ORIGINAL ARTICLE

THE CLINICAL EXPERIENCE OF THE EFFECTIVE USE OF DAPAGLIFLOZIN IN COMORBID CARDIAC PATIENTS WITH CONCOMITANT TYPE 2 DIABETES MELLITUS AND ARTERIAL HYPERTENSION ON THE BACKGROUND OF OVERWEIGHT IN OUTPATIENT SETTING

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ABSTRACT

The aim: To assess the efficacy and safety of dapagliflozin in the treatment of comorbid cardiac patients with type 2 diabetes mellitus (T2DM) in combination with arterial hypertension (AH) and overweight in outpatient setting.

Materials and methods: Under observation were 19 patients who were treated in outpatient setting during 2019-2021 for AH and had T2DM, overweight or obesity. As part of complex treatment, patients received dapagliflozin 10 mg once a day for 12 months.

Results: The normalization of blood pressure, elimination of heart failure symptoms on the background of increased ejection fraction, improved indicators of the functional capacity of the kidneys, and a decrease in the degree of proteinuria/albuminuria were noted after treatment. The patients had an easier time losing weight (body mass index and waist circumference decreased; $p<0.05$) and decreased levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C). None of the monitored patients had cases of hypoglycemia or urinary tract infection. The number and/or doses of antihypertensive, hypouricemic and diuretic drugs were gradually reduced.

Conclusions: Using dapagliflozin in a standard dose of 10 mg/day in the complex therapy of patients with T2DM in combination with arterial hypertension and overweight contributes not only to the normalization of blood pressure, but also to a reduction in body weight and waist circumference. The proposed therapy can be an alternative for the treatment of patients with T2DM with concomitant overweight or obesity, arterial hypertension, with or without heart and/or renal failure as a first-line antidiabetic drug.

KEY WORDS: arterial hypertension, type 2 diabetes mellitus, body weight, dapagliflozin

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INTRODUCTION

The cardiovascular disease (CVD) remains the leading cause of death and disability worldwide. However, Ukraine, where the mortality from CVD is 64.3% [1], is a region with a very high cardiovascular risk [2] for various, primarily socio-economic, environmental and mental reasons. The main risk factors for cardiovascular mortality in Ukraine include smoking, unhealthy diet, low physical activity, alcohol abuse, obesity, and air pollution [1]. An additional risk factor has become daily life problems, burdened by "covid" restrictions and stresses, which often lead to AH, atherogenic dyslipidemia, T2DM, and their complications. That is why comorbid patients with various combinations of cardiometabolic syndrome (obesity, arterial hypertension, dyslipidemia, hyperuricemia, impaired glucose tolerance or diabetes mellitus) dominate today among cardiac patients. This leads to long-term prescribing of a large number of medications by various specialists, often without taking into account possible drug interactions. Therefore, the search for drugs with combined mechanisms of action and physiological effects that would have a positive effect on various links of the pathogenesis of cardiometabolic syndrome is extremely relevant.

From this point of view, a relatively new group of oral drugs for the treatment of T2DM – sodium-glucose co-transporter-2 inhibitors (SGLT-2 inhibitors) is considered promising. SGLT-2 ensures tubular reabsorption of up to 90% of glucose from the ultrafiltrate, and their inhibitors, due to the reduction of glucose reabsorption and, accordingly, glucosuria, have a hypoglycemic effect. Along with the hypoglycemic effect, SGLT-2 inhibitors have natriuretic and diuretic, and therefore hypotensive effects, and due to glucosuria, they contribute to a decrease in body weight [3]. The number of randomized studies of the effectiveness of SGLT-2 inhibitors in the treatment of T2DM revealed a positive effect on the cardiovascular system and kidneys even in patients without established atherosclerotic CVD and chronic kidney disease [4,5]. Further studies of SGLT-2 inhibitors revealed their effectiveness in reducing the risk of cardiovascular and renal complications both in patients with T2DM and heart failure (HF), and without them [6,7]. Since all the mechanisms of favorable cardioprotective effects of SGLT-2 inhibitors have not been fully established, the study of this issue is relevant.

THE AIM

The aim was to assess the efficacy and safety of dapagliflozin in the treatment of comorbid cardiac patients with T2DM in combination with AH and overweight in outpatient setting.

MATERIALS AND METHODS

The studies were conducted with the informed consent of the patients, and their methodology was in line with the Declaration of Helsinki of 1975 and its revision of 1983 and was approved by the local bioethics commission of UzhNU (Protocol No. 1 dated 10.01.2020), and its participants read and signed the consent letter, the structure of which corresponded officially accepted. There were 19 comorbid patients under observation who were treated in outpatient setting by a cardiologist during 2019-2021 for hypertension and had various combinations of cardiometabolic syndrome, overweight or obesity, and T2DM. All patients were consulted by an endocrinologist and received dapagliflozin 10 mg once a day as part of complex treatment, as a new antidiabetic drug.

