Kozioł Magdalena, Krasowska Danuta, Lewicki Marcin, Pawlicki Mateusz, Łopuszyńska Anna, Krasa Aleksandra, Piekarska Ewa. The analysis of a wide spectrum of activity of Sodium-Glucose co-transporter-2 inhibitors. A literature review. Journal of Education, Health and Sport. 2020;10(8):439-449. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2020.10.08.054
https://apcz.umk.pl/czasopisma/index.php/JEHS/article/view/JEHS.2020.10.08.054
https://zenodo.org/record/4008150

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

Received: 01.08.2020. Revised: 05.08.2020. Accepted: 30.08.2020.

The analysis of a wide spectrum of activity of sodium-glucose co-transporter-2 inhibitors. A literature review

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ABSTRACT

Introduction: The discovery of sodium-glucose co-transporter-2 inhibitors is attributed to phlorizin, which after oral administration caused the excretion of glucose in urine. Later studies showed that this effect was conditioned by SGLT-2 inhibition. However, this substance has not been used in the treatment of diabetes mellitus due to its non-selective action. Beeing also active against SGLT-1 transporters in alimentary tract, it causes osmotic

diarrhea, dehydration and eventually malnutrition. Currently in Poland, gliflozins are used only in the treatment of diabetes mellitus, mainly type 2, especially with coexisting obesity and high cardio-vascular risk. However, as many human and animal studies show, the effect of SGLT2 inhibitors can be observed in many systems and organs.

Results: The best known non-anti-diabetic action is the reduction of body fat and protection against fat accumulation following a high-calorie diet. These compounds reduce the production of endogenous fatty acids. Moreover, gliflozines lower the levels of cholesterol, triglycerides, uric acid and aminotransferases. They have a protective effect on the liver because they cause remission of nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD). They lower the cardiovascular risk and have an anti-inflammatory effect. Moreover, they inhibit vascular remodeling and improve hemodynamic conditions.

Conclusions: According to many research, gliflozines have many collateral effects which can be used in the clinic as a treatment of diseases other than diabetes or coexisting with it. Obesity and cardiovascular diseases are among the most important health problems in the modern world. SGLT-2 inhibitors can prevent the above-mentioned diseases and reduce them.

Key words: Sodium-glucose co-transporter-2 (SGLT2) inhibitors; obesity; weight loss; mechanisms; kidney.

Introduction: The beginning of the group of drugs, i.e. sodium-glucose 2 cotransporter inhibitors, is attributed to the discovery of phlorizin. This compound, after oral administration, caused glucose excretion in the urine, which resulted in a reduction of blood glycemia [1]. As it emerged from later studies, this effect was conditioned by the inhibition of sodium-glucose co-transporters-2 (SGLT-2) in the kidney [2]. Unfortunately, this substance has not been introduced into antidiabetic therapy. Firstly, it is poorly absorbed from the gastrointestinal lumen. Secondly, it is characterized by non-selective action, inhibiting both sodium-glucose symporters (SGLT1 and SGLT2), which are present in various body tissues [3]. The effects of phlorizin on SGLT1 located in the intestine resulted in increased adverse effects, such as osmotic diarrhea (due to malabsorption glucose-galactose) dehydration and malnutrition [4]. For this reason, this compound was not approved for the treatment of diabetes, but it did compel–further research on more selective compounds acting only on SGLT-2 receptors. In Poland, these substances are used mainly in the treatment of diabetes mellitus with insulin resistance, in particular diabetes coexisting with obesity, in monotherapy (in patients with poor tolerance of metformin) or in combination with other oral medications or insulin. However, as studies show, this substance also affects the functioning of other tissues and organs, including a protective effect on the kidneys, cardiovascular system. In addition, many results indicate that phlosines decrease visceral fat, remission NAFLD and mitigate chronic obesity-related inflammation.

