



Experience of Using Sodium-dependent Glucose Cotransporter Type 2 Inhibitors in Comorbid Patients in Real Clinical Practice

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Abstract

Inhibitors of sodium-dependent glucose cotransporter type 2 (SGLT2i) are drugs that protect against cardiovascular diseases and mortality in patients with diabetes mellitus (DM) type 2 of various age groups with the presence of comorbid pathology and numerous complications. The huge number of achieved results may vary in different cases, but already existing data prove the importance and necessity of prescribing such innovative drugs as SGLT2i. So far, the effectiveness and necessity of using SGLT2i has been proven not only in patients with type 2 diabetes, but also in patients with heart failure and chronic kidney disease without diabetes.

The Aim of the Study: An analysis of the long-term results of the influence of combined therapy with dapagliflozin and metformin on the state of carbohydrate, lipid and protein metabolism, indicators of liver tests and synthetic liver function in patients with type 2 diabetes, representatives of the Ukrainian population, who have signs of high cardiovascular risk.

Materials and Methods: The study included 60 patients with type 2 diabetes, of whom 34 were men and 26 were women. The average age of the patients was (57.52 ± 0.96) years. 39 (65.0%) patients had diabetes of moderate severity, 21 (35.0%) had severe diabetes. 11 patients (18.3%) received combined therapy including insulin. Treatment of patients with type 2 diabetes included adherence to dietary recommendations, namely, nutritional correction and the appointment of tableted oral hypoglycemic agents: dapagliflozin in a daily dose of 10 mg and metformin in a daily dose of 1500 to 2000 mg; 11 patients were additionally prescribed insulin therapy in addition to the oral hypoglycemic drugs. Determination of the level of carbohydrate, lipid, and protein metabolism, indicators of liver tests, and liver synthetic function were performed in all patients.

Results: Long-term treatment with dapagliflozin in combination with metformin in patients with type 2 diabetes with a high cardiovascular risk has proven its effectiveness. A significant improvement in carbohydrate, lipid, and protein metabolism indicators, liver test results, and liver synthetic function was established in the treated patients.

Conclusions: The expediency and effectiveness of using the combination of the drug dapagliflozin in combination with metformin as a long-term glucose-lowering therapy for patients with type 2 diabetes with comorbid pathology and high cardiovascular risk have been substantiated.

Keywords: Comorbid Patients; Type 2 Diabetes; High Cardiovascular Risk; Sodium-dependent Glucose Cotransporter Type 2 Inhibitors

Relevance

The American College of Endocrinologists, 2020 [1] regarding the management of patients with type 2 diabetes and established

atherosclerotic cardiovascular diseases or signs of high risk of cardiovascular complications or heart failure recommends the SGLT2i or glucagon-like peptide-1 receptor agonists (GLP-1) with

proven benefits for the cardiovascular system and prescribes these drugs as part of hypoglycemic therapy regardless of the level of glyated hemoglobin (HbA1c). Currently, the safety of all hypoglycemic drugs is determined by cardiovascular risk. In large-scale clinical studies, the cardiovascular efficiency of the most promising group of drugs - SGLT2i has been proven [2-7].

The combination of diabetes and cardiovascular diseases is a very urgent problem of modern medical science. It is now known that 85% of all cardiovascular deaths in patients with type 2 diabetes are caused by atherosclerotic cardiovascular disease, including stroke and heart attack. Numerous studies have proven that patients with diabetes can develop heart failure, which occurs as a result of both atherosclerotic and atherosclerotic-independent mechanisms. Medical researchers are very concerned about the fact that heart failure remains undiagnosed in almost 30% of patients, and the majority of patients with heart failure have a preserved ejection fraction [8-11]. Undiagnosed heart failure occurs more often in women, overweight and obese patients, and elderly patients [13,14].

It is established that SGLT2i or gliflozins reduce the level of blood pressure with the help of osmotic diuresis, as they exert a glucosuric effect. Inhibition of SGLT2 reduces the reabsorption of glucose from the glomerular filtrate in the proximal part of the renal tubules with a simultaneous decrease in sodium reabsorption, which leads to the excretion of glucose in the urine and osmotic diuresis. Thus, dapagliflozin increases sodium delivery to the distal tubules, which increases tubuloglomerular pressure. This, in combination with osmotic diuresis, helps reduce volume overload, lower blood pressure, preload and afterload, which has a positive effect on heart remodeling. Also, these drugs lead to a decrease in insulin resistance (IR), glucose toxicity, a decrease in the level of oxidative stress and inflammation, which contributes to the improvement of endothelial function and the reduction of arterial stiffness. The results of large international studies have confirmed the positive effect of dapagliflozin and other SGLT2i on the cardiovascular system. In the study of real clinical practice «CVD-REAL», which involved more than 300,000 patients from 6 countries of the world, it was established that the use of SGLT2i compared to other hypoglycemic drugs contributed to a decrease in mortality from any cause due to heart failure on 46%, and the risk of hospitalization for the aforementioned reason decreased by 39% [4,15].

