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**Review**

# Inhibitors of type 2 sodium glucose co-transporters – a new strategy for diabetes treatment

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**Abstract:**

In the last few years, the type 2 sodium glucose co-transporters (SGLT2) have been the subject of particular attention as a new, potent group of anti-diabetic drugs.

SGLT2 inhibitors block glucose reabsorption in the kidneys, which prompts urinary excretion of glucose and results in lowering of its plasma levels. Although this group of medications is still under investigation, their efficacy in the treatment of type 2 diabetes mellitus (T2D) is very promising, with some of these inhibitors currently undergoing clinical trials.

**Key words:**

diabetes, sodium-glucose co-transporters, SGLT2 inhibitor

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## Introduction

Type 2 diabetes mellitus (DM2, T2D), which was formerly known as non-insulin-dependent diabetes mellitus (NIDDM), is characterized by the failure of sensitive tissues to respond to insulin (insulin resistance) and by the  $\beta$ -cell dysfunction that results in hyperglycemia. Untreated hyperglycemia leads to tissue damage that results in micro- and macro-vascular pathologies (i.e., heart disease, blindness, kidney failure, stroke), it also inhibits wounds healing, thereby prompting lower limb infections and gangrene. High glucose levels exacerbate insulin resistance and promote  $\beta$ -cell damage leading to their apoptosis [11, 18].

Almost half of patients with T2D are treated with oral medications [28, 32], and sometimes insulin is

added to some of these drugs. The aim of standard treatment, which combines pharmacotherapy with dietary and exercise intervention, is to reduce hyperglycemia and other risk factors for cardiovascular diseases, especially hypertension and dyslipidemia [21, 23, 28] because those disorders lead to inflammatory disease. Inflammatory disease results in atherosclerosis, which is why proper treatment should not only correct those parameters but also inhibit the inflammatory state [24].

Combinations of oral anti-diabetic medications are routinely used to help patients maintain a level of glycated hemoglobin (HbA<sub>1c</sub>) recommended by the American Diabetes Association and the European Association for the Study of Diabetes [1, 23].

Although an advanced and aggressive strategy for therapy of type 2 diabetes manages to lower blood

pressure and lipid levels, recent studies have shown that only about 7% to 15% of patients with diabetes are able to meet their glycemic target [4, 7]. These patients are a challenge for standard therapies, which drives the search for potential, new diabetes medications. It is for this purpose that the type 2 sodium-glucose co-transporters (SGLT2) inhibitors are now being evaluated by a number of pharmaceutical companies [11–13, 23]. The mechanisms of the most widely used anti-diabetic drugs have primarily focused on maintaining normal glucose levels with insulin, hypoglycemic agents, increasing insulin release, improving glucose disposal, controlling hepatic release or inhibiting intestinal glucose absorption (Tab. 1) [2, 23].

SGLT2 inhibitors represent a new strategy in the treatment of diabetes by inhibiting glucose reabsorption in kidneys, thereby prompting glucose urinary excretion. This not only results in lowering glucose levels in the plasma, but also shifts the energy balance in a negative direction [11–13].

### Function, structure and distribution of a low-affinity sodium-glucose type 2 co-transporters

There are two primary sodium-dependent co-transporters (SGLT) responsible for renal glucose re-absorption. Those two belong to the sodium glucose

co-transporter gene family (SLC5A), which has twelve constituents. They are found only in transporting epithelial cells and they move the substrate (glucose) actively from the external to the internal environment.

The first type of high-affinity/low-capacity sodium glucose/galactose transporter (SGLT1) is a product of the SLC5A1 gene and is found mostly in the intestine brush border, as well as the brain, skeletal and heart muscle, liver, lungs and kidneys. SGLT1 co-transporters present in the intestine brush are mainly responsible for normal absorption of dietary glucose, while those found in the S3 segment of the proximal renal tubule are for the residual renal glucose transport [35]. Because the SGLT1 is expressed beyond the kidney, its inhibition would be undesirable [11].