Current status and future perspective: The main mechanism of action of gliflozin is a strong selective inhibition of sodium-dependent glucose cotransporter-2 [5]. In a healthy adult human with normoglycemia, approximately 140-180 g of glucose is filtered during a day and is almost completely reabsorbed in the proximal nephron tubules. About ninety percent of this process takes place in the convoluted tubule as an active transport along the sodium ion concentration gradient, which is determined by the activity of the ATP-Na / K pump. By symport, one glucose molecule enters the epithelium from the lumen of the tubule together with one sodium ion molecule thanks to SGLT-2. Another ten percent of the filtered

glucose is reabsorbed in the straight segment of the proximal tubule by SGLT-1. By reabsorbing the filtered glucose, the kidneys contribute to the maintenance of blood glucose homeostasis. The selective inhibition of SGLT-2 manifests itself in the inhibition of the reabsorption of glucose from the renal tubules and the resulting glucosuria. This process is not insulin dependent. It lowers serum glucose level, so it has been used primarily in the treatment of insulin-resistant diabetes [3,6].

Studies show that SGLT-2 inhibitors are effective in long-term glycemic control in monotherapy and in combination with other hypoglycemic drugs [7,8]. Kashiwagi A and Maegawa H. proved that canagliflozin lowers glycated haemoglobin level by about 0.74% [9]. This was confirmed by the results of other independent studies [10]. Moreover, it has been shown that the addition of gliflozin to insulin therapy in patients with type 2 diabetes, significantly reduces the amount of insulin intake (decrease by 7.28% after three months of therapy) [11].

SGLT-2 inhibitors have their receptors not only in the kidneys but also in other body tissues, for example in the liver. A study by Kern M. et al. demonstrated that empagliflozin increases glucose uptake by the liver while reducing gluconeogenesis. This improves insulin sensitivity. However, increased glucose uptake by muscles and adipose tissue was not demonstrated, which indicates the lack of SGLT-2 receptors in those locations [12].

At present, the problem of obesity is widespread all over the world. This condition predisposes, among others, to hypertension, kidney diseases. Moreover, excessive body weight is a risk factor of diabetes, because it leads to metabolic complications such as hyperinsulinemia, dyslipidemia and insulin resistance. Studies show that dapagliflozin has a positive effect on patients struggling with obesity. Calorie excretion with urine helps to reduce the amount of fat tissue. In 2018, Dong Wang and others conducted a mouse study, which was administered dapagliflozin for 26 weeks. Four groups fed on different diets were created. The first group of animals was burdened with obesity induced by a western high-fat diet (WD), the second group was fed a low-fat diet (LF), the third WD with dapagliflozin and the last (LF) with dapagliflozin. The growth curve showed a significant weight increase in mice fed on a WD diet in comparison to the group fed on LF. Simultaneous intake of dapagliflozin reduced the rate of weight gain by about 9%. Diet with dapagliflozin also reduced plasma triglycerides by about 21.83% in WD groups and by 3.3% with LF diet. Moreover, a diet with SGLT-2 inhibitor caused a decrease in plasma cholesterol, glucose and insulin levels. Unfortunately, the study also showed that this compound did not affect the appetite center as the diet with dapagliflozin did not reduce the quantity of food intake [13].

Moreover, a systematic review carried out by Orme et al. in patients previously treated with sulfonylurea derivatives, dapagliflozin was the most effective in reducing body weight (by 1.54kg) compared to the GLP-1 (exenatide) used (loss of 0.65kg and the DPP4 inhibitor, which caused an average weight increase of 0.57 kg. [14]. Another study confirming the influence on body weight loss among antidiabetic drugs was a paper published by Jabbour et al. It has been proved that adding dapagliflozin to the therapy of patients already treated with metformin and sitagliptin resulted in a 2.1 kg reduction (95% CI -3.2 to -1 kg) compared to placebo [15].

