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Antidiabetic drugs and cognitive impairment in type 2 diabetes

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Type 2 diabetes is a metabolic disease that is a risk factor for cognitive impairment, some antidiabetic medication may be associated with the survival of neurons. *Objective:* To study the association of antidiabetic medication and cognitive functions in patients with type 2 diabetes. *Materials and methods:* we examined 240 patients with type 2 diabetes. The patients were divided into 4 groups depending on glucose-lowering therapy: group 1 - insulin, group 2 - tableting medication, group 3 - combined therapy, group 4 – analogues of glucagon-like peptide 1. All patients underwent general clinical examination, cognitive functions test based on the Montreal scale. Statistical analysis was performed using the R-system software package. *Results:* The overall score of the MoCA test was higher in the group of patients receiving glucagon-like peptide-1 compared with the patients in groups 1, 2 and 3, whose cognitive functions declined. Patients receiving only biguanides medication performed the cognitive test significantly better. The correlation analysis revealed that cognitive functions are affected by age, disease duration, complications presence, and HbA1c level. *Conclusion:* In type 2 diabetes glucagon-like peptide-1 and biguanides treatment is accompanied by better performance of the cognitive function assessment tests.

INTRODUCTION

Type 2 diabetes mellitus (DM) is a progressive metabolic disease that is associated with the constant selection and correction of therapy for the complication prevention and the life prolongation. At the present stage, doctors have a wide range of antidiabetic medication that is heterogeneous in their action, safety profiles and tolerability. There is growing evidence that some types of antidiabetic therapy can improve cognitive function and even have a preventive effect in the dementia development (Unsal Avdal et al. 2017; Mostafa Madmoli et al. 2019). It is known that some antidiabetic medication, in addition to normalization of glycemia, have a positive effect on mitochondrial and synaptic function, reduce neuroinflammation and improve brain metabolism (Zhong, 2018). Thus, 19 studies were included in the PROSPERO meta-analysis (n = 4855), where the efficacy (i.e., pro-cognitive effects) and the acceptability of antidiabetic agents for the treatment of Alzheimer's disease and mild cognitive impairment were compared. As a result, it was shown that pioglitazone in a dose of 15 to 30 mg has the greatest efficacy compared with placebo (Cao, 2018). Since December 2010, the CAROLINA study (n = 6042 patients) has been conducted, comparing the effects of linagliptin and glimepiride with respect to the prevention rate of accelerated cognitive decline in type 2 diabetes. The final results are expected in 2019 (Biessels, 2018). Another study showed that sitagliptin therapy is associated with the cognitive function increase according to a brief mental status scale for patients with and without Alzheimer's disease (p = 0,024 / 0,047sootvtestvenno) (Isik, 2017). Experimental models revealed that glucagon-like peptide-1 provide a neuroprotective effect (Chalichem, 2017). In the study, patients who used metformin achieved better results in terms of memory and executive functions, and this effect persisted for 4 years after the start of therapy (Herath, 2016). Thus, there are various data regarding the effect of antidiabetic medication on cognitive function in diabetes, however, there is no clear connection between certain groups, dosages and other factors that may in some way affect the complications of the patient central nervous system. The purpose of this research was to study the effect of various antidiabetic medications on cognitive function of patients with type 2 diabetes.

