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Sodium Glucose Co-Transporter 2 (SGLT-2) Inhibitors: A Review

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ABSTRACT
Worldwide, the number of individuals with diabetes is projected to rise from 366 million in 2011 to 552 million by end of 2030. Despite therapeutic advances, the incidence and prevalence of diabetes continues to surge exacting a tremendous economic burden on countries. The major problem with diabetes is that just 50% of population is able to achieve target glycaemic control with available medications. Type 2 diabetes nearly doubles the risk of cardiovascular and macro vascular complications. Meeting the treatment goal is elusive for many patients. Sodium glucose co-transporter 2 (SGLT2) inhibitors are new class of antidiabetic drug with insulin-independent mechanism of action. The remarkable advantage of these drugs is to increase urinary glucose excretion without inducing hypoglycaemia and promoting body weight loss. This review focuses on physiology underlying the use of SGLT2 inhibitors, their mechanism of action and clinical pharmacology.
Keywords: *Sodium glucose co-transporter 2 inhibitors, Anti-diabetic drugs, Dapagliflozin, Canagliflozin, Empagliflozin.*

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive, chronic metabolic disease characterised by hyperglycaemia.[1] Diabetes is a highly prevalent disease affecting more than 194 million people worldwide and according to Indian Council of Medical Research- Indian Diabetes study (ICMR-INDIAB), India currently has 62.4 million people with diabetes.[2] This is set to increase to over 100 million by 2030. According to International Diabetes Federation, it is predicted that there will be >0.5 billion patient with diabetes worldwide by the year 2030 and two-third of these patients will die prematurely from cardiovascular complications.[3] Type 2 diabetes accounts for nearly 95% of diabetes and reduces life expectancy by at least 10-15 yrs.[4]

Typical features of T2DM are insulin resistance of various organs such as liver, muscle, and adipose tissue, abnormal hepatic glucose production and reduced glucose- stimulated insulin secretion. Hyperglycaemia is a characteristic feature of T2DM. Beyond being a diagnostic marker, elevated glucose is a key factor in the two abnormalities that are at the core of type 2 diabetes: pancreatic beta cell failure and insulin resistance. Chronic hyperglycaemia can induce apoptosis of beta cells that is not countered by a

compensatory increase in beta cells neogenesis and can lead to insulin gene transcription. The detrimental effect of excessive glucose concentration is referred as "glucotoxicity".[5]

The mechanism of action of the existing anti-hyperglycaemic drugs used for the treatment of type 2 diabetes includes increasing insulin release, insulin sensitivity, controlling hepatic glucose release or inhibiting intestinal glucose absorption.[6] Currently available drugs work primarily either by improving beta-cell secretion of insulin (eg sulphonylureas and the new incretin agents) or by improving peripheral and hepatic insulin sensitivity (eg metformin and pioglitazones). Additional mechanisms for managing hyperglycemia, eg promoting satiety and decreasing glucagon release also contribute in long term management of Type 2 diabetes.

The ultimate goal of any pharmacological intervention in T2DM is to limit microvascular and potentially macrovascular complications by maintaining plasma glucose levels within a relatively normal range.[7] The poor glycaemic control leaves diabetics susceptible to develop both macrovascular and microvascular complications, that increase morbidity and mortality. Furthermore, although the existing drugs have proven efficacy, the long term control of blood glucose becomes difficult when the treatment is accompanied by the body weight gain during the therapeutic process.[8] Among commonly used oral antidiabetic agents thiazolidinediones and sulphonylureas are known to contribute in weight gain.[9] There is significant unmet need for effective therapies, having lesser side effects, increase glycaemic control, and target new mechanism of action.

A recent therapeutic approach for long term successful control of blood sugar and improving insulin resistance in diabetic patient has been energy control in reverse direction. From this point of view, several researchers have focussed on renal sodium linked glucose transporter 2 (SGLT-2) to reduce blood glucose level by blocking the renal glucose reabsorption system. This led to clinical development of a new class of antidiabetic drugs: SGLT2 inhibitors, use of which results in therapeutically induced excretion of glucose in urine. These drugs serve two medical needs: glycaemic control and reduction of already ingested calories.

