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Assessment of the risk of developing cerebrovascular complications in patients with type 2 diabetes mellitus on program hemodialysis

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Introduction

Today, the prevalence of diabetes is increasing worldwide, with the largest increases in low- and middle-income countries. In many developed countries, type 2 diabetes mellitus (T2DM) is now not only the leading cause of end-stage chronic kidney disease (CKD), but also a major risk factor for cardiovascular disease.[1] In contrast to chronic glomerulonephritis, which in the last 2-3 decades has been considered the main cause of BCS, type 2 diabetes is increasingly causing end-stage glomerulonephritis. This forces all countries of the world to spend more and more funds allocated for health care. Therefore, it is important to determine effective methods of diagnosis and treatment in the early stages of the disease.[2]

In the world, the incidence of CKD is on average 100-600 people per 1 million population in different countries, and this figure is 1-3 cases per 10,000 population in children, 4-10 in adults, especially in people over 70 years old. The main cause of SBC in adults is type 2 diabetes, in connection with which a number of scientific studies are being carried out to create new methods of diagnosis and treatment, as well as to improve existing ones.[3] According to the WHO, the incidence of diabetes mellitus complicated by CKD, its prevalence and mortality among these patients is actually much higher than the available data. Therefore, it is important to develop targeted programs to identify and prevent risk factors that cause complications in patients on hemodialysis as a result of CKD developed as a result of type 2 diabetes.[4]

Despite of numerous scientific studies, scientific and technological achievements, type 2 diabetes mellitus and CKD, which developed as a complication, still remains one of the unexplored problems of modern medicine. According to the literature of late 20th-early 21st century, the spread of CKD was epidemic in nature, and this was confirmed by the data of large epidemiological studies, such as NHANES (National Health and Nutrition Examination Survey) and PRE VEND (Prevention of end-stage renal and vascular pathology). In 2002, the European and American Association of Nephrologists and Hemodialysis Physicians was established to unify approaches to the diagnosis, treatment and prevention of kidney disease. In particular, Inoue Hideaki, Jun Shirakawa in their studies found that CKD is the main cause of cardiovascular complications in diabetes.[5] Also, according to Fesler P., Mimran A., diabetic nephropathy (DN) is the leading cause of this severe complication worldwide - in developed countries. In particular, they found that 40% of patients dying on hemodialysis are patients with diabetes mellitus, and 11% are patients with cardiovascular complications.[6]

Modern studies have shown that the basis for the formation of cognitive dysfunction in patients with type 2 diabetes and CKD at the pre- and dialysis stages is cerebrovascular insufficiency, which occurs under the influence of cardiovascular risk factors. At the same time, the issues of predicting these complications using biomarkers in combination with assessing the quality of life of patients with type 2 diabetes on program hemodialysis still remain unexplored.[7]

In recent years, it can be observed in Uzbekistan that the number of patients with type 2 diabetes and DN increased significantly between 2010 and 2019. It should also be noted that in the next 10 years, the incidence rate in some regions of our country - Kashkadarya, Bukhara, Namangan, Jizzakh, Surkhandarya regions increased by 200%, and the highest rate (286%) in the city of Tashkent. Kadirova I.A., Mindubaeva F.A. in their studies, they observed that changes in the nervous system in patients with stage V CKD largely determine their fate and cause disability and death. Eralina S.N., Ismailov E.L. in their conclusions studied various neurological complications arising from the use of programmed hemodialysis in patients with end-stage CKD.[8]

In particular, today the problem of early detection and treatment of diabetic nephropathy and CKD, which developed as a result of diabetes mellitus, remains relevant, despite the fact that it has been studied by a number of scientists. Based on the foregoing, improving the treatment of various neurological complications arising from the use of program hemodialysis (PGD) is considered an important problem in modern medicine.[9]

The above discussed issues were the reasons for the present study.

Purpose of the study: to assess the risk of developing cerebrovascular complications in patients with type 2 diabetes mellitus on program hemodialysis

Material and research methods

The clinical material of the study was 150 patients with type 2 diabetes with DN and CKD V stage, examined and treated in RSNPMC Endocrinology M3 RUz from 2000 to 2022, who were on program hemodialysis.The duration of CKD ranged from 1 year of life to 15 years.

Of these, there were 55 women and 95 men. The average age of men was 67 ± 4.2 years, and the average age of women was 64 ± 5.6 years. 20 patients of the corresponding age made up the control group. The number of hemodialysis sessions in patients varied from 2x to 162.

Table 1 shows the distribution of examined patients by sex and age.

As can be seen from Table 1, men and women in most cases made up the age group from 45 to 74 years - 72/44 patients, respectively.