The second transporter is the low-affinity/high-capacity sodium-glucose co-transporter – SGLT2, which is the SLC5A2 gene product. This transporter plays a major role in the re-absorptive mechanism for glucose in kidneys because it is responsible for 90% of glucose absorption. It has the capacity to transport glucose across the membrane against a concentration gradient. SGLT2 is 59% identical to SGLT1 and is expressed almost exclusively in the S1 and S2 segments of renal proximal tubule. SGLT2 was described in the early 1990s and nonsense homozygous and compound heterozygous mutations have been identified in patients with renal glucosuria. SGLT2 was mapped to chromosome 16 p11.2 after being isolating from a human kidney library. The secondary structure of this protein is predicted to contain 14 transmembrane  $\alpha$ -helices, with the hydrophobic amino and carboxy termini of transmembrane  $\alpha$ -helice 14 facing the extracellular solution and the consensus N-linked glycosylation site between  $\alpha$ -helices 6 and 7.

The regulatory mechanisms of SGLT2 are still under investigation but according to Lee et al. [19], it appears that the activity of renal SGLT can be regulated by hyperglycemia through the ROS-NF- $\kappa$  (reactive oxygen species-nuclear factor- $\kappa$ ) pathways, as well as being inhibited by angiotensin II (ANGII) and epidermal growth factor (EGF). Hypothetically, high glucose levels activate protein kinase C (PKC), which induces the formation of ROS that subsequently stimulate the nuclear translocation of NF- $\kappa$ . PKC also induces activation of Ca<sup>2+</sup>-dependent cytosolic phospholipase A<sub>2</sub> (cPLA<sub>2</sub>), which leads to the release of arachidonic acids (AA). ANGI and EGF work through a tyrosine kinase (TK)-protein kinase C-mitogen activated protein kinase (MAPK)-cPLA<sub>2</sub> signal transduc-

Tab. 1. Currently used hypoglycemic medications

Class of medication	Mechanism of action
Biguanide (metformin)	Reduction of hepatic gluconeogenesis and glucose absorption from the gastrointestinal tract, increase of peripheral glucose uptake and insulin sensitivity through the AMPK activation
Sulfonylureas	Stimulation of insulin secretion
Acarbose	Inhibition of alpha-glucosidase
Thiazolidinediones	Activation of PPAR-gamma
DPP-IV inhibitors	Enhancement of incretin action
Exenatide	Stimulation of insulin secretion by GLP-1 stimulation
Insulin	Direct activation of insulin receptor

**Tab. 2.** Clinical studies on SGLT2 inhibitors

SGLT2 inhibitor	Clinical development	Clinical study	Dose of medication (mg)	Blood glucose reduction (mg%)
Dapagliflozin	III phase	12-weeks prospective, randomized parallel-group, double-blind, placebo-controlled (study from the II phase)	2.5, 5, 10, 20, 50	16–31
Remogliflozin	II phase	randomized, double-blind, parallel assignment, safety/efficacy study	no publication to date	no publication to date
Sergliflozin	II phase	double-blind, randomized, placebo-controlled study (evaluation weight loss, safety, tolerability and pharmacokinetics in obese subjects following 12-week dosing*)	500, 1000 *	–
AVE - 2268	phase IIb	–	–	–
JNJ-28431754	II phase	double-blind, randomized, placebo-controlled, double-dummy, parallel group, multicenter, dose-ranging	50, 100, 200, 300	no publication up to date
ISIS 388626	Preclinical	–	–	–

tion cascade, which results in the release of AA and the subsequent downregulation in expression of SGLT2.

Due to inhibition of SGLT2, glucose reabsorption from the renal filtrate is reduced and the bulk of the glucose appears in the urine. Therefore, SGLT2 is a potential drug target for the treatment of diabetes mellitus (Tab. 2) [12, 13, 16, 19, 26, 27, 31, 35].

### SGLT2 inhibitors – mechanism of action, benefits and side effects

The kidneys play an important role in the control of blood glucose levels. When the capacity of glucose reabsorption has been exceeded, the surplus glucose is excreted in the urine and a state known as glucosuria develops. Although substances that suppress renal glucose reabsorption have been long known, the mechanism of action at the molecular level was not described until the early 1990's [12].