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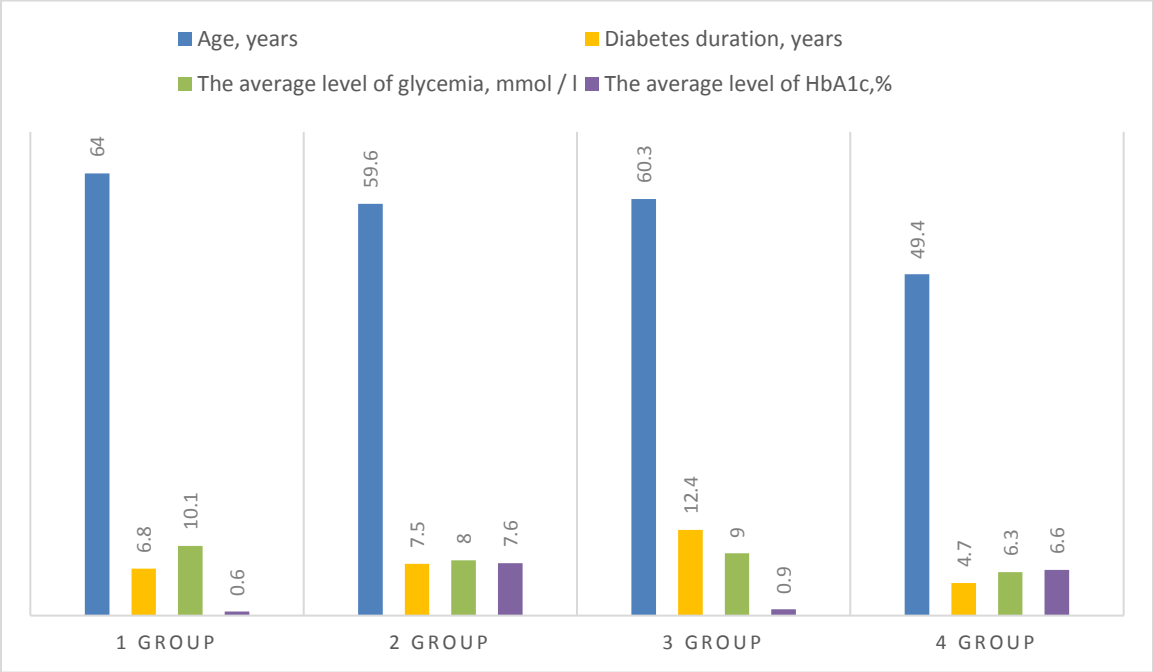

Chart 1 Characteristics of the examined patients

MATERIALS AND METHODS

The study was approved by the Ethics Committee of Siberian State Medical University (No. 5265) of 05/02/2017.

Design - observational, transverse, one-time study. The observation group included patients with type 2 diabetes who were seen by an endocrinologist on an outpatient basis at "Health" Center clinic and receiving treatment as a day patient at the endocrinology clinic of Siberian State Medical University of the Ministry of Health of Russia, from 18 to 85 years old.

Exclusion criteria were: an organic brain lesion (tumor, stroke); use of drugs and substances that alter cognitive functions (psychotropic, narcotic substances); chronic alcoholism; condition after severe injuries and operations, hematological, oncological, severe infectious diseases, severe hypoglycemia and diabetes ketoacidosis for the last 6 months before being included in the study. The period of inclusion in the study was 6 months. All patients were sampled venous blood in an amount of 5 ml to evaluate biochemical blood parameters. During the visit, patients together with the doctor filled out a cognitive function assessment questionnaire.

Clinical characteristics of patients: 240 people were examined with type 2 diabetes, at the age of 57.6 years, the disease duration was 7 years; among all patients, 90 men and 150 women. Patients were divided into 4 groups: 1 group - received insulin, group 2 - received tableting medication, group 3 - combination therapy, group 4 - analogues of glucagon-like peptide 1 (Victoza). Patients 1st group received insulin: Lantus or Levemir plus Novorapid or Chumalog on basis-bolus regime. In 2nd group brand names of biguanids was - Glucophage or Siofor (1000-2000 mg), sulfonylureas - Diabeton MR (60 mg -120 mg) or Manninil (3,5-7 mg), sodium-glucose cotransporter type 2–Jardiance (10-25 mg) or Forxiga (5-10 mg). As a combined therapy they received insulin Levemir or Lantus on basis regime plus Glucophage or Siofor, sometimes plus Jardiance or Forxiga. The dose of the drugs taken by the patients was individual, depend on glycaemia and acceptable taking into account pharmacodynamics. The study included patients who took glucose-lowering therapy for 6 months, at the time of the visit, they did not perform titration therapy. Despite the fact that the literature describes the negative effect of urea sulfonyl drugs in type 2 diabetes in elderly patients, today these drugs are available, inexpensive and are given out to patients with state support, and therefore are the drugs of choice for many patients with type 2 diabetes type.

