

Gliflozins or SGLT2 Inhibitors: Still More Questions To Be Answered

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Abstract

Approximately 350 million people have diabetes and only fifteen percent achieve the glycemic target. It is achieved by different drugs targeting liver, intestine, beta cells and adipose tissue. SGLT2 inhibitors are the new emerging group targeting kidney and inhibiting the sodium glucose co transporters hence renal reabsorption of glucose in proximal renal tubule. In present review we investigate SGLT2 inhibitors for their potential role in management of diabetes with focus on their advantages and limitations. We searched pubmed, medline database with the term SGLT, SGLT2 inhibitors, Gliflozins for published research work. Searched articles critically evaluated for information including abstracts. Free accessible full articles and abstracts were included for review due to financial limitation. SGLT2 inhibitors show promise due to oral administration, insulin independent mechanism of action, additional weight loss, no risk of hypoglycaemia and reproductive effects while increase risk of urinary tract infection, drug- drug interactions and lack of evidences for consequences of renal glycosuria on long term seems limiting factor to their use.

KEYWORDS:

SGLT, SGLT2 inhibitors, Gliflozins, Diabetes

INTRODUCTION:

As per World Health Organization, 346 million people have diabetes mellitus worldwide, and may be double by year 2030^[1].

Among the different subtypes, diabetes mellitus type 2 is associated with insulin resistance and impaired glucose stimulated insulin secretion,^[2] that is positively correlated with obesity^[3], high fat intake,^[4] glucose toxicity^[5] and pancreatic beta cell necrosis^[6-7] if remain uncontrolled^[8]. Management of diabetes includes reduction in blood sugar level by insulin or Oral Hypoglycaemic Agents,^[9-10] treatment of associated disorders like hypertension, dyslipidemia,^[11-12] obesity and insulin resistance^[13] and to prevent or manage secondary complications.

Drugs reduce blood sugar level by different mechanism including release of insulin from pancreatic beta cells, sensitize the peripheral tissues for action of insulin, inhibit the intestinal absorption of glucose, modify action of glucagon like peptide etc. (Refer Fig 1: Mechanism of action of different oral hypoglycaemic) –