It has been demonstrated that the majority of dapagliflozin-related weight loss is caused by the reduction of total body fat mass, abdominal fat volume (VAT) and

subcutaneous fat volume (SAT) [16]. In a study published in 2020. Dr. Lars Johansson et al. studied the effect of dapagliflozin, saxaglyptin and metformin on the volume of fat and liver fat. This was a multicenter study, randomized on a group of 823 patients. After 52 weeks from the start of therapy 59 patients underwent MRI. It turned out that therapy with dapagliflozin significantly reduced liver fat volume (by about 30%) and subcutaneous fat volume by over 10%). In patients in the group treated with dapagliflozin in combination with saxagliptin and metformin, body weight was reduced from 90.8 ± 19.7 kg to 88.4 ± 18.1 kg in week 52 [17]. The mechanism of fat tissue reduction during SGLT-2 inhibitors therapy is not fully understood. It is believed that this compound decreases liver lipogenesis and increases insulin secretion. Additionally, it alleviates obesity-related inflammation by suppressing proinflammatory cytokines and relieving oxidative stress [18,19].

In addition to the beneficial effect on glycemic levels and obesity rates, SGLT-2 inhibitors have a protective effect on the liver. This is manifested not only by a decrease in liver fat volume but also by a decrease in aminotransferase levels in people with type 2 diabetes, which was verified in the study by Sattar N. et al. in 2018. ALT and AST levels were analyzed before the therapy and after 24 weeks of empagliflozin administration. A decrease in enzyme levels by 2.96 ± 0.18 U/l was observed, with an insignificant change in the placebo group. Transaminases, especially ALT are correlates of hepatic fat levels. Changes in the levels of these indicators are consistent with a decrease in the liver fat content. [20] The beneficial effect on the reduction of liver adipocyte volume was confirmed by Eriksson JW. et al. describing a study carried out on 84 patients with type 2 diabetes. As a result of the study, 12-week therapy with dapagliflozin resulted in the decrease of liver fat volume by 13% and in association with Omega-3 acids by 21%.Moreover, dapagliflozin monotherapy resulted in decreased markers of hepatocyte damage such as alanine aminotransferase, aspartate aminotransferase, γ-glutamyltranspeptidase, cytokeratin CK 18-M30 and CK 18-M65 and plasma fibroblast growth factor 21 [21].

Many articles about the complex influence of gliflozins on the organism, contributing to the reduction of risk and progression of metabolic disease. A group of researchers from Taiwan at the beginning of 2020 described a mouse study conducted with the use of the latest NGI001 gliflozin. This compound has been proven to protect against metabolic diseases and related complications. The decrease in the deposition and synthesis of fatty acids was most probably related to the reduced activity of acetyl-CoA carboxylase. Moreover, gliflozin improved the regulation of carbohydrate metabolism and decreased insulin resistance [22].

The SGLT-2 inhibitors also have an anti-inflammatory effect, which was described from the studies in 2016 by Jojim T et al. It has been proven that empagliflozin protects against NASH development [19]. This thesis was confirmed in 2017 by Tobit H et al. Patients were administered dapagliflozin, which resulted in NASH remission and improvement of hepatic steatosis markers [23].

Cardiovascular disease (CVD) is one of the major causes of mortality in many countries. [24] Obesity, particularly visceral adipose tissue excess is one of the major risk factors of cardiovascular disease [25]. Excess adipokines produced by fat cells are involved in the pathogenesis of CVD [26,27]. The studies demonstrate that perivascular adipose tissue (PVAT) may be an important modifiable factor. The ectopic deposition of fat in PVAT may cause, among other things, remodeling of arterial walls leading to atherosclerosis [28]. Some

results suggest that SGLT-2 inhibitors may prevent the mentioned processes. The study carried out by Mori Y et al. described the effects of luseogliflozin on PVAT remodeling and neointima formation after vascular wire damage in mice. The animals were divided into four groups. Two of them were fed a low-fat diet (LFD), another two high-fat diet (HFD). After 60 days luseogliflozin was added to the diet for one group of LFD and one HFD. After 75 days, femoral artery damage and unilateral removal of surrounding PVAT were performed. At the end of the experiment tissues were taken for examination, which showed a significant decrease in the thickness of neointima and intima-media ratio in mice treated with luseogliflozin. The same result was found for the removal of PVAT. Moreover, the drug administered weakened PVAT remodeling in HFD-fed mice, increased adiponectin gene expression around the lesion and decreased the number of infiltrating macrophages with PDGF-B expression. This study suggests that SGLT-2 inhibitors may be used as prevention of restenosis after balloon or stent angioplasty [29].