Among the patients were 5 people with newly diagnosed T2DM (1 patient with estimated glomerular filtration rate (eGFR) of 48 ml/min, 4 patients with existing cardiovascular and renal pathology), who received dapagliflozin as the first and only antidiabetic drug; 6 patients received metformin 1000 mg + dapagliflozin due to insufficient effectiveness of metformin; 3 patients were prescribed dapagliflozin instead of sulfonylurea derivatives; 5 patients received dapagliflozin to replace the combination of metformin with sulfonylurea derivatives due to eGFR less than 60 ml/min (2 patients) or the presence of cardiac and renal pathology (3 patients).

Only patients who received dapagliflozin 10 mg for more than 12 months were included in the study. Among them were 17 men and 2 women, aged from 42 to 63 years.

All patients underwent a general clinical examination and special examination methods, which included: ECG, echocardioscopy, ultrasound examination of extracranial vessels, eGFR, general urinalysis, fasting blood glucose, glycated hemoglobin, blood insulin and insulin resistance index, total cholesterol, low and high density lipoproteins, triglycerides, uric acid, and potassium level in the blood. All studies were carried out in certified laboratories. Also, body mass index (BMI) was calculated and waist circumference (WC) was determined for all patients.

Due to quarantine restrictions, the current control was carried out online, laboratory tests were carried out at the place of residence on an outpatient basis, taking into account the need once every 3-6 months, ECG and echocardioscopy – once every 6-12 months.

At the same time, patients continued to receive basic therapy, which included the standard prescription of lisinopril and losartan, amlodipine and verapamil, spironolactone or eplerenone, and torasemide (furosemide if there is a risk of hyperkalemia). Beta-blockers were prescribed only in case of direct indications, preference was given to metabolically neutral nebivolol. When antiatherothrombotic therapy was indicated, statins (atorvastatin, rosuvastatin) and an antiplatelet agent were prescribed (taking into account the frequent presence of hyperuricemia, clopidogrel was preferred). In case of hyperuricemia (uric acid over 360 μmol/l in patients with gout and over 400 μmol/l in patients without gout), allopurinol was prescribed (if eGFR is less than 60 ml/min – flebuxostat).

The criteria for the effectiveness of the therapy were the normalization of blood pressure ((BP) 120/70-130/80 mm Hg) and heart rate (HR) (60-80 bpm), carbohydrates (glycated hemoglobin 6-7%), lipid (LDL-C < 2.4 mmol/l), electrolyte (blood potassium 3.5-5.0 mmol/l) and purine (blood uric acid 200-360 μmol/l) exchanges. The ultimate aim of therapy was the reduction or absence of symptoms of heart failure: shortness of breath and edema against the background of increased left ventricular ejection fraction (EF), signs of kidney damage (proteinuria or albuminuria) and renal failure (decrease in urine albumin/creatinine index and increase in eGFR). The analysis and processing of the results of the examination of patients was carried out using the Statistics for Windows v.7.0 computer program (StatSoft Inc, USA) using parametric and non-parametric methods of evaluating the obtained results. The difference was considered probable at $p<0.05$.

RESULTS

After the treatment, a gradual improvement of the cardiovascular system was observed in all patients, which consisted in a decrease in shortness of breath, leg's edema, and after 12 months of treatment, shortness of breath remained only in 3 patients, and none of the patients had leg's edema. BP normalization was noted (on average from 176/103 mm Hg to 135/84 mm Hg, $p<0.05$) with a gradual reduction in the total number of antihypertensive drugs; elimination of HF symptoms against the background of an increase in EF on average from 56±2.4 to 57±1.3% (only 3 patients had HF symptoms with moderately reduced HF). Indicators of the functional ability of the kidneys improved, in particular, eGFR increased from 72±2.6 to 81±3.8 ml/min/1.73 m2 on average, $p<0.05$, and the degree of proteinuria/albuminuria decreased. Patients noted that it was easier for them to lose weight than before, as evidenced by the dynamics of the degree of obesity (BMI decreased from 36±1.6 to 31±1.2 kg/m2, WC – from 144±3.2 to 126±2.2 cm, respectively; $p<0.05$). A positive effect of dapagliflozin on lipid metabolism was noted, as the levels of total cholesterol and LDL-C significantly decreased (from 6.4 mmol/l to 5.2 mmol/l, and from 4.2 mmol/l to 2.6 mmol/l, respectively; $p<0.05$) (Table I).

Were established that the appointment of dapagliflozin leads to a reduction in the need for diuretics. Thus, the number of patients taking diuretics decreased from 8 to 4. In four patients without atherosclerotic CVD, temporarily, under the control of the lipid profile, statins were discontinued. None of the monitored patients had cases of hypoglycemia or urinary tract infection.