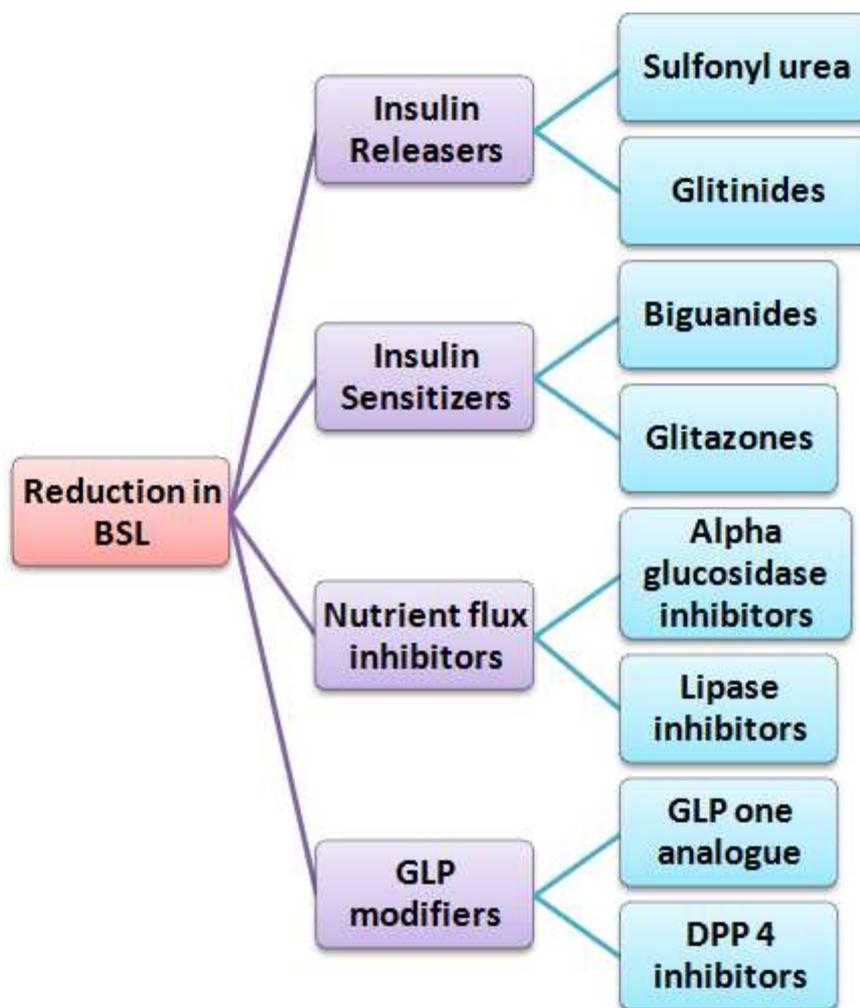


Figure 1: Mechanism of action of different oral hypoglycemics

These drugs act on different site including pancreatic beta cells, liver, adipose tissues, intestinal absorption and gut hormones. At present only 7 to 15% patients achieve the glycemic target,^[14-15] hence there is ever felt need of search for new therapeutic target and drugs acting on it^[16-17] and has been discussed time to time^[18,19].

METHOD FOR COLLECTION OF DATA

In present review we investigate SGLT2 inhibitors for their potential role in management of diabetes. We searched pubmed, medline database with the term SGLT, SGLT2 inhibitors, Gliflozins for published research work. Searched articles critically evaluated for information including abstracts. We studied current status, potential mechanism for beneficial pleotropic effects as well as their limitation and long term outcome in diabetes.

Glucose transporters (GLTs)

Glucose Transporters are membrane proteins that transport ions, vitamins, amino acids, glucose and osmolytes across the brush-border membrane of intestinal epithelium and proximal renal tubules. Filtered Glucose is reabsorbed from the S1 segment of proximal tubule^[20] till renal threshold and beyond it, excreted in urine.^[21] Glucose transport across the cell membrane is transported by 2 transporters: (SGLTs) sodium glucose co transporters and (GLUTs) glucose transporter.

1. GLUTs are facilitative or passive transporters expressed in each cell of body. They belong to SLC2 gene family and consisting of 13 members i.e. GLUT1 to GLUT12 and H⁺ myoinositol co transporter ^[22-23]
2. SGLTs are member of SLC5 gene family, consisting of 9 members including sodium and glucose transporter that is inhibited through Oral Rehydrating Solution in diarrhea ^[24-25]. Molecular characteristics of SGLT have been studied in animals ^[26-28] as well as in humans ^[29]. SGLT2 is the low-affinity sodium glucose co transporters, expressed predominantly in proximal tubule to reabsorb renal glucose.

Genetic and Molecular variations of SGLT family

SGLT1 transports glucose and galactose ^[30] not only in the renal tubules but also in intestine for glucose absorption ^[31]. In addition, it is expressed in various organs such as the lungs, heart, liver, ^[30] skeletal muscles, and S3 segment of PCT of kidney. Inhibition of SGLT1 is undesirable due to side effects ^[6] and mutation may cause glucose/galactose malabsorption. ^[25]

