Review on Role of Sodium Glucose Cotransporter-2 Inhibitors (SGLT2) In Type 2 Diabetes

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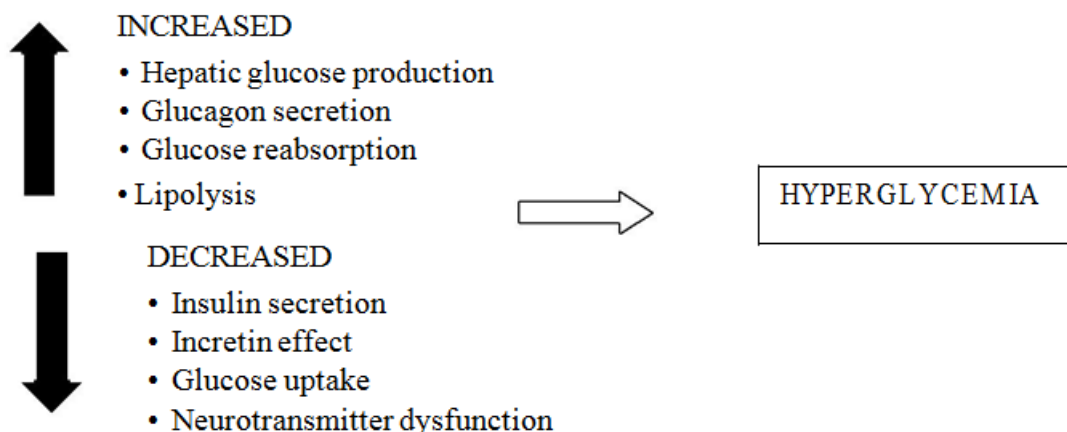[1]*Consultant Diabetologist , Sri Ramakrishna Hospital, Coimbatore.*
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Abstract*: Hyperglycemia is the major factor responsible for the development of diabetic microvascular complications and plays an important role in the pathogenesis of type 2 diabetes (T2DM) by means of glucotoxicity. Effective glycemic controlnot only reduces the incidence of microvascular complications, but also corrects the metabolic abnormalities that contribute to the progression of the disease. Progressive beta cell failure and side effects including weight gain and hypoglycemia associated with many current therapies present obstacles to the achievement of optimal glycemic control in type 2 diabetes mellitus (T2DM).Current treatment for type 2 diabetes does not achieve good glycemic change.Existing treatments have dose limiting safety or tolerability issues such as hypoglycaemia (sulphonylureas), oedema (glitazones), weight gain(sulphonyl ureas , glitazones) gastro intestinal adverse events (glucagon – like peptide 1 analogues). This has led to the discovery of novel therapeutic agents in treating T2DM that limits the side effects of existing drugs at the same time improving glycemic control. The vital role of kidneys in maintaining glucose homeostasis has given the impetus in developing sodium glucose co-transporter2(SGLT2) inhibitor, a new pharmacological class of anti-diabetic agent. Kidneys are currently considered as the mainstay in treating diabetes, as it maintains glucose homeostasis. The kidney maintains blood glucose levels by effectively reabsorbing the filtered glucose by receptors present in the apical membranes of the proximal convoluted tubule called the sodium glucose co-transporters (SGLT's). The underlying mechanism of SGLT2 inhibitors are independent of insulin secretion or action and is not related to beta cell function.SGLT2 inhibitors act on the kidneys and inhibit the effective reabsorption of glucose into circulation instead eliminate it causing glucosuria. It should also be pointed out that the mechanism of SGLT2inhibitors are complimentary and are not alternative to other existing anti-hyperglycemic drugs. SGLT2 inhibitors induce glucose excretion, resulting in calorie loss thereby reducing the weight which is also an advantage over most other therapies in diabetes.*
Key Words*: SGLT2, glucosuria, HbA1C, UGE, hypoglycemia, GLUT's, phlorizin*