RENAL PHYSIOLOGY OF GLUCOSURIA

Healthy individuals are able to maintain tight glucose homeostasis by closely regulating glucose production, reabsorption, and utilisation, and inspite of extreme variations in glucose intake, relatively very few people develop either diabetes or hypoglycaemia.[10] The kidney plays a critical role in filteration and reabsorption of glucose. 180gm of plasma glucose are filtered by the kidney per day of which 99% is reabsorbed into plasma in the proximal tubules. In normoglycaemic individuals this translates to approximately 180 gm of glucose.[11] Under period of hyperglycaemia the amount of filtered glucose reabsorbed increases in proportion to the plasma glucose concentration. Glucose starts appearing in the urine once its level exceed the maximum capacity(Tm) of the carrier protein which usually corresponds to a plasma glucose level of 200 mg/dl. In patients with diabetes, hyperglycemia results in hyperfilteration of glucose in the kidney and the increased luminal glucose exceeds the maximum reabsorption rate resulting in glucosuria.[12]

MECHANISM OF GLUCOSE TRANSPORT ACROSS MEMBRANE

The reabsorption of glucose filtered into the glomerular filterate is the primary mechanism by which the kidney influences glucose homeostasis.[13] Cell membrane being composed of lipids, is impermeable to glucose, which is a polar compound. Reabsorption occurs in proximal convoluted tubule and transport of glucose across the cell membrane requires carrier protein located in the cell membrane. Glucose enters eukaryotic cells via 2 different type of cell membrane associated carrier protein: the facilitated glucose

co-transporters (GLUTs) and the active sodium coupled co-transporters (SGLTs).[14] Glucose transport through the apical membrane of intestinal and kidney epithelial cells depend on the presence of secondary active Na^+/ glucose symporters: SGLT1 and SGLT2. The active transport of glucose is linked to downhill sodium transport, which is maintained by active extrusion of sodium across the basolateral surface into intracellular fluid. The energy provided by co-transport of Na^+ ions down their electrochemical gradient is used to concentrate glucose inside the cells. Facilitated diffusion of glucose across the basolateral membrane, catalysed by the GLUTs is an energy independent cellular process (Figure 1). There are 13 members in the GLUT family, each with different substrate specificity, kinetic properties and tissue expression profiles. GLUT4 is primarily involved in insulin mediated glucose uptake in muscles and adipose tissue.[15]

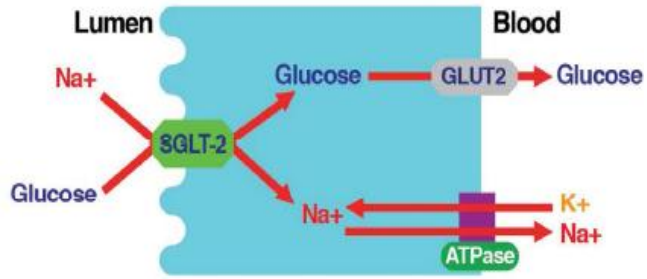

Figure 1: Glucose reabsorption mediated by SGLT2 in Kidney. Glucose is actively transported coupled with Na^+ across the luminal membrane catalysed by SGLT2. Further glucose is diffused out of cell with help of basolateral transporter GLUT2. Adapted from Ref. 15

SGLT2 CARRIER PROTIEN: THE UNIQUE THERAPEUTIC TARGET

Six sodium-glucose co-transporter have been identified in the kidney (SGLT1-SGLT6). SGLT2 is exclusively expressed in the brush border of epithelial cells in S1 segment of proximal tubule of the kidney whereas SGLT1 is expressed primarily in the small intestine and distal S2/S3 segment of proximal tubule of kidney and myocardium.[16] SGLT2 is a low affinity high capacity transporter of glucose and in healthy individuals it reabsorbs about 90% of filtered glucose. SGLT1 governs glucose transport in S3 segment and is a low capacity high affinity glucose transporter that reabsorbs the remaining 10% of filtered glucose (Figure 2). Inhibition of SGLT2 leads to the decrease in blood glucose due to increase in renal glucose excretion. The mechanism of action of this new class of drug also offers further glucose control by allowing increased insulin sensitivity and uptake of glucose in muscle cells, decreased gluconeogenesis and improved first phase insulin release from beta cells. The selective inhibition of SGLT2 does not hamper glucose transport in other major organs of the body such as brain, liver and muscle.[17]