SGLT2 is product of SLC5A2 gene and mapped on chromosome 16p11.2. HNF – 1 α is SGLT2 gene activator ^[32], its mutation is associated with MODY3 ^[33-36] having precocious nephropathy ^[37-38] and renal malformation. ^[39] Renal glycosuria ^[40] due to SGLT2 mutation may lead to compensatory rise in serum renin and aldosterone levels ^[41]. SGLT2 is low affinity/ high capacity co transporter, found exclusively in S1 S2 segment of proximal renal tubule ^[42] and reabsorb filtered glucose from lumen to blood up 90% against the concentration gradient. ^[43] The rationale for the clinical evaluation of these agents is their beneficial effects on glycaemia, blood pressure and body weight ^[44]. SGLT3 senses glucose in small intestine, skeletal muscles and kidneys rather than transporting sugar. ^[45] SGLT4 is highly expressed in the small intestine and kidneys ^[46-47] while SGLT5 is predominantly in kidneys only. ^[48] SGLT6 ^[49] and SMIT1 ^[50] are sodium-dependent MI transporters expressed in various organs. Inhibition of MI transport by methylene-*myo*-inositol may impair function of kidneys, because MI, an organic osmolyte, mediates osmolarity and maintains cell volume and fluid balance in various cells. ^[51] For example, an MI transporter inhibitor causes acute renal failure in normal rats by injuring renal epithelium, ^[52] however, the precise roles of these SGLTs remains unclear.

Regulation of SGLT activity

The regulation of SGLT activity is by glucose level in blood as well as by Angiotensin II and Endothelial Growth Factor. ^[53] Angiotensin II and EGF inhibits the SGLT2 expression while increased blood glucose stimulate the SGLT2 expression and action. (Refer Figure 1: Regulation of SGLT2 gene expression)

