of the quantitative variables. None of the quantitative data were normally distributed. The quantitative data are presented as a median value with the first and the third quartiles. The nominal data are presented as a percentage (%) and its odds ratio (% ± OR%). Differences in quality characteristics between the groups were established using the Chi-square test and Fisher's exact test. The correlation coefficient was established according to Spearman's criterion. The *p-value* was set at 0.05.

Results

3.1. Assessment of Cognitive Disorders Using Montreal Cognitive Assessment

The median MoCA of the studied patients was 26 [24; 28] points. The control group median MoCA - 28.0 [27.0; 28.8] points, in the DM2 group median MoCA – 25 [24; 27] points, *p-value* < 0.05. MoCA values of healthy volunteers in the control group were reliably different from those of the patients in the DM2 group (**Table 1**).

Table 1. Montreal Cognitive Assessment parameters in volunteers (the control group) and patients in the of DM2 group.

MoCA parameter	Control group Me (Q1-Q3)	DM2 group Me (Q1-Q3)
Visuoconstructive skills	4 [4; 5]	4 [3; 4]*
Naming	3 [3; 3]	3 [3; 3]
Attention	5 [5; 6]	5 [4; 6]*
Speech	3 [2; 3]	3 [2; 3]
Abstraction	2 [2; 2]	2 [2; 2]
Memory	4 [4; 5]	4 [3; 4]*
Orientation	6 [6; 6]	6 [6; 6]
Total score	28.0 [27.0; 28.8]	25 [24; 27]*

Note: MoCA - Montreal Cognitive Assessment; * p < 0.05— reliability of differences compared with similar values of the control group.

Patients from the DM2 group were established to have negative correlation between MoCA test parameters and the serum level of HbA1 (r = - 0.381, *p-value* < 0.05). The median MoCA score was 26.0 [24.5; 27.0] points in DM2 subgroup 1 patients (HbA1c ≤ 7.0%) and 24.5 [21.3; 27.0] points in subgroup 2 (HbA1c ≥ 7.0%), *p-value* > 0.05. MoCA values of the patients in DM2 subgroup 1 (HbA1c ≤ 7.0%) and subgroup 2 (HbA1c ≥ 7.0%) were reliably different upon evaluation of short-term memory: the 5-word memorisation test (**Table 2**).

Table 2. Cognitive function parameters according to Montreal Cognitive Assessment in patients of DM2 subgroup 1 and subgroup 2.

MoCA parameter	DM2 subgroup 1 (HbA1c ⩽ 7.0%) Me (Q1-Q3)	DM2 subgroup 1 (HbA1c ⩾ 7.0%) Me (Q1-Q3)
Visuoconstructive skills	4 [3; 4]	3 [2; 4]
Naming	3 [3; 3]	3 [3; 3]
Attention	5 [4; 6]	5 [4; 5.8]
Speech	3 [2; 3]	3 [2; 3]
Abstraction	2 [2; 2]	2 [2; 2]
Memory	4 [3; 5]	4 [2; 4]*
Orientation	6 [6; 6]	6 [6; 6]
Total score	26.0 [24.5; 27.0]	24.5 [21.3; 27]

Note: MoCA - Montreal Cognitive Assessment; * *p-value* < 0.05— reliability of differences compared with similar values of the control group.

3.2. Assessment of Cognitive Disorders Using Frontal Assessment Battery

DM2 patients had cognitive disorders associated with frontal lobe dysfunction in 1/3 of the cases (18 pers., 29.5 ± 15.6%), including mild (94.5%) and moderate (5.5%) cognitive disorders.

The median total FAB score of the studied patients was 17 [16; 18] points. The median value was 17.5 [16.0; 18.0] points in the control group, and 16.0 [15.0; 17.5] points in the DM2 group (*p-value* < 0.05) (**Table 3**).

Table 3. Cognitive function parameters according to Frontal Assessment Battery in the volunteers (the control group) and the patients in the DM2 group.

FAB parameter	Control group Me (Q1-Q3)	DM2 group Me (Q1-Q3)
Conceptualisation	3 [3; 3]	3 [2; 3]*
Lexical fluency	2 [2; 3]	2 [2; 3]
Dynamic praxis	3 [3; 3]	3 [3; 3]
Simple choice reaction	3 [2; 3]	3 [2; 3]
Complex choice reaction	3 [3; 3]	3 [3; 3]
Grasp reflex	3 [3; 3]	3 [3; 3]*
Total score	17.5 [16.0; 18.0]	16 [15.0; 17.5]*

Note: FAB - Frontal Assessment Batter; * *p-value* < 0.05— reliability of differences compared with similar values of the control group.

The median FAB16.0 [15.5; 17.5] in DM2 subgroup 1 (HbA1c ≤ 7.0%) points and 16.0 [15.0; 17.8] points in subgroup 2 (HbA1c ≥ 7.0%), *p-value* > 0.05.

Therefore, the median total FAB score was > 16 points in both subgroups of DM2 patients. This attested to general absence of clinically significant cognitive disorders

associated with frontal lobe dysfunction. However, a small number of the observed DM2 patients had FAB scores ≤ 15 points.

3.3. Assessment of Depressive Disorders using Hospital Anxiety and Depression Scale

In the control group, subclinical anxiety was registered in 4 subjects (1.12 ± 3.9%), subclinical depression was found in 1 subject (0.3 ± 2.02%). The median HADS scores: the anxiety subscale: 5.0 [4.0; 6.0] points (normal: < 7 points); the depression subscale: 2.0 [0.0; 4.0] points (normal: < 7 points); the total score according to both subscales was 7.0 [5.3; 9.8] points (normal: < 14 points).

In the DM2 group, subclinical anxiety was registered in 14 subjects (23 ± 10.6%), subclinical depression was found in 6 subjects (9.8 ± 7.5%). The median HADS scores: the anxiety subscale: 5.0 [3.5; 7.0] points (normal: < 7 points); the depression subscale: 4.0 [3.0; 5.0] points (normal: < 7 points); the total score according to both subscales was 9.0 [7.0; 11.5] points (normal: < 14 points), *p-value* < 0.05 (**Figure 4**).

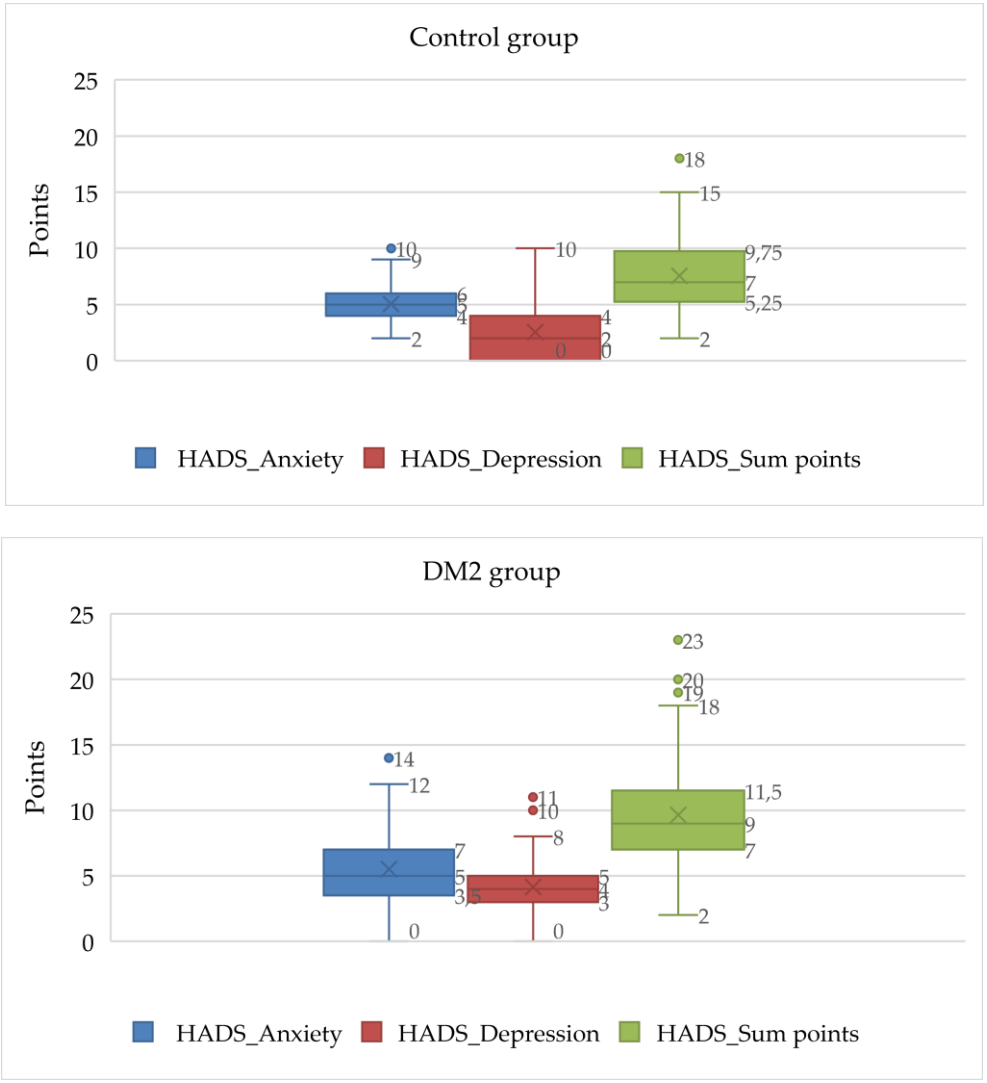

Figure 4. Depression and anxiety parameters according to Hospital Anxiety and Depression Scale in the control group and the DM2 group.

3.4. Serum Level BDNF in the Control and DM2 Groups

In the control group, the median serum BDNF level amounted to 2.3 [2.1; 2.5] ng/ml, and to 1.6 [1.3; 2.0] ng/ml in the DM2 group (*p-value* < 0.05). The median serum BDNF level was 1.8 [1.5; 2.2] ng/ml in patients of the DM2 subgroup 1 (HbA1c ≤ 7.0%) and 1.5 [1.0; 1.8] ng/ml in the DM2 subgroup 2 (HbA1c ≥ 7.0%), *p-value* < 0.05.

No statistically significant correlation was found between the serum BDNF level and the age of healthy volunteers (r = - 0.193; *p-value* > 0.05).

Statistically significant inverse correlation between the serum BDNF level and DM2 duration was established for DM2 patients (r = - 0.266, *p-value* < 0.05), as well as between the serum BDNF level and HbA1c (r = - 0.512, *p-value* < 0.05).

Analysis of the association between cognitive disorders (MoCA and FAB) and the serum BDNF level in the DM2 group has shown a statistically significant direct correlation with separate parameters of the cognitive tests (**Table 4, Table 5**).

Table 4. The interrelation between the serum BDNF level and Montreal Cognitive Assessment parameters in DM2 group patients.

MoCA parameter	**BDNF ng/ml, Spearman's correlation coefficient (r)**
Visuoconstructive skills	0.575**
Naming	0.278*
Attention	0.437**
Speech	0.341*
Abstraction Абстрактное	0.201
Memory	0.693**
Orientation	0.088
Total score	0.832**

Note: MoCA - Montreal Cognitive Assessment; * *p-value* < 0.001, ** *p-value* < 0.05 — the correlation significance (two-tailed)

Table 5. The interrelation between serum BDNF level and Frontal Assessment Battery parameters in patients of the DM 2 group.

FAB parameter	**BDNF ng/ml, Spearman's correlation coefficient (r)**
Conceptualisation	0.253*
Lexical fluency	0.335*
Dynamic praxis	0.140
Simple choice reaction	0.101
Complex choice reaction	0.413**
Grasp reflex	0.016
Total score	0.553**

Note: FAB - Frontal Assessment Battery; * *p-value* < 0.001, ** *p-value* < 0.05 — the correlation significance (two-tailed)

Discussion

Cognitive disorders develop in over 50% DM2 patients and directly affect the quality of life, labour and social adaptation of these patients [8–12]. Assessment of cognitive disorders using MoCA has shown that the median score in the DM2 patients is reliably lower than that of the healthy volunteers in the control group. Detailed analysis of MoCA results of DM2 patients has established a decrease in cognitive functions manifested by disorders in spatial orientation, attention and short-term memory. The results obtained attest to the presence of cognitive disorders in DM2 patients against the background of chronic hyperglycaemia. In our study, a statistically significant inverse correlation has been established between hyperglycaemia and cognitive disorders in DM2 patients.

Approximately 30% of the DM2 patients had frontal lobe dysfunction, predominantly manifested by impairment of conceptualisation and grasp reflex. However, no statistically significant differences in general assessment of cognitive functions according to FAB were found in the control or DM2 group. MoCA was the more sensitive cognitive test for DM2 patients as compared with FAB.

Anxiety and depression are wide-spread among DM2 patients. The comorbidity of DM2 and anxiety/depression elevates the risk of complications of this endocrine disease and deteriorates the patients' quality of life [13]. The frequency of this comorbid condition (the overlap syndrome) varies between 25% and 76%, which is significantly higher than the average populational values [14–17]. Analysis of anxiety and depression parameters of HADS in our patients has shown significantly higher frequency of anxiety-depressive disorders (21.3%) in comparison with the volunteers in the control group (14.3%).