Cognitive functions of all patients were screened based on the Montreal scale (MoCa test). The MoCa test is designed for mild cognitive disorders screening. The scale gives an assessment of various cognitive aspects: attention and memory, executive functions, concentration, language, visual and constructive skills, counting, abstract thinking and orientation. The time to complete the study is approximately 10 minutes. The maximum possible score is 30; cognitive dysfunction is verified with 26 or less score. The HbA1c level was determined in capillary blood using the liquid chromatography method on the analyzer "DS5 Glycomat" (DrewScientific, Netherlands). To calculate sample sizes, the minimum group volume estimation formula was used comparing the indicator in two independent groups.

Statistical processing of the data was performed using the IBM SPSS Statistics 19.0.0 program in Russian (IBM SPSS Inc). Normality was tested by using the W-test, Shapiro-Wilk. During the descriptive analysis with the normal distribution, the arithmetic mean of the value (X), the error of the mean (m) calculation was used, and for abnormal distribution the calculation of quartiles (Me, Q1-Q3) was used. A comparative analysis was performed based on the Student's t-test f for normal distribution and based on the Mann-Whitney Z-test for abnormal distribution. The Wilcoxon test was used for dependent data. The level of significance was considered critical at 0.05 level. Qualitative data was evaluated using frequency analysis. The Spearman coefficient was used in the correlation analysis.

RESULTS

During the study, data on the age, duration of the disease, the level of fasting glucose and HbA, were obtained. The data are presented in chart 1. As a result of the study, it was found that most patients met target

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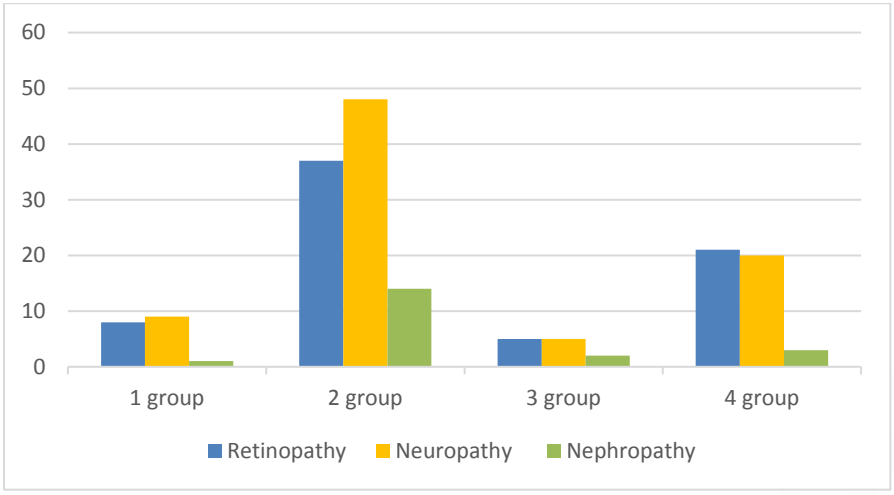

