SGLT-2 inhibitors: a novelty in the treatment of type 2 diabetes

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Abstract

Sodium glucose co-transporter-2 (SGLT-2) inhibitors are the newest group of drugs for the treatment of type 2 diabetes mellitus, which have been in clinical use for the past few years. They act in the proximal renal tubules by reducing the glucose reabsorption, the glucose then being excreted in the urine. Consequently, by decreasing blood glucose levels, they exert a favourable effect on the glycaemic control and importantly, do not increase the risk of hypoglycaemia. SGLT-2 inhibitors also possess favourable metabolic effects, especially on weight, blood pressure and serum uric acid level reduction. They also slow down the progression of diabetic kidney disease. For some SGLT-2 inhibitors it was shown that they exert beneficial effects on the cardiovascular system by reducing cardiovascular events and complications through yet unknown mechanisms, which are subject of intensive research. SGLT-2 inhibitors rarely cause serious side effects. This manuscript describes the mechanism of action of SGLT-2 inhibitors, their effect on the glycaemic control, metabolic effects, effects on the incidence of cardiovascular disease, as well as the most common adverse effects and prescribing restrictions for SGLT-2 inhibitors in Slovenia.

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1 Introduction

Diabetes is a metabolic disease characterised by chronically increased blood glucose levels. The incidence of diabetes has been increasing and has reached pandemic proportions. It was estimated that in 2017 there were 425 million adults with diabetes in the world. The number of patients with diabetes is predicted to rise to 642 million by 2040. Additionally, by 2025, the number of deaths attributable to diabetes and its complications will increase by 50 % (1,2).

As the available medications do not provide optimal glycaemic control, there is a need for the development of new antihyperglycaemic drugs. Sodium-glucose co-transporter 2 (SGLT-2) inhibitors represent a novel approach to the management of type 2 diabetes. They were approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) between 2012 and 2014 (3). The first SGLT-2 inhibitor was phlorizin, which was extracted from the bark of apple trees. This molecule has

been known for more than 200 years. It is a non-selective inhibitor of both SGLT-2 and SGLT-1. Phlorizin provides effective glycaemic control and reduces insulin resistance in diabetic animals. Clinical use of this drug is restricted by its poor absorption after oral administration, as well as by nausea and diarrhea due to SGLT-1 inhibition. Its metabolic product, phloretin, also inhibits the glucose transporter type 1 (GLUT-1) expressed in erythrocytes and blood-brain barrier. Nevertheless, the phlorizin molecule was succesfully used as the basis for synthesis of several selective SGLT-2 inhibitors, such as empagliflozin, dapagliflozin, canagliflozin and others (1).

2 Mechanism of action

In individuals without diabetes, 180 g of glucose is filtered by the renal glomerulus, daily, and virtually all of it is subsequently reabsorbed in the proximal tubule. Thereby the kidney prevents glucose loss (1,4). Once the renal threshold for glucose is exceeded in healthy individuals, i.e with glucose levels above 11 mmol/L, glycosuria results (5). This protective action of the kidney prevents further increase in plasma glucose and the associated harmful effects (6).

In the proximal renal tubule, glucose can be reabsorbed passively via GLUT transporters or actively via SGLT transporters (4,6). The latter transports glucose into the cells using sodium gradient created by Na/K ATPase pump at the basolateral border of the cell membranes (1). SGLT transporter has two variants: SGLT-1 and SGLT-2. SGLT-1 is found mostly in the small intestine, kidney, heart and skeletal muscles, where it is responsible for active absorption of glucose into these tissues. SGLT-2 is found almost exclusively in the proximal renal tubules, where it reabsorbs 80–90 % of the filtered glucose load. SGLT-1 is responsible for less than 10 % of the glucose reabsorption in kidneys (4-7). It has been demonstrated that the number of SGLT-2 transporters is increased in diabetic patients (1). With rising plasma glucose concentrations, kidneys' SGLT-2 expression increases, causing an increased renal threshold for glycosuria. Additionally, this causes enhanced renal glucose reabsorption in proximal tubules, which leads to further elevation of its plasma levels (5).