Many studies suggest that gliflozins show extremely beneficial effects on the cardiovascular system. There are many hypotheses about the mechanisms that determine this effect [30,31,32,33]. Firstly, they improve the haemodynamic state of the body by lowering blood pressure, increasing haematocrit and acting diuretically. Secondly, they condition the negative energy balance by excretion of glucose with urine, production of ketone bodies [34] and reduce atherogenic risk factors such as high levels of uric acid [11,35] and triglycerides. At the same time, they increase the HDL level [36,37]. However, many authors claim that rapid improvement of the cardiovascular system suggests a higher proportion of haemodynamic factors as the main mechanism of beneficial effect. A large EMPA-REG OUTCOME study has shown a statistically significant reduction in the risk of cardiovascular death and number of hospitalizations for heart failure in patients treated with empagliflozin. Moreover, a decrease in early diabetic complications in nephrops was observed. [38] More recent independent studies with other SGLT-2 inhibitors such as CANVAS [39] and CREDENCE [40] have confirmed the previously stated conclusions.

Hypertension is another disease affecting many people in the world, which often occurs in combination with other diseases, including the previously mentioned T2 diabetes, obesity. It turns out that SGLT-2 inhibitors reduce systolic and diastolic pressure. It is believed that these drugs reduce sympathetic tension, increase osmotic diuresis and minimally increase natriuresis [41,42]. Such action additionally reduces the risk of cardiovascular events [43]. The study with dapagliflozin showed that this drug decreases the plasma volume and increases haematocrit, reticulocytes and red blood cell count. This effect was partially explained by increased erythropoietin production and therefore increased erythrocyte production [44]. Both systolic and diastolic blood pressure decreased significantly by 2.8 and 1.6 mmHg, respectively, in a collective analysis of five studies developed by Kashiwagi A et al. The pressure decrease was significantly higher at initial systolic pressure >140 mmHg [37]. Another systematic review and meta-analysis proved a decrease in systolic and diastolic pressure by 4 mmHg and 1.6 mmHg, respectively, when using SGLT-2 inhibitors [9, 45]. The studies suggest that the observed benefits are affected by diuretic effects. The EMPA-REG OUTCOME study reported a 38% reduction in the number of patients who required loop diuretics after empagliflozin [46].

An important advantage of SGLT-2 inhibitors is their nephroprotective effect. Receptors for gliflozins are located in the kidneys, which results in reduced glomerular

hyperfiltration (due to reduced sodium reabsorption and modification of the glomerular-globular return concentration) [47] modulation of RAS and increase in erythropoietin production. These compounds prevent damage to proximal tubular cells by inhibiting glucose absorption. This protects against glucotoxicity and oxidative stress [48]. Moreover, the systolic pressure reduction alone determines the inhibition of arteriovenous reconstruction. The randomized double-blind study carried out by V. Perkovic et al. was to determine the effect of canagliflozin on kidneys. It turned out that the relative risk of end-stage renal failure was 32% lower, while the risk of doubling creatinine concentration or death from renal causes was 34% lower in the group of patients taking canagliflozin compared to the placebo group. [40]

Diabetic nephropathy is one of many complications of untreated or poorly controlled diabetes. It is known that in this disease the expression of SGLT-2 protein is increased. Studies on cultured human proximal tubular cells have shown that insulin, not elevated glycemic level, increases the expression of SGLT-2 protein. It turns out that this increase was associated with an increased content of reactive oxygen species. [49] Wang Xiaoxin et al. indicated that inhibition of SGLT-2 protein decreases the accumulation of lipids, inflammation and thus slows down the development of nephropathy in mice with diabetes. The immunofluorescence study showed that SGLT2 inhibition prevented the accumulation of extracellular matrix. Moreover, protective effect on podocytes with WT1 and synaptopodine was demonstrated. However, the drug used was not able to stop the decrease in the amount of nephrin [50].

