

Sodium Glucose Co transporter 2 (SGLT2) Inhibitors: A New Sword for the Treatment of Type 2 Diabetes Mellitus

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Abstract

The low affinity sodium glucose cotransporter (SGLT2) plays a major role in physiology of glucose reabsorption from proximal part of kidney. Almost all glucose excreted through glomerular filtration, is reabsorbed via SGLT2 until blood glucose level reaches to its threshold value for glucose excretion i.e. ~180mg/dl. Increasing the glucose excretion by inhibiting the SGLT2 is the novel approach for the treatment of diabetes. Safe and normal life of patients having familial renal glucosuria due to SLC5A2 gene mutation is accelerating the development of SGLT2 inhibitors. Weight loss and very low risk of hypoglycemia are the potential benefits of these inhibitors. There are number of molecules in this class under the stage of development.

Key Message

SGLT2 inhibitors have the potential to be useful as add-on agents in patients taking oral hypoglycemic drugs or insulin, with a low risk for hypoglycemia and the potential for weight loss. Results of ongoing phase III clinical trials are awaited and the risk-benefit ratio of this new class of drug will decide the place for the management of type 2 diabetes mellitus.

Key Words

Type 2 diabetes mellitus, SGLT2 inhibitors, Glucosuria

Introduction

Type 2 Diabetes mellitus (T2DM) is characterized by an increase in blood glucose concentration due to resistance of insulin action. High blood glucose (hyperglycemia) is the main pathogenic factor for the development of diabetic complications including coronary heart disease, retinopathy, nephropathy, and neuropathy.^{1,2} In addition, chronic hyperglycemia leads to progressive impairment of insulin secretion and to insulin resistance of peripheral tissues which is known as glucose toxicity.³⁻⁶

Treatment of diabetes has been mainly focused on maintaining normal blood glucose levels by using either insulin or oral hypoglycemic agents (OHAs).⁷ The mechanism of action of the anti-diabetic agents used for the treatment of type 2 diabetes, include increasing insulin release, increasing insulin sensitivity, controlling hepatic glucose release or inhibiting intestinal glucose absorption.⁸

Often, therapy with insulin and OHAs become less effective in controlling hyperglycemia, particularly as a result of weight gain, worsening insulin resistance and progressive failure of insulin secretion due to glucose toxicity. Insulin therapy alone or with hypoglycemic agents can produce weight gain due to reducing glucose excretion.⁹⁻¹¹ Among commonly used OHAs, thiazolidinediones and sulphonylurea contribute to weight gain, whereas metformin causes weight loss and dipeptidyl peptidase-4 inhibitors are weight neutral.^{7,12} Overall, there is a need for novel agents which can effectively control blood sugar level without producing weight gain or hypoglycemia.

A number of new targets have indicated promise for the treatment of T2DM, including sodium glucose transport inhibition, glucokinase activation, glucagon receptor antagonism, fibroblast growth factor-21 receptor activation, 11 β -hydroxysteroid dehydrogenase type 1 inhibition, and others.¹³⁻¹⁶ SGLT2 is a molecular target to directly induce glucose excretion and to safely normalize plasma glucose in the treatment of type 2 diabetes. SGLT2 inhibitors increase the glucose excretion and control the blood sugar level without any risk of hypoglycemia and weight gain. Currently the upcoming molecule of this class is in phase 3 development.

In this article our focus is mainly on SGLT2 inhibitors and its advantages in treatment of T2DM.

Renal sodium glucose transport

The kidney plays an important role for the body's energy control. Glucose filtered from the blood in the glomerulus is reabsorbed mainly in the S1 segment of the kidney's proximal tubule,¹⁷ but when the capacity for glucose reabsorption reaches saturation, excess glucose is excreted in the urine.¹⁸ Approximately 180 g of glucose is filtered on a daily basis, with 90% reabsorbed in the convoluted segment of the proximal tubule, and the remaining 10% in the distal straight segment of the proximal tubule.¹⁹

In healthy persons, glucose present in the plasma is filtered by the kidneys, but virtually all of it is reabsorbed, such that less than 1% of glucose is excreted in urine due to not reaching to threshold value for glucose excretion.²⁰ In patients with diabetes, however, hyperglycemia can lead to hyperfiltration, and the increased luminal glucose exceeds the maximal reabsorption rate, resulting in glucosuria. As well, maximal renal glucose reabsorption can further contribute to high plasma glucose levels. The inhibition of renal glucose reabsorption may result in decreased plasma glucose levels.