SGLT-2 inhibitors act by inhibiting SGLT-2 in the proximal tubules, thereby preventing glucose reabsorption. Increased urinary glucose excretion lowers its plasma concentrations, leading to efficient glycaemic control (8). SGLT-2 inhibitors induce urinary excretion of 20–100 g of glucose and cause a daily loss of 90–450 kcal (4). The efficacy of SGLT-2 inhibitors depends on the plasma glucose levels: low glucose levels reduce their efficacy. The decrease in glucose levels caused by SGLT-2 inhibitors in non-diabetic individuals differs from that in patients with diabetes. SGLT-2 inhibitors act independently of insulin secretion and therefore do not cause beta-cells failure nor do they increase the risk for hypoglycaemia (6). The mechanism of action of SGLT-2 inhibitors is presented in Figure 1.

3 Basic antihyperglycaemic effects

Several previous studies have shown that SGLT-2 inhibitors decrease HbA1c. This was dependent on the baseline values: HbA1c droped by 0.51–1.45 % with the baseline HbA1c of 7–9.1 % (1). A mean reduction in HbA1c levels induced by SGLT-2 inhibitors was 0.69 % compared to placebo (3). In the »Empagliflozin Cardiovascular Outcomes and Mortality

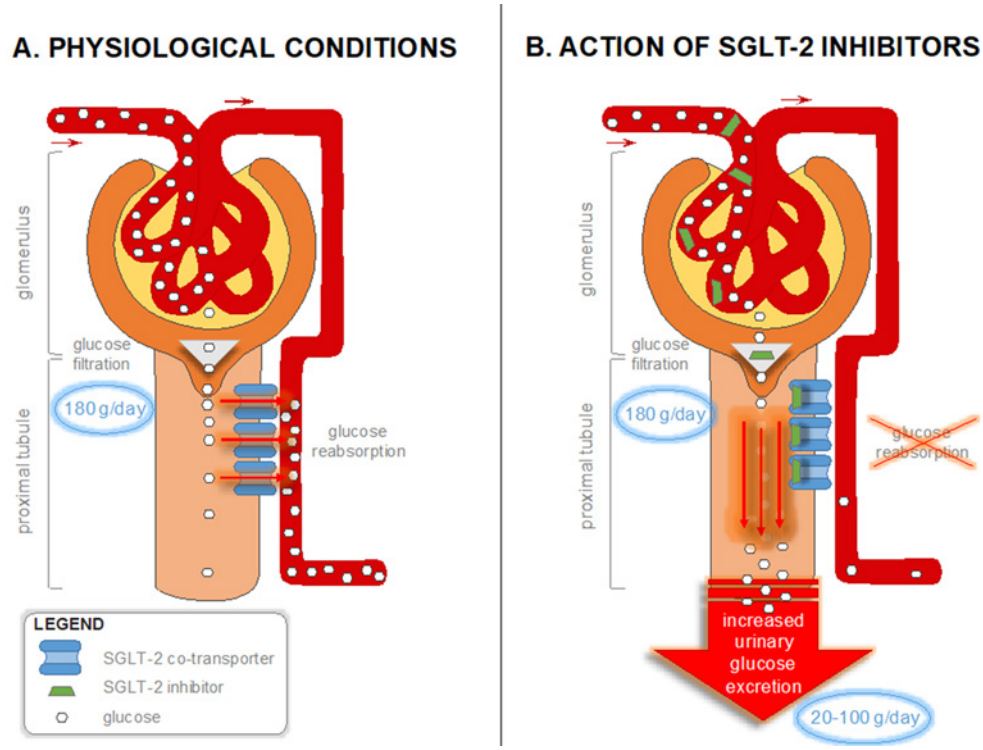

Figure 1: Schematic presentation of SGLT-2 inhibitor action in the renal glomerulus and proximal tubule. Adopted by (5).

in Type 2 Diabetes« (EMPA-REG OUTCOME) trial, empagliflozin 10 mg daily decreased HbA1c levels by only 0.54 %, and empagliflozin 25 mg daily by 0.6 % (9). Treatment with SGLT-2 inhibitors was reported to reduce fasting glucose levels by an average of 0.9 mmol/L as compared to placebo (3).

