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Possibilities of therapeutic intervention in non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus: role of SGLT-2-inhibitors

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Republican Specialized Scientific-and-Practical Medical Centre of Endocrinology named after Academician Ya.Kh.Turakulov under the Ministry of Health of the Republic of Uzbekistan.

Aim of studying the efficacy of the SGLT-2 inhibitor empagliflozin (Jardins, Boehringer Ingelheim International GmbH) at a daily dose of 25 mg for 12 weeks on liver function in patients with type 2 diabetes and NAFLD.
Material and methods: 33 patients were observed, of which 64% were men, 36% were women. The average age of the surveyed was 51.9 ± 8.0 years, the average experience of diabetes mellitus was 6.9 ± 2.3 years. All patients received monotherapy with metformin at an average dose of 1909 ± 140.0 mg per day, statins and antihypertensive therapy, in which one of the drugs was an ACE inhibitor.
Results: Liver function while taking empagliflozin. The coefficient of steatosis decreased by 16.3 (95% CI 15.6-16.9), fibrosis - by 0.99 (95% CI 0.94-1.03). At the same time, a significant decrease in the calculated data on the FIB-4 and NAFLD scales is also shown. The average decrease in fasting glycemia after 12 weeks of taking empagliflozin was 2.1 mmol / L (95% CI 2.0-2.19), postprandial glycemia decreased by 2.3 mmol / L (95% CI 2.18-2.43), НвА1с - by 1.38% (95% CI 1.34-1.43).
Conclusion: The therapeutic options for the treatment of NAFLD are aimed at various mechanisms of pathogenesis, and the use of SGLT2 inhibitors seems to be one of the effective and pathogenetically justified methods of treating NAFLD in patients with type 2 diabetes.

Keywords: type 2 diabetes mellitus, non-alcoholic fatty liver disease, sodium glucose co-transporter 2, non-alcoholic steatosis

Introduction. The urgency of the problem of non-alcoholic fatty liver disease (NAFLD) is in the significant acceleration in the increase in the prevalence of this pathology among the population around the world. This phenomenon accompanies an

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increase in the prevalence of obesity, in particular, abdominal one, and type 2 diabetes mellitus [1,2].

NAFLD and diabetes mellitus are mutually aggravating diseases that require a sensitive diagnostic vigilance from doctors, since the timing of non-alcoholic transformation of steatohepatitis (NASH) into liver cirrhosis and hepatocellular carcinoma is reduced to 6 years [3,4], while the stage of moderate severe fibrosis can be reversed [5,6].

Screening for NAFLD is recommended in patients at high risk for cardiovascular disease [7,8]. And since patients with type 2 diabetes are classified as individuals with a high and very high risk of cardiovascular disease, early detection of NAFLD in patients with type 2 diabetes is essential.

Currently, non-pharmacological interventions such as weight loss, low-carbohydrate diet, increased physical activity and optimal control of diabetes mellitus are in the first place in the standards of treatment for NAFLD [9].

Of the pharmacological preparations, vitamin E and pioglitazone have the most convincing evidence base; studies are ongoing on GLP-1 receptor agonists. However, the effectiveness of vitamin E was showed in patients with NASH without diabetes; there is insufficient data on its use in patients with diabetes and cirrhosis. In addition, potential adverse events with vitamin E supplementation are bleeding and hemorrhagic stroke, prostate cancer, and increased overall mortality with high doses of the vitamin [10,11].

The use of pioglitazone is associated with weight gain, fluid retention, and this drug is contraindicated to patients with congestive heart failure and decreased bone mass [12].

Studies are being conducted on the use of a number of other drugs for the treatment of NASH: PPARα/PPARδ agonists, thyroid hormone-receptor agonists,

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chemokine receptor 2 / chemokine receptor 5 antagonists, farnesoid X receptor agonists. These studies are in phases 2 and 3. From a practical point of view, it is interesting to study the effect of drugs used to treat type 2 diabetes, with proven cardiovascular safety, in particular, SGLT2 inhibitors, on the course of NAFLD.