I. Introduction

Type2 Diabetes is a progressive, chronic metabolic disease characterized by hyperglycemia. The effect of excessive glucose concentration regarded as "glucotoxicity" contributes to pancreatic beta cell failure and insulin resistance. The incidence and prevalence of diabetes keeps uncontrollably increasing inspite of various treatment modalities being available. The incidence could triple to one in three by 2050 in general population.[6].Typical features of T2DM are insulin resistance to various organs as liver, muscle and adipose tissue, abnormal glucose production and reduced glucose stimulated insulin secretion.[6] There are various factors that lead to increased blood glucose levels such as increased hepatic glucose production, increased glucagon secretion, impaired insulin secretion, decreased incretin effect, increased lipolysis, increased glucose re-absorption, decreased glucose uptake and neurotransmitter dysfunction collectively called as ominous octet.[1] In normal healthy individuals glucose homeostasis is maintained through a control over glucose production, re-absorption, and utilization.[2] In healthy individual, about 180 g of glucose is filtered daily by the renal glomeruli, and is then reabsorbed in the proximal convoluted tubules.[1] This is achieved by passive transporters, facilitated glucose transporters (GLUT's) and active co-transporters namely sodium glucose co-transporters (SGLTs).There are currently 6 identified SGLTs of which two (SGLT1 & SGLT2) are considered important.[2] In the early stages of T2DM there is increased production of pancreatic insulin to overcome insulin resistance but as the disease progress the depletion of pancreatic beta cells leads to decreased insulin secretion which results in absolute insulin deficiency and increased plasma glucose levels.[2] The U.K. Prospective Diabetes Study showed that, a decline in 1% in mean A1C was associated with a reduction of 37% in micro vascular complications and 21% reduction in the risk of any diabetes related complication or death. [6]

INCREASED
- Hepatic glucose production
- Glucagon secretion
- Glucose reabsorption
- Lipolysis

DECREASED
- Insulin secretion
- Incretin effect
- Glucose uptake
- Neurotransmitter dysfunction

⟹ HYPERGLYCEMIA

Kidney plays a vital role in regulation of glucose homeostasis by gluconeogenesis, utilizing glucose from the circulation and by reabsorbing glucose from the glomerular filtrate. Because of the low molecular weight of glucose, it is filtered into the urine and is recovered later by the kidneys. With the glomerular filtration rate of 180 liters per day kidneys filter around 160– 180 g of glucose per day maintaining a mean day long plasma glucose concentration of 100 mg/dl. In normal healthy individuals almost no glucose is excreted into the urine because all filtered glucose is reabsorbed by the proximal renal tubules (PCT) and returned into the circulation.[2] There is increased glucose re-absorption in PCT with rising plasma glucose levels until the maximum transport for glucose (Tmax) is reached. Tmax is considered to occur at a GFR of 260 – 350 mg/min/1.73 m^2. Renal glucose threshold is the plasma glucose concentration above which the SGLT capacity becomes saturated. The excess glucose cannot be reabsorbed,which results in urinary glucose excretion (UGE) or (glucosuria).This occurs at an estimated plasma glucose concentration of approximately 200 mg/dl.[2]

The currently available anti-diabetic agents bring about a reduction of elevated glucose levels by various mechanisms as increasing insulin sensitivity (metformin and thiazolidinediones), decreasing hepatic glucose production,glucogenolysis (metformin), increasing insulin secretion from the pancreas (sulfonylureas, DPP-4 inhibitors, meglitinides), reducing glucagon secretion (DPP-4 inhibitors), preventing post prandial release of glucagon from alpha cells of pancreas (incretin/ GLP-1 agonists and amylin analogues), delaying absorption of glucose(alpha glucosidase inhibitors), increasing glucose uptake by tissues, increasing glycogen levels, decreasing glycogen breakdown (insulin), releasing of insulin from beta cells of pancreas during hyperglycemia (incretin), increasing satiety (incretin and amylin analogues).[13,1]

Sodium Glucose Co-Transporter (Sglt-2) Proteins:

SGLTs are membrane-bound proteins that actively transport glucose against the concentration gradient which requires an energy source to drive the sodium pump. The regulation of glucose homeostasis by kidneys is attained through the SGLTs. [2] A family of 6 SGLT receptors encoding the gene SLC5A (11 genes) are distributed in various parts of the body.[1] SGLT1 is present in distal proximal convoluted tubule, loop of henle and in the gastro intestinal tract, as a high affinity, low capacity transporter. Besides its presence in the kidneys SGLTs are also present in small intestine, trachea, heart, and plasma membrane. [2]

Table 1: Sodium glucose co-transporter (SGLT) family :

SGLT MEMBER	SUBSTRATE	DISTRIBUTION		
SGLT1	Glucose, Galactose	Intestine,trachea,		kidneys,
		heart, brain, testis		
SGLT2	Glucose	Kidney, brain,	liver,	thyroid,
		muscle, heart		
SGLT3	Glucose	Intestine, testis,	lung,	thyroid,
		brain, uterus		
SGLT4	Glucose, Mannose	Intestine, liver, kidney, brain		
SGLT5	Glucose, Galactose	Kidney		
SGLT6	D – Chiro - Inositol	Brain, kidney, intestine		

SGLT2 is a high capacity, low affinity transporter extensively located in the proximal tubule.[1] Act as a transporter for both dietary glucose and galactose. SGLT2 contributes for reabsorption of 90% of the glucose and SGLT1 contributing to about 10%.[2] SGLT2 is encoded by SLC5A2 gene and any mutation in this gene results in loss of function and a rare disorder of familial renal glucosuria which is characterized by UGE in the presence of normal plasma glucose concentration without any signs of renal tubular dysfunction.[2]

Table 2: Characteristics of SGLT1 and SGLT2.