The rate of hypoglycaemic episodes in patients treated with SGLT-2 inhibitors did not exceed that in placebo groups. This may be due to the insulin-independent action of these drugs. In addition, the effects of SGLT-2 inhibitors decrease when the plasma glucose levels are decreasing thereby preventing hypoglycaemia (5). The rate of hypoglicaemia was higher in patients taking SGLT-2 inhibitors in combination with other glucose-lowering drugs that may cause hypoglycaemia, such as sulfonylureas or insulin (6). SGLT-2 inhibitors caused statistically less mild hypoglycaemia episodes than sulfonylureas, their rate being higher by 30 % in patients taking sulfonylureas than in patients taking placebo (10). A meta-analysis showed that the incidence of mild hypoglycaemia in the treatment with dapagliflozin and empagliflozin was low and comparable with placebo (3). Figure 2 summarizes basic, additional favourable and adverse effects of SGLT-2 inhibitors (see further text).

4 Favourable metabolic effects

4.1 Reduction of body mass

Patients receiving SGLT-2 inhibitor lose 1–5 kg, which usually represents 2–5 % of their body mass. A greater loss was recorded in patients with long-stan-

ding diabetes and higher baseline body mass (6). Lioudaki et al. found that the effects of SGLT-2 inhibitors on weight loss are dose-dependent: body weight loss of 1.61 kg was reported with lower doses, and a loss of 2.66 kg with higher doses. Importanlty, weight loss was associated with a decrease in waist circumference (7). Another meta-analysis demonstrated that treatment with SGLT-2 inhibitors led to significant loss of body weight: by 1.3–2.24 kg with dapagliflozin and by 1.84–1.93 kg with empagliflozin. A statistically significant association between weight reduction and higher doses was reported for dapagliflozin but not for empagliflozin (11). Weight gain due to insulin treatment was prevented when SGLT-2 inhibitor was added (6).

During the initial 12–26 weeks of treatment with SGLT-2 inhibitors, a fast body weight loss was recorded, whereafter it stopped or showed only a minimal decrease. Body weight reduction in the initial period seems to be due to the loss of fluid through osmotic diuresis, and later on due to the loss of body fat. Dual energy x-ray absorptiometry (DEXA) measurements demonstrated that 30 % of body weight loss was caused by osmotic diuresis and 70 % of weight loss was attributable to loss of adipose tissue (mostly visceral and, to a lesser extent, subcutaneous tissue) (1). The most probable cause of body fat loss is a metabolic shift from carbohydrate to lipid utilization mediated by SGLT-2 inhibitors, which leads to enhanced glucose excretion and the resulting relative glucose deficiency (1). The effects of SGLT-2 inhibitors on body weight reduction are not yet fully understood. A greater weight loss would be expected considering that in patients treated with SGLT-2 inhibitors, up to 100 g of glucose is excreted in the urine per day (11).

4.2 Lowering of uric acid levels

Many patients with type 2 diabetes have elevated serum uric acid levels, which may be responsible for chronic complications of diabetes (6,12). SGLT-2 inhibitors lower serum uric acid levels by 10–13 %; a greater decrease occurring in individuals with higher baseline values (7). Therapy with canagliflozin normalised uric acid levels in 20–30 % of patients with elevated uric acid. Dapagliflozin also lowered uric acid levels, but the effect wore off after treatment discontinuation. Empagliflozin was also shown to posess uric acid-lowering effect (12). The most probable mechanism is enhanced glycosuria with the resulting exchange of uric acid at the apical membrane of the proximal tubular cell, and increased excretion of uric acid in the urine, most likely due to the effect on the uric acid transport in the renal proximal tubules, e.g. GLUT-9 (12).