Similar results were obtained in the «CVD-REAL2» study, where 470,000 patients participated, 73% of whom did not have confirmed cardiovascular diseases. Dapagliflozin, which was administered to 75% of patients, reduced all-cause mortality by 49% compared with other hypoglycemic drugs and the rate of heart failure hospitalizations by 36%. The frequency of myocardial infarction decreased by 19%, and cerebral stroke - by 32% due to the use of SGLT2i [4,16].

It is very important that dapagliflozin has a multi-component effect: it not only lowers glycemia, body weight, increases diuresis, contributing to a moderate decrease in blood pressure, but also demonstrates antifibrotic activity in non-alcoholic fatty liver disease (NAFLD).

In a randomized, double-blind, placebo-controlled trial DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events) evaluated the safety of dapagliflozin. The above-mentioned study on cardiovascular consequences against the background of the use of SGLT2i is currently the largest. It evaluated the use of dapagliflozin in comparison with placebo over a period of 5 years in more than 17,000 adults with type 2 diabetes from 33 countries of the world and analyzed the development of cardiovascular events, which were characterized by the presence of several factors of cardiovascular diseases at once or established cardiovascular pathology. The results of the large-scale DECLARE-TIMI 58 study are of great interest to scientists and doctors, as they concern not only patients with existing cardiovascular diseases, but also patients with risk factors for their development, which is almost every second patient with type 2 diabetes [21-25].

In the study on the effect on cardiovascular events - DEFINE-HF (Dapagliflozin Effect on Symptoms and Biomarkers in Patients With Heart Failure - «Dapagliflozin Effect on Symptoms and Biomarkers in Patients With Heart Failure») [26] demonstrated an improvement in health, which was associated with heart failure, according to the Kansas Cardiomyopathy Questionnaire, in patients with heart failure with reduced ejection fraction treated with SGLT2i.

Thus, it can be concluded that SGLT2i are drugs that protect against cardiovascular diseases and mortality in patients with type 2 diabetes of different age groups with the presence of comorbid

pathology. Numerous metabolic and cardiorenal effects of SGLT2i have been demonstrated so far, but they require further study. [18,27,28].

Therefore, the goal of this study is to analyze the results of combined therapy with dapagliflozin and metformin on the status of carbohydrate, lipid, and protein metabolism, indicators of liver tests, and synthetic liver function in patients with type 2 diabetes who have signs of a high risk of cardiovascular complications.

Materials and Methods

60 patients with type 2 diabetes were under observation, 34 of which were men and 26 were women. The average age of the patients was (57.52 ± 0.96) years. 39 (65.0%) patients had diabetes of moderate severity, 21 (35.0%) had severe diabetes. Insulin dependence was observed in 11 patients (18.3%). Treatment of patients with type 2 diabetes included adherence to dietary recommendations, namely, nutritional correction - when developing dietary recommendations for patients with type 2 diabetes with NAFLD, the basis was the composition of end glycation products (EGP) in food products (average daily consumption of products with with a EGP content of $(14,700 \pm 580)$ kilo/unit/day), proposed by the American Nutrition Association, the EGP content of only those foods consumed by the Ukrainian population was evaluated, while typical cooking methods were used and the EGP value was expressed for each sample of food as EGP kJ/100 g of food; appointment of tableted oral hypoglycemic agents: dapagliflozin in a daily dose of 10 mg and metformin in a daily dose of 1500 to 2000 mg, 11 patients were additionally prescribed insulin along with the tableted hypoglycemic drugs.

The analysis of clinical and biochemical indicators included the determination of glycemia indicators during the day, including fasting blood glucose (BGf), postprandial glycemia (BGpp) by the glucose oxidase method using the express analyzer «Biosen C line», the average daily glycemia (BGa) was also calculated, amplitude of glycemia, HbA1c by colorimetric method. The level of immunoreactive insulin (IRI) in the blood was determined by the immunochemiluminescence method using the Insulin Elisa kit («ELISA» DRG Diagnostics, USA). The IR index (HOMA2-IR) was calculated using the improved model of the HOMA calculator. The study of the concentration of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) was carried out