Table 1 Distribution of patients by sex and age (WHO, 2017)

Age, years	Number of men	Number of women
18-44 (young age)	15 (15.8%)	6 (10.8%)
45-59 (average age)	52 (54.7%)	30(54.5%)
60-74 (old age)	20 (21.0%)	14(25.4%)
75 and older (senile age)	8 (8.4%)	5 (9.0%)
Total: n = 150	95 (63.3%)	55(36.7%)

According to the degree of chronic cerebral ischemia (CCI), the patients were divided into 3 groups: 1gr. – 50 (33.3%) patients with diabetic nephropathy, stage 5 CKD with stage 1 CI; 2 gr. – 50 (33.3%) patients with diabetic nephropathy, stage 5 CKD with stage 2 CI; 3 gr. - 50 (33.3%) patients with diabetic nephropathy, stage 5 CKD with stage 3 CCI. The control group consisted of 20 persons with CKD 1-2 st.

Inclusion Criteria: patients with type 2 diabetes who were on program hemodialysis with CKD stage V.

Exclusion Criteria: pregnant women, children and young people with type 1 diabetes, oncology, stage 1-4 CKD, autoimmune thyroiditis (hypothyroidism).

We conducted a study of patients according to the generally accepted scheme, starting with complaints, an anamnesis of the disease, data on objective, endocrine, neurological, ophthalmological statuses.

The diagnosis of type 2 diabetes mellitus and CKD stage was established on the basis of standard clinical indicators (complaints, anamnesis data, severity and time of development of endocrinological symptoms, examination different bottom, etc.), research (general blood test, biochemical blood parameters), as well as paraclinical methods (ECG, Dopplerography of the main arteries of the head, MRI of the brain), etc.

Biochemical methods of blood analysis included the determination of fasting blood sugar, glycemic profile, electrolytes, lipid spectrum, coagulogram, urea, creatinine, glucose, glycated hemoglobin, O AK and determined the presence of MAU. In addition, we have studied in patients the content of neuromarkers in the blood S-100, NSE and BDNF.

The quality of life was assessed using 3 scales: according to the WHO Qol-BREF questionnaire, the MMSE test and the Hamilton anxiety scale.

Results

Complaints of a cerebrovascular nature (headaches, dizziness, noise in the head, memory loss, sleep disturbance) - most often encountered in group 3 patients with chronic cerebral ischemia 3 degrees.

Hereditary burden was observed in 14 (9.3%) cases and 150. The duration of hypertension prevailed in patients of the 3rd group, reaching 14.8 ± 5.2 years. The duration of CCI ranged from 8.5 ± 1.2 in the first group to 28.8 ± 6.8 months in the 3rd group of patients. ($p < 0.005$). The duration of type 2 diabetes also dominated in group 3 compared to group 1, reaching 26.5 ± 4.1 years ($p < 0.005$). Such anthropometric indicators as BMI and WC were unsignificantly increased in the 3rd group of patients ($p > 0.005$). The average data of biochemical parameters (glycated hemoglobin, hyperdyslipidemia) were also significantly higher in the 3rd group of patients ($p < 0.005$). AH was also significantly higher in the 3rd group of patients ($p < 0.005$).

The reliability of differences between the data of biochemical parameters of blood in the groups in comparison with the control was established. At the same time, the average values of creatinine and urea were especially significantly increased in patients in group 3 ($p < 0.001$, $p < 0.001$, $p < 0.05$.). The levels of total protein were also the most reduced in the 3rd group of patients ($p < 0.001$).

Table 2 gives a comparative analysis of the content of brain-derived neurotrophic growth factor (BDNF) in the serum of patients in the compared groups. As shown in Table 1, serum levels of BDNF in the groups of patients with type 2 diabetes significantly decrease in comparison with the control group as the degree of CCI increases.

The next step was to study the content of S100, NSE in groups. Tables 3 and 4 present the comparative results by groups.

As can be seen from the data in Table 3, in groups 1 and 2, there were no significant differences in the content of S100B in the blood in comparison with the control ($p > 0.05$), while in group 3 these differences were observed to be significant. S100b was significantly higher in these patients ($p < 0.05$). An increase in the level of S100b in group 3 patients highlights the presence of brain damage in this group and is a poor prognostic criterion.

As can be seen from the data in Table 4, in groups 2 and 3, significant differences were found in the content of NSE in the blood ($p < 0.05$) compared to control: values tended to increase as the degree of CCI increased. An increase in the NSE marker in groups 2 and 3 also indicates damage to brain neurons in these patients.

Doppler ultrasound (USDG) was used to assess the main blood flow in the common carotid arteries (CCA), middle cerebral arteries (MCA) and posterior cerebral arteries (PCA).

Next, we examined the results of ultrasound examination of the vessels of the head in 3 groups. Revealed a significant decrease in the parameters of USDG mainly in the 3rd group of patients before

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treatment ($p < 0.05$). Significant changes in the pulse index, narrowing of the vessel diameter by 2.8 times, and a decrease in blood flow velocity were revealed. At the same time, thickening of the vessel wall along the common carotid, internal carotid and vertebral arteries were observed in all groups.