Characteristics	SGLT1	SGLT2
Location	Small intestine, DCT	PCT
Capacity	Low	High
Affinity	High	Low
Mutation & loss of function	Glucose-galactose malabsorption	Familial renal glucosuria
Contribution to glucose re-absorption	10%	90%

Homozygous mutations in the gene encoding SGLT2 may lead to maximum UGE(>10-$100g/1.73m^2$/day), whereas heterozygous mutation may lead to lower degrees of UGE($<10g/1.73m^2$/day).[2] Another group of glucose transporters, the facilitative glucose transporters or GLUTs are involved in the passive diffusion of glucose from the basolateral membrane of cells in the proximal convoluted tubule into the blood stream, mainly via GLUT2 and to a minor degree via GLUT1.[2]

Sodium Glucose Co-Transporter 2 (Sglt2) Inhibitor:

The SGLT2 inhibitor drugs arguably dates back 178 years. In 1835, French chemists first isolated a substance called phlorizin from the bark of apple trees and in 1886, German physician and early diabetes pioneer Joseph von Mering demonstrated that ingestion of high doses of phlorizin caused people to shed glucose in their urine pharmacologically denoted as glucosuria[13]. It was identified that phlorizin blocked the glucose transport in several tissues including kidneys and small intestines, which was later found to be due to inhibition of SGLT proteins. Phlorizin turns out to be a competitive inhibitor of both SGLT1 and SGLT2 but has a greater affinity for SGLT2[12]. In 1980, a study conducted on rat models with diabetes proved phlorizin was found to improve the glycemic levels and caused glucosuria without hypoglycemia[13]. Phlorizin also shown to normalize the insulin sensitivity in partially pancreatectomized rats but had no effect on insulin in control group. Thus ensuing glucosuria reversed insulin resistance and discontinuation of phlorizin resulted in insulin resistance and hyperglycemia. Phlorizin is converted into number of other compounds like phloretin in the GIT because of beta- glucosidase. This is also associated with unpleasant gastro-intestinal problems[13]. As a result of this massive dosing is required in humans compared to animal models. Moreover it is a potent inhibitor of GLUT1, suppression of which can lead to reduce glucose transport to other tissues such as the central nervous system. Various other studies revealed that phlorizin has a disadvantage of low bioavailability, poor absorption, decreased glucose-galactose absorption, dehydration and diarrhoea. It was also found to be non-selective in its inhibition of SGLT2 and SGLT1. So it became evident that phlorizin would not be applicable to the human DM populations. Still counting on the underlying mechanism, the entire class of SGLT2 has really been about the search of compounds that are capable of replicating the ability of phlorizin in causing glucosuria side stepping all the undesired effects and dosing requirements.In clinical trials a majority of drugs under trial are discontinued due to safety concerns. Various phlorizin derivatives that possess increased stability, bioavailability, SGLT2 selectivity and candidates with both O- and C- glucoside activity have been evaluated. Candidates such as sergliflozin and T – 1095 of O- glycosides were evaluated first, but were discontinued earlier due to non-selective SGLT2 inhibition and/or bioavailability issues. Number of C-glucoside compounds progress to marketing application and approval because of increased resistance to enzymatic breakdown activity.

The major challenge in pharmacological innovation of diabetic treatment is development of medication that is efficacious and has lower side effects such as weight gain and hypoglycemia common with oral anti – diabetic agents. SGLT2 inhibitors posses a novel mechanism in reducing the serum glucose level to a greater extent by increasing the renal elimination of glucose without causing much side effects. The challenge is to select the agent that inhibits only SGLT2 which is primarily responsible for regulating glucose reabsorption in the kidneys, without inhibition of SGLT1 as it is abundant in the gastro-intestinal tract, and its inhibition may lead to undesirable effects. Recent developments have focused on increased selectivity to SGLT2. Only Canagliflozin and Dapagliflozin has been approved by the DCGI and marketed in India.