The mechanism of action of SGLT2 inhibitors is to interfere with sodium-glucose co-transporters in the S1 segment in the proximal tubule of the kidneys. However, there is still little information regarding the

molecular mechanism of action of SGLT2 inhibitors. According to Pajor et al. [25], the inhibitor involves competitive binding of the glucose moiety of the SGLT2 inhibitor to the glucose moiety binding site on the transport protein and the aglycone moiety probably interacts with hydrophobic or aromatic residues on SGLT. Their studies also suggested that a conserved residue at Cys 615 in human SGLT2 appears to participate in maintaining the structure of the inhibitor binding site, but this cysteine probably does not bind directly to the inhibitors.

Because the SGLT2 are responsible for reabsorption of most of the glucose filtered in glomeruli, the SGLT2 inhibitors induce glucosuria by suppressing 90% of glucose reabsorption [10, 12, 13, 17].

In patients with diabetes, SGLT2 inhibition may bring paradoxical benefits since excessive glucose excretion lowers the plasma glucose levels, extinguishes glucose toxicity and results in a loss of energy [10, 13], which leads to better control of diabetes and improvements in the disorders correlated with it [10, 12, 17].

Depending on the dose, SGLT2 inhibitors exhibit a variety of effects ranging from lowering plasma glucose levels to possible reductions of plasma insulin and glycated hemoglobin levels [11, 20].

Another therapeutic effect of SGLT2 inhibitors includes a reduction in hepatic gluconeogenesis and decreased glucotoxicity [15]. Thus, by lowering the

plasma glucose, the liver sensitivity is improved, which leads to a suppression of hepatic glucose production as a result of glucose-6-phosphatase inhibition. In addition, these inhibitors increase sodium excretion, which can theoretically lead to a mild reduction in arterial blood pressure [3, 20]. However, this effect is not common for all drugs of this category [17].

Contrary to some of the currently used anti-diabetic medications, SGLT2 inhibitors act only on the transporters in the kidneys. Therefore, they do not stimulate insulin secretion and the risk of hypoglycemia has been predicted to be low [5, 6, 10, 17, 20].

Furthermore, high patient compliance can be expected, because there are no common gastrointestinal disturbances associated with these inhibitors [10].

Additionally, a well-controlled serum glycemia lowers glomerular hyperfiltration, which results in a reduction of the nephropathy caused by longstanding diabetes [20, 22, 30].

The convenience of oral administration is another advantage of these potential antidiabetic drugs [6, 17, 20].

Importantly, concerns regarding the safety of this group of inhibitors does not appear to be relevant. This point is demonstrated by patients with familial renal glucosuria who have inherited defects in SGLT2; yet, they have normal kidney function [26, 29]. Furthermore, polyuria and increased thirst, as well as bacterial and fungal infections [8, 9, 20] commonly associated with glucosuria do not seem to be a significant problem while using SGLT2 inhibitors.

## Representatives of SGLT2 inhibitors

### Phlorizin and phlorethin

Phlorizin was one of the first natural phenol glycosides identified and was isolated from fruit tree bark in 1835. It was used as a research tool in “phlorizin-induced” glucosuria and as its aglycone form, phlorethin. It is a  $\beta$ -D-glucoside consisting of a glucose moiety and an aglycone (with two aromatic carbocycles joined by an alkyl spacer) [5]. They have not been used for the treatment of diabetes because their oral bioavailability is very low and they inhibit other transporters in addition to SGLT2, which leads to concerns about their undesirable side effects [10, 12].

All of the SGLT2 inhibitors are glycosides derived from phlorizin. There are carbocyclic and heterocyclic O-glycosides, carbocyclic and heterocyclic C-glycosides, as well as N-glycosides and O-glycosides with modified glucose moieties [13].

### T-1095, T-1095A and TA-7284

One of the next generation of SGLT2 inhibitors is T-1095A, which is the active form of T-1095. This inhibitor has a better bioavailability and can be orally administered. *In vitro*, it inhibits SGLT2 four times better than SGLT1 (IC<sub>50</sub> value of 50 nM for human SGLT2 and 200 nM for SGLT1). Development of T-1095 by Tanabe and Johnson & Johnson pharmaceutical companies reached the second phase of clinical trials before being discontinued [12].