Glucose transportation in the body is mainly mediated by two types of transporters: sodium glucose linked transporters (SGLT) and facilitative glucose transporters (GLUTs).²¹ SGLT are the members of sodium substrate co-transporters, the solute carrier family 5A (SLC5A). Six members of this family named SGLTs transport sugars coupled to sodium ion (Table 1).

Table 1: Sodium glucose-linked transporter (SGLT) isoforms.^{22,23}

Gene	Protein	Substrates	Tissue Distribution
SLC5A1	SGLT1	Glucose & Galactose	Small intestine, heart, trachea & kidney
SLC5A2	SGLT2	Glucose	Kidney
SLC5A4	SGLT3	Glucose sensor	Small intestine, uterus, lungs, thyroid & testis
SLC5A9	SGLT4	Mannose, glucose, fructose & 1,5-AG	Small intestine, kidney, lung, liver
SLC5A10	SGLT5	Glucose & Galactose	Kidney
SLC5A11	SGLT6	Myo-inositol, xylose & chiro-inositol	Spinal cord, kidney, brain, Small intestine

Two types of sodium glucose cotransporters mediate glucose reabsorption. The low affinity sodium glucose cotransporter (SGLT2) is found almost exclusively in the kidney,²⁴ and several mutations in the human SGLT2 gene can cause renal glucosuria.^{25,26} Although the high-affinity sodium glucose cotransporter (SGLT1) is expressed to some extent in the kidney and contributes to glucose reabsorption, it is mainly expressed in the small intestine, where it is important in glucose absorption.^{27,28} Genetic mutations in the SGLT1 gene leading to a functional defect are responsible for glucose/galactose malabsorption.²⁹

SGLT 2 Inhibitors

Discovery from Phlorizin

The potential target SGLT2 to treat hyperglycemia was discovered in 1835 from phlorizin, originally isolated from the bark of apple trees. Since extracts from the willow and cinchona trees were known for their antipyretic properties, phlorizin was first investigated for this activity as well, but further study revealed the glucosuric effect of phlorizin.³⁰ It could induce glucosuria in humans by inhibiting renal glucose reabsorption. Administration of phlorizin to partially pancreatectomized diabetic rats induces glucosuria and lowers blood glucose.³¹ Secondary effects include reversal of secondary insulin resistance due to amelioration of glucose toxicity.³² Phlorizin is a competitive inhibitor of both SGLT1 and SGLT2, and therefore also inhibits intestinal glucose-galactose absorption which results in glucose-galactose malabsorption. Apart from this disadvantage, phlorizin is poorly absorbed from the gastrointestinal (GI) tract due to easily hydrolyzed by lactase-phlorizin hydrolase. Because of these demerits it has not been developed further as a medication for the treatment of diabetes, but it has been a useful tool that has been used to study the potential effects of blocking renal glucose reabsorption in the treatment of diabetes.³⁰

Subsequently, a phlorizin derivative T-1095 which is a prodrug of the active molecule T-1095A was developed with improved oral bioavailability.³³ In streptozotocin- induced diabetic rats, T-1095 increases urinary glucose excretion, lowers plasma glucose levels, and lowers glycated hemoglobin (HbA1c).³⁴ However, this compound also had significant activity against the SGLT1 transporter, and may be a nonspecific SGLT inhibitor.^{34,35} Although T-1095 has not proceeded to clinical development, it has demonstrated proof of principle, such that many pharmaceutical companies are now developing SGLT2 inhibitors as potential treatments for T2DM.