Chart 2 Microvascular complications in patients with type 2 diabetes

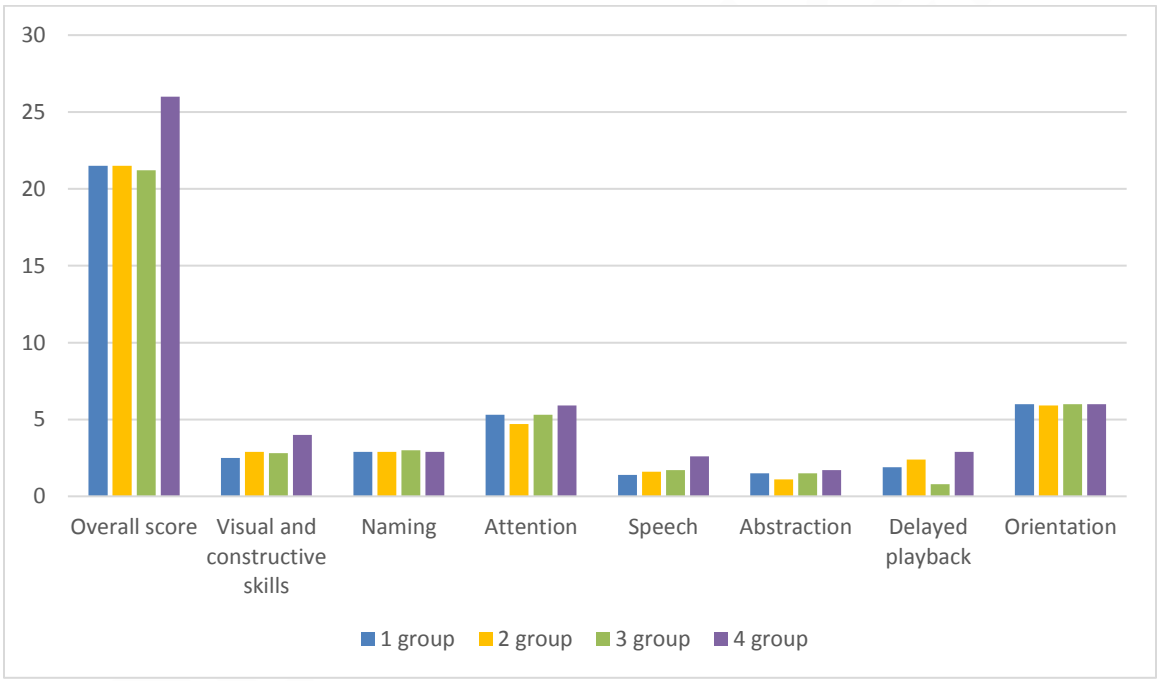

Chart 3 Results of the Montreal Cognitive Dysfunction Assessment in Patients with Type 2 Diabetes

levels of glycemic control for HbA1c level, with the exception of the group on combined antidiabetic therapy (U = 502.5, p = 0.000; U = 13.0, p = 0.004, respectively). However, the fasting blood glucose level was the lowest in group 4 (U = 49.5, p = 0.005; U = 524.0, p = 0.000; U = 22.5, p = 0.005). Also, patients from group 4 had a longer disease duration associated with therapy intensification during treatment (U = 134.5, p = 0.043; U = 28.5, p = 0.004 respectively). Moreover, group 4 patients were significantly younger compared with the other groups, apparently, due to the cost of glucagon-like peptide-1 medication (U = 58.5, p = 0.001; U = 625.0, p = 0.001; U = 50.5, p = 0.042, respectively).

The assessment of the microvascular complications among patients was carried out according to the recommended algorithms of specialized medical care for diabetic patients in 2017 (Dedov, 2017). Characteristics of the complications are presented in chart 2. During the diabetes chronic complications assessment, the most frequently retinopathy was verified from 46 to 73%, and polyneuropathy from 60% to 75%. Whereas nephropathy occurred in 8-28 % less often. Additionally, it was found that retinopathy was least frequently recorded in patients on tablet antidiabetic therapy (U = 831, p = 0.029).