Sodium glucose co-transporter 2 (SGLT2) is produced in large quantities in the proximal tubule cells of the renal nephrons. This protein is required for the reabsorption of glucose filtered into the primary urine [13]. In addition to the kidneys, SGLT2 is found in the alpha cells of the islets of the pancreas [14]. SGLT2 inhibitors lead to excretion of glucose in the urine, increase osmotic diuresis, reduce body weight, including fat mass, lower blood pressure, and improve glycemic control [15]. Cardio- and renoprotective effect of a number of drugs of this group is also shown [16,17]. In the literature, there is more and more data arising on the effectiveness of drugs in this group in the treatment of NAFLD in patients with type 2 diabetes. Therefore, we set ourselves the goal of studying the efficacy of the SGLT-2 inhibitor empagliflozin (Jardins, Boehringer Ingelheim International GmbH) at a daily dose of 25 mg for 12 weeks on liver function in patients with type 2 diabetes and NAFLD.

Materials and methods.

We conducted a prospective study of patients with type 2 diabetes and NAFLD who were inpatient at the republican Specialized Scientific-and-Practical Medical Centre of Endocrinology in 2019, followed by outpatient follow-up. Inclusion criteria were the presence of diagnosed type 2 diabetes, the absence of achieving target glycemia on metformin monotherapy, and the presence of confirmed NAFLD.

The exclusion criteria were the presence of chronic kidney disease (C3A2 and higher), the presence of a urinary tract infection, acute complications of diabetes mellitus, and the presence of cardiovascular accidents at the time of hospitalization.

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All patients underwent determination of anthropometric indicators: measurement of height on a stadiometer in a standing position, weight measurement on a floor scale, with the calculation of body mass index (BMI) according to the formula: BMI = weight (kg) / height^2 (m^2). Heart rate (HR) was measured at rest after at least 15 minutes sitting, twice for a minute. The arithmetic mean was recorded. Blood pressure was measured with a hand-held tonometer according to the Korotkov method in a sitting position at rest twice. The arithmetic mean was recorded. Glycemia was determined on an automatic biochemical analyzer BS-380 "Mindray" by the glucose oxidase method in venous blood at fasting state and 2 hours after breakfast using HUMAN "Glucose" reagents (Germany). Glycated hemoglobin was determined by the HbA1c analyzer (automatic machine) Huma Nex A1c with HUMAN reagents (Germany). Liver enzymes were determined on an automatic biochemical analyzer BS-380 "Mindray" by the kinetic method using "ASAT", "ALAT" HUMAN reagents (Germany). Thrombocyte counting was carried out on an automatic hematology analyzer VS-5800. Blood albumin was determined on an automatic biochemical analyzer BS-380 "Mindray" using the "Albumin" HUMAN reagent (Germany).

The HOMA-IR index was calculated using the formula HOMA-IR = fasting glycemia (mmol/L) * fasting insulin (pg/mL)/22.4.

The diagnosis of NAS and NASH was made on the basis of ultrasound of the liver in the presence of: diffuse hyperechoicity of the liver parenchyma and heterogeneity of its structure; fuzziness and / or accentuation of the vascular pattern; distal attenuation of the echo signal. The steatosis coefficient (S, db/m) according to the controlled parameter of ultrasound attenuation and the fibrosis coefficient (F, kPa) were recorded according to the results of elastography on a Fibroscan 502 TOUCH F60276 apparatus before and after 12 weeks of taking the drug [18].

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All patients were calculated on the FIB-4 scale using the formula:

FIB-4 = age * AST / platelets (10^9 / L) * √ALT

In this case, the result of 0-2 was regarded as mild fibrosis, from 3 to 4 - moderate fibrosis, 5-6 - severe fibrosis / cirrhosis.

Also, all patients were calculated using the NAFLD fibrosis score using the formula:

NAFLD Score = -1.675 + 0.037 × age (years) + 0.094 × BMI (kg / m^2) + 1.13 × IGT / DM (yes = 1, no = 0) + 0.99 × AST / ALT - 0.013 × Platelets (× 10^9 / L) - 0.66 × Albumin (g / dl).

The assessment of the presence of fibrosis was carried out as follows:

A score of less than -1.455 was regarded as the absence of significant fibrosis (F0-F2);

A score above 0.675 was considered significant fibrosis (F3-F4);

Intermediate scores (from -1.455 to 0.675) were regarded as F2-F3.

Statistical processing of the results was carried out using Microsoft Excel 2013 and SPSS (version 23). Values are presented as arithmetic mean ± standard deviation. The reliability of the indicators was assessed at $p < 0.05$. To compare the indicators before and after the start of therapy, the t-test for paired samples with a CI of 95% was used with the calculation of two-tailed significance.

Results and discussion.