At present, another SGLT2 selective inhibitor, TA-7284, is being developed by Tanabe Co. This agent is in the first phase of clinical development in Japan and is licensed to Johnson & Johnson as JNJ-28431754 and is in the second phase of trials in United States and Europe [14, 27].

### Sergliflozin

In 2007, Katsuno et al. [17] from Kissei Pharmaceutical Co., Ltd. published a report examining sergliflozin etabonate (2-[(4-methoxyphenyl)methyl]phenyl 6-O-(ethoxycarbonyl)- $\beta$ -D-glucopyranoside), which is based on a benzylphenol glucoside and differs from the structure of phlorizin (Fig. 1) [17, 34]. The results ob-

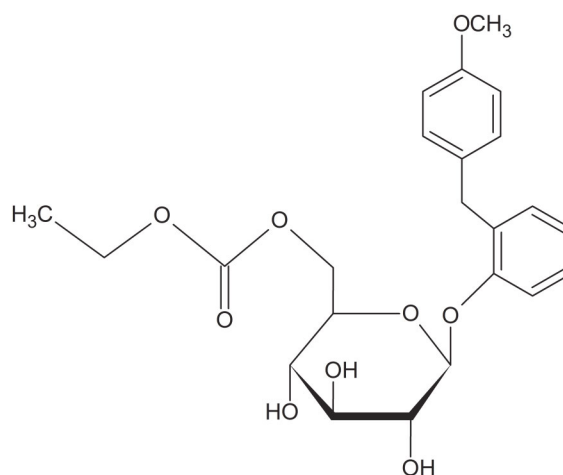


Fig. 1. Chemical structure of sergliflozin

tained by Katsuno suggested that sergliflozin-A (an active form of sergliflozin) is a potent and selective SGLT2 inhibitor. Their study also showed that sergliflozin-A was approximately seven times more active against SGLT2 compared to phlorizin. In addition, it was five times less active against SGLT1 compared to phlorizin.

Sergliflozin-A has a high selectivity ratio (296:1) for SGLT2. Moreover, this agent has no influence on GLUT 1 activity. In diabetic rats, oral administration of sergliflozin lowers plasma glucose levels, improves postprandial hyperglycemia, while it does not cause hypoglycemia and does not affect urinary electrolyte excretion. Sergliflozin (KGT-1251, GW 869682), which is being investigated by Kissei Pharmaceutical in cooperation with GlaxoSmithKline, is now in the second phase of clinical development.

### Remogliflozin

Remogliflozin etabonate (5-methyl-4-[4-(1-methylethoxy)benzyl]-1-(1-methylethyl)-1H-pyrazol-3-yl] 6-O-(ethoxycarbonyl)- $\kappa$ -D-glucopyranoside), another SGLT2 inhibitor (GSK 189075) that was also synthesized by Kissei Pharmaceutical belongs to new category of SGLT2 inhibitors. The structure of this inhibitor differs from that of phlorizin, T-1095 and sergliflozin (as its structural scaffold is based on a benzylpyrazole glucoside) (Fig. 2). Remogliflozin has a selectivity ratio of 365:1 and is a highly selective inhibitor for human SGLT2. It is also more selective than sergliflozin-A. For human SGLT2, the inhibitory effect of remogliflozin was approximately three times greater than that

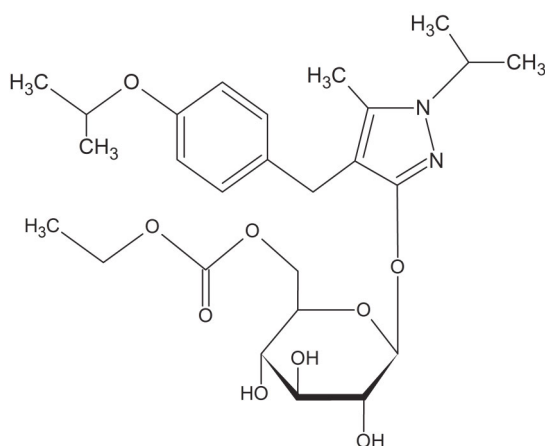


Fig. 2. Chemical structure of remogliflozin

of phlorizin and inhibition of SGLT1 was five times lower than that of phlorizin [6].