Dapagliflozin

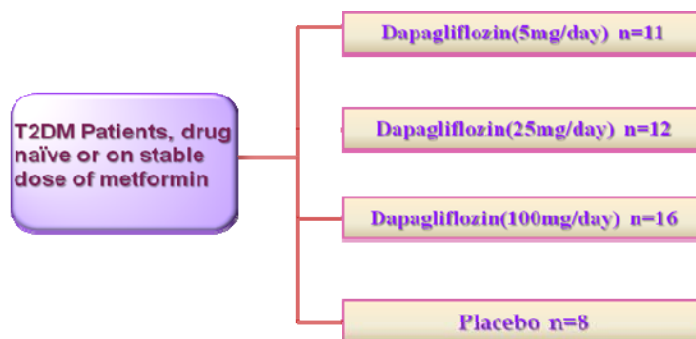
Dapagliflozin is a highly selective SGLT2 inhibitor under clinical development by Bristol-Myers Squibb and AstraZeneca. It is a C-aryl glucoside which is highly selective (~1,200-fold) for hSGLT2 vs. hSGLT1. It is 32-fold more potent than phlorizin against human SGLT2 and 4-fold less potent than phlorizin against human SGLT1.³⁶ Dapagliflozin stimulated significant excretion of glucose in the urine in both normal nondiabetic rats, as well as in rats that were already glucosuric because of diabetes. However the pre clinical data are suggestive of a greater impact of dapagliflozin in the diabetic kidney to reduce the renal glucose threshold.³⁶ Dapagliflozin treatment of Zucker diabetic fatty (ZDF) rats with 0.5mg/kg dose over 15 days results in reduced fasting plasma glucose, increased glucose infusion rate and glucose utilization rate, decreased endogenous glucose production, and increased glucose uptake into liver. The potency of dapagliflozin in stimulating glucosuric responses in normal rats appears to be greater than that observed with sergliflozin,³⁷ T-1095, or phlorizin administered subcutaneously.³³

The safety, tolerability, pharmacokinetics, and pharmacodynamic of the drug were evaluated in single-ascending-dose (SAD; 2.5–500 mg) and multiple-ascending-dose (MAD; 2.5–100 mg daily for 14 days) studies in healthy subjects. Dapagliflozin exhibited dose-proportional plasma concentrations with a half-life of ~17 h and glucosuria was also dose-dependent i.e. Dapagliflozin produced glucose excretion in a range from 18 to 62 gm relating to doses from 2.5–100 mg (MAD) on day 1.³⁸

In 2007, 14 days Phase IIa trial was carried out to assess the safety and efficacy of multiple doses of dapagliflozin administered alone or along with metformin in T2DM patients.³⁹ This double blinded, placebo controlled, randomized, parallel group study was carried out in 47 subjects of T2DM and who were treatment naïve or on a stable dose of metformin for at least 4 weeks prior to randomization. The design of phase IIa is shown in figure-1. Dapagliflozin demonstrated dose related glucosuric action. On day 14, urine glucose values were 36.6, 70.1, and 69.9 g/day for the 5, 25, and 100mg doses (as compared with no change for placebo), which were slightly lower than those on day 1. On day 2, FSG significantly decreased from baseline after a single dose of 100 mg of dapagliflozin (-9.3%, P<0.001). On day 13, dapagliflozin treatment was associated with dose-dependent reductions in fasting serum glucose (FSG) of -11.7% (P<0.05), -13.3% (P<0.05), and -21.8% (P<0.0001) representing the absolute mean reductions in FSG of 18.8, 28.8, and 38.7 mg/dl in the 5, 25,

and 100mg dose groups, respectively. No significant reduction in FSG was observed in subjects who received the placebo. There were no discontinuations due to adverse events and no serious adverse events occurred. Hypoglycemia was observed in two subjects received dapagliflozin with metformin and vulvovaginal infection was occurred in two subjects, in which one subject received dapagliflozin alone and other received dapagliflozin with metformin. Other minor events like nausea, constipation and diarrhoea were observed non specific to dapagliflozin.

Figure.1: Design of Phase IIa study.



In other 12-week study of dapagliflozin in 389 drug-naïve patients with T2DM randomized to 5 different doses of dapagliflozin, 2.5, 5, 10, 20, or 50 mg, metformin, or placebo.⁴⁰ The primary objective was to compare changes in the mean HbA1c levels from baseline for each group versus placebo after 12 weeks. Secondary objectives compared dapagliflozin versus placebo for fasting plasma glucose change from baseline, dose-dependent trends in glycemic efficacy, proportion of patients achieving HbA1c <7%, and change in 24-h urinary glucose-to creatinine ratio. At 12 weeks, all dapagliflozin groups achieved significant reductions in mean HbA1c change from baseline versus placebo, ranging from -0.55% to 0.90% for dapagliflozin in a non-dose-dependent fashion, -0.18% for placebo, and -0.73% for metformin. Fasting plasma glucose reductions ranged from -0.89 mmol/L to -1.72 mmol/L for dapagliflozin in a dose-dependent fashion, -0.33 mmol/L for placebo, and -1.0 mmol/L for metformin, with statistically significant reductions in the 5 mg to 50 mg dapagliflozin groups versus placebo. Proportions of patients achieving an HbA1c <7% at week 12 ranged from 40%-59% for dapagliflozin, 32% for placebo, and 54% for metformin. Total body weight reductions occurred in all groups, ranging from -2.5% to -3.4% body weight for dapagliflozin, -1.2% for placebo, and -1.7 % for metformin. Adverse events were reported at similar frequencies across all groups. No deaths or drug-related serious adverse events occurred. Hypoglycemic events were reported in 6%-10% of dapagliflozin-treated patients with no dose relationship, 4% for placebo, and 9% for metformin, urinary tract infections; infections were reported in 5%-12% of dapagliflozin-treated patients without a clear dose relationship, 6% for placebo, and 9% for metformin. There were small changes from baseline in serum blood urea nitrogen (BUN), but no change in serum creatinine at Week 12 in all dapagliflozin doses.