Table 3: **Comparison of Canagliflozin and Dapagliflozin.**

Details	Canagliflozin	Dapagliflozin
Indication	To improve glycemic control in patients in adults with T2DM	To improve glycemic control in patients in adults with T2DM
Dose	Starting dose: 100 mg orally once daily Maximum dose : 300 mg orally once daily	Starting dose: 5 mg orally once daily Maximum dose:10 mg orally once daily
Administration	Take prior to the first meal of the day, may reduce postprandial hyperglycemia via delayed intestinal glucose absorption.	Take in the morning with or without food.
Pharmacokinetics	Onset of action: within 24 hours Protein binding: 99% mainly to albumin Oral bioavailability:68% Elimination halflife:18.6 hours	Onset of action: within 24 hours Protein binding: 91% mainly to albumin not affected by renal or hepatic impairment Oral bioavailability:75%
Metabolism	Major metabolism through O-glucuronidation by UGT2B4 to two inactive metabolites. Minor oxidative metabolism(7%) through CYP3A4 substrate of P-gp and MRP2	Primarily metabolized by UGT1A9 to an inactive metabolite CYP- metabolism is a minor clearance pathway in humans weak substrate of P-glycoprotein

Mechanism Of Action Of Sglt2 Inhibitors:

SGLT2 is a low – affinity, high capacity glucose transporter located in the proximal convoluted tubule in the kidneys and is responsible for re-absorption of 90% glucose back into the plasma.[2] SGLT-2 reabsorbs vast majority of glucose filtered by the kidney in the S1 and S2 segments of the PCT and the rest being reabsorbed by SGLT-1 in the S3 segment. Inhibition of SGLT-2 causes decreased blood glucose levels since there is increased renal glucose excretion.[5] Inhibition of SGLT-2receptors in the PCT prevents re-absorption of glucose and facilitates its excretion in urine. As a result plasma glucose levels are lowered resulting in caloric loss. There is an improvement in all glycemic parameters since the plasma level of glucose decreases as it is excreted in the urine. Unlike the action of thiazolidinediones the mechanism of action of SGLT2 inhibitors is independent of the action of insulin and is dependent only on blood glucose levels.

This results in minimal potential for hypoglycemia and there is no risk of overstimulation or fatigue of the beta cells. SGLT2 inhibitors correct hyperglycemia by lowering the renal threshold for glucose excretion and suppress renal glucose re-absorption.[8] In normal healthy individuals, the filtered glucose load is < 375 mg/min (maximum glucose transport capacity Tm), and all the filtered glucose is reabsorbed into circulation. In uncontrolled T2DM the glucose load exceeds 375 mg/min, and all the excess glucose is excreted in the urine. When renal threshold to reabsorb glucose is exceeded, the glucose excretion rate increases linearly and parallels to the glucose filtration load. Thereby the reabsorption and excretion curves shows a non-linear transition as the threshold is reached, this "rounding" of the curves is termed splay. Increased glucose reabsorption is observed in diabetic patients which is associated with increased expression and activity of the SGLT2 transporter in the proximal tubule. It is desirable in diabetic patients to restore normoglycemia by allowing the kidneys to eliminate the glucose. On the basis of pathophysiologic considerations the development of specific inhibitors of SGLT2 inhibitors provides a rational approach for treating diabetic patients.
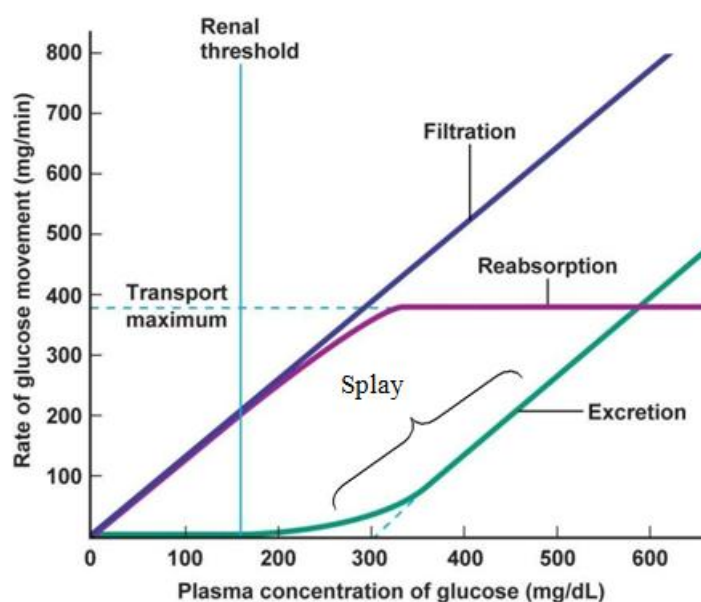
The mechanism of action of this new class of drugs offers further glucose control by allowing increased insulin sensitivity and uptake of glucose in muscle cells, decreased gluconeogenesis and improved first phase insulin release from the beta cells. This approach does not only decreases the blood glucose levels but also has metabolic benefits such as calorie loss (due to loss of calories in the urine).