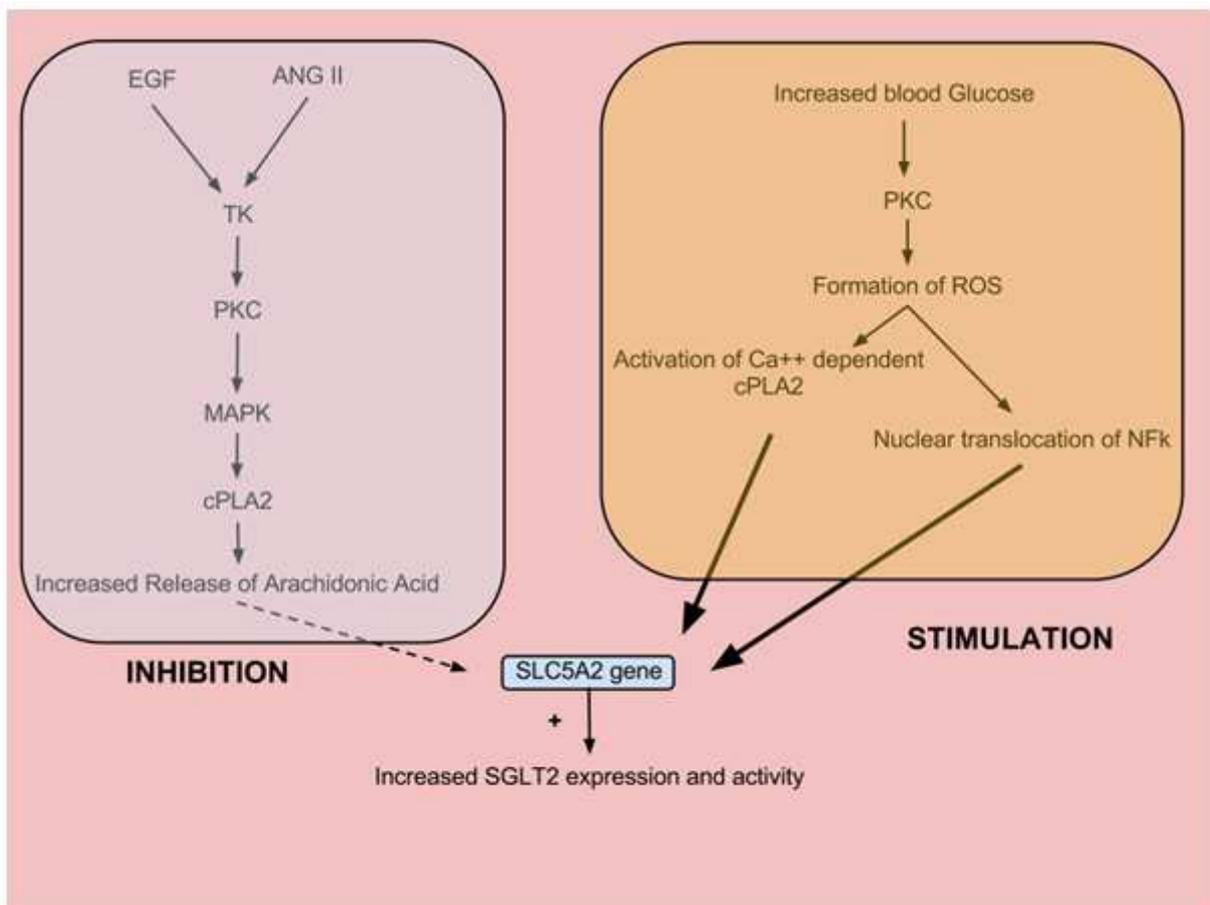


Figure 2: Regulation of SGLT2 gene expression

Renal Glucose transport in health

At less than 180 mg% of filtered glucose in proximal renal tubule all glucose is reabsorbed in blood but if it is more than renal threshold, glycosuria develops.^[54] In diabetics, there is up regulation of renal GLUTs and SGLT2s^[55, 56] secondary to increased gene expression.^[57-59] That means inhibition of SGLT2 will lead to more glycosuria as compare to non-diabetics.^[60]

Development of SGLT inhibitors

Glucosuria due to SGLT2 inhibition results in caloric loss and beneficial weight loss.^[61] Currently several SGLT2 inhibitors with various degrees of selectivity toward SGLT2 versus SGLT1 selectivity are being tested in clinical trials.^[62-65]

Phlorizin, a first natural phenolic O-glucoside, isolated from fruit tree bark in 1835, has been known to induce glucosuria for more than 100 years. It is a non-selective SGLT inhibitor, used to explore the effects of SGLT^[66] and its effects in diabetic animal models^[67-69] but not to distinguish between two subtypes^[60] due to non specific inhibition of SGLTs causing unacceptable side effects.^[66]

All SGLT2 inhibitors are Phlorizin derivatives and substituted on glucose moiety as carbocyclic glycosides, heterocyclic glycosides, N-glycosides and O-glycosides^[70].

Phloretin, metabolite of phlorizin inhibits GLUT1^[71] while Phlorizin derivative, T-1095 (T-1095A) inhibits both SGLT1 and SGLT2^[72]

SGLT2 inhibitors have been developed preferentially^[73-77] as new approach in management of diabetes^[16] due to selective expression in renal proximal tubule hence

unimpaired glucose supply to RBC and brain by GLUT1,^[78] weight loss and no risk of hypoglycaemia.^[68] **Mechanism of Action of SGLT2 inhibitors**

SGLT 2 inhibitors bind competitively to glucose binding site of transporter and inhibit glucose reabsorption at molecular level.^[16] They are composed of two domains:^[79]

A. Sugar binding domain bind to glucose and induce conformational changes in aglycone motif

B. Aglycone domain which influence the binding affinity of the transporter.

SGLT2 inhibitor binds to glucose binding domain due to structural similarity and prevents glucose transport. (Refer Figure 2: Mechanism of action of SGLT2 inhibitors)

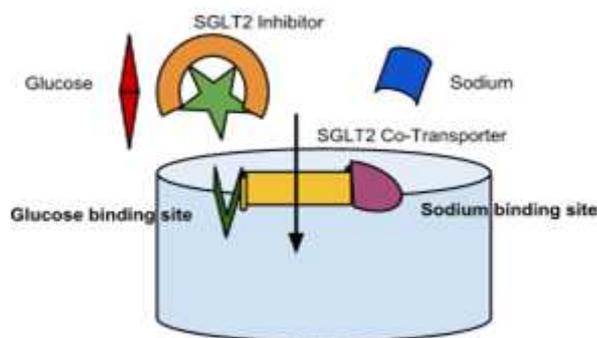


Figure 3: Mechanism of action of SGLT2 inhibitors

Many SGLT inhibitors are in development due to their novel mechanism of action for management of diabetes.^[16-17, 40, 42-43, 53, 56, 65]