In total, 33 patients were observed, of which 64% were men, 36% were women. The average age of the surveyed was 51.9 ± 8.0 years, the average experience of diabetes mellitus was 6.9 ± 2.3 years. All patients received monotherapy with metformin at an average dose of 1909 ± 140.0 mg per day, statins and antihypertensive therapy, in which one of the drugs was an ACE inhibitor. The initial

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anthropometric and laboratory-instrumental characteristics of patients are presented in Table 1.

Tab. 1. Anthropometric and laboratory-instrumental characteristics of patients at baseline and after 12 weeks of therapy.

№	Characteriscits (units)	Baseline		In 12 weeks after treatment started		P (two-tailed)
		Mean	SD	Mean	SD	
1	Weight (kg)	88.1	14.8	83.8	12.4	<0.001
2	BMI (kg/m^2)	30.1	4.0	28.7	3.4	<0.001
3	Waist circumference (sm)	91.1	11.3	88.1	10.4	<0.001
4	Hips circumference (sm)	96.0	11.1	94.9	10.6	<0.001
5	SBP (mm Hg)	132.6	18.1	122.4	11.5	<0.001
6	DBP (mm Hg)	84.5	9.2	76.6	7.0	<0.001
7	Heart rate (bpm)	80.9	8.7	75.0	5.9	<0.001
8	Fasting glycemia (mmol/L)	9.4	3.1	7.3	1.5	<0.001
9	Postprandial glycemia (mmol/L)	11.3	3.3	8.9	1.2	<0.001
10	HbA1c (%)	9.2	1.5ë	7.8	0.9	<0.001
11	Haemoglobin (g/L)	133.2	14.3	133.3	8.6	=0.575
12	Platelets (*10^9/L)	263.9	75.6	265.8	55.8	=0.001
13	ALT (U/L)	38.2	24.1	30.1	13.2	<0.001
14	AST (U/L)	29.9	16.1	25.7	10.3	<0.001

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15	GGT (U/L)	53.3	33.3	44.8	26.9	<0.001
16	Total cholesterol (mmol/L)	4.9	1.3	4.5	0.9	<0.001
17	Triglycerides (mmol/L)	2.7	1.6	2.3	1.1	<0.001
18	HDL (mmol/L)	1.11	0.62	1.17	0.52	<0.001
19	LDL (mmol/L)	2.30	0.92	2.08	0.82	<0.001
20	VLDL (mmol/L)	1.32	0.8	1.17	0.67	<0.001
21	Alkaline phosphatase (U/L)	259.2	69.3	253.7	70.7	<0.001
22	Creatinine (μmol/L)	82.4	20.4	75.9	16.3	<0.001
23	eGFR (mL/min/1.73m^2)	86.3	17.2	91.6	16.1	<0.001
24	Ferritin (pg/mL)	246.3	153.2	214.5	128.0	<0.001
25	CRP (U)	5.6	2.8	3.5	1.8	<0.001
26	Fibrinogen (g/L)	3.3	0.8	2.7	0.6	<0.001
27	Interleukin-6 (pg/mL)	8.1	5.4	5.6	3.8	<0.001
28	HOMA-IR	8.4	4.7	5.5	2.2	<0.001
29	Steatosis coefficient (S) according to elastography, dB/m	304.7	42.8	288.4	43.5	<0.001
30	Fibrosis coefficient (F) according to elastography, kPa	8.5	2.8	7.5	2.3	<0.001
31	FIB-4 score results	1.1	0.57	0.99	0.36	<0.001
32	NAFLD score results	-0.97	1.07	-1.20	0.83	<0.001

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As one can see from Table 1, the patients examined by us had several components of the metabolic syndrome. 92% of patients were overweight or obese. All patients were on antihypertensive drugs, but 15% of patients did not reach target blood pressure levels. The HbA1c was higher than the target values (7%) in 88% of patients, 82% had fasting glycemia above 6.1 mmol/L, and in 58% postprandial glycemia exceeded 10.0 mmol/L.

Liver enzymes were slightly increased or corresponded to the upper limit of the reference range. The lipid spectrum corresponded to atherogenic dyslipidemia.

Such indicators of inflammation as CRP, interleukin-6, and fibrinogen were moderately increased. The average ferritin level was 246.3 pg/mL.