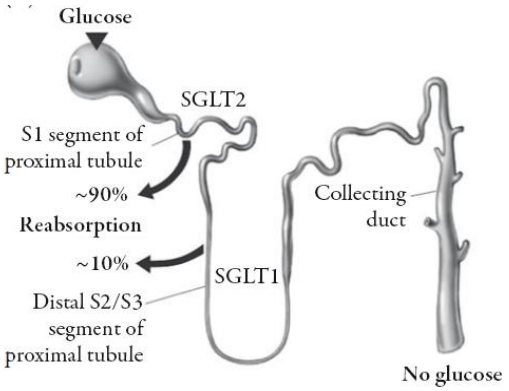

Figure 2: Renal glucose handling. The majority of glucose is reabsorbed by SGLT-2 in the S1 and S2 segments of the proximal convoluted tubule, and the remaining is reabsorbed by SGLT-1 in the S3 segment. Adapted from Ref. 16

SGLT2 INHIBITORS: MECHANISM OF ACTION

SGLT2 inhibitors provide a novel insulin-independent mechanism for the treatment of T2DM. There is an inter-individual variability in the renal threshold for glucose excretion, but in T2DM there seems to be an upregulation of glucose reabsorption in the proximal tubule. The maximal transport rate for glucose is up to 20% higher in patients with poorly controlled T2DM.[18] Increasing urinary glucose excretion through an

inhibition of glucose reabsorption represents an attractive method of maintaining blood glucose control. Sodium-glucose co-transporter-2 (SGLT2) inhibitors act by inhibiting SGLT2 in the proximal collecting duct of renal tubules, to prevent reabsorption of glucose and facilitate its excretion in urine.

The mode of action is dependent on blood glucose levels and independent of the actions of insulin. Thus, there is minimal risk of accompanying hypoglycaemia seen with other other antidiabetes medications that increase insulin secretion. Furthermore, there is minimal risk of overstimulation or fatigue of beta cells.[19] In addition the, the caloric loss (1gm of glucose=4Kcal) associated with excreted glucose facilitates weight loss.[20] Since the rate of urinary glucose excretion is proportional to glomerular filteration rate, the glucose lowering efficacy of SGLT2 inhibitors is expected to be compromised in patients with renal impairment. In the pursuit for attractive clinical candidate a number of specific SGLT2 inhibitors have been developed (Table 1).

Table 1: SGLT2 inhibitors: Current regulatory status

Compound	Daily Dose	Phase of Development
Dapagliflozin	5, 10 mg	Approved by European Medicines Agency
Canagliflozin	100, 300 mg	Approved by U.S. Food and Drug Administration
Empagliflozin	10, 25 mg	Phase 3
Ipragliflozin	25,50 mg	Phase 3(Approved in Japan)
Tofogliflozin	20 mg	Phase 3
Luseogliflozin	2.5, 5 mg	Phase 3
Ertugliflozin	5, 10 mg	Phase 2
LX4211	Not yet determined	Phase 2
EGT0001442	Not yet determined	Phase 2
ISIS 388626	Not yet determined	Phase 1
Sergliflozin		Discontinued due to nonselectivity
Remogliflozin		Discontinued due to nonselectivity

Phlorizin: the first known SGLT inhibitor was isolated from the root and bark of apple trees. Phlorizin non-selectively blocks both SGLT2 and SGLT1. Phlorizin was not developed for use in humans because of its low bio-availability (~15%) and its action on SGLT1 which can result in GI side effects like diarrhoea.[21]

Dapagliflozin: Dapagliflozin, an orally active sodium glucose cotransporter type2 inhibitor, is rapidly absorbed after oral administration, reaching peak plasma concentration in 2 hrs, and with a half-life of approximately 16-17 hrs. Dapaliflozin is highly protein bound, with oral bioavailability of 78% and primarily metabolised via uridine diphosphate-glucuronosyltransferase (UGT)1A9 to form inactive metabolite.[22] Dapagliflozin is approved as 10mg once daily drug, as monotherapy, or as add-on to metformin, sulfonylurea, dipeptidyl peptidase-4 inhibitors, and/or insulin. Dapagliflozin is specifically indicated as an adjunct to diet and exercise to improve glycemic control in adult with type II diabetes mellitus. The recommended dose is 5 mg once daily taken in the morning with or without food in severe hepatic impairment.[23] Renal functions should be assessed before initiating dapagliflozin. Dapagliflozin has got US Food and Drug Administration approval on January 2014 based on monotherapy and combined therapy studies.