Analysis of cognitive functions was carried out based on MoCA test (chart 3). During the MoCA test analysis, it was found that the overall score for this test was higher in the group of patients receiving glucagon-like peptide-1 compared with among patients in groups 1, 2 and 3, who experienced a decline of cognitive functions (U = 26.0, p = 0.001; U = 234.0, p = 0.000; U = 8.0, p = 0.002, respectively). Also, patients from the first 3 groups completed the tests of visual-constructive skills, attention and speech, significantly worse than patients of group 4 (U = 57.0, p = 0.001; U = 342.0, p = 0.000; U = 28.5 , p = 0.01, U = 52.0, p = 0.024; U = 234.5, p = 0.000; U = 22.0, p =

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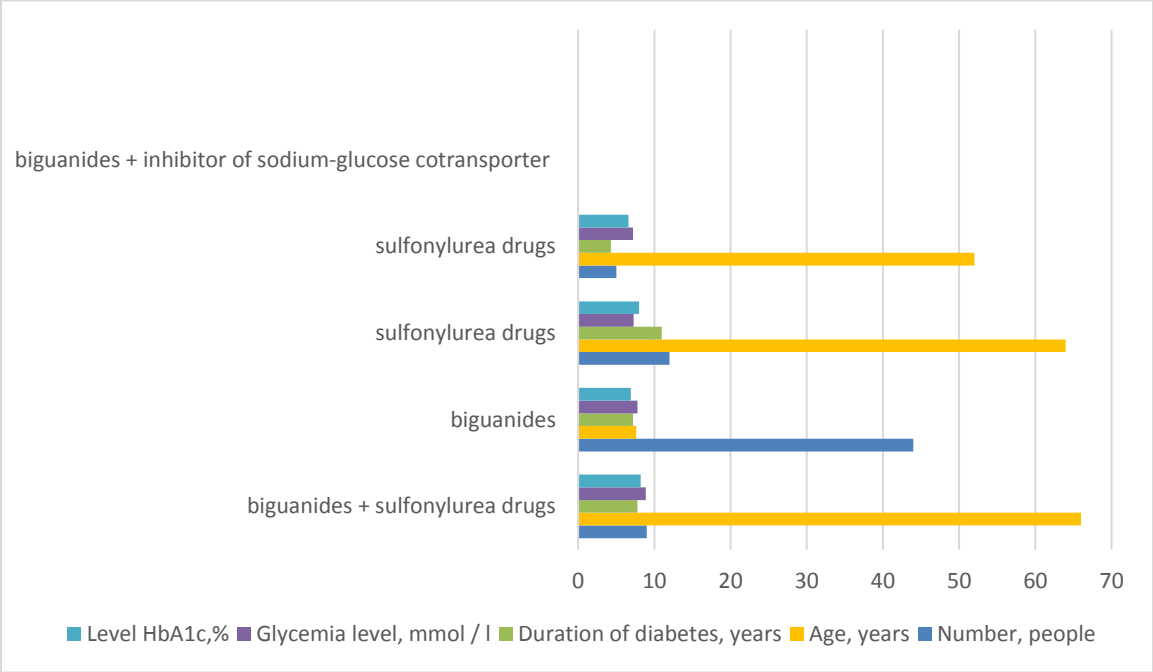