Table 5: Pharmacokinetic data of SGLT2 inhibitors

Drug	Oral BA	Elimination	Dose adjustments
Canagliflozin 100mg – 300mg	65%	UGT1A9 and 2B4	If eGFR is > 45 <60ml/min/1.73m^2. Stop in patients if eGFR is <45ml/min/1.73m^2.
Dapagliflozin 5-10 mg	78%	Hepatic and renal UGT1A9	Should not be given if eGFR is<60ml/min/1.73m^2.

eGFR estimated glomerular filtration rate, UGT – uridinediphosphateglucuronosyl-transferase.

Pharmacokinetics Of Sglt2 Inhibitors:
Absorption: The SGLT2 inhibitors are extensively and rapidly absorbed on oral administration. An oral bioavailability of 75% and more is seen for a dose of 10mg. The time to achieve maximum concentrationis slowed down in the presence of food.[13]

Metabolism: Dapagliflozin is metabolized in the liver into its inactive conjugate dapagliflozin 3-0- glucuronide. It is then eliminated by the kidneys. In patients with renal impairment, the glucosuric effect of the drug is reduced. Therefore dapagliflozin should not be used in patients with moderate to severe renal impairment. Half life of dapagliflozin may be increased in patients with severe hepatic impairment and hence the drug should not be used in this setting but no adjustment in dose is necessary for patients with mild to moderate hepatic impairment.[13]

Elimination: Approximately 40% of canagliflozin that is administered is excreted unmetabolized in feces, while minor metabolism of canaglifozin occurs via uridine 5[1]- diphospho-glucuronosyltransferase that results in two pharmacologically inactive metabolites (canagliflozin O- glucuronides) which are mainly excreted via urine.[13]

FDA Warning:

The U.S Food and Drug administration (FDA) has given safety information on using SGLT2 inhibitors that may lead to a serious condition where the body produces high levels of blood acids called ketoacidosis. Close monitoring of the patients for symptoms like nausea, breathing difficulty, vomiting, sleepiness, unusual fatigue and confusion is required. Symptoms usually occur within 2 weeks of using the drug. On the occurrence of these symptoms patients are recommended to consult the physician before discontinuing the drug. FDA identified 20 cases of ketoacidosis and diabetic ketoacidosis (DKA) since March 2013 to June 2014 from FDA Adverse Event Reporting System (FAERS) database and all these cases required hospitalization for further treatment. Elevated blood or urine ketones are usually associated with a high anion gap metabolic acidosis. Factors that contribute to the development of high anion gap metabolic acidosis in these documented cases were acute renal failure, hypovolemia, hypoxemia, history of alcohol use. Some factors like infection, urosepsis, trauma, reduced caloric or fluid intake and reduced insulin dose contributed to DKA.[7] Although SGLT2 inhibitors are a new class of anti-diabetic drugs, they are still in the post marketing surveillance phase of trials and have been recently identified to have certain major drug – drug interactions. When canagliflozin, a SGLT2 inhibitor is given along with digoxin there is an increased digoxin exposure. UDP – glucoronyltransferase enzyme inducers when given along with canagliflozin results in decreased canagliflozin exposure.

Clinical Safety Data:

1) Urinary Tract Infection And Genital Tract Infection:

Results of a meta-analysis in eight studies comparing canagliflozin and dapagliflozin to other anti-diabetic agents revealed that urinary tract infections (UTI) and genital tract infections –yeast infections called vulvovaginitis in females and balanitis or balanoprosthitis in males were found to be more common with SGLT2 inhibitors. As reviewed by Nauck, safety data from pooled retrospective analysis of data from the short term, double blind periods of 12 placebo controlled trials (n=4,545) using dapagliflozin resulted in gential tract infection and lower urinary tract infection were more common with dapagliflozin compared with the placebo controlled groups (genital tract infections 4.1-5.7% dapagliflozin versus 0.9% placebo and urinary tract infection 3.6-5.7% dapagliflozin versus 3.7% placebo). A pooled analysis of four 26 weeks phase III analysis (n=3,313) of canagliflozin revealed that risk of urinary tract infection and genital tract infection is more with canagliflozin than the placebo control groups (UTI 5.1% canagliflozin versus 4% placebo ; genital tract infections 7.5% canagliflozin versus 1.9% placebo). These effects are found to be more common in women than in men.[2]

2) Hypoglycemia :