4.3 Effects on fat metabolism

Individuals with type 2 diabetes usually have increased triglyceride levels, low levels of high-density lipoproteins (HDL) and high levels of low-density lipoproteins (LDL). Patients treated with SGLT-2 inhibitors showed mild reduction of triglyceride levels and an increase in the HDL levels. The mechanisms responsible for these changes most likely include weight loss and decrease in glucose levels, leading to reduced production of very low density lipoproteins (VLDL) in the liver. Consequently, plasma triglyceride levels decrease (7). In comparison with placebo, SGLT-2 inhibitors increase HDL levels by 0.05 mmol/L, and are expected to reduce triglyceride levels by 0.09 mmol/L (3). On the other hand, an increase in LDL levels, which is linked to

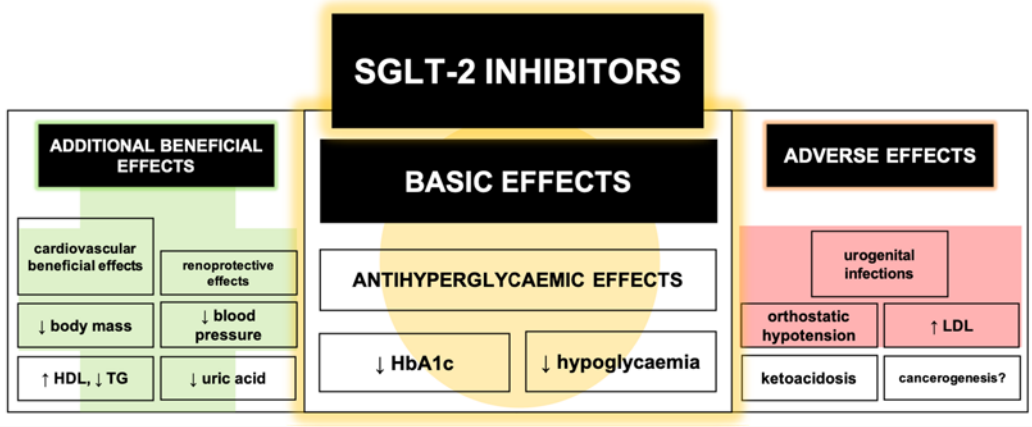

Figure 2: Overview of basic effects, additional beneficial effects and adverse effects of SGLT-2 inhibitors. HDL – high density lipoprotein, TG – triglycerides, HbA1c – glycated haemoglobin, LDL – low density lipoprotein.

higher risk for cardiovascular diseases, is one of adverse effects associated with SGLT-2 inhibitor therapy.

4.4 Effects on hepatic function

SGLT-2 inhibitors decrease alanine aminotransferase (ALT) levels by 2.8 IU/L, thereby exerting a beneficial effect on non-alcoholic fatty liver disease. Whether ALT reduction is due to the body weight decrease caused by SGLT-2 inhibitors or it occurs because of their direct effects on the liver remains unclear (3).

5 Beneficial non-metabolic effects

5.1 Blood pressure reduction

SGLT-2 inhibitors were shown to significantly reduce systolic and diastolic blood pressure in several studies. A larger decrease was observed for systolic blood pressure and this correlated with the active substance and dosage of the SGTL-2 inhibitor used. The effect on blood pressure did not depend on the degree of glycaemic control and weight loss (noted soon after the initiation of SGLT-2 inhibitor treatment). Greater decrease of blood pressure occured in patients with higher baseline systolic blood pressures (6,7). In their meta-analysis, Shyangdana et al. showed that SGLT-2 inhibitors used as monotherapy or in combination with metformin led to decreased blood pressure compared to placebo; i.e. to –2.6 mmHg by empagliflozin 10 mg/day, and to –6 mmHg by canagliflozin 300 mg/day. The same study showed that SGLT-2 inhibitors induced a mean decrease in systolic pressure of –3.77 mmHg and a mean decrease in diastolic pressure of –1.75 mmHg. It should be emphasized that blood pressure reduction caused by SGLT-2 inhibitors was not associated with increase in heart rate (13). The greatest decrease in blood pressure was seen in patients treated with canagliflozin (3).