Dapagliflozin has been shown, in multiple clinical studies, to reduce both HbA1c and fasting plasma glucose. Dapagliflozin administration led to significant placebo-adjusted reductions in HbA1c of −0.58%, −0.77%, and −0.89% in 485 newly diagnosed, treatment-naïve T2DM patients controlled by diet and exercise administered 2.5, 5, and 10 mg of dapagliflozin, respectively. The HbA1c change in the placebo group was −0.23%.[24] Patients with diabetes uncontrolled with oral diabetes agents for six weeks or more – metformin ≥1,000 mg and/or pioglitazone ≥30 mg or rosiglitazone 4 mg – and on at least 12 weeks of insulin and at least 6 weeks of a stable insulin dose at ≥50 units daily demonstrated mean changes in HbA1c of −0.70% for dapagliflozin 10 mg and −0.78% for dapagliflozin 20 mg at twelve weeks.[25] When combined with insulin for 24wks, dapagliflozin10 mg dose provided statistically

significant improvement in Hb1Ac, reduction in mean insulin dose(0.79%) and a statistically significant reduction in body weight compared with placebo in combination with insulin of up to 2.4 kgs.[26] Analysis of 208-week data comparing dapagliflozin in combination with metformin versus glimepiride with metformin showed an increase of 0.2 mmHg (95% CI -1.66, 1.61) in the glimepiride group while those on dapagliflozin showed a reduction of 3.69 mmHg (95% CI -5.24, -2.14).[27] Data from 21 clinical studies, were included in prespecified meta-analysis (n=9,339) to assess the cardiovascular safety of dapagliflozin. The results suggested that there was no increase in cardiovascular risk in a study that included more patients and substantial proportion of older patients.[28]

Canagliflozin: Canagliflozin was first approved by the US Food and Drug Administration on 29 March 2013 and recently also in Australia. Canagliflozin is a potent, competitive, reversible, highly selective once daily orally-administered SGLT2 inhibitor.[29] The starting dose approved for canagliflozin is 100 mg once daily, before first meal of day, and increased to 300mg daily for those not responding adequately, provided renal function is normal.[30] The oral bioavailability is 65% achieving maximal plasma concentration 1-2 hr after administration. The drug is metabolised by glucuronidation by UGT1A9 and UGT2B4.[31] Canagliflozin is indicated in adults aged 18 yrs and older with type 2 DM to improve glycemic control. As monotherapy when diet and exercise alone donot provide adequate glycemic control in patients for whom the use of Metformin is considered inappropriate due intolerance or contraindication, or as add on therapy with other antihyperglycemic products including insulin when these together with diet and exercise donot provide adequate glycemic control.

European commission approval was based on a comprehensive global phase 3 clinical trial programme which enrolled 10,285 pts in 9 studies.[32] Three studies have compared canagliflozin to current standard treatment, of which two compared canagliflozin to sitagliptin[33,34] and another with glimeperide.[39] The phase three programme also included three large studies in special populations: patients over 55 with type 2 diabetes[35], patients with type 2 diabetes, who had moderate renal impairment[36] and patients with type 2 diabetes who were considered to be at high risk for cardiovascular risk.[37] Results from the programme showed that both 100 mg and 300 mg dose of canagliflozin improved glycaemic control compared to baseline . A second endpoint showed that there was body weight reduction in the canagliflozin group compared to those on placebo group. Phase 3 results showed that canagliflozin was generally well tolerated. The hypoglycaemia was low when canagliflozin was used as monotherapy or as add on to metformin.