The high level of the HOMA-IR index in patients (8.4±4.7) deserves attention, which corresponds to the literature data and is fully explained by the role of steatosis in the formation and maintenance of insulin resistance in the liver and other tissues. The coefficients of steatosis and fibrosis corresponded to non-alcoholic steatosis in 32 patients and steatohepatitis in one patient, which was confirmed by the data on the FIB-4 and NAFLD scales.

Table 2. Dynamics of indicators on the background of daily intake of 25 mg of the SGLT-2 inhibitor empagliflozin for 12 weeks.

Paired Samples Criterion								
	Paired differences							
Characteriscits (units)	Mean	Mean square deviation	Average error of mean	95% confidence interval for difference		T	degrees of freedom	P (two-tailed)
				Lower	Upper			
Weight (kg)	4.3047	3.1355	.0757	4.1562	4.4532	56.855	1714	.000
BMI (kg/m^2)	1.4362	.9924	.0240	1.3892	1.4832	59.933	1714	.000
Waist circumference (sm)	2.954	2.011	.060	2.837	3.072	49.171	1119	.000

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Hips circumference (sm)	1.018	2.074	.075	.871	1.165	13.605	767	.000
SBP (mm Hg)	10.248	9.019	.218	9.821	10.675	47.055	1714	.000
DBP (mm Hg)	7.878	5.373	.130	7.623	8.132	60.721	1714	.000
Heart rate (bpm)	5.892	7.080	.171	5.557	6.227	34.465	1714	.000
Fasting glycemia (mmol/L)	2.1017	2.0212	.0488	2.0060	2.1975	43.062	1714	.000
Postprandial glycemia (mmol/L)	2.3065	2.5765	.0622	2.1844	2.4285	37.072	1714	.000
HbA1c (%)	1.3827	.9198	.0222	1.3392	1.4263	62.259	1714	.000
Haemoglobin (g/L)	-.143	7.068	.255	-.644	.357	-.562	767	.575
Platelets (*10^9/L)	-1.940	24.957	.603	-3.122	-.758	-3.219	1714	.001
ALT (U/L)	8.111	12.508	.302	7.518	8.703	26.854	1714	.000
AST (U/L)	4.224	8.645	.209	3.814	4.633	20.233	1714	.000
GGT (U/L)	8.511	9.042	.218	8.083	8.940	38.981	1714	.000
Total cholesterol (mmol/L)	1.0445	.4579	.0116	1.0217	1.0674	89.773	1548	.000
Triglycerides (mmol/L)	2.1732	.9447	.0240	2.1261	2.2203	90.536	1548	.000
HDL (mmol/L)	-.46453	.15963	.00406	-.47249	-.45658	-114.529	1548	.000
LDL (mmol/L)	.56908	.53167	.01351	.54259	.59558	42.127	1548	.000
VLDL (mmol/L)	.27846	.32444	.00824	.26229	.29463	33.780	1548	.000
Alkaline phosphatase (U/L)	26.455	35.766	.864	24.761	28.149	30.632	1714	.000
Creatinine (μmol/L)	6.4017	8.0553	.1945	6.0202	6.7833	32.912	1714	.000
eGFR (mL/min/1.73m^2)	-5.327	7.796	.188	-5.696	-4.957	-28.294	1714	.000
Ferritin (pg/mL)	31.7369	34.7824	.8399	30.0896	33.3843	37.787	1714	.000
CRP (U)	2.1242	1.5949	.0385	2.0487	2.1997	55.155	1714	.000
Fibrinogen (g/L)	.5843	.4932	.0119	.5610	.6077	49.058	1714	.000
Interleukin-6 (pg/mL)	2.4767	2.4338	.0588	2.3615	2.5920	42.143	1714	.000
Insulin (ng/mL)	3.0315	4.6215	0.116	2.8127	3.2504	27.165	1714	.000
HOMA-IR	2.93424	3.05155	.07369	2.78972	3.07877	39.821	1714	.000
Steatosis coefficient (S) according to elastography, dB/m	16.253	13.305	.321	15.623	16.883	50.588	1714	.000

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Fibrosis coefficient (F) according to elastography, kPa	.9886	.9455	.0228	.9438	1.0334	43.299	1714	.000
FIB-4 score results	.1124289 5	.307752 76	.00743 139	.097853 41	.127004 49	15.129	1714	.000
NAFLD score results	.2319776 3	.452054 54	.01091 588	.210567 78	.253387 48	21.251	1714	.000

Dynamics of anthropometric indicators.