Primary mechanisms involved in blood pressure reduction seem to include osmotic diuresis and enhanced urinary sodium excretion (decreased amount of sodium in the body). Increased delive-

ry of sodium to the macula densa with SGLT-2 inhibition reduces renin secretion and in the long term leads to inhibition of the renin-angiotensin-aldosterone system with beneficial effects on blood pressure. The absence of heart rate increase supports this theory (7). Reduction of arterial stiffness is another factor contributing to a decrease in blood pressure, as shown in young patients with type 1 diabetes (14).

5.2 Renoprotective effects

SGLT-2 inhibitors provide renal protection by improving glycaemic control, reducing blood pressure, and most probably, by exerting direct effects on the kidney (reduction of glomerular hyperfiltration, inflammation and fibrosis). Progression of diabetic nephropathy is associated with a gradual decrease in glomerular filtration rate (GFR), leading to reduced efficacy of SGLT-2 inhibitors. In patients with GFR < 45 ml/min, their effects on HbA1c eventually disappear, but they continue to exert other non-metabolic effects (15).

Diabetic nephropathy develops due to several factors. The mechanisms responsible for the development of glomerular hyperfiltration include impaired neurohumural activation (haemodynamic effect) and tubular factors. The former involves a decrease in afferent arteriole tone compared to the efferent one, and increase in intraglomerular pressure, leading to glomerular hyperfiltration. This is due to increased activity of angiotensin II with affinity for efferent arteriole constriction. Another mechanism involves increase in glucose burden in the proximal renal tubule and the associated SGLT-2 and SGLT-1 hyperactivity and increased glucose and sodium reabsorption in the proximal tubules, with the resulting activation of tubulo-glomerular feedback because of diminshed delivery of sodium to the macula densa in the distal tubule of the nephron. As a result, vasodilation of the afferent arteriole and glomeular hyperfiltration occur. Hyperfiltration is followed by a progressive decrease in GFR. At early stages, hyperfiltration causes glomerulosclerosis, and the compensatorily increased filtration rate in other, previously unaffected glomeruli, leads to sclerosis of these glomeruli too (1,6,15).

SGLT-2 inhibitors increase delivery of the filtered burden, especially sodium, to the distal nephron segment and macula densa, thereby enhancing local adenosine excretion leading to adenosine-induced constriction of the afferent arteriole. The resulting decrease in intraglomerulal pressure and GFR has protective glomerular effects (15,16). Empagliflozin has been shown to reduce inflammation and decrease the level of renal fibrosis due to improved glycaemic control, thereby limiting glucose-induced impairment of proximal renal tubules. Also, it was found that the treatment with SGLT-2 inhibitors for 24 weeks decreased urinary albumin-creatinine ratio in patients with diabetes and albuminuria by 41 % compared to placebo (7). Thanks to the above described mechanisms, the use of SGLT-2 inhibitors in combination with angiotensine-converting enzyme inhibitors has proved to be the most effective way to prevent progression of diabetic nephropathy and is superior to the use of a single drug (1).

5.3 Cardiovascular benefits

According to the requirements issued by the FDA in 2008, all new glucose-lowering drugs should be investigated for their potential cardiovascular risks. Two such studies have been conducted so far for SGLT-2 inhibitors, i.e the EMPA-

