Review Article

SGLT-2 inhibitors and the metabolic fulcrum

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Treatment potential of sodium glucose transporter-2 (SGLT-2) inhibitors in diabetes was first reported more than two decades ago, but their recently testified effect on reduction of major cardiovascular endpoints in outcome trials has led to renewed enthusiasm in them. Their role in the management of type 2 diabetes assumes more significance given that it is known that kidneys are not just innocent bystanders in this chronic disease, but are also involved in its pathogenesis. Pragmatic use of SGLT-2 inhibitors entails classifying patients based on their metabolic state- the so called metabolic fulcrum. When used in carefully selected patients, these drugs not only help in glycemia control, but also have a variety of favourable effects, like reduction of blood pressure and cardiovascular mortality, and improvement in clinical renal endpoints. In this mini review, we briefly describe the rationale of use of SGLT-2 inhibitors, their effects, usage and major side effects.

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Key words **: Type 2 diabetes, sodium glucose transporter-2 inhibitors, splay, metabolic fulcrum, glucosuria.**

Type 1 and 2 diabetes mellitus are chronic metabolic diseases which adversely affect both micro and macrovasculature. They are characterised by hyperglycemia which is a proven risk factor for the microvascular complications- nephropathy, neuropathy and retinopathy. Association of hyperglycemia, however, is less robust with the macrovascular complications- stroke, coronary artery disease (CAD) and peripheral artery disease (PAD). More so, any meaningful advantage of maintaining euglycemia in diabetes on macrovascular complications can take up to a decade to manifest. Neither glucose lowering drugs, nor therapeutic lifestyle changes had shown reduction in development of macrovascular complications before 2015[1,2]. Last 2 years have however drawn huge interest in two classes of drugs- Sodium Glucose Transporter-2 (SGLT-2) inhibitors and Glucagon Like Peptide-1 (GLP-1) receptor agonists -that were shown to reduce major adverse cardiovascular endpoints (MACE) in trials of patients with T2DM[3,4]. We discuss here the former class of drugs, three of which are currently US FDA approved for use in selected patients of type 2 diabetes- canagliflozin, empagliflozin, and dapagliflozin.

Kidneys in Glucose Homoeostasis- in Health and in Diabetes Mellitus :

The kidneys actively participate in normal glucose homeostasis in more ways than one. First, they use glucose as a metabolic fuel, second, they are sites of glucose production via gluconeogenesis, and finally, they reabsorb all filtered glucose and prevent glucosuria. Under physiological conditions, SGLT-2 in the initial part of proximal convoluted tubule reabsorbs the majority (80-90%) of filtered glucose, while SGLT-1 reabsorbs the remaining 10-20%[5]. There is difference between the 'theoretical' threshold and 'actual' threshold for glucosuria. In normal humans, the maximum renal glucose reabsorptive capacity or the tubular maximum for glucose (TmG) is about 375 milligrams per minute and this corresponds to a plasma glucose concentration of 300 mg/dl. The 'actual' threshold for glucosuria is however a plasma glucose concentration of 180 mg/dl. This difference is referred to as splay and characterizes the nonlinear transition between the renal glucose reabsorption and excretion curves as the TmG is approached. Splay has been explained by the presence of either functional and/or morphological glomerulotubular imbalance. Glucosuria can result from three mechanisms- decrease in the threshold for glucosuria, increase in splay, or reduction in TmG.

It is now known that the kidneys are not innocent bystanders in the pathogenesis of type 2 diabetes (Table 1). They contribute to the development of hyperglycaemia by producing excess amounts of glucose, by increasing glu-

- **Cardiovascular disease (CVD) is a significant cause of morbidity and mortality in diabetic patients.**
- **SGLT-2 inhibitors are new armamentarium to control hyperglycemia in T2DM patients.**
- **This drug has favorable effects on BP, cardiovascular mortality and renal functions apart from HbA1c reduction in carefully selected patients.**
- **However, researches are in progress regarding long term use of these drugs.**

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Table 1 — *Showing Kidneys in Type 2 Diabetes Mellitus and Effects of SGLT-2 inhibitors*

Kidneys in Type 2 diabetes mellitus	Effects of SGLT-2 inhibitors
1. Increase in gluconeogenesis	1. Reduce TmG
2. Increase in TmG	2. Reduce glucosuria threshold
3. Increase in threshold for glucosuria	3. Increase splay
4. Decrease in splay	4. Ameliorate beta cell glucotoxicity
	5. Reduce blood pressure and proteinuria
	6. Promote utilization of fat for energy production- the ROBINHOOD effect.
	7. Promote ketogenesis
	8. Reduce weight and visceral fat

cose reabsorption in response to an elevated threshold for glucosuria and an increase in the TmG. So, the use of SGLT2 inhibitors to target this aspect of the 'dirty octet' has drawn interest.

SGLT-2 Inhibitors—Mechanism of action :

SGLT2 inhibitors improve glucose tolerance by reducing both the threshold for glucosuria and the TmG and by ameliorating glucotoxicity leading to enhanced ß-cell function and improved insulin sensitivity in muscle[6,7]. The efficacy of SGLT2 inhibitors, however, is partially offset by an increase in endogenous glucose production and enhanced glucose reabsorption by SGLT1.

Multiple publications have described the effect of the three US FDA approved SGLT-2 inhibitors on HbA1c levels in drug-naive T2DM patients and as an add-on therapy in patients with poorly controlled T2DM (HbA1c >7.0%) treated with metformin, sulfonylureas, pioglitazone, metformin plus sulfonylureas, metformin plus pioglitazone, and insulin compared to placebo (8-10). These studies demonstrate that in T2DM patients with HbA1c 7.8–8.2%, a reduction in HbA1c of ~0.7–1.0% is achievable with SGLT2 inhibitor therapy. In long-term studies (>1 year duration) SGTL2 inhibitors cause a more durable reduction in HbA1c than do sulfonylureas and DPP-4 inhibitors[11,12].

Effect on Blood Pressure and the Kidney :

As the reabsorption of glucose and sodium in the proximal tubule are coupled, SGLT2 inhibition is associated with mild negative salt and water balance and a durable decrