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STUDY OF THE HYPOGLYCEMIC AND CARDIOPROTECTIVE EFFECT OF EMPAGLIFLOZIN IN THERAPY OF PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract:

The aim of our study was to study the hypoglycemic and cardioprotective effect of empagliflozin in patients with type 2 diabetes mellitus cardiovascular diseases.

Keywords: type 2 diabetes mellitus , atherosclerotic cardiovascular disease, sodium glucose cotransporter type inhibitors, empagliflozin

The prevalence of diabetes mellitus (DM) in the world is steadily increasing every year. According to the International Diabetes Federation (IDF), in 2021, about 537 million people had this disease, and according to forecasts, by 2045 this patient population is expected to increase to 783 million people [7]. Type 2 diabetes mellitus (DM2) is strongly associated with atherosclerotic cardiovascular disease (ASCVD) and is a risk factor for heart failure (HF); Patients with DM are hospitalized for HF 4 times more often than patients without impaired carbohydrate metabolism [2,3]. The consequences of delayed intervention are micro- and macrovascular complications. Real-world data suggest that patients with HbA1c ≥ 7.0% (as opposed to those with HbA1c <7.0%) in the absence of intensification of therapy within a year after diagnosis significantly increase the risk of myocardial infarction (67%), stroke (51%), heart failure (64%), combined cardiovascular outcomes (62%) at 5.3 years. This confirms the need for earlier intensification of treatment [4].

The progressive course and complications of DM2 (nephropathy, retinopathy, neuropathy, severe cardiovascular diseases), the high cost of treating DM2 and its complications determine not only the medical, but also the high social and economic significance of this disease and justify the search for new effective methods of treatment. Patients with type 2 diabetes have a high risk of developing heart failure and a high incidence of cardiovascular mortality, with every 1% increase in glycated hemoglobin in the >7.5% range accompanied by a 15% increase in the risk of developing heart failure. Since treatment with secretagogues and insulin is associated with an increase in body weight and an increased risk of hypoglycemic episodes, sodium-glucose cotransporter inhibitors began to take second place after metformin in the treatment of type 2 diabetes. type 2 (and SGLT2) , the effectiveness of which was similar to that obtained in controlled clinical trials [1,2,6,8,9].

At present, the appointment of pharmacological therapy for T2DM is not seen as a failure of dietary therapy, lifestyle changes, but is the key to successful multifactorial disease management.

On the the pharmaceutical market has another effective a group of oral hypoglycemic drugs – iNGLT-2.

The results of large randomized clinical trials have demonstrated the ability of a relatively new class of drugs - iSGLT-2 not to only effectively influence indicators of glycemic control, but and reduce frequency of adverse cardiovascular events and renal outcomes in patients with DM2 [9,10,11,12].

AT connection with this use of iSGLT-2 in daily clinical practice is of interest not only endocrinologists, but and at doctors of related specialties.

The mechanisms of renal reabsorption of glucose are currently receiving much attention. The main role in them belongs to the sodium-glucose cotransporter, encoded by the *SLC 5 A gene.* [four]. To date, 13 types of cotransporters of the SGLT family are known , the first two types of them have been studied in the most detail: SGLT- 1 and SGLT-2 having various functional features. This cotransporter has low affinity, but high capacity, it simultaneously and unidirectionally transfers sodium (Na+) and glucose in a ratio of 1:1. The sodium cation passing through the apical membrane of the epithelial cells of the proximal tubule creates an electrochemical gradient that allows glucose to passively enter the cell. With the help of SGLT- 2, about 90% of the filtered amount of glucose is reabsorbed by the end of the proximal convoluted tubule [5,7].

Natriuresis is the second most important effect of SGLT-2 and is directly associated with glucosuria, since each unreabsorbed glucose molecule leads to the

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excretion of a sodium cation. However, it can be assumed that natriuresis may be transient , since the activation of the renin-angiotensin- aldosterone system (RAAS) caused by it will contribute to a compensatory increase in sodium reabsorption downstream. After some time, the excretion of excess sodium induced by hyperglycemia will stop and a new one will be established - reduced relative to the initial balance of sodium in the body [5].

Active excretion of sodium and glucose - osmotically active agents increases diuresis, which is also a direct and even targeted effect of SGLT-2 , since patients with type 2 diabetes, as studies of the last decade have shown, have a higher sodium content and hypervolemia in the body than in a healthy population. The high point of application of their mechanism of action at the level of the proximal tubules of the nephron makes SGLT2 unique diuretics, devoid of the usual disadvantages of traditional diuretic drug groups. The expert community, when analyzing the results of the EMPA-REG OUTCOME study [14] , points to a decrease in circulating blood volume (CBV) as one of the key factors that determined the benefits for the cardiovascular system.