SODIUM GLUCOSE CO TRANSPORTERS (SGLT) TYPE 2 INHIBITORS: CURRENT STATUS

In Diabetes, renal glucose production^[80] is increased by gluconeogenesis at proximal convoluted tubule^[81] that is surmountable by insulin.^[82] SGLT2 inhibitors are being studied in preclinical models,^[73-75] undergoing clinical development^[83] and few have been approved recently to be marketed for management of diabetes.^[17]

SGLT 2 inhibitors have found to have beneficial effects on diabetes and its complication in various animal models^[72, 84-89] including GK rats, diabetic models with age-dependent impaired insulin secretion.^[90, 64]

Diabetes increases the expression of SGLT2 mRNA,^[56] HNF-1alpha,^[55] Interleukin 6^[91] in kidney of diabetic rats causing diabetic kidney disease. Treatment with the SGLT2 inhibitor lowered blood glucose, improved glucose tolerance and normalized insulin sensitivity as well as oxidative stress of Ins2(C95S) mutants.^[92]

Dapagliflozin

Dapagliflozin reduced blood glucose levels in hyperglycaemic streptozotocin (STZ) rats,^[93] reduced hyperglycaemia in Zucker diabetic fatty (ZDF) rats as well as weight loss in diet induced obese rats.^[94] It showed significantly increased glucose utilization rate, significantly reduced glucose production,^[95] significantly improved islet morphology without change in mean β -cell mass. Sustained glucose lowering might prevent the continued decline in functional adaptation of pancreatic β -cells.^[96] It has shown linear pharmacokinetics, absorption not effected by food, and predominantly urinary excretion.^[97]

Dapagliflozin was first in the class of oral SGLT 2 inhibitor undergoing various phase 3 trials^[95, 98] for an insulin-independent treatment approach for type 2 diabetes

mellitus (T2DM) either in mono therapy or in combination^[99] to demonstrate efficacy and safety of this agent across various patient populations and clinical scenarios.

The safety, tolerability, Pharmacokinetics (PK) and pharmacodynamics (PD) of dapagliflozin and its inactive major metabolite, dapagliflozin 3-O-glucuronide were evaluated for single-ascending dose study in healthy Japanese and multiple-ascending dose study with T2DM Japanese. In both group, dapagliflozin absorbed rapidly reaching maximum plasma concentration in 0.5-1.3 h. Safety and tolerability were similar in placebo verses treated groups.^[100] Plasma half-life of approximately 17 h rendering it suitable for once-daily administration^[101] without regard to meals.^[102-103]

Dapagliflozin in doses of up to 100-mg inhibits up to 40% of glucose resorption and excretes 70g of glucose per day,^[95] significantly reduced fasting serum glucose (FSG), improved oral glucose tolerance test (OGTT), decreased urine glucose in type 2 DM as compared to placebo probably due to the decreased filtered glucose load following improved glycemic control.^[104]

Add-on dapagliflozin with Metformin or Glipizide were accessed in type 2 diabetes. Mean HbA(1c) reduction^[62] was similar to glipizide while dapagliflozin produced significant weight loss as compare to weight gain with glipizide, and less hypoglycemia versus glipizide.^[105]

Bollinder demonstrated that reduction in weight was by reduced total-body fat mass (FM), visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) volume, and not just by osmotic water loss in urine^[106] and weight loss was dose independent.^[107]

It also reduced blood pressure,^[107] lipid profile, waist circumference, serum uric acid and high sensitivity C-reactive protein levels although did not cause electrolyte disturbances, hepatotoxicity, or nephrotoxicity.^[108]

Genital and lower urinary tract infections were more frequent although responded to standard treatment without study discontinuation^[105] while 8% of patient had vulvovaginal fungal infection and required treatment.^[107] Increased hematocrit and serum parathyroid levels,^[109] are the major negative effects to be considered^[110] along with other adverse event profile.