The incidence of hypoglycemia is found to be low in SGLT2 inhibitor therapy, except for the groups undergoing background therapy of sulfonylureas or insulin, with minor effects where the plasma blood glucose levels go below 63 mg/dl. Based on the results of these clinical trial data, prescribing information for both canagliflozin and dapagliflozin recommended using a low dose of insulin or insulin secretagogue to reduce the risk of hypoglycaemia when used in combination.[2]

3) Renal Safety And Dehydration Effects:

A phase III trial of canagliflozin used in T2dm patients with CKD (estimated GFR >30 and <50 ml/min/1.73m^2) resulted I larger reduction of GFR (-9.1% for 100mg and -10.1% for 300 mg of canagliflozin versus -4.5% for placebo) from the baseline in canagliflozin treatment groups compared to the placebo groups and these reductions were found to be high in 3 weeks of treatment period and it returned back to baseline over 26 week treatment period. Lower number of people in canagliflozin 100 mg and 300 mg progressed to albuminuria.Various data also studied volume depletion effects of canagliflozin lead to hypotension which occurred in about 1.3%-1.4% in 100 mg and 300 mg respectively versus 1.1% in placebo group, which were not serious or led to discontinuation of the study.[2] A 12 placebo controlled studies (n>4, 500) on dapagliflozin revealed that approximately 375 ml extra urinary volume is produced per day with dapagliflozin 10 mg therapy, volume depletion occurred in 0.6%-1.2% for 2.5 – 10 mg of dapagliflozin versus 0.4% for placebo groups, indicating a slightly elevated risk and a need to maintain an adequate fluid intake. Hypotension occurred more frequently for elderly people and subjects treated with loop diuretics. It does not cause acute renal toxicity also the GFR came to normal by week 24 and was maintained till week 102.[2]

4) Venous Thromboembolic Events :

The events causing VTE were monitored in the SGLT2 inhibitor clinical trials and the effects were found to be because of volume depletion. It was found to be 0.2% and 0.3% in patients receiving canagliflozin 100 and 300 mg respectively versus 0.2% for placebo group which is not statistically relevant or significant.[2]

5) Bone Safety:

Treatment for about 26 weeks with canagliflozin revealed that no meaningful changes in bone demineralization were observed, but there was increased in overall fracture events (2.5% for 100 mg and 2.3% for 300 mg compared to control 1.7%). No clear reports were documented on dapagliflozin induced bone demineralization or increased fracture risk rates in people with diabetes and acute renal failure but bone fractures were documented in patients with moderate renal failure(estimated GFR >30 to <60 ml/min/1.73m^2). [2]

6) Cardiovascular Safety :

SGLT2 inhibitors have favorable effects on cardiovascular risk but the changes in lipid profile have caused some CV effects as stroke, heart attack, and other vascular complications. There was a dose related increase in low density lipo-protein cholesterol (LDL-C) about 4.5% to 8% for 100 mg and 300 mg of canagliflozin. So the dosing recommendations were included while initiating canagliflozin therapy as to monitor the LDL-C levels and treat accordingly.[2]

7) Malignancies :

Monitoring of breast, bladder and renal cell cancer were monitored in patients treated with canagliflozin and the incidences were found to be 0.38%-0.46% versus 0.4% for breast cancer, 0.06%-0.09% versus 0.11% for bladder cancer and 0.06%-0.09% versus 0.08% for renal cell carcinoma. The data revealed from pooled analysis documented that dapagliflozin have increased risk of causing bladder and breast cancer than canagliflozin so it is to be used carefully or used in caution with people who already have previous history of the disease.[2]

Safety of SGLT2 Inhibitors in Pregnancy and Breast Feeding:

Pregnancy: In animal studies, exposure to the drug during periods of animal development corresponding to the late second and third trimesters of human development, showed increased kidney weights and renal pelvic and tubular dilation at doses expected during human exposure. Canagliflozin is rated as FDA category C, as there are no adequate and well – controlled studies in pregnant women. The use of canagliflozin is not recommended, especially during the second and third trimesters. The potential benefits should always outweigh the risks.

Breast Feeding: There are studies which prove that the drug is excreted into human milk. A proper decision should be made whether to discontinue breast feeding or to discontinue the drug, taking into account the importance of the drug to the mother.