SGLT2 is particularly attractive due to its additional positive effect on body weight and blood pressure, as well as the possibility of using them in combination with other antidiabetic agents or as monotherapy in patients at any stage of T2DM. While most antihyperglycemic agents have little or no effect on CV risk reduction, some are associated with adverse effects on body weight and CV events, and SGLT2 have demonstrated robust glycemic control as mono- and combination therapy, and their the unique effects on the kidneys independent of insulin modulation provided additional metabolic benefits. Cardiac microvascular dysfunction contributes to the development of diabetic cardiovascular complications. Empagliflozin has cardioprotective effects that go beyond its hypoglycemic effect.

The aim of our study was to study the hypoglycemic and cardioprotective effect of empagliflozin in patients with type 2 diabetes mellitus cardiovascular diseases.

MATERIALS AND RESEARCH METHODS

The study involved 42 patients with type 2 diabetes mellitus and cardiovascular disease , including 21 women and 21 men, who sought advice from the 2nd therapy department at the multidisciplinary clinic of the Tashkent Medical Academy. The duration of the disease ranged from 3 to 8 years, the mean age was 56.6±9.8 years.

All examined patients had ASCVD, such as arterial hypertension (100%), coronary artery disease (28.5%). Most patients received micronized aspirin , B-blockers, ACE inhibitors, calcium antagonists , and 50% of them received statins, and not regularly. Most (60%) of them were on monotherapy ACE inhibitors , the rest on combination therapy, but many of them (80 %) did not reach the target levels of blood pressure. All patients were overweight - their body mass index (BMI) exceeded 25 kg/m^2. Obesity (BMI ≥30 kg/ m2) was registered in 32 (71.2 %) patients , overweight in 10 (28.8%) patients. The average waist circumference was 105.1±8.0 cm for men and 108.3±9.0 cm for women. The study included patients with unsatisfactory carbohydrate metabolism, while glycated hemoglobin (HbA 1 c) did not exceed 9%. Male smokers were not included in the study. The study included patients who were on monotherapy before the study. metformin (M) at a dose of 500 mg to 1500 mg per day . These patients were divided into 2 groups: group 1 - 18 patients, to metformin at a dose of 2000 mg / day , an oral hypoglycemic drug (PSSP) from the group of sulfonylurea drugs - gliclazide MB with a slow release at a dose of 60 mg / day was added , group 2 included In 24 patients, empagliflozin was added to metformin at a dose of 10 mg per day, if necessary, the dose was increased to 25 mg per day for 12 weeks. The control group consisted of 20 adults without DM, 5 (25%) of them had AH, comparable in age, 55.9±7.5 years.

Exclusion Criteria studies: previous myocardial revascularization, acute coronary syndrome, decompensation of chronic heart failure, exacerbation of concomitant pathology, decrease in glomerular filtration rate (GFR) less than 30 ml/min/1.73m2, age over 85 years on moment of inclusion in research, acute inflammatory processes or exacerbation of chronic inflammatory processes of the urinary system.

All patients underwent a general clinical examination, studied fasting and postprandial glycemia, glycated hemoglobin (HbA 1 c), blood lipid spectrum. From instrumental studies, studies of ECG, EchoCG , blood pressure were carried out . Blood glucose was examined by biochemical method (SPINREACT kits , S.A.U.) . The study of glycated hemoglobin (HbA1c) was carried out by the method of biochemistry (FILTERSAMPLER kits). EchoCG was filmed on the SSI - 6000 apparatus. Weight and height were also measured to calculate BMI. To identify safety, hepatic transaminases - AlT, AsT, as well as a general urine test were investigated .

At the beginning of the course of therapy and after 12 weeks, laboratory control was carried out, which included a study of blood biochemistry (blood

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glucose on an empty stomach and 2 hours after a meal, HbA 1 c), EchoCG (EF) and ECG.

Table 1.

Characteristics of the examined patients Indicator	Control n-20	Group 1 M+Gliclazide MB n -18	Group 2 M+Empagliflozin n-24
Men , n (%)	8(40 %)	5(28)	3 (12.5)
Women n(%)	12(60 %)	13(72%)	21 (87.5%)
Age, years	55.9±7.5	55.9±3.8	56.5±7.1
Body mass index, kg/m2	29.5±6.4	33.4±8.1	34.4±5.9
History of hypertension, n (%)	5 (25%)	18 (100%)	24 (100%)
Duration history of DM 2, years	-	5.5 (3.0 ; 8.0) _ _	4.5 (3.5 ; 8.0) _ _
GARDEN, mm Hg _	1 33 .5 ± 1 1 .3	157.2±13.5	157.7±14.3
DBP, mm Hg _	8 8.7 ± 5.8 _ _	98.1±7.4	98.34±7.6
Heart rate, bpm min	76.0±9.1	77.11±8.89	78.28±9.07
LVH, %	59.7 %	83.7%	89.5%
Angina pectoris FC I - II (n , %)	-	4 (9.5%)	8 (19.0)