Another study accessed clinically significant effect on the QT interval in healthy subjects as compare to moxifloxacin and in suprathreshold doses^[111] and found no increase in risk.

It has been approved by US FDA in January 2014 to be used in DM type 2 with potential of additional benefit to reduce BP, and improved insulin sensitivity^[112]

6-deoxydapagliflozin is developed as more potent SGLT2 inhibitor as compare to dapagliflozin.^[113]

Ipragliflozin

Ipragliflozin selectively inhibited SGLT2 in KK-A(y) type 2 diabetic mice, streptozotocin-induced type 1 diabetic rats and may be beneficial in type 1 diabetes too, and normal mice at nanomolar concentration with stability against intestinal glucosidases.^[114]

In phase 2 clinical trial, Ipragliflozin once daily significantly reduced fasting plasma glucose, glycosylated hemoglobin, and mean amplitude of glucose excursions compared with placebo.^[115]

It is approved in Japan to be used as monotherapy or in combination with other hypoglycemics.^[116] It reduces body weight with reduction in visceral and subcutaneous fat without affecting lean mass and bone mass. It may be due to increased lipolysis and fatty acid oxidation.^[117]

Sergliflozin

Sergliflozin etabonate reduced postprandial blood glucose level after a single oral administration, plasma insulin in the 4-day administration, improved hyperglycemia and prevented body weight gain in 8-week study, reduction in fatty liver and pancreatic beta-cell abnormalities in the 9-week study in female KK-A(y) mice.^[118] It was studied in COS-7 cells expressing hSGLT1 and hSGLT2^[119] in normal and diabetic rats in comparison with gliclazide and voglibose whereas improved postprandial hyperglycemia in neonatal streptozotocin-induced diabetic rats was seen with Sergiflozn but not with gliclazide. Antihyperglycemic effect was correlated with the severity of the diabetic condition and no reduction in plasma glucose level of normal rats as seen with gliclazide. Chronic treatment reduced the levels of glycated hemoglobin, fasting plasma glucose, and improved glycemic response in Zucker fatty rats without affecting body weight or food intake.^[120]

Sergliflozin-A (active form) was highly selective and potent inhibitor of human SGLT2 in Chinese hamster ovary-K1 cell line in mice, rats, and dogs in a dose-dependent manner.^[121]

The active metabolite of benzylphenol glycoside based sergliflozin etabonate, was evaluated in healthy volunteers and patients with type 2 diabetes mellitus.^[122] It has high selectivity ratio (296:1) with no effect on GLUT1 activity, developed by Glaxosmithkine and in phase 2 and 3 clinical trial.

Tofogliflozin

Tofogliflozin is identified as potent and highly selective SGLT2 inhibitor^[123] with increased renal glucose clearance in ZDF rats, GK rats and db/db mice^[124] Additionally no inhibition of lysosomal glucosidases suggests a low-risk of various lysosomal diseases^[125]

Long-term treatment with Tofogliflozin preserved β -cell function due to the reduction of oxidative stress through the sustained glucose-lowering effects.^[126] It is well absorbed, highly metabolised in liver with subsequent excretion in urine. Hydroxyl metabolite with ketone successor is the minor metabolite^[127] and associated with hyperketonemia, ketonuria and pollakiuria.^[128]