After 12 weeks of empagliflozin therapy, there was an average weight loss of 4.3 kg (95% CI: 4.15-4.45). At the same time, the number of people with normal BMI increased due to a decrease in the number of people with obesity of 1 and 3 degrees. Also, there was a significant decrease in waist circuference by 2.9 cm (95% CI: 2.8-3.07) and in hips circumference by 1.0 cm (95% CI 0.87-1.17).

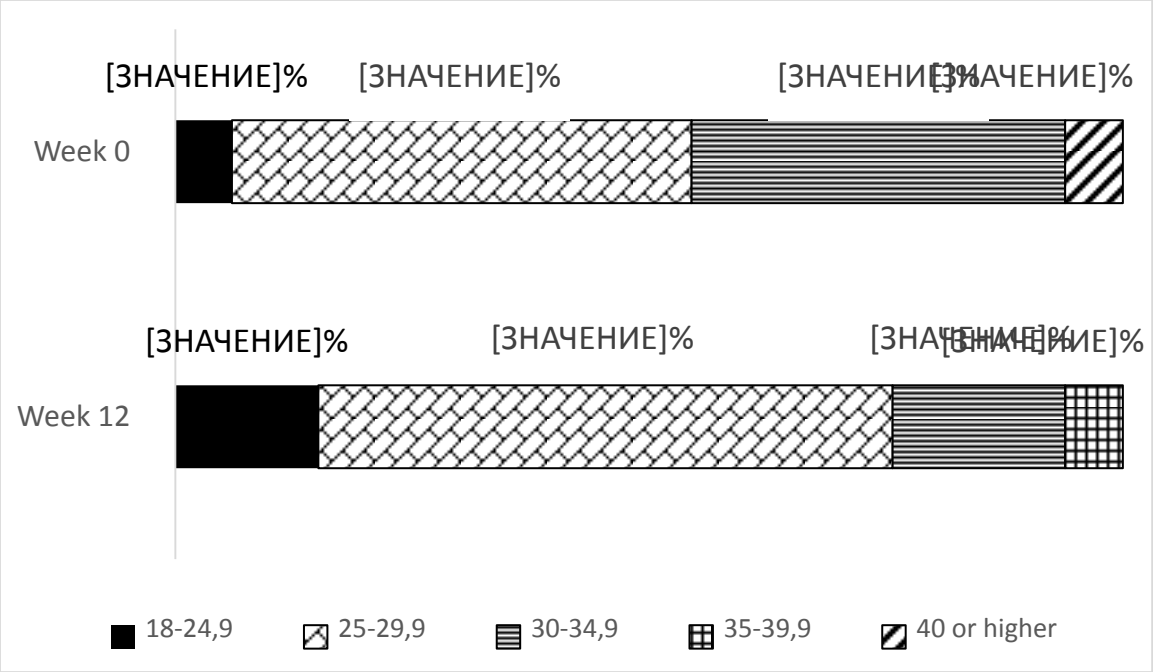

Fig. 1. ***Distribution of body weight categories (normal weight, overweight, obesity 1, 2 and 3 degrees) according to BMI among patients (in% of the number of patients) before and after 12 weeks of taking empagliflozin.***

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Dynamics of blood pressure and heart rate while receiving empagliflozin.

By the 12th week of taking empagliflozin, there was a decrease in systolic blood pressure (SBP) by an average of 10.2 mm Hg. (95% CI 9.8-10.7), diastolic - by 7.9 (95% CI 7.6-8.1) and heart rate by 5.9 beats per minute (95% CI 5.6-6.2). At the same time, 15% of patients did not reach target blood pressure levels before the initiation of SGLT2 inhibitor in therapy, and after 12 weeks from the start of taking the drug, only 6% had blood pressure levels above the target.

Dynamics of glycemia while taking empagliflozin.

The average decrease in fasting glycemia after 12 weeks of taking empagliflozin was 2.1 mmol / L (95% CI 2.0-2.19), postprandial glycemia decreased by 2.3 mmol / L (95% CI 2.18-2.43), НвА1с - by 1.38% (95% CI 1.34-1.43). However, 76% of patients still did not reach the target HbA1c level below 7%, although at the beginning of follow-up 88% of patients were outside the target HbA1c range. From our point of view, it is important that over 12 weeks of taking empagliflozin, the number of people with a target level of postprandial glycemia increased from 58% to 79%. Achieving target fasting glycemic levels is more challenging, but in 9% of patients it was possible with SGLT2 inhibitor.