As the data of Table 1 show, the examined patients have obesity of the 1st degree, 83.7% and 89.5% of the examined patients have left ventricular hypertrophy (LVH). LVH is regarded as the main predictor of cardiovascular mortality. The term " remodeling ", which replaced the concept of LVH, means the whole complex of changes that occur at various levels [11]

Analysis of carbohydrate metabolism data showed that all patients had unsatisfactory values of carbohydrate metabolism at admission. So, in 2 examined groups, there was an increase in carbohydrate metabolism compared to the control group, while fasting glycemia was increased by 52% and 54%, postprandial by 48% and 43% and HbA 1c by 37% and 39%, respectively. It should be noted that all these patients were on monotherapy prior to inclusion in the study. Also, patients had dyslipidemia with an increase in TC, triglycerides, LDL and a decrease in HDL. It is known that poor glycemic control and dyslipidemia are important risk factors for the development of cardiovascular diseases in patients with type 2 diabetes [10].

Table 2.

Biochemical parameters of blood in patients with type 2 diabetes before and during treatment

Indicators	Control n-20	Group 1 M+Gliclazide MB n -18	R	Group 2 M+Empagliflozin n-24	R
Glycemia on an empty stomach , mmol / l					
Initially	4.5 ± 1.0 _ _ _	8.5 ± 1.0 _ _ _	>0.05	8.7 ± 1.7	0.031
After 12 weeks		7.1 ± 1.9		6.7 ± 1.6	
Postprandial glycemia, mmol/l					

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Initially	6.3 ± 1.3 _ _ _	14.5 ± 3.0 _ _ _	>0.05	13,9 ± 1.0	0.044
After 12 weeks		9.9 ± 1.9 _ _		9 , 0 ±2.1	
HbA1c, %					
Initially	5.5 ± 0.9 _ _ _	8.8±1.0	>0.05	8, 8 ±1.3	0.0019
After 12 weeks		7.4±1.6		7.1±1.2	
Total cholesterol, mmol/l					
Initially	4.3 ± 0.7 _ _ _ _	5.1 ±1.7	>0.05	4.8 ± 1.4	>0.05
After 12 weeks		4.5±1.9		4.6±1.7	
Triglycerides , mmol /l					
Initially	1.5 ± 0.0 8 _	2.46±1.51	0.028	2.51±1.82	0.014
After 12 weeks		1.95±1.23		1.82±1.55	
HDL, mmol/l					
Initially	1.35 ± 0.0 4 _	0.92±0.33	>0.05	0.96±0.37	>0.05
After 12 weeks		0.98±0.31		1.01±0.40	
LDL, mmol/l					
Initially		2, 12 ±1.8	>0.05	2.5 5 ±1.30	>0.05
After 12 weeks		2.03 ± 2.16		2, 1 8±1.84	
AST , U/l					
Initially	17.9 ± 3.9 _ _	3 1 .6±7.2	0.0034	3 3 .1±6.8	0.0028
After 12 weeks		22.6±8.4		21.4±7.0	
ALT , U / l					
Initially	21.8 ± 3.4 _ _	37.5 ±9.6	>0.05	39.8 ±10.1	0.00 19
After 12 weeks		31.3 ±9.1		27.1±8.8	

Note: p<0.05 ; p <0.001 – the presence is significant in relation to the studied group

Patients of the 1st group metformin was added gliclazide MB at a dose of 60 mg/day. The 2nd group of patients took the drug from the iSGLT2 group - empagliflozin at a dose of 10 mg/ day. The dose of metformin was increased to 2000 mg/day.

Against the background of treatment, there are positive dynamics in carbohydrate metabolism. So, in patients of group 1, fasting glycemia was reduced by 17% (>0.05) , in group 2 - by 21% (p<0.05), postprandial glycemia by 16 (>0.05) and 33% (p<0.05), HbA1c by 16 and 20.5% (p<0.05), respectively. There is a positive trend in the lipid spectrum of the blood, so OH in both was reduced by 7 and 18% (p>0.05), respectively. There is a decrease in liver enzymes by 17 and 31% (p<0.001), respectively. Empagliflozin is the drug of choice in patients with DM2 and atherosclerotic CVD, hypertension, visceral obesity, and hyperuricemia , and has a cardiovascular and nephroprotective effect [14]. As part of any combination of 2 or more hypoglycemic drugs, metformin should be used in the absence of contraindications [5], taking into account the leading role of insulin resistance in the pathogenesis of DM2 [5].