Table I. Dynamics of clinical and laboratory indicators on the background of taking dapagliflozin

Indicators	Before treatment (n=19)	After 6 months of treatment (n=19)	After 12 months. treatment (n=19)
BMI (kg/ m2) (M±m)	36±1,6	33±1,6	31±1,2*
WC (cm) (M±m)	144±3,2	134±3,6	126±2,2*
Overweight (number of the patient)	5	7	7
Obesity class I	8	7	8
Obesity class II	6	5	4
Obesity class III	0	0	0
HR (bpm.) (M±m)	86±1,8	74±1,3	72±1,3
BP systolic (mm Hg.) (M±m)	176±3,4	136±1,9	135±1,8*
BP diastolic (mm Hg.) (M±m)	103±2,3	85±1,4	84±1,2
Normal (number of the patients)	0	4	4
High normal (number of the patients)	0	11*	12*
Grade 1 hypertension (number of the patients)	6	4	3
Grade 2 hypertension (number of the patients)	10	0	0
Grade 3 hypertension (number of the patients)	3	0	0
EF (%): (M±m)	56±2,4	56±1,8	57±1,3
Preserved (number of the patient)	12	13	14
Moderately reduced (number of the patients)	6	6	5
Reduced (number of the patients)	1	0	0
Symptoms of HF:			
Shortness of breath (number of the patients)	18	8*	3*
Edema of the lower legs (number of the patients)	12	2*	0
Fasting blood glucose (mmol/l)	8,6±0,4	7,8±0,3	6,8±0,4*
Glycated hemoglobin (%)	7,4±0,2	6,6±0,3	6,4±0,3
Insulin (μIU/ml)	28±1,2	34±2,2	24±1,8
Index of insulin resistance	12,5±0,8	14,4±	7,8±0,6*
Total blood cholesterol (mmol/l)	6,4±0,5	5,4±0,4	5,2±0,4
LDL-C (mmol/l)	4,2±0,2	3,0±0,3*	2,6±0,2*
Uric acid (μmol/l)	398±12	286±8*	234±11*
Blood potassium (mmol/l)	4,2±0,08	4,5±0,1	4,4±0,1
Blood creatinine (μmol/l)	112±4,8	98±3,6	96±4,2
eGFR (ml/min/1.73 m2)	72±2,6	80±4,4	81±3,8
Albuminuria (number of the patients)	11	9	7
Proteinuria (number of the patients)	6	4	3
Albumin/creatinine index (mg/mmol) (number of the patients)			
< 3.4 - normal	6	9	12
3.4 - 33.9 - abnormal	9	7	6
>33.9 - high abnormal	4	3	1

Note: The significance of the difference:* – with the indicator before treatment (the indicator is calculated according to the Mann-Whitney test, $p<0.05$).

DISCUSSION

In the observed patients the cardioprotective effect of dapagliflozin was manifested in the reduction of the number of persons with shortness of breath from 19 to 3, the disappearance of edema on the lower legs in all patients, and the increase of the ejection fraction. The mechanisms of favorable cardioprotective effects of SGLT-2 inhibitors have not been fully established, but it is believed that they are based on the reduction of pre- and afterload on the heart due to natriuresis and diuresis, a positive effect on energy

metabolism in the myocardium, prevention of its fibrosis and remodeling [8]. The improvement of indicators of the functional capacity of the kidneys, in particular, an increase in eGFR and a decrease in the degree of proteinuria/albuminuria, may be one of the factors in reducing the further need for antihypertensive, hypouricemic, and diuretic drugs. The decrease in body weight registered by us in all patients is obviously caused by glucosuria, due to a decrease in glucose reabsorption, which is a characteristic feature of SGLT-2 inhibitors and coincides with the data of other researchers [3].

The fact that there were no patients with decompensated T2DM among the patients, and no sharp improvement in the indicators of carbohydrate metabolism was observed. Nevertheless, a year after the appointment of dapagliflozin, only five patients were also taking metformin, and one, with contraindications to it (eGFR less than 60 ml/min/1.73 m2) – a sulfonylurea derivative (glurenorm). At the same time, the improvement of health indicators occurred against the background of a gradual decrease in the number and/or dose of antihypertensive, hypouricemic, and diuretic drugs.

That why, can be talked about the pleiotropic effects of dapagliflozin, which are not directly related to its effect on carbohydrate metabolism. A temporary increase in insulin resistance and compensatory hyperinsulinemia in those patients who were prescribed dapagliflozin to replace metformin deserves additional study.

At the end of the study, all patients continued to take dapagliflozin 10 mg, as there was no case of a decrease in the functional capacity of the kidneys or the development of hypoglycemia.

The data was obtained confirm the positive effect of dapagliflozin both on the components of the cardiometabolic syndrome (obesity, hypertension, T2DM), and the prevention of cardiovascular complications, in particular, heart and kidney failure. Thanks to these properties, dapagliflozin is included in the European and American guidelines not only for the treatment of T2DM [9,10], but also for the prevention of cardiovascular pathology in general [2].

Analyzing the obtained data, we the conclusion that dapagliflozin is effective and safe and can be an alternative for the treatment of patients with T2DM with overweight or obesity and arterial hypertension, with or without heart and/or renal failure.

CONCLUSIONS

Using dapagliflozin in a standard dose of 10 mg/day in the complex therapy of patients with T2DM in combination with arterial hypertension on the background of overweight or obesity contributes not only to the normalization of blood pressure, but also to a reduction in body weight and waist circumference. The absence of unwanted effects of the therapy makes it possible to use it widely and for a long time in outpatient clinical practice. The proposed therapy can be an alternative for the treatment of patients with T2DM with concomitant overweight or obesity, arterial hypertension with or without heart and/or renal failure as a first-line antidiabetic drug.

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