Chart 4 Patients combination for glucose-lowering oral medication analysis

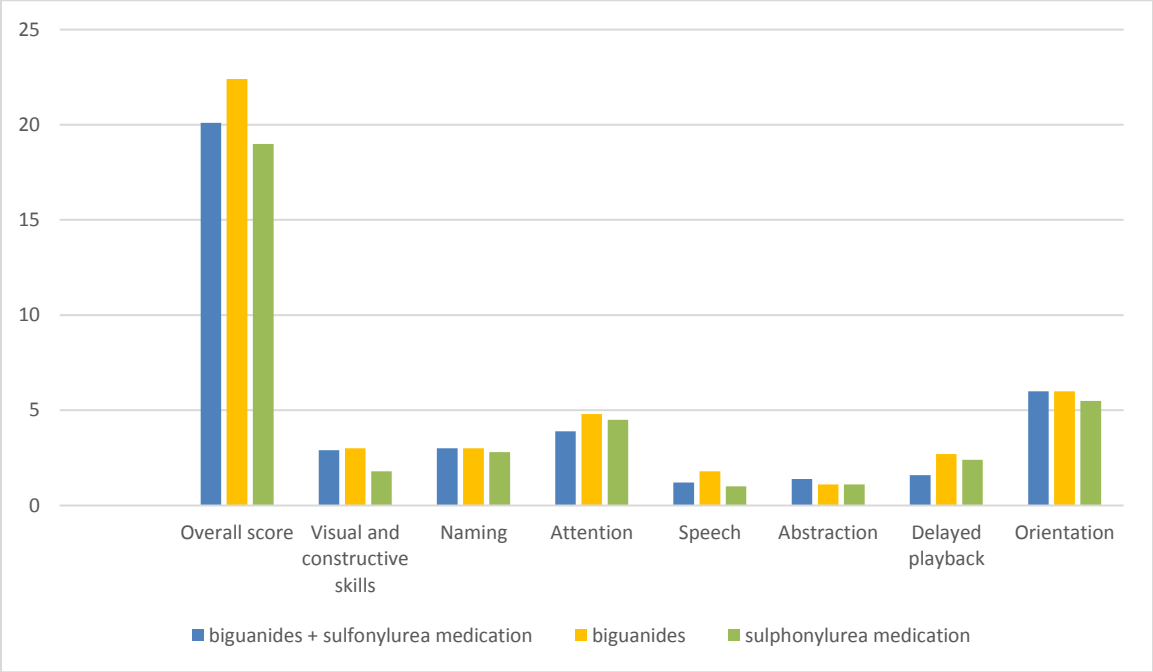

Chart 5 Results of the Montreal Cognitive Dysfunction Assessment in Patients with Type 2 Diabetes, receiving hypoglycemic tableting therapy

0.026, U = 32.5, p = 0.002; U = 328, 5, p = 0.000; U = 20.0, p = 0.019, respectively). Furthermore, patients receiving combined therapy performed a memory test (delayed reproduction) worse than group 2 and 4 (U = 110.5, p = 0.032; U = 13.0, p = 0.005, respectively). At the same time, patients on oral therapy registered lower scores on abstraction test compared with group 4 (U = 513.0, p = 0.038).

Additionally, a glucose-lowering oral medication analysis was carried out. Patients were divided based on their combination, which is presented in chart 4. During the oral hypoglycemic medication groups evaluation, it was found that patients most often took biguanides, and sulfonylureas, and their combination of biguanides and sodium-glucose-co-transporter type 2 inhibitors, in approximately equal parts. The age among patients taking the combination of biguanides and sulfonylurea drugs was significantly higher than in other groups (t = 2.02, p = 0.049; t = 2.21, p = 0.044, respectively). In patients taking sulfonylurea medication, the duration of the disease was significantly longer, and the level of glycemia was significantly less compared with the patients on sodium-glucose cotransporter type 2 inhibitors (U = 14.5, p = 0.044, U = 94.5, p = 0.038). Moreover, a comparative analysis of the parameters of cognitive functions of this group of patients was carried out (Chart 5).

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The overall score of the MoCA test was significantly lower among patients receiving only sulfonylurea drugs than among patients receiving biguanides (U = 133.5, p = 0.022). Results of visual-constructive skills and speech tasks showed the same correlation (U = 137.5, p = 0.028; U = 95.0, p = 0.001, respectively).

During the correlation analysis, it was revealed that the age of the patients with type 2 diabetes affects total scores on the MoCA test (as well as its individual tasks: visual-constructive skills, attention and speech) (R = -0.341, p = 0.000; R = -0.416 , p = 0.000; R = -0.197, p = 0.04; R = -0.292, p = 0.002, respectively). A positive correlation was also established between such complications as retinopathy and the duration of diabetes (R = 0.2, p = 0.038) and nephropathy with HbA1c levels (R = 0.197, p = 0.043). Moreover, it was shown that patients with high HbA1c completed the speech task of the MoCA test much worse (R = -0.288, p = 0.003).