Analysis of serum BDNF has shown its reliably lower level in DM2 patients than in healthy volunteers in the control group. In our study, we have established a statistically significant inverse correlation between hyperglycaemia (HbA1c) and serum BDNF in DM2 patients. The lowest serum BDNF level was registered in patients of the DM2 subgroup 2 (HbA1c ≥ 7.0%) with medically non-stable DM2. Analysis of the interrelation between serum BDNF and MoCA parameters has demonstrated statistically significant positive correlation with visuoconstructive skills, attention and short-term memory in DM2 patients. Positive correlation has been determined between the serum BDNF level and FAB parameters – conceptualisation, lexical fluency, complex choice reaction – in DM2 patients.

Therefore, the serum level of BDNF correlated with both the DM2 severity and the severity of metabolic (diabetic) cognitive disorders. Possibly, it is associated with the fact that BDNF is not only expressed in the brain but also in pancreas (**Figure 5**). In earlier studies, the level of BDNF was lower in men than in women [17]; in our study, the level of BDNF in serum did not depend on the sex. Although the level of BDNF expression in pancreas is much lower than in the brain, BDNF, apparently, is a clinically significant serum biomarker of comorbidity of DM2 and other metabolic disorders. We have demonstrated that analysis of blood serum BDNF was a more sensitive test in comparison with FAB. We assume that dynamic evaluation of the serum BDNF level in DM2 patients may become a good alternative to neuropsychological testing using scales and questionnaires, for which a degree of subjectivity remains possible as well as influence of depressive disorders on the overall assessment [19]. It is known that depression may mimic cognitive disorders [20]. This hypothesis is also supported by our finding of more severe depressive disorders in DM2 patients in comparison anxiety disorders. On the contrary, evaluation of the serum BDNF level in patients with DM2 makes it possible to avoid the influence of depression on assessment of cognitive disorders, i.e. this biomarker is clinically significant, objective and economically justified. The economic effect may consist in economy of time for the attending physician (endocrinologist or general practitioner) and absence of the need for additional specialists' (a neurologist or a neuropsychologist) consultations for diagnosis of comorbid cognitive disorders.

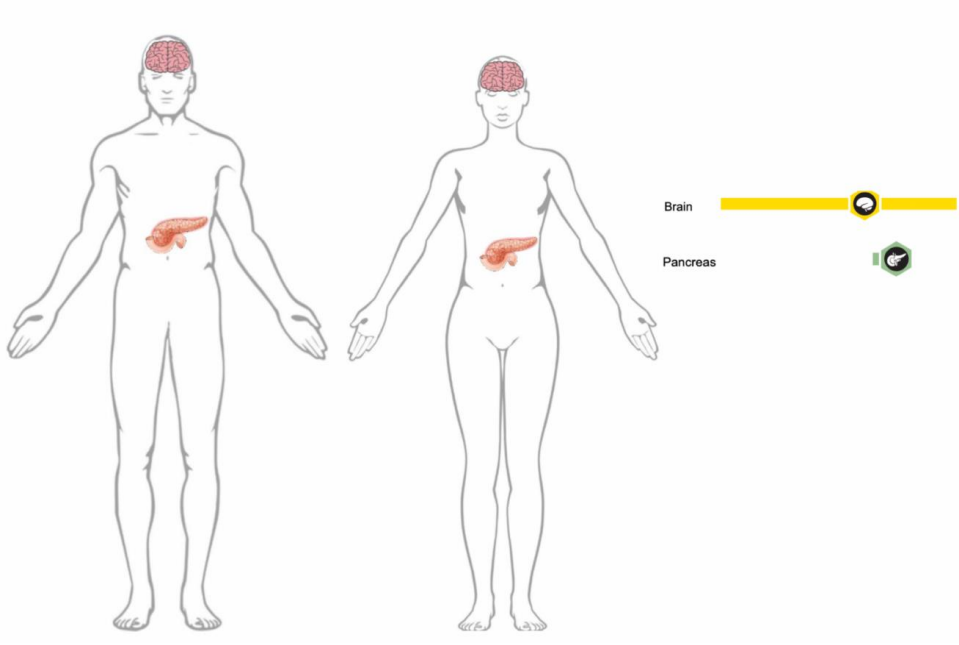

Figure 5. BDNF expression level in the human brain and pancreas

Limitations

- We could not investigate the effectiveness of других methods in the diagnosis of cognitive расстройств in patients with DM2, and we could not compare these results with the results of magnetic imaging of brain.
- We could not study the effectiveness of serum level of BDNF compared with the use of other laboratory tests (other serum biomarkers of cognitive disorders).

Conclusions

There are significant differences between MoCA and FAB based on cognitive disorders assessment using various cognitive subscales in patients with DM2. Serum level of BDNF may by potential biochemical marker of metabolic cognive disorders in DM2.

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Data Availability Statement: Not applicable.
Conflicts of Interest: The author declares that there is no conflict of interest.

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