It was initially suggested that gliflozin may increase the risk of AKI by sudden decrease in GFR. In 2016, FAERS reported 101 cases of AKI in type 2 diabetic patients treated with canagliflozin and dapagliflozin at the beginning of treatment. However, up 83% of these patients took drugs predisposing to this disease (e.g. NSAIDs, ACE inhibitors, diuretics) [51]. In order to determine the safety of SGLT-2 inhibitors, Nadkani et al. conducted large cohort studies among patients suffering from T2 diabetes. It was demonstrated that these drugs even lower the risk of AKI [52]. A similar conclusion was reached by the scientists conducting the CANVAS study demonstrating that the administration of canagliflozin was not associated with an increased risk of AKI compared to placebo [39]. Another confirmation is the EMPA-REG study, which described the protective effects of empagliflozin on acute renal failure [38].

The use of insulin in patients with type 1 diabetes is often associated with marked fluctuations in blood glucose levels and hypoglycemia. A study to evaluate the safety and efficacy of dapagliflozin in patients with type 1 diabetes mellitus [59]. Finally, dapagliflozin has been approved in the EU at a dose of 5 mg / day as an additive to insulin in adults with type 1 diabetes (T1D) and a body mass index (BMI) $\geq$ 27 kg / m^2 when insulin alone is not sufficient to maintain a normal blood glucose level [60].

Conclusions

Sodium-glucose co-receptor-2 inhibitors have a broad activity in many organs and tissues of the body due to abundance of these receptors. They reduce the level of glucose by excreting it in the urine, and reduce the rate of adipose tissue growth (even in individuals fed a high-fat diet). In addition, they lower blood pressure and reduce the risk of atherosclerosis through their anti-inflammatory and neointimal proliferation inhibiting effects. Another

important action is the inhibition of NASH and NAFLD development. Among the positive effects that we can find in laboratory tests are lowering of LDL, TG, uric acid level, ASPAT, ALAT and increase of HDL levels. All these effects contribute to the reduction of cardiovascular risk and the occurrence of metabolic disease. It is known that a large volume of visceral and hepatic fat promotes cardiovascular complications and type II diabetes mellitus [53,54]. In addition, higher overall mortality was demonstrated in patients with coexisting diabetes T2 and NAFLD. Therefore, any effective therapy leading to weight loss and liver fat reduction can protect obese and/or DM2 patients against other diseases.

Another problem for people with diabetes is progressive kidney dysfunction. The pathogenesis of diabetic kidney diseases is multifactorial [55,56]. That is why, despite the introduction of all known prophylactic measures, including strict control of glycemia, strict control of blood pressure, inhibition of angiotensin-converting enzyme, angiotensin II receptor or mineralocorticoid receptor antagonism, kidney disease inevitably progresses in these patients [57]. Therefore, there is a need to introduce a new treatment method, which would affect many pathways associated with diabetic nephropathy.

Nowadays, the use of SGLT-2 correceptor inhibitors is mainly limited to the antidiabetic effect, because this effect has been best studied so far. However, according to the studies presented by me, the possibilities of these drugs are much greater, so there is a clear need for large, multi-centre studies assessing the effect of gliflozin to finally prove all the beneficial health effects. One such study is a randomized controlled trial that started on May 29, 2019 in Mexico. The study included patients with diabetes or pre-diabetes coexisting with obesity of the 3rd degree. The main outcome of the study is to establish whether the combination of dapagliflozin and metformin is more effective than metformin alone at reducing weight. [58] Similar research should be promoted to supply trustworthy recommendations.

The DAPA-HF study by AstraZeneca showed that dapagliflozin reduces the risk of worsening heart failure or death from cardiovascular causes, regardless of diabetes [61]. Thanks to this, on May 6, 2020. The FDA has approved AstraZeneca Forxiga dapagliflozin for the treatment of heart failure with reduced ejection fraction (HFrEF) in adults with type 2 diabetes (T2D). Moreover, EMPEROR Reduced will probably allow the registration of empagliflozin as a drug used in cardiology.

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