Dynamics of insulin resistance indicators.

Insulin levels decreased by 3.0 ng/mL (95% CI 2.8-3.2) after 12 weeks of taking SGLT2 inhibitor. However, we consider important a significant decrease in the NOMA-IR index - by 2.9 units (95% CI 2.8-3.1).

Liver function while taking empagliflozin.

After 12 weeks of taking an SGLT2 inhibitor, there was a decrease in the level of hepatic aminotransferases - ALT by 8.1 U/L (95% CI 7.5-8.7), AST by 4.2 U/L (95% CI 3.8-4.6), gamma-glutamyl transferase by 8.5 U/L (95% CI 8.1-8.9), alkaline phosphatase by 26.5 U/L (95% CI 24.8-28.1).

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The coefficient of steatosis decreased by 16.3 (95% CI 15.6-16.9), fibrosis - by 0.99 (95% CI 0.94-1.03). At the same time, a significant decrease in the calculated data on the FIB-4 and NAFLD scales is also shown.

Dynamics of indicators of inflammation.

The average decrease in ferritin levels by the end of the observation period was 31.7 U/L (95% CI 30.1-33.4), the level of C-reactive protein significantly decreased by 2.1 U/L (95% CI 2.0- 2.2), the fibrinogen level increased by 0.58 g/L (95% CI 0.56-0.61). Also, a significant decrease in the level of interleukin 6 by 2.48 units was obtained (95% CI 2.36-2.59).

Dynamics of lipid spectrum indicators.

Despite the fact that the doses of statins did not change, we observed a significant ($p<0.001$) decrease in total cholesterol levels by 1.04 mmol/L (95% CI 1.01-1.07), triglycerides by 2.17 mmol/L (95% CI 2.11-2.24), LDL by 0.57 mmol/L (95% CI 0.53-0.60), VLDL by 0.28 mmol/L (95% CI 0.26-0 , 30), as well as an increase in HDL levels by 0.46 mmol/L (95% CI 0.45-0.47).

Effect of empagliflozin on renal function.

By the end of the follow-up period, there was a significant ($p<0.001$) decrease in creatinine levels by 6.4 μmol/L (95% CI 6.0-6.8) and an increase in eGFR by 5.3 ml/min/1.73 m^2 (95% CI 4.9-5.7).

Of the side effects when using SGLT2 inhibitors, hypovolemia and euglycemic ketoacidosis are possible, probably associated with an increase in glucagon levels, which stimulates β-oxidation of fatty acids and the formation of ketone bodies by the liver [19,20].

In addition, there is a risk of developing urogenital infections, urosepsis and amputations with the use of some drugs in this group [15,21].

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There were no side effects such as hypovolemia, ketoacidosis, or urogenital infections while taking empagliflozin at a dose of 25 mg for 12 weeks.

Discussion of the results obtained.

Weight loss while taking SGLT2 inhibitors is described in the literature and is explained not only by the loss of extracellular fluid volume, but also by a decrease in visceral fat mass [22], which is confirmed by a significant decrease in waist, hip circumference and BMI in our study.

Even 3% weight loss is enough to reverse steatosis. In the case of balloon transformation of hepatocytes and signs of inflammation, weight loss of 5% or more is necessary. For the treatment of NASH, it is necessary to reduce weight by 7% or more, and in the case of fibrosis - by 10% or more from the baseline [23-25]. In our study, we observed a weight loss of 4.9% from baseline, which is significant for such a short observation period.

As for the absolute values, according to the literature, weight loss while taking SGLT2 inhibitors occurs on average by 3 kg. During the first 4 weeks of taking the drug, water and electrolytes are lost, and subsequently, weight loss occurs mainly due to fat mass [26]. Our results showed a significant weight loss of 4.3 kg, which is consistent with the literature.

When using SGLT2 inhibitors in patients with NAFLD, some increase in appetite is possible due to the loss of calories in the urine [27]. In our study, we did not observe an increase in appetite and an increase in the portion of food consumed.

As in the studies of other authors, in parallel with a decrease in glycemia, we observed a decrease in insulin levels, which significantly reduces the synthesis of fats in the liver de novo [19,20].