Magnetic resonance imaging (MRI) was performed to assess the presence and severity (scale of age-related white matter changes) of white matter lesions (WWH) and lacunae. Studies have shown that microvascular disease in type 2 DM, which manifests as white matter abnormalities on MRI, is associated with reduced cerebral blood flow velocity, increased resistance in the middle cerebral arteries, and inflammation.

MRI of the brain revealed such changes as atrophy of the cerebral cortex (12 (36.3%) observations out of 33), white matter hyperintensity (7 (21.2%) observations out of 33), intracranial hypertension (11 (33.3%) %) of observations out of 33). In 5 (15.1%) cases, the norm was revealed. Foci of demyelination, periventricular leukoaraiosis, foci of chronic ischemia (indications of previous transient ischemic attacks or acute cerebrovascular accident were detected in 8 (67%) out of 12 patients of group 3.

The correlation analysis of the studied parameters revealed that the level of BDNF in the blood statistically significantly correlated with glycated hemoglobin ($r = 0.68$; $p < 0.001$) with blood creatinine ($r = 0.71$; $p < 0.001$), with eCKF ($r = 0\ .66$; $p < 0.001$), with albumin/creatinine ($r = 0.56$; $p < 0.001$). A significant positive correlation was also found with the levels of neuromarkers: S100b ($r = 0.48$; $p < 0.001$), ($r = 0.59$; $p < 0.001$).

In addition, a significant positive moderate correlation was established between blood BDNF, CRP, albuminuria, and alkaline phosphatase ($r = 0.36$, $p < 0.01$, $r = 0.30$, $p < 0.01$, $r = 0, 29$, $p < 0.01$).

It was found that in patients with type 2 diabetes with DN and CKD, stage V. with albuminuria, reduced eGFR, hyperlipidemia, increased creatinine, uric acid in the blood, decreased cognitive function, changes in MRI of the brain and Dopplerography of the main arteries of the head, there is a significant decrease in the concentration of BDNF, and a significant increase in S100b, NSE in the blood, which indicates the need carrying out preventive measures to prevent the development of cerebrovascular disorders.

Table 5 shows the average scores of the three questionnaires used in patients with type 2 diabetes by group.

Our studies showed that in patients with DM 2, depending on the degree of CCI, the data on 3 questionnaires significantly differed from the control group (healthy individuals) when assessing 4 indicators of the WHO QoL-BREF, the MMSE Test, and the Hamilton Depression Scale. This indicated a decrease in criticism of one's own health and the presence of low self-esteem in general on the WHOQoL-BREF questionnaire.

When determining the degree of depression on the Hamilton scale, it was found that in these patients, as the degree of CCI increased, so did the degree of depression.

As for the MMSE test, its results showed the presence of a decrease in cognitive functions at the level of mild dementia in group 1 and severe dementia in group 3 patients.

The next stage of our work was the assessment of the degree of conditionality and the etiological proportion of risk factors for mortality and developed a scale for the degree of conditionality and the etiological share of risk factors for mortality in CKD stage 5 (table 6).

Table 2 Comparative analysis of the content of brain-derived neurotrophic growth factor (BDNF) in the serum of patients of the compared groups

Index	Control group n=20	1 group n=36	2 group n=32	3 group n=22	p-value
BDNF, ng/ml	2.1 ± 0.23	0.8 ± 0.04**	0.5 ± 0.09**	0.2 ± 0.06**	0.001

Note: normal BDNF is from 1.5 to 2.4 ng/ml

Table 3 Average S100 content μg/l in the blood of patients by groups

Groups				R		
1 gr n = 36	2 gr n = 32	3 gr n = 22	Control (n = 20)	p1	p2	p3
0.07 ± 0.005	0.09 ± 0.008	0.3 ± 0.06*	0.02 ± 0.009 μg/l	> 0.05	> 0.001	< 0.005

Note: p1 - significance of differences between 1 g and control, p2 - significance of differences between 2 g and control, p 3 - significance of differences between 3 g and control

Table 4 Average values of NSE content (ng/ml) in the blood of patients by groups

Groups				R		
1 gr n = 36	2 gr n = 32	3 gr n = 22	Control (n = 20)	P1	P2	P3
8.9 ± 0.05	18.4 ± 1.9	22.1 ± 4.6	9.01 ± 0.09	> 0.05	< 0.05	< 0.05

Note: p1 - significance of differences between 1 g and control, p2 - significance of differences between 2 g and control, p 3 - significance of differences between 3 g and control. The range of determinations is 0 – 16 ng/ml.