Advantages Of Sglt-2 Inhibitors:
1) Glycemic Effects

About 58 clinical trials involving canagliflozin and dapagliflozin reported that there are favorable effects on reducing glycosylated haemoglobin (HbA1C). About a 52 weeks study involving canagliflozin as monotherapy showed an overall mean change from baseline in HbA1C and this is maintained for over long periods.[8]Clinically relevant improvements in glycemic control were reported from dapagliflozin 10mg (reduction of about-0.5% to -0.7% compared to placebo).[13] As reviewed by Kalra, a comparison of canagliflozin 300mg and sitagliptin for a period of 52 weeks proved that the efficacy of canagliflozin overcome the effect of sitagliptin in reducing the HbA1C levels.[8]

2) Effects On Weight Reduction

SGLT-2 inhibitors use leads to a reduction in body weight ranging from about 1 to 5 kg.In patients with higher base line weight and long standing diabetes a greater reduction in body weight is seen.The weight loss is sustained after upto 2 years of use of dapagliflozin,and may be linked to a reduction in insulin dose requirements of patients with long standing diabetes.Evidences suggest that two-third of the decreased weight is lost from fat mass(especially visceral abnormal fat);as compared to lean mass.Initially there is rapid decline in weight followed by slower rate of weight loss.It is also associated with marked reduction in waist circumference.If given in combination with insulin SGLT-2i can attenuate weight gain due to insulin.Treatment with dapagliflozin10mg produced a statistically significant decrease in body weight of up to 2.4kg compared to an increase of 0.43 kg in the placebo group.[8] Dual-energy X-ray absorbimerty revealed that body weight reduction is mainly due to reduction in the body fat mass rather than a loss of fluid or lean tissue. [2,9]

3) Effects on Blood Pressure

SGLT-2 inhibitors cause significant reduction in both systolic and diastolic blood pressure.These effects are more markedly presented in reduction of systolic BP and are not dose dependent.The associated symptoms of tachycardia and hypotension have not been reported.The effects on BP are found to be greater in

patients with high baseline systolic BP and is independent of glycemic or body weight reduction.Initially BP reduction with SGLT2i occurs due to osmotic diuresis and in later stages it is due to inhibition of renin – angiotensin system.Studies reported a reduction of upto 13.4-17mmHg insystolic BP with empagliflozin, canagliflozin at the dose of 100 and 300mg dose reduced systolic and diastolic BP compared with glimepiride with no notable changes in pulse rate.[8] Canagliflozin attains a relevant lowering of systolic(-3.9 and -5.3mmHgfor the 100 and 300mg dose respectively) and diastolic (-2.1 and - 2.5mm Hg for the 100 and 300mg dose respectively).Canagliflozin treatment is correlated with a mild diuretic effect and haemoconcentration(reflected by increased haemoglobin and haematocrit).Decline in diastolic BP were smaller and less consistent across clinical trials.[9]

4) Effects On Uric Acid

Evidences suggest that there are potentially beneficial effects of SGLT2 in hyperuricemia as it reduces serum uric acid levels by acting directly on its transport system or indirectly by producing sodium re-absorption in the PCT. This effect is improved if insulin is co-prescribed in patients with type2 diabetes. This is independent of risk factors for hypertension renal disease and cardio-vascular disease.[6]

5) SGLT2 Inhibitors And Cancer

Studies performed on animals and molecular evidences do not suggest a positive link between exposure to SGLT2 inhibitors and the risk of developing cancer. Studies were conducted in Sprague – dawley rats which were associated with increased risk of neoplasms of renal tubules, leydig cells and testicular cells and also had carbohydrate malabsorption and disrupted calcium homeostasis. But these effects are not proved in humans. Through 8 phase 3 clinical trials with canagliflozin there were no documented cases of testicular cancer or pheochromocytoma, one case was reported with testicular cancer. The patient developed enlarged scrotum and had scrotal pain. A particular study was done where SGLT2 inhibitor (canagliflozin) was given to a group of people who were compared with placebo group, from the study it was concluded that the overall incidence of bladder, renal and breast cancers does not increase in canagliflozin treatment group while being compared to the non-canagliflozin groups. In 11 phase 3 clinical trial,the incidence of bladder cancer for dapagliflozin was about 0.16% and breast cancer in females about 0.09%. Within 6-12 months of treatment bladder cancer was found in almost half treated patients out of which 6-9 cases presented hematuria.[4]

6) Effects On Lipids

SGLT2 inhibitors do not have a very prominent role on blood lipid levels. But evidence shows thatCanagliflozin increases high density lipoproteins (HDL) by 7.1 – 10.6%, low density lipoproteins (LDL) by 7.1% and reduces triglycerides by 2.3%.[8] Small increases are seen in the HDL cholesterol and LDL cholesterol and small reductions in triglycerides in patients who are also treated with dapagliflozin.[6] This may be how SGLT2 attributes to weight reduction. An increase in HDL-C and LDL-C was observed in patients treated with canaglifozin for 104 weeks and this increase was a consistent finding at week 52. However, the proportion of patients who started lipid-modifying agent's therapy was 13% in canagliflozin 100mg, 11.5% in canagliflozin 300mg and 13.3%in glimipride groups. After a period of 4 years on using the drug, a sustained and stable weight loss was observed with dapagliflozin whereas weight gain was observed with glimipride (-3.95 vs. +1.12kg).[8]