Currently dapagliflozin is in phase III development.

Sergliflozin

Sergliflozin (KGT-1251), a prodrug of SGLT2 inhibitor Sergliflozin A was developed by Kissie Pharmaceuticals, Japan and currently, it is being developed by GlaxoSmithKline. It has been shown 7-fold selectivity for human SGLT2 Vs human SGLT1 in cell culture system. It has been induced glucosuria in healthy mice, rats and dogs., and also lower postprandial blood glucose in diabetic rats independently of insulin secretion.⁴¹

According to study conducted by Hussey et al, sergliflozin has shown dose dependent glucosuric effect.⁴² The study was conducted in 18 healthy over weight and obese subjects (18-55 years) to evaluate safety, pharmacokinetic and pharmacodynamic of sergliflozin over 14 days of dosing. These eighteen subjects were

divided in two cohorts of equal subjects and six subjects of each cohort were kept on 500 and 1000 mg of sergliflozin and rest of three subjects in each cohort were on placebo. The treatment was given three times per day for 14 days. Sergliflozin was well tolerated in both cohorts and had stable pharmacokinetic parameters. After 14 days treatment, subjects treated with sergliflozin reduced bodyweight of average 1.5kg compare to placebo treated subjects. Hypoglycemia was not reported. The urinary electrolyte level was raised on day1 in sergliflozin treated subjects but it was resolved by day 14.

Two randomized, double blinded, placebo controlled and single dose escalation crossover studies were done to evaluate safety, pharmacokinetic and pharmacodynamic of sergliflozin.⁴³ In one study sergliflozin was given in a dose range of 5-500 mg in 14 healthy subjects while in other study dapagliflozin was given in dose range of 50-500 mg in 8 type 2 diabetes patients. No variation was observed in pharmacokinetic parameters between two groups and segliflozin has shown dose dependent glucose excretion in urine. The duration of glucose excretion was related to plasma concentration of sergliflozin A. In subjects with type 2 diabetes, 500 mg reduced mean plasma glucose from 18.2 mmol to 11.2 mmol/L, with minor, transient alterations in urine electrolytes. Some minor adverse events like headache, sore throat in healthy subjects and headache, dyspepsia in diabetic patients were seen.

Thus, sergliflozin have shown promising profile for treatment of diabetes along with obesity and also excellent safety profile.

Remogliflozin etabonate

Remogliflozin etabonate is a prodrug based on benzylpyrazole glucoside and is metabolized to its active form, remogliflozin, in the body. Currently it is in development phase and developed by Kissei Pharmaceutical Corporation and GlaxoSmithKline. Remogliflozin is a selective SGLT2 inhibitor and orally administered remogliflozin etabonate increased urinary glucose excretion in a dose-dependent manner in both mice and rats. In normal rats, remogliflozin etabonate inhibited the increasing plasma glucose level after glucose infusion without increasing insulin secretion. Remogliflozin etabonate also showed antihyperglycemic effects in both streptozotocin-induced diabetic rats in oral glucose tolerance and in diabetic (db/db) mice in the fed condition. Chronic treatment with remogliflozin etabonate reduced the levels of fasting plasma glucose and glycated hemoglobin. In high-fat diet-fed Goto-Kakizaki rats, remogliflozin etabonate improved hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and insulin resistance.⁴⁴

Thus study performed on rodent models by Fujimori et al suggests that remogliflozin etabonate may be a new and useful drug for the treatment of diabetes.