Canagliflozin

Canagliflozin is also highly potent and selective SGLT2 inhibitor with pronounced anti-hyperglycemic effects in high-fat diet fed KK (HF-KK) mice, in db/db mice, In ZDF rats.^[129] It reduced the renal threshold for glucose but preserved relationship between blood glucose and urinary glucose excretion i.e. no Urinary Glucose Excretion when Blood Glucose is below Renal Threshold. It decreased glycated hemoglobin (HbA1c), improved measures of insulin secretion, decreased body weight gain, epididymal fat, liver weight, and respiratory exchange ratio in rodent models of T2DM and obesity.^[130]

Canagliflozin was studied in type 2 DM not controlled on insulin and oral antihyperglycaemic therapy, as add on drug found efficacious and improves beta cell function^[131] and well tolerated without evidence for glucose malabsorption.^[132]

Remogliflozin etabonate (RE)

Remogliflozin etabonate, prodrug of active form, remogliflozin, increased urinary glucose excretion in a dose-dependent manner in both db/db mice in the fed condition and streptozotocin-induced diabetic rats. It reduced triglycerides, blood sugar, serum insulin, and insulin resistance in high-fat diet-fed Goto-Kakizaki rats.^[133]

With selectivity ratio of 365:1, It changed body weight and blood pressure in drug naive or metformin intolerant diabetic patients. Headache and flatulence were most frequent adverse events.^[134]

Empagliflozin

Although renal impairment decreases the clearance but dose adjustment is not required in renal impairment^[135] and with other drugs affecting UGT pathway like gemfibrozil, Rifampicin or probenecid. It decreases the arterial stiffness and blood pressure in type one diabetes mellitus may be due to its pleotropic action^[136]

Others in initial phase of development

BI-10773 once-daily, in phase I clinical trials in patients with T2DM suggested coadministration with metformin is safe and well tolerated and now undergoing in phase III clinical trials.^[137] T 1095 and T1095a are orally given with better bioavailability, they have 4 times higher ratio of inhibition of SGLT2. It has prevented functional and histological changes as well as abnormal expression of GLUT2 in kidney of streptozotocin (STZ)-induced diabetic rats by reducing blood sugar^[84] and in phase 2 clinical trial by Tannabe and Johnson and Johnson pharmaceutical.^[16]

TA 7284 is in phase 1 clinical trial in Japan and phase 2 trial in USA and Europe^[65] TS-071 is another potent and selective SGLT2 inhibitor that improves glucose levels in rodent models of type 1 diabetes too^[138] while EGT1442 is investigated in rats and dogs after a single dose and in db/db mice after chronic administration showing favourable properties both in vitro and in vivo.^[139]

AVE2268 is also a new SGLT2 inhibitor in the stream line^[140] N-linked β -D-xylosides were synthesized and evaluated for (SGLT2) inhibition in a cell-based assay. Of these, the 4-chloro-3-(4-cyclopropylbenzyl)-1-(β -D-xylopyranosyl)-1H-indole 19m was found to be the most potent inhibitor in Sprague-Dawley (SD) rats and streptozotocin (STZ) induced diabetic SD rats.^[141]

Antisense oligonucleotide, ISIS 388626 once weekly reduce the SGLT2 mRNA expression by 80% in Zucker rats with high kidney specificity^[142] and persistent effect for several weeks after stopping the therapy and undergoing phase 1 clinical trial.^[143]

A unique dioxo-bicyclo[3.2.1] octane motif is under development with full control of stereochemistry by Pfizer.^[144] While derivatives of a novel scaffold, C-phenyl 1-thio-D-glucitol are also under evolution for SGLT2 inhibition.^[145]

ADVANTAGES OF SGLT2 INHIBITORS

SGLT2 inhibitors inhibit up to 90% of glucose reabsorption in kidney.^[16-17,95, 121] Increase excretion will reduce the glucotoxicity in tissue, induce calories loss^[95, 17] with better control of diabetes, reduced level of plasma insulin and glycated haemoglobin^[6,107] and prevent complications.^[16,95, 121] On long term use, reduction in glomerulus hyperfiltration may lead to reduced risk of nephropathy^[146-147] by limiting kidney growth, inflammation and albuminuria.^[148]

Other beneficial effects are No risk of hypoglycemia due to insulin independent mechanism^[66,133,149] No gastrointestinal disturbances, convenient Oral route of administration,^[147,149] Less weight gain,^[149] improved liver sensitivity, decreased hepatic gluconeogenesis,^[150] increased sodium excretion leading to reduced blood pressure and beneficial effect in hypertension,^[151] and benefit in type 1 diabetes^[152] although not seen by all SGLT2 inhibitors.