7) Effects On Cardio Vascular Risk Pathways

One of the major complications of hyperglycemia is leukocytosis which is effectively reduced by SGLT2 inhibitors. SGLT2 inhibitors also reduce inflammation and oxidative stress which are different processes involved in the pathophysiology of atherosclerosis. SGLT2 inhibition leads to glucosuria which usually accompanies diuresis, weight reduction and also a reduction in blood pressure which are all very beneficial in patients with heart failure, also convinced that impaired ventricular function and remodeling could be improved. It was also proved from a study that patients receiving dapagliflozin were likely to experiences light reductions in the incidence of myocardial infarction by 13.8%, stroke by 9.1%and cardiovascular death by 9.6% and all – cause death by 5.0%.[5]

II.   Discussion

The renal glucose handling by inhibiting SGLT2 has proved to be successful in treating T2DM. None of the anti-hyperglycemics available are recognized to reduce CV risks. SGLT2 inhibitors, a modest therapy in T2DM reduces the glycemic levels independent of insulin secretion, reducing the blood pressure and body weight. Hence there is a strong rationale that these compounds will not only protect against microvascular complications but also against macrovascular complications. It is proved from certain studies that SGLT1 is involved in glucose uptake in many cancers. From this outlook, inhibition of SGLT1 and SGLT2 might even be

protective in certain types of cancer.SGLT2 inhibitors when used as combination therapies in individuals with T2DM had a poorly controlled blood glucose level, proved to be effective in,

➢ Reducing HbA1C
➢ Weight reduction
➢ Lowering systolic blood pressure
➢ Decreasing fasting plasma glucose levels.[3]

Considering the mechanism of SGLT2 inhibitors the incidence of occurrence of hypoglycaemia seemed to be very low. As evaluated by Nauck et al, one of the largest studies with 801 participants found that there is significantly less hypoglycaemia associated with SGLT2 inhibitors compared to sulfonylureas.[3] Recently U.S FDA documented 20 cases of diabetic ketoacidosis (DKA) on using SGLT2 inhibitors and labeling changes will be based on additional information in this class of drugs which is under investigation.

Future of Glycemic Control With Sglt2 Inhibitors

SGLT2 inhibitors are efficacious in treating T2DM as monotherapy in patients who are intolerant to metformin because of its side effects, but there are also studies saying that it can be used in combination with metformin, insulin, sulfonylureas, DPP4 inhibitors and thiazolidinediones. The next level of glycemic control in patients with T2DM includes INVOKAMET (Invokana + Metformin)(documented to have increased risk of lactic acidosis and vitamin B12 deficiency) and XIGDUO (Dapagliflozin + Metformin). The added advantage of preserving beta cell function and improving insulin sensitivity is to be recognized. The various factors to be considered when using SGLT2 inhibitors are

➢ Effects on reduction in HbA1C and glycemic control.
➢ Effects on weight compared to others which produced significant weight gain.
➢ Genital and urinary infections.
➢ Effectiveness: other drugs may decline in effectiveness as the disease progress because of its effects in stimulating insulin release; since SGLT2inhibitors are independent of insulin secretion, its effectiveness does not diminish with time.
➢ Ease of use by oral administration

The fear of hypoglycemia may have an impact in quality of life of the patients. Future trials may examine patients for combination therapy with other agents available and also monitor hypoglycemic episodes. There is the potential for evaluating their use in uncontrolled type 1 diabetes.

III.   Conclusion

The SGLT2 inhibitors are a novel approach in reducing glucose levels by promoting the urinary excretion of glucose without causing hypoglycemia in subjects with T2DM. Canagliflozin and Dapagliflozin have demonstrated a good safety profile, modest weight loss, a decrease in A1C. Because the SGLT2 inhibitors have a mechanism of action that is independent of insulin secretion or the presence of insulin resistance, the efficacy of this class of drug is not anticipated to decline with progressive beta cell failure or in the presence of severe insulin resistance. A reduction in sodium is seen, which is beneficial in decreasing Blood Pressure in hypertensive patients. FDA reported that diabetic ketoacidosis may occur on using SGLT2 inhibitors. This class of drugs can be used in combination with all other ant diabetic medications with anticipated additive efficacy on glycemic control.

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