Taking into account the negative impact of type 2 diabetes on the course and prognosis of EF parameters, the optimal therapeutic intervention will be such a treatment that will simultaneously positively affect the glycemic status and LV diastolic function. And here, great prospects are associated with inhibitors of the sodium-dependent type 2 glucose transporter (or gliflozins). Gliflozins reduce blood glucose by blocking the glucose transporter of the same name and reducing its reabsorption in the proximal nephron, which leads to glucosuria, calorie loss and a decrease in blood pressure (BP). In addition to hemodynamic unloading of the heart, gliflozins are believed to be able to directly improve LV diastolic function. In a number of experimental studies, empagliflozin accelerated the processes of active relaxation and reduced the severity

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of myocardial inflammation, oxidative stress, myocardial hypertrophy and fibrosis [12]

Table 3
Study of the left ventricular ejection fraction (%) in patients with type 2 diabetes during treatment

Index	Group 1 M+Gliclazide MB n -18	Group 2 M+Empagliflozin n-24
Initially	61.3±9.78	60.1±8.93
After 12 weeks	62.9±7.46	64.1±5.68

After 12 weeks, there were no statistically significant differences between the 1st and 2nd groups in the effect of the type of therapy on LV contractility (EF), while the use of empagliflozin positively affects heart function, as evidenced by an increase in EF (on EchoCG) by 7 .8% (P > 0.05), compared with group 1, where this indicator did not change (61.3±9.78% before and 62.9±7.46 after treatment). According to the Algorithms of specialized medical care for patients with diabetes mellitus (2019), patients with DM2 and ASCVD are recommended to use iSGLT2 or glucagon-like peptide-1 receptor agonists, which have proven cardiovascular benefits, as part of hypoglycemic therapy [5]. The results show that the administration of empagliflozin in addition to previously taken metformin allowed a statistically significant reduction in HbA1c levels. By the end of the study, 73.7% of patients in group 1 achieved their individual target HbA1c levels, with the greatest decrease in glycemic parameters observed in the group of patients with initially non-target HbA1c levels. In group 2, by the end of the study, target HbA1c values were achieved in 55.4% of patients. But in this group, 8 (44.5%) patients noted symptoms of hypoglycemia (feeling hungry at night, sweating, insomnia), most of them at night, compared with patients in group 1, where these symptoms were absent.

Effective therapy for type 2 diabetes is associated with weight gain. Weight gain, for example, is the most common side effect of insulin therapy with conventional SSSPs. This is fraught with aggravation of insulin resistance, deterioration of the clinical picture of the disease, and an increase in the cost of treatment. Thus, over 12 weeks of treatment and observation, patients of group 1 showed an average increase in body weight by 3.1 ± 0.09 kg compared with patients of group 1, who had a decrease in body weight by 4.9 ± 0.78 kg. Also, in patients of group 2, there was a decrease in systolic blood pressure from 157.7±14.3 mm Hg . up to 139 ±9.7 mm Hg Art. (p<0.05), diastolic with 98.34±7.6 mm Hg up to 85.7±4.4 mm Hg (p<0.05). In patients of group 1, there was also a decrease in blood pressure, but these indicators were not significant, despite the fact that patients in both groups were on combined antihypertensive therapy. Thus, the results of this study largely coincide with the conclusions of foreign authors.

Analyzing the side effects of empagliflozin, it should be noted that in 2 patients (including women) there was an exacerbation of urinary tract infections, but in a mild degree of severity, which was stopped by taking uroseptics and maintaining personal hygiene.

CONCLUSIONS.

1. Empagliflozin + metformin dual combination therapy is the optimal choice in patients with type 2 diabetes and very high cardiovascular risk. During treatment, patients who took empagliflozin at a dose of 10 mg/ day in combination with metformin at a dose of 2000 mg/ day showed positive dynamics in carbohydrate metabolism. Thus, fasting glycemia was reduced by 21% (p<0.05), postprandial glycemia by 33% (p<0.05) and HbA 1c by 20.5% (p<0.05), respectively.

2. To date, iSGLT-2 has an extensive evidence base with confirmed cardioprotective effects in patients with type 2 diabetes. The drug empagliflozin has a positive effect on heart function, as evidenced by an increase in EF (on echocardiography) by 7.8% (P > 0.05), compared with group 1, where this indicator did not change (61.3±9.78 % before and 62.9±7.46 after treatment).

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3. Empagliflozin is a safe drug. Empagliflozin practically does not increase the risk of hypoglycemia, since it does not stimulate insulin secretion and does not suppress the synthesis of endogenous glucose in the liver, unlike sulfonylurea drugs.

4. Taking into account the multidirectional mechanism of action of the drugs used, the data obtained on their efficacy and safety in preventing the risk of adverse cardiovascular and renal events, the low risk of hypoglycemia, and the positive effect on visceral adipose tissue, we can confidently speak about the multifactorial management of T2DM.

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