Other SGLT2 inhibitors

A number of other SGLT2 inhibitors are under development like:^{45,46}

- AVE-2268- Sanofi-Aventis(USA)
- KGT-1681- Kissei Pharmaceutical Co. Ltd/ GlaxoSmithKline
- TS-033- Taisho Pharmaceuticals Co. Ltd, Tokyo, Japan*
- YM-543- Astellas Pharmaceutical Inc., Tokyo, Japan
- JNJ-28431754/ TA-7284 (Canagliflozin)- Johnson & Johnson Pharmaceutical, USA/ Mitsubishi Tanabe Pharma, Japan

*Taisho Pharmaceutical Company recently announced the discontinuation of the development of TS-033, although they have announced a backup compound that is in Phase 1 clinical trial.

Clinical Trials of SGLT2 Inhibitors

All clinical trials of SGLT2 inhibitors which are registered to clinical trial.gov are given in Table 2.⁴⁷

Table 2: Clinical trials of SGLT2 inhibitors

SGLT2 Inhibitor	Clinical Trial	Status
A	A Phase III Study of BMS-512148 (Dapagliflozin) in Patients With Type 2 Diabetes Who Are Not Well Controlled With Diet and Exercise.	1
A	Efficacy and Safety of Dapagliflozin, Added to Therapy of Patients With Type 2 Diabetes With Inadequate Glycemic Control on Insulin.	1
A	Efficacy and Safety of Dapagliflozin in Combination With Metformin in Type 2 Diabetes Patients.	1
A	Efficacy and Safety of Dapagliflozin in Combination With Glimepiride (a Sulphonylurea) in Type 2 Diabetes Patients.	1
A	Pharmacokinetic Drug Interaction Study With Dapagliflozin and Glimepiride in Healthy Subjects.	2
A	Pharmacokinetic Drug Interaction Study of Dapagliflozin and Valsartan or Simvastatin in Healthy Subjects.	2
A	An Efficacy & Safety Study of BMS-512148 in Combination With Metformin Extended Release Tablets.	2
A	Drug Interaction With Metformin.	2
A	Study to Evaluate the Potential Pharmacokinetic Interaction and Pharmacodynamic Effects on Renal Parameters of Bumetanide (1mg) and Dapagliflozin (10 mg) When Co-administered in Healthy Subjects.	2
A	Effects of Single Oral Dose Dapagliflozin QT Study.	2
A	Glycemic Efficacy and Renal Safety Study of A in Subjects With Type 2 Diabetes Mellitus and Moderate Renal Impairment.	1
A	Trial to Evaluate the Efficacy and Safety of Dapagliflozin in Japanese Type 2 Diabetes Mellitus Patients.	1
A	Study of the Effect of Dapagliflozin on the Pharmacokinetics of Warfarin or Digoxin in Healthy Subjects.	2
A	A Phase III Study of BMS-512148 (Dapagliflozin) in Patients With Type 2 Diabetes Who Are Not Well Controlled on Metformin Alone.	1
A	Pharmacokinetic Drug Interaction Study of Dapagliflozin and Glimepiride or Sitagliptin in Healthy Subjects.	2
A	Study of Dapagliflozin in Combination With Metformin XR to Initiate the Treatment of Type 2 Diabetes.	1
A	Bioavailability Study of Fixed Dose Combination (FDC) Formulations of Dapagliflozin and Metformin XR Versus Individual Component Coadministered to Healthy Subjects in a Fasted State.	3
A	Evaluation of the Effect of Dapagliflozin in Combination With Metformin on Body Weight in Subjects With Type 2 Diabetes.	1
A	Dapagliflozin DPPIV Inhibitor add-on Study.	3
A	Add-on to Thiazolidinedione (TZD) Failures.	1
A	Safety and Efficacy of Dapagliflozin as Monotherapy in Subjects With Type 2 Diabetes.	1
A	Effects of Dapagliflozin on Insulin Resistance and Insulin Secretion in Subjects With Type 2 Diabetes.	3
A	Effects of Dapagliflozin on Kidney Function (Glomerular Filtration Rate) in Subjects With Type 2 Diabetes.	3
A	A Trial of BMS-512148 in Patients With Type 2 Diabetes Mellitus.	2
A	Efficacy and Safety in Patients With Type 2 Diabetes Mellitus and Cardiovascular Disease.	4
A	Efficacy and Safety in Patients With Type 2 Diabetes Mellitus, Cardiovascular Disease and Hypertension.	4
A	Study of the Absolute Oral Bioavailability of Dapagliflozin in Healthy Subjects.	2
A	A Phase IIA Study of BMS-512148 to Assess Safety, Exposure, and Biological Effects in Stable Type 2 Diabetic Subjects.	2
A	A Pilot Study of BMS-512148 in Subjects With Type 2 Diabetes.	2