Interestingly, in the alpha cells of the pancreatic islets, SGLT2 decreases intracellular glucose, which is an important signal for glucagon release. Suppression

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of SGLT2 leads to an increase in glucagon secretion, which ultimately stimulates β-oxidation of fatty acids and causes a shift in metabolism from carbohydrate to fatty acid, which also reduces the content of triglycerides in the liver [19]. So, the main mechanism for reducing the fat content in the liver under the action of SGLT2 inhibitors is a decrease in de novo lipid synthesis by reducing the level of glycemia and insulin and an increase in beta-oxidation of fatty acids.

It turns out that if the number of glucagon receptors is reduced, this, on the one hand, leads to improved glycemic control in type 2 DM, and on the other hand, it significantly increases the ALT level and the fat content in the liver. Therefore, a potential mechanism for reducing the fat content in the liver under the influence of SGLT2 inhibitors may be precisely the effect by increasing the level of glucagon [28].

Another potential mechanism of action of SGLT2 inhibitors may be an increase in the metabolism of VLDL, but this fact has been shown in rats and has not yet been proven in humans [29]. In our study, we observed a significant decrease in the level of atherogenic fractions of the lipid spectrum and an increase in the level of HDL cholesterol within 12 weeks of taking empagliflozin.

Studies investigating the efficacy and safety of SGLT2 inhibitors in humans have shown a significant reduction in ALT levels [30]. Initially, this effect was associated with a decrease in body weight and the level of HbA1c [31]. However, further studies have shown that a decrease in the level of liver enzymes can occur regardless of changes in body weight [32]. In addition, it has been shown that weight loss with the use of SGLT2 inhibitors is not so significant and quickly reaches a plateau [15]. Therefore, it was suggested that the decrease in the level of liver enzymes is associated with the mechanisms described above [33].

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In a small study among 24 patients in whom, despite therapy with GLP-1 receptor agonists or DPP-4 inhibitors, increased ALT levels remained, the addition of SGLT2 inhibitors (in this study, ipragliflozin) led to a significant decrease in ALT levels and the results of calculations on the FIB-4 scale in about half of patients regardless of initial treatment [34].

In our work, the liver enzymes significantly decreased while taking empagliflozin, which also affected the dynamics of the calculated indicators of the FIB-4 and NAFLD scales.

A study that examined the potential effect of the SGLT2 inhibitor ipragliflozin on NAFLD in patients with type 2 diabetes showed that after 4 weeks of therapy, along with a decrease in the levels of glycemia, insulin, and the degree of insulin resistance, there was a decrease in the level of markers of inflammation and liver damage, in particular, tumor necrosis factor-alpha and interleukin 6 [35]. Similar results were shown for dapagliflozin - in patients with type 2 diabetes and NAFLD, a decrease in the level of markers of oxidative stress (myeloperoxidase and ROS) was shown [36].

Our results on the reduction of CRP, fibrinogen and interleukin-6 also suggest a decrease in inflammation and progression of fibrosis on the background of empagliflozin use.

The use of canagliflozin led to a decrease in the results of the FIB-4 index and the level of ferritin, a marker of liver oxidative stress, which suggests a decrease in the degree of liver fibrosis [37]. In our study, the ferritin level also significantly ($p<0.001$) decreased by 31.7 units.

In a study of the effect of dapagliflozin on the course of NAFLD in patients with type 2 diabetes, there was a decrease in the level of damage to hepatocytes and fibroblast growth factor 21 while taking dapagliflozin [38]. Since biopsy is the gold

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standard for the diagnosis of NAFLD, it would be reasonable to evaluate the histological changes while taking SGLT2 inhibitors. However, the invasiveness of this procedure limits its use in routine clinical practice. In our work, we did not determine fibroblast growth factor 21 and did not perform liver biopsy. However, Japanese researchers performed a series of liver biopsies on the background of canagliflozin use for 24 weeks. The authors showed a statistically significant improvement in the histological picture of NASH up to the disappearance of NAS signs (1 patient) and a shift to the initial histological changes (in 4 patients) [39].

The dynamics of creatinine and GFR levels in our study confirms the safety of the drug and some nephroprotective effect, which manifests itself within a sufficiently short observation period.

Thus, the therapeutic options for the treatment of NAFLD are aimed at various mechanisms of pathogenesis, and the use of SGLT2 inhibitors seems to be one of the effective and pathogenetically justified methods of treating NAFLD in patients with type 2 diabetes. We propose the use of SGLT2 inhibitors as the drug of choice in combination with therapeutic doses of metformin in the treatment of patients with type 2 diabetes and NAFLD.

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