REG OUTCOME trial for empagliflozin and the Canagliflozin Cardiovascular Assessment Study (CANVAS) for canagliflozion, both in patients with type 2 diabetes. The studies differed in that the EMPA-REG OUTCOME trial included 99.5 % of patients who had suffered a previous cardiovascular event, and the CANVAS study included only 67 % of such patients. The primary aim of both studies was to determine the effect of SGLT-2 inhibitors on the following three major adverse cardiovascular events (MACE): cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. The results of both investigations confirmed the efficacy of SGLT-2 inhibitors, which decreased MACE by 14 % as compared to placebo. Yet, a difference was found between the two drugs when concerning the individual elements of MACE. In the EMPA-REG OUTCOME study the cardiovascular mortality decreased by 38 % during the study period (3.1 years), whereas in the CANVAS trial by 13 % during the study period (6.0 years). There seem to be several reasons for these results: different characteristics of the patients studied (different proportions of cardiovascular patients), effects of other cardioprotective drugs, selectivity of SGLT-2 inhibitors for SGLT-2 versus SGLT-1 (> 2500-fold for empagliflozin and > 250-fold for canagliflozin), and statistical analysis. Also, there was a difference in the time to the separation of survival curves. Based on data of the EMPA-REG OUTCOME the effect was noted early, i.e. after three months, and was attributed to haemodynamic effects, hypothesis of changes in cardiac fuel, improved fat metabolism and improved endothelial function. In the CANVAS trial these results were recorded later, i.e.after one year, which is attributable to positive effects of canagliflozin which slowed the progression of atherosclerosis (1,7,17-19). Importantly, in both groups treated with SGLT-2 inhibitors significanly less patients were hospitalised for heart failure compared to those receiving placebo: 35 % in EMPA-REG OUTCOME and 33 % in CANVAS trial (17-19). The described beneficial effects cannot be explained solely by the impact of drugs on glycaemia. It is assumed that the benefit is independent of glycaemic control, yet further studies are needed. In previous studies, it was shown that SGLT-2 inhibitors decrease plasma volume, enhance urinary sodium excretion and improve the response to diuretic therapy. In addition, they enhance a metabolic shift to improved myocardial bioenergetics (improved balance between oxygen consumption and work efficiency with ketone bodies utilization as compared to glucose). An interesting and important cardiovascular protective mechanism involves the increase in serum magnesium levels. The role of magnesium in protecting the myocardium against significant arrhythmias is well established (20). Thanks to their renoprotective action, SGLT-2 inhibitors reduce the degree of renal failure in patients with heart failure. Beneficial effects on endothelial function are also important. Thanks to the above decribed effects, SGLT-2 inhibitors may be an effective treatment option for patients with heart failure with preserved ejection fraction, for whom no such treatment has been available so far (8,21).

The mechanisms underlying positive cardiovascular effects of SGLT-2 inhibitors have not yet been fully investigated . Most probably, cardiac overload and oxygen consumption are reduced through lowered arterial pressure and decreased arterial stiffness, which decreases myocardial oxygen consumption and improves cardiac function. In addition, effects of protective mechanisms invol-

ved in SGLT-2 inhibition include body weight reduction, absence of stimulatory effect on sympathetic nervous activity, increase in urinary sodium excretion, reduction of oxidative stress, stimulation of glucagon excretion and other beneficial effects mediated by as-yet unidentified mechanisms of action (1,7,17).

An intensive research effort is currently underway to identify these mechanisms. The results obtained are expected to significantly contribute to improved prevention of cardiovascular events in patients with diabetes.

6 Adverse effects

The rate of adverse effects associated with SGLT-2 inhibitors reported by large-scale studies was similar to that found for other groups of antihyperglycaemic agents. It is estimated that serious adverse effects occur in 1.0 % to 12.6 % of cases (6). The most common adverse effects include urinary tract infections (vulvitis, vulvovaginitis, balanitis and balanoposthitis). Genital infections can be prevented by appropriate genital hygiene. Higher rates of urinary tract infections were not documented (6). Increased genital infection rates were attributed to increased amounts of glucose in urine, which encourage fungal and bacterial growth (1). SGLT-2 inhibitors induce osmotic diuresis with the resulting relative hypovolaemia, which may lead to orthostatic hypotension, reported in less than 3 % of patients. Using SGLT-2 inhibitors as an add-on to diuretics increases the risk for its onset (1,6). Therefore, drinking an extra amount of at least 500 mL of unsweetened fluid is recommended to prevent dehydration during the course of therapy (3). SGLT-2 inhibitors tend to increase LDL cholesterol (by up to 10 %), a finding documented in all patients (average increase – 0.9 mmol/L) (3). Minimal reduction of bone tissue formation, as well as an increase in bone resorption markers were reported, but there were no significant changes in mineral bone density (6). However, the CANVAS trial reported a 23 % increase in the rate of low-energy fractures, especially those involving the upper arm and ribs (17), which was attributed to a small increase in serum phosphate levels. It was found that reduced sodium reabsorption in the proximal renal tubule leads to increased reabsorption of sodium and phosphate through another transporter expressed in the proximal tubule. The net effect of elevated serum phosphate is enhanced parathormone activity and increased bone tissue resorption. Reduction of vitamin D production and calcium absorption occur for the same reason and lead to a decrease in bone mineral density (20). Canagliflozin has been shown to cause a minimal increase in serum potassium levels as well, especially in patients with impaired renal function and subjects who had been treated with drugs exerting effects on potassium levels, such as renin-angiotensin-aldosterone system inhibitors. This phenomenon was not documented in patients treated with empagliflozin or dapagliflozin. The net increase in serum potassium levels is the result of opposing mechanisms, the predominant effects being those responsible for potassium retention (20).