A	Renal Mechanism of Action/Splay vs. TmG.	3
A	Renal Impairment in Type 2 Diabetic Subjects.	2
A	Phase I Multiple-Ascending Dose (Japan).	2
B	A Study To Compare Effects Of GSK189075 In Combination With Either Furosemide Or Hydrochlorothiazide.	2
C	Weight Loss In Obese Subjects Taking Either GW869682 Or Placebo 3 Times Per Day For 12 Weeks.	2
B and C	Investigation Of Weight Loss And Body Composition Changes After Dosing With Either Placebo Or One Of Two Active Drugs	2
D	An Efficacy, Safety, and Tolerability Study for TA-7284 in Patients With Type 2 Diabetes.	3
D	CANagliflozin Treatment And Trial Analysis-Sulfonylurea (CANTATA-SU) SGLT2 Add-on to Metformin Versus Glimepiride.	3
D	An Efficacy, Safety, and Tolerability Study for JNJ-28431754 in Patients With Type 2 Diabetes.	2
D	To Evaluate the Safety, Tolerability, Pharmacokinetics (PK) and Pharmacodynamics (PD) of Single and 14-Day Multiple Oral (by Mouth) Doses of JNJ-28431754 in Patients With T2DM.	2
D	A Study of the Safety and Effectiveness of JNJ-28431754 in Promoting Weight Loss in Overweight and Obese Patients Who do Not Have Diabetes.	2
D	CANVAS – CA Nagliflozin cardioVascular Assessment Study.	3
AVE2268	Dose-Ranging Study Evaluating AVE2268 in Patients With Type 2 Diabetes Not adequately Controlled by a Metformin Treatment.	2
YM543	A Safety and Efficacy Study With YM543 in Type 2 Diabetes Mellitus Subjects.	2

A: Dapagliflozin B: Remogliflozin Etabonate C: Sergliflozin D: Canagliflozin

1: Active, not recruiting 2: Completed 3: Recruiting 4: Not yet recruiting

Advantages

There are many advantages of SGLT2 inhibitors to treat diabetes by increasing excretion of glucose in urine:

- Weight loss or weight maintenance, a key target for any type 2 diabetes treatment.
- No hypoglycemia because SGLT2 inhibitors do not induce insulin secretion or inhibit hepatic glucose production.
- Improve insulin sensitivity and indirectly preserve β -cells by depletion of toxic glucose concentration in blood.
- SGLT2 inhibitors also produce osmotic diuretic effect which may be advantageous in patients with hypertension and CHF.
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Disadvantages

Apart from above advantages, SGLT2 inhibitors may have some disadvantages. There may be a risk of negative effect of glucosuria on the kidneys, polyuria and increased thirst, but the lack of such evidences in patients with familial renal glucosuria provides some reassurance. Another theoretical problem in relation to the genitourinary tract is increased risk for either bacterial or fungal infection, but only long term clinical trial can answer about this risk. The final concern that may be directly related to the mechanism of action of SGLT2 inhibitors is whether some patients would experience salt-wasting, as has been described in one individual with an SLGT2 mutation.⁴⁸ The small trials have not suggested a major problem in this respect, but it remains a possibility to be considered in ongoing and future studies.

Conclusion

Inhibition of SGLT2 represents a novel approach in diabetes treatment. SGLT2 inhibitors have significant potential in the treatment of type 2 diabetes as a class of drugs that can effectively lower blood glucose without the risk of hypoglycemia. Additionally SGLT2 inhibitors improve both fasting and post prandial serum glucose level and produce weight loss. Due to such a remarkable profile, SGLT2 inhibitors can be used to treat co morbidities like hypertension, obesity and dyslipidemia. SGLT2 inhibitors would be expected to be beneficial in treatment of T2DM either as a monotherapy or in combination with insulin or other OHAs. The results of longer-term clinical trials of safety and efficacy will ultimately determine whether SGLT2 inhibition can be added to the list of drugs that have a place in the management of T2DM.

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