It has also been confirmed that oral administration of remogliflozin etabonate increased urinary glucose excretion in a dose-dependent manner in mice and rats. In normal and streptozocin-induced rats, it reduced the plasma glucose without stimulating insulin secretion and lowered plasma glucose levels during the oral glucose tolerance test in a dose-dependent fashion. Additionally, in diabetic (db/db) mice with insulin resistance, it decreased the blood glucose and improved the abnormal glucose metabolism. When administered constantly, remogliflozin reduced the levels of plasma glucose, plasma insulin, and glycated hemoglobin in a dose-dependent manner, and suppressed the development of hypertriglyceridemia in GK rats fed a high-fat diet [6].

### Dapagliflozin

Dapagliflozin (Fig. 3), which was known earlier as BMS 512148 (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol, is the SGLT2 inhibitor furthest along in clinical development. Currently, it is now in the third phase of studies and clinical data from a 12-week study is quite promising (Tab. 1) [10, 20]. Bristol-Myers Squibb is developing dapagliflozin in cooperation with AstraZeneca.

In normal and diabetic rats, the potency of dapagliflozin in inducing glucosuria seemed to be greater than that observed with sergliflozin. In ZDF (Zucker diabetic fatty) rats, a single oral doses of dapagliflozin lowered hyperglycemia [10, 17].

The data from a clinical trial, which was conducted with 389 treatment-naive patients with T2D, demonstrated that after 12 weeks of dapagliflozin treatment there was a significant reduction in HbA1c levels, as well as in fasting plasma glucose and postprandial glucose levels. Randomized patients were adminis-

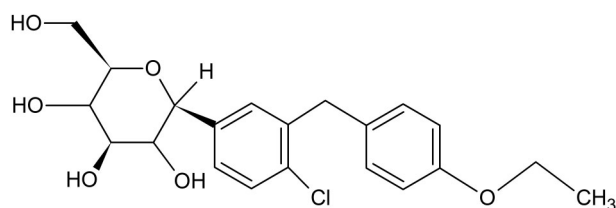


Fig. 3. Chemical structure of dapagliflozin

tered either dapagliflozin orally (doses ranging from 2.5 to 50 mg) once per day, 1.5 g of extended-release metformin or placebo. Compared to minimal glucosuria, which was observed with placebo and metformin, the treatment with dapagliflozin led to glucosuria between 52 and 85 g/day. Another effect of dapagliflozin treatment, regardless of dosage, was significant weight loss. Weight loss ranged from 2.5 to 3.4 kg, while that of metformin and placebo were 1.7 kg and 1.2 kg, respectively [20]. The effect of weight depletion is supposed to be connected with the diuretic effect of dapagliflozin. According to a previous study [20], during the first week of dapagliflozin treatment there was an acute weight reduction provided by fluid loss.

The diuretic effect induced by dapagliflozin could be also responsible for the observed decrease of systolic blood pressure [20].

## Conclusion

The SGLT2 inhibitors possess a convenient oral route of administration, low weight gain potential, and a low hypoglycemia risk. Hence, these agents should be considered as alternatives to the second-line diabetes therapies in patients with inadequately controlled glycemia treated with monotherapy.

Additionally, since there is a lack of medications than can be used to control energy balance in a negative direction, the SGLT2 inhibitors offer distinct advantages over existing antidiabetic drugs. In addition, conditions other than diabetes such as those associated with metabolic syndromes may be future indications for SGLT2 inhibitors. However, the therapeutic potential for the treatment of metabolic syndromes such as obesity, as well as the probable beneficial treatment of type 1 diabetes mellitus will need to be assessed in further studies. In addition, careful evaluation of the adverse effects of drug-induced glucosuria should be carried out.

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