Patients treated with canagliflozin in the CANVAS trial showed twice the risk for lower limb amputation compared to the placebo group. A higher rate of amputations was documented in men and in subjects with previous amputation, neuropathy or peripheral artery disease. The risk for amputation was not dose-related. The exact cause is yet unknown, but it is supposed to be related to increased haemoconcentration due to osmotic diuresis and hypovolaemia (17,19).

Treatment with SGLT-2 inhibitors was also reported to cause diabetic ketoacidosis. The majority of affected individuals were patients with type 1 diabetes who received the drug off-label. There were several patients with type 2 diabetes in whom ketoacidosis was triggered by a variety of factors, including acute disease, infection, reduced food and fluid intake, missed insulin dose, surgical procedure or alcohol consumption. In some patients glucose levels were lower than usually noted in diabetic ketoacidosis; in some of them glucose levels were even within the normal range. Potential mechanisms underlying the development of ketoacidosis in patients receiving SGLT-2 inhibitors include: increased glucagon-insulin ratio, enhanced production of free fatty acids, shift from oxidative carbohydrate metabolism to oxidative free fatty acid metabolism, and reduced excretion of ketone bodies (1,22). SGLT-2 inhibitors should be discontinued prior to any major surgery or other invasive procedure associated with potential bleeding risk in order to prevent the development of diabetic ketoacidosis. Preparation for some interventions, e.g.colonoscopy, may cause dehydration. Also, SGLT-2 inhibitor therapy should be discontinued in patients anticipating severe stressful physical activity (e.g.running a marathon). It is recommended to discontinue the medication at least three days before the planned activity, i.e. at least five half-lives of the drug (23). In acute situations, such as vomiting, urgent surgery, or shock, SGLT-2 inhibitors should be discontinued immediately (24). However, no recommendations are available for minor investigations, especially contrast studies. Discontinuation of the treatment is suggested for patients undergoing contrast studies which may cause acute kidney injury with the resulting acidosis. Previous studies have shown that ketoacidosis due to treatment with SGLT-2 inhibitors is preventable because it could be anticipated and recognisable. Routine measurements of ketone levels in urine, however, are not recommended (1,22,24).

Patients treated with SGLT-2 inhibitors may be at higher risk of developing breast and bladder cancer. No definitive conclusions have yet been reached because of small cohorts and because it was not clear whether the disease was present before the treatment began. Nevertheless, treatment with SGLT-2 inhibitors is not advised for patients with bladder cancer (at present or in the past) (1).

7 Availability of SGLT-2 inhibitors in Slovenia

Currently, two agents from this group, i.e. empagliflozin and dapagliflozin, are available in Slovenia.