by the enzymatic colorimetric method: when determining TC and TG using SpineLab kits (Kharkiv, Ukraine) using the Fluorate-02 analyzer -AVLF-T, when determining HDL-C - using a kit from the company «SpineLab» CJSC (Kharkiv, Ukraine). The concentrations of low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C) and the atherogenic index (AI) were calculated by the calculation method according to generally accepted formulas. Determination of total bilirubin was carried out by the Jendraszyk method using the Fluorat-02-AVLF-T and Photometer RM 2111- In «Solar», the study of thymol sample and alkaline phosphatase activity in blood serum was carried out according to the McLagan method; the activity of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in blood serum was determined by the Reitman-Frenkel method on Fluorate-02-AVLF-T devices and Photometer RM 2111-U «Solar». Recalculation of AST - $1 \mu\text{mol/l per second} = 1 \text{ unit/l}$. The total protein in blood serum was determined by the biuret method, the fractional composition of blood serum proteins was determined by the turbidimetric method; creatinine, blood urea - by Popper's method.

During the clinical study, safety measures for the patient's health, protection of his rights, human dignity and moral and ethical standards, provided for in such cases, were observed in accordance with the principles of the Helsinki Declaration of Human Rights (1964), the Council of Europe Convention on Human Rights and Biomedicine, relevant laws of Ukraine. All patients signed an informed consent to participate in the study.

Statistical processing of the received data was carried out using the package of statistical programs «Statistica 8.0» (StatSoft Inc, USA), Microsoft Office Excel-2003. Quantitative signs with a normal distribution were presented as mean \pm standard error of the mean ($M \pm m$), Student's test was used to compare the means of two samples. The assessment of differences between groups with a distribution close to normal was carried out using the Pearson test.

Research Results and their Discussion

Reduction of IR and improvement of glycemic control are the main results expected from the use of hypoglycemic drugs. At the same time, these drugs currently have great requirements, namely, along with lowering blood glucose, they should not only not cause

cardiovascular complications and prevent their occurrence, but also not have a negative impact on internal organs of patients, in particular liver and kidneys, etc., and if possible, have an organoprotective effect. All of the above is of interest regarding the use of the combination of metformin and dapagliflozin in patients with type 2 diabetes.

In patients who were under observation for 2 years, the dynamics of indicators of carbohydrate metabolism against the background of treatment with dapagliflozin in combination with metformin is shown in table 1. From the presented data, it can be seen that the average indicators of carbohydrate metabolism in patients with type 2 diabetes were in a state of decompensation. Against the background of the therapy, there was a positive trend in reducing their levels, namely: fasting, postprandial, and average daily glycemia.

Indicators	Group and number of patients, n = 60	
	Before treatment	After treatment
BGf, mmol/l	11,94 ± 0,45	8,37 ± 0,44 p < 0,001
BGpp, mmol/l	12,08 ± 0,52	10,50 ± 0,49 p < 0,05
Amplitude of glycemia, mmol/l	5,11 ± 0,38	5,04 ± 0,33
BGa, mmol/l	11,24 ± 0,37	9,73 ± 0,38 p < 0,01
HbA1c, %	8,24 ± 0,13	7,41 ± 0,14 p < 0,001
IRI, mU/ml	19,78 ± 1,72	14,12 ± 1,68 p < 0,05
HOMA2-IR	3,06 ± 0,1	2,04 ± 0,3 p < 0,01

Table 1: Indicators of carbohydrate metabolism in patients with type 2 diabetes on the background of long-term therapy with dapagliflozin in combination with metformin.

Remark: p – the significance of the differences between indicators before and after treatment according to the Student’s t-test.

Indicators	Group and number of patients, n = 60	
	Before treatment	After treatment
Total bilirubin, μmol/l	14,07 ± 0,82	13,21 ± 0,79
Thymol test, U	4,92 ± 0,39	4,75 ± 0,42
AST, U/l	38,72 ± 1,22	31,14 ± 1,19 p < 0,001
ALT, U/l	58,12 ± 2,66	47,38 ± 1,99 p < 0,001
AST/ALT	0,79 ± 0,04	0,66 ± 0,04 p < 0,05

Table 2: Indicators of liver tests in patients with type 2 diabetes during the long-term therapy with dapagliflozin in combination with metformin.

Remark: p – the significance of the differences between indicators before and after treatment according to the Student’s t-test.

HbA1c, IRI and index HOMA2-IR (p < 0,001; p < 0,05; p < 0,01; p < 0,001; p < 0,05; p < 0,01, respectively). A statistically significant decrease in IRI testifies to a tendency to decrease insulin resistance and increase sensitivity to insulin, according to the calculated HOMA index. Also, during the analysis of the long-term results of the use of dapagliflozin in combination with metformin, positive dynamics of liver test indicators in patients with type 2 diabetes (Table 2) are confirmed.