During the intragroup assessment among patients receiving only insulin, positive correlations was found between such complication as the retinopathy and the level of HbA1c (R = 0.802, p = 0.009); between the glycemic level and the speech task of the MoCA test - (R = 0.726, p = 0.041). During the assessment of patients receiving hypoglycemic tablet medication, correlation was found between the age and the total scores on the MoCA test (R = -0.324, p = 0.005) and its individual tasks: visual-constructive skills (R = -0.381, p = 0.001), speech (R = -0.274, p = 0.018), delayed reproduction (R = -0.233, p = 0.046). The duration of the diabetes also affects speech and naming tasks (R = -0.246, p = 0.038; R = -0.263, p = 0.027, respectively). Evaluating patients group receiving a combination therapy, positive associations were found between the age and the delayed reproduction task (R = 0.892, p = 0.017); fasting glycemic level and the total scores on the MoCA test (R = 0.975, p = 0.005) and attention setting (R = 0.206, p = 0.044). Furthermore, in this group of patients negative correlations were also found: between the neuropathy presence and the glycemic level (R = -0.84, p = 0.036) and the total scores of the MoCA test (R = -0.84, p = 0.036).

DISCUSSION

Diabetes is a common and multi-component metabolic disease that can lead to target organs damage, including the brain (Craft, 2004). The relationship between diabetes and cognitive impairment may be due to the following parameters: macrovascular and microvascular changes, impaired glucose metabolism, chronic inflammation, hyperinsulinemia, insulin resistance or oxidative stress, cardiovascular risk factors (Strachan, 2011). Similarly, in the conducted study, the relationship of the development of cognitive impairment with age, duration of the disease, the presence of complications, as well as chronic hyperglycemia in this category of patients was identified. This study revealed relationship of cognitive impairment development with age, duration of the disease, the presence of complications, as well as chronic hyperglycemia in this patient's category.

The treatment of diabetes, including oral hypoglycemic agents and insulin, which minimize the symptoms of the disease and potentially prevent complications such as cognitive decline, is becoming increasingly important (Banks, 2012). In the research cohort, the best results of cognitive tests were recorded in patients receiving therapy with glucagon-like peptide-1 compared with insulin, oral hypoglycemic agents, or their combination. In the study cohort, the best results of cognitive tests were recorded in patients receiving therapy with glucagon-like peptide-1 compared with insulin, oral hypoglycemic agents, or their combination. Moreover, a deeper analysis of hypoglycemic tablet therapy revealed the positive effect of biguanides on cognitive function compared to urethane preparations, their combination, or sodium glucose-cotransporter type 2 inhibitors.

Modern groups of glucose-lowering medication with a significant degree of evidence can improve cognitive characteristics in patients with type 2 diabetes, affecting both vascular and neurodegenerative complications, providing anti-inflammatory effects (Kodl, 2008; Testa Маб 1998). Clinical studies showed that improved glycemic control has a positive effect on the objective indicators of cognitive functioning (Gradman, 1993; Meneilly, 1993). The limitation of this study is a small sample of patients, as well as insufficient group spread of patients prescribed hypoglycemic medication. However, research in this area is of undoubted scientific and practical interest.

CONCLUSION

Type 2 diabetes is accompanied by cognitive impairment, but to a lesser extent in patients receiving treatment with glucagon-like peptide-1 and biguanides.

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Authors' Contribution
MariiaV. Matveeva: search literature review**,** patient recruitment, data processing, statistical processing, description of results
IuliiaG. Samoilova: research design, article correction
Natali G. Zhukova: research design, article correction
O.A. Oleynik: patient recruitment, statistical processing
Maria A. Rotkank: search literature review, patient recruitment
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