Canagliflozin therapy induced glucosuria of 70gm/day additionally leads to an energy deficit of 300Kcal/day, which translates into body weight reduction of −1.84 and −2.43 kg (100 and 300 mg canagliflozin respectively).[38] The weight loss was caused by fat mass loss and not due to osmotic dieresis.[39] A desirable additional effect was small but consistent reductions in systolic(−3.9 and −5.3 mmHg for 100 and 300mg dose) and diastolic (−2.1 and −2.5 mmHg for the 100 and 300mg dose) blood pressures. The changes are more prominent for systolic BP, but not accompanied by increased compensatory heart rate.[40] Canagliflozin, in contrast to Dapagliflozin, shows moderate but sustained efficacy even in patients with moderately impaired renal functions(GFR in range 30-50 ml/min/ 1.73 m^2) Canagliflozin has been shown to increase high density lipoprotein by 7.1-10.6%, low density lipoprotein by 7.1% and reduce triglycerides by 2.3%.[41]

Ipragliflozin: The drug has been approved in Japan for the treatment of T2DM either alone or in combination with metformin, SU, pioglitazone, α-glucosidase inhibitor, DPP-4 inhibitor, or with nateglinide.[42]

Empagliflozin: The drug is currently under Phase III evaluation. Empagliflozin is being studied in

daily doses of 10 and 25mg. Trials have shown that the molecule causes a greater reduction in HbA1c value as compared to sitagliptin, but similar to that shown with metformin. The trials for long term safety and efficacy are undergoing.

ADVERSE EFFECTS

The incidences of adverse effects with SGLT2 inhibitors are reported to be similar as that observed with other anti-diabetic drugs. Among the most important safety aspects of SGLT2 inhibitors is their low propensity to cause hypoglycaemia, for the reason, that the glucose excretion decreases along with decreasing plasma glucose concentrations and lack of response from counter-regulatory mechanisms as the mode of action is independent from insulin. However, it is expected to happen if these medicines are used in combination with other anti-diabetic drugs. A 208 week comparison of dapagliflozin plus metformin compared with glipizide plus metformin showed a tenfold reduction in episodes of hypoglycaemia.[27] This significant finding provides hope and succour for long term treatment and patient compliance.

The most frequent adverse event observed is uro-genital tract infections.[43] Glucosuria in most probability results in increased risk of genital fungal and urogenital infections: most commonly vulvitis and vulvovaginitis in females and balanitis and balanoposthitis in males. Adequate perineal hygiene and treatment with antifungal agents is suggested for prevention. Volume depletion and orthostatic hypertension are presumed to occur as a result of osmotic diuresis, but incidence of these adverse event has been observed to be minimal (<3%).[28]

Although, SGLT2 inhibitors can be used in combination with other anti-diabetic drugs and diuretics, caution need to be exercised with concomitant use of loop diuretics, because of potential risk of volume depletion. An increase in the dose of SGLT2 inhibitors should be considered if concurrent use of drugs which induce metabolising enzymes, for example, rifampicin, phenytoin, pheenobarbitone are used.[30]

Recently, US FDA has issued a safety warning for occurrence of acidosis after use of SGLT2 inhibitors. The FDA Adverse Event Reporting System (FAERS) data base identified at least 20 cases of acidosis reported as diabetic ketoacidosis (DKA), ketoacidosis, or ketosis in patients treated with SGLT2 inhibitors in a span of one year, all of whom required hospitalisation. The factors identified for precipitating such events were major illness, reduced food and fluid intake, and reduced insulin dose.[44]

THERAPEUTIC APPLICATIONS

The aim of the treatment in T2DM is to achieve near normal glycaemia toprevent the development and progression of vascular complications. SGLT2 inhibitors are a novel class of drugs with novel mechanism of action. These drugs can be used as initial monotherapy in treatment naive persons, in whom metformin is not indicated, or not tolerated. SGLT2 inhibitors can also be used as add-on to metformin or dual glucose lowering therapy, in persons inadequately controlled by these medications or are obese and failing to achieve HbA1c goals.

CONCLUSION

SGLT2 inhibitors are promising novel class of antidiabetic drugs which will help in achieving effective glycaemic control with a low risk of hypoglycaemia. Their unique mechanism of action, independent of insulin, and additional benefits such as weight loss and blood pressure make them attractive choice for combination with other antidiabetic drugs as an add-on therapy. However, more clinical data is required to assess their effect on clinical consequences of poor glycaemic control such as micro and macro vascular complications. Caution needs to be exercised while using these drugs in elderly patients who are prone to dehydration, genital infections and patients with reduced renal functions.

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