As a result, a significant decrease in transaminases and the de Ritis coefficient (p < 0.001; p < 0.001 and p < 0.05, respectively) was established during the use of dapagliflozin therapy in combination with metformin for 2 years. The levels of total bilirubin and thymol test also tended to decrease, but no definite difference was found. The above indicates a positive effect of the combination of dapagliflozin and metformin on the indicators of liver tests.

The effect of the above-mentioned combination of drugs on the parameters of lipid metabolism in patients with type 2 diabetes mellitus was monitored (Table 3).

Thus, it was established that during a long-term therapy with dapagliflozin in combination with metformin, there was a positive trend in relation to a definite decrease in the levels of TC, TG, LDL-C and an increase in the level of HDL-C (p < 0.001; p < 0.01; p < 0.01 and p < 0.001, respectively).

Indicators	Group and number of patients, n = 60	
	Before treatment	After treatment
TC, mmol/l	7,41 ± 0,23	5,76 ± 0,22 p < 0,001
TG, mmol/l	2,48 ± 0,19	1,55 ± 0,17 p < 0,01
HDL-C, mmol/l	1,21 ± 0,04	1,38 ± 0,04 p < 0,01
LDL-C, mmol/l	3,63 ± 0,18	2,62 ± 0,17 p < 0,001
VLDL-C, mmol/l	1,09 ± 0,13	0,79 ± 0,13
AI	3,75 ± 0,34	3,04 ± 0,32

Table 3: Indicators of lipid metabolism during the long-term therapy with dapagliflozin in combination with metformin.

Remark: p – the significance of the differences between indicators before and after treatment according to the Student’s t-test.

Indicator	Group and number of patients, n = 60	
	Before treatment	After treatment
Total protein, g/l, p < 0,001	77,68 ± 0,35	81,22 ± 0,36
Albumin, %	54,31 ± 0,47	55,17 ± 0,44
Globulin α1, %	4,99 ± 0,12	5,15 ± 0,13
Globulin α2, %	11,21 ± 0,11	11,31 ± 0,10
β- Globulin, %	12,17 ± 0,22	12,37 ± 0,23
Globulin γ, %	15,05 ± 0,16	14,89 ± 0,17
Fibrin, mg	11,91 ± 0,17	11,62 ± 0,15
Fibrinogen, g/l	2,94 ± 0,04	2,89 ± 0,03
Prothrombin index, %	98,05 ± 0,49	98,69 ± 0,47
Platelets, 10 ⁹ /l	264,45 ± 3,19	282,38 ± 3,16 p < 0,001

Table 4: Dynamics of indicators of protein metabolism and liver synthetic function in patients with type 2 diabetes during the long-term therapy with dapagliflozin in combination with metformin.

Remark: p – the significance of the differences between indicators before and after treatment according to the Student’s t-test.

Taking into account the importance of assessing the state of the protein-synthetic function of the liver during the long-term (2 years) use of dapagliflozin in combination with metformin, the parameters of protein metabolism were determined (Table 4).

A significant increase in the content of total protein and platelets (p < 0.001), as well as an improvement in other indicators of the protein-synthetic function of the liver, indicates its improvement, which demonstrates the positive effect of receiving hypoglycemic therapy one year after the start of treatment.

Thus, the analysis of the obtained results of the long-term treatment with dapagliflozin in combination with metformin in patients with type 2 diabetes showed its effectiveness. Improvements in carbohydrate, lipid, and protein metabolism, liver function tests, and liver synthetic function were found in patients with type 2 diabetes, representatives of the Ukrainian population, who had a high risk of developing cardiovascular complications.

Conclusions

- Long-term use of dapagliflozin in combination with metformin contributed to the improvement of indicators of carbohydrate metabolism, in particular, a statistically significant decrease in IRI indicates a tendency to decrease insulin resistance and increase insulin sensitivity, according to the calculation index of HOMA.
- A significant decrease in transaminases and the de Ritis coefficient (p < 0.001; p < 0.001 and p < 0.05, respectively) and a tendency to decrease the levels of total bilirubin and thymol test indicate a positive effect of the combination of dapagliflozin and metformin on indicators of liver tests in patients with type 2 diabetes.
- A positive trend was noted in relation to a definite decrease in the levels of TC, TG, LDL-C and an increase in the level of HDL-C (p < 0.001; p < 0.01; p < 0.01 and p < 0.001, respectively). A significant increase in the content of total protein and platelets (p < 0.001), as well as an improvement in other indicators of the protein-synthetic function of the liver, indicates its improvement against the background of long-term use of dapagliflozin and metformin in patients with type 2 diabetes.
- The feasibility of using the combination of dapagliflozin in combination with metformin as long-term glucose-lowering therapy in patients with type 2 diabetes with a high cardiovascular risk has been substantiated.

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