Table 5 Mean scores of the questionnaires used in patients depending on the degree of chronic cerebral ischemia

No. gr	Total	WHO QoL-BREF				Test MMSE	Hamilton Depression Scale
		1	2	3	4		
1	n = 50	19 ± 2.3*	22 ± 3.2	11 ± 0.6	33 ± 5.7*	23 ± 1.4	11 ± 0.2
2	n = 50	13 ± 3.5*	14 ± 1.2*	8 ± 0.7*	34 ± 3.9*	19 ± 1.7*	18 ± 1.4*
3	n = 50	12 ± 1.2*	10 ± 0.5*	4 ± 0.2*	15 ± 0.2*	9 ± 1.2*	25 ± 1.6*
Control							
2	n = 20	50 ± 7.6	46±4.2	39±0.6	58±5.7	30±1.2	3±0.4

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Table 6 The scale of the degree of risk factors for mortality in DM2 with CKD 5 tbsp

Degree of conditioning	OR range	Factors
High	**> 3.0**	GFR less than 15 ml/min, reduced BDNF level to 0.2-0.3 ng/ml, increase in S100B from 0.3 and > μg/l, increase in NSE more than 22 ng / ml, decrease in the thickness of the intima media MAH, increased urea, creatinine, low urine density, albuminuria, increased AU / Cr, low HDL, elevated triglycerides, hyperglycemia, increased cholesterol level, stroke, heart attack, Charcot foot, blindness, Hamilton scale score over 23 points, MMSE score below 10 points, WHOQol-BREF score below 30 points
Medium	**2.0-3.0**	GFR less than 25 ml / min, hyperglycemia, elevated urea, creatinine, elevated cholesterol levels; reduced level of BDNF 0.4 -0.7 ng/ml, increased S100B0.1-0.2μg/l, increase in NSE from 15 to 21 ng / ml, the sum of points on the Hamilton scale from 14 to 22 points, the sum of points on the MMSE test from 10 to 20 points, the sum of points on the WHOQol-BREF questionnaire from 30 to 49 points
Low	**1.5-2.0**	GFR 25 to 45 ml/min; increased urea, creatinine, decreased BDNF from 0.8 to 0.9 ng/ml, increased S100B from 0.08 to 0.09 μg/l, an increase in NSE from 8 to 14 ng / ml, the sum of points on the Hamilton scale from 0 to 13 points, the sum of points on the MMSE test is more than 25 points, the sum of points on the WHOQol-BREF questionnaire is less than 50 to 80 points

Note: MA, main arteries of the head; AU, albuminuria; Cr, creatinine; GFR, glomerular filtration rate.

Thus, the developed scale of the degree of conditionality and the etiological proportion of risk factors for mortality made it possible to identify factors by 3 degrees, allowing to develop a set of measures for the prevention of complications and a decrease in the incidence of deaths.

Figure 1 shows the risk assessment of cerebrovascular complications developed by us in patients with DM2 on program hemodialysis.

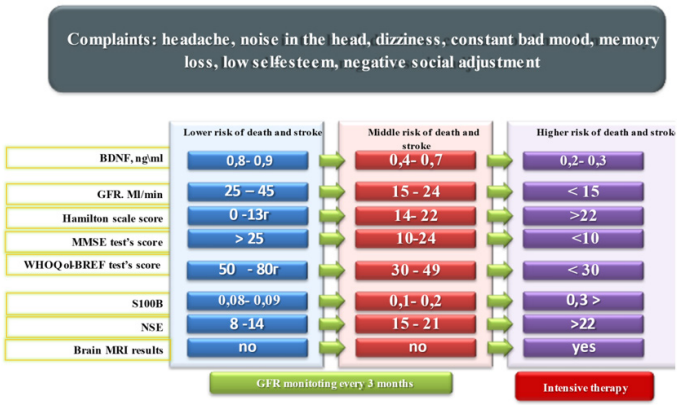

Figure 1 Assessment of the risk of developing cerebrovascular complications in patients with type 2 diabetes mellitus on program hemodialysis.

Conclusion

1. A direct correlation was found with the level of fasting glycemia, glycated hemoglobin, BDNF, S100B, NSE in the blood with the duration of the disease, blood flow velocity in the carotid artery, in the vertebral artery. In the 2nd and 3rd groups of patients, a direct correlation was found with the quality of life indicators according to 3 questionnaires - WHOQoL-BREF, the MMSE test and the Hamilton Depression Scale.
2. A reliable prognostic value was established for assessing the serum levels of BDNF, S100B, NSE in the groups of patients with type 2 diabetes and CKD stage V both before and during program hemodialysis in order to determine the risk of developing cerebrovascular complications.
3. Comprehensive assessment of the quality of life of patients with DM2 and CKD stage V using scales WHOQoL-BREF, Hamilton and MMSE have a high predictive value of the risk of developing cerebrovascular complications.

Acknowledgments

None.

Conflicts of Interest

None.

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