Empagliflozin is a selective SGLT-2 inhibitor. It exhibits rapid absorption and reaches peak plasma levels one to two hours after administration (25). Its half-life in plasma is 10.3–18.8 hours. The recommended dose of empagliflozin is 10–25 mg once daily. Current guidelines recommend that in patients with impaired renal function the dosage of empagliflozin should be adjusted as follows: with GFR < 60 mL/min the maximum daily dose is 10 mg, while with GFR < 45 mL/min empagliflizin is contraindicated or should be discontinued. With GFR < 60 mL/min, the therapy should not be restarted. In hepatic impairment, dose adjustments are not required, yet data on this subject are scarce (6,25). In Slovenia, empagliflozin, marketed as Jardiance, is also available in combination with metformin, under the brand name Synjardy.

Dapagliflozin shows greater selectivity for SGLT-2 than for SGLT-1. It exhibits rapid absorption and reaches peak plasma levels one to two hours after administration. Its bioavailability is 78 %. Dapagliflozin metabolism occurs predominantly in the liver and kidney via uridine diphosphate-glucuronosyltransferase (UGT1A9). The recommended dose is 5–10 mg once daily. In hepatic impairment the dose should be reduced from 10 mg to 5 mg daily. According to current guidelines, dapagliflozin is contraindicated in patients with GFR < 60 ml/min (6,25). In Slovenia dapagliflozin is marketed as Forxiga; in combination with metformin it is available under the brand name Xigduo. Results from recent studies suggest that GFR-related restrictions will be relaxed or even removed.

8 SGLT-2 inhibitor usage restrictions in Slovenia

Based on the world literature data SGLT-2 inhibitors can be prescribed as monotherapy or in combination with other glucose-lowering drugs, such as metformin, sulfonylureas, dipeptidyl peptidase 4 (DPP-4) inhibitors or insulin (3).

According to the guidelines on the use of SGLT-2 inhibitors in the treatment of type 2 diabetes issued by the Health Insurance Agency of the Republic of Slovenia, they can be prescribed only in the folowing cases:

1. in combination with metformin or sulfonylurea/repaglinide, when the use of sulfonylurea/repaglinide or metformin is contraindicated, or when adverse effects occured;
2. in triple therapy with optimal doses of metformin or sulfonylurea/repaglinide, when the doctor or the patient have reservations about insulin treatment;
3. in combination with insulin and metformin (or without metformin when it is contraindicated or adverse effects occur).

The drug can be prescribed only on the basis of the report and recommendation provided by a specialist diabetes clinic (26).

9 Potential for future use

The reported beneficial effects of SGLT-2 inhibitors go far beyond glycaemic control and open up new possibilities for their wider use. Diabetes is a disease associated with high cardiovascular risks. Therefore, not only good glycaemic control, but also appropriate protection against cardiovascular events, is of vital importance to diabetic patients. SGLT-2 inhibitors provide both benefits. Moreover, positive effects are exerted also in diabetic patients with a history of past cardiovascular events. Even more, renoprotective effects of SGLT-2 inhibitors are particularly welcome in early-stages of diabetic nephropathy. Additionally, very important is their weigth-loss effect, considering that the majority of patients with type 2 diabetes are overweight. Therefore, ideal candidates for treatment with SGLT-2 inhibitors would be overweight diabetic patients with high cardiovascular risk and early-stage diabetic renal disease. In view of the beneficial effects, one would expect SGLT-2 inhibitors to be more widely used and should be prescribed as a second line treatment (after metformin), yet their wider use seems to be limited by high cost. Another reason for their not being prescribed more frequently is that they have been available for clinical use only for a past few years, so more studies are needed to investigate their long-term effects.

10 Conclusion

SGLT-2 inhibitors are a novel group of antihyperglycaemic drugs. Previous studies have confirmed their effectiveness on glycaemic control and also additional beneficial metabolic effects, particularly those associated with weight loss. Additional advantage of SGLT-2 inhibitors is that they decrease blood glucose levels independent of the secretion and action of insulin and therefore do not increase risks for hyperglycaemia. Empagliflozin and canagliflozin have been shown to provide protection against cardiovascular events and the associated complications. After only a few years of clinical use, SGLT-2 inhibitors have proved to be very promising antidiabetic agents, yet further investigations are required to assess possible additional effects on metabolism and potential adverse long-term treatment effects.

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