PROBLEMS WHICH ARE ASSOCIATED WITH SGLT2 INHIBITORS

Some commonly seen adverse events were polyuria and increased thirst that may be due to osmotic water loss in urine. High level of glucosuria associated with bacterial

and fungal infection especially of urinary tract is another problem that cannot be ignored. Subclinical and initial clinically significant infection may go unrecognized due to neuropathy in diabetics. As diabetics are already on high risk of infection, further increase in infection may predispose them to septicaemia and hospitalization. Further studies are needed to define the risk and consequences of UTI in diabetics by Gliflozins.

As most of the diabetic patients are on multiple drugs, incidence of drug - drug interaction has to be studied in detail to prevent and monitor the clinical relevant events. Drugs affecting the uridine diphosphate glucuronosyltransferase (UGT) pathway i.e. Rifampicin results in significant effect on metabolic pathway. Further attention is needed in patients with liver or renal impairment while using Gliflozins especially due to kidney being primary site of their action.^[153]

Increased endogenous glucose production^[154] by Gliflozins is another area of concern and further study. Whether is compensatory mechanism of the body in response to increase excretion of glucose or independent action of Gliflozins yet to be answered?

There is also increased activity of SGLT1 in response to inhibition of SGLT2 transporter that is responsible for only 50 to 60% excretion of filtered glucose.^[155] Increased SGLT1 activity may result on extra burden on renal cell with unknown consequences on other SGLT1, and demands further long term studies.

CONCLUSION

SGLT2 inhibitors are welcomed in the drug management of diabetes due to their novel site of action targeting kidney, oral administration and no risk of hypoglycemia due to self check on action below renal threshold for glucose absorption in peripheral tissues including liver and muscles, additional reduction in blood pressure and body weight, less gastro intestinal side effects and their potential to reduce the nephropathy put them in much of the sought drug in management of type 2 diabetes and probably in type 1 diabetes too.

At the same time increased polyuria, thirst and risk of urinary tract infection are the limitations of these drug class. In diabetes even subclinical infection cannot be overlooked due to impaired tissue defence. Gliflozins put the diabetic patients at increased risk of bacterial and fungal infections of urinary tract and with its own complication like septicaemia, hospitalization and additional antimicrobial administration to treat these infections.

Risk of drug- drug interactions increased many fold due to multi drug therapy in diabetes with additional antimicrobial and should be sought thoroughly in all diabetics with liver and renal impairment.

Long term effects on kidney function has to be accessed in light of sustained exposure of renal cell to glycosuria as well as increased risk of nephropathy due to repeated UTI in diabetics. Future potential of use in diabetes type one is to be explored as well as newer SGLT2 inhibitors acting through antisense oligonucleotide therapy.

To conclude, although SGLT2 inhibitors have advantages of insulin independent mechanism to reduce the blood sugar level with additional advantages of reduced blood pressure, increased insulin sensitivity, weight loss and reduced nephropathy, their limitations can not be overlooked.

Increased risk of UTI is to be kept in mind while prescribing the drug. Patient should be educated and intimated about the urinary tract infection and periodically examination to diagnose and treat the infection is advisable to prevent the

complications. Cost benefit analysis of lab investigations, and pharmacotherapy of infections as well as long term assessment to study effect of increased SGLT1 activity and endogenous glucose production is required further. Further evidences would make their place more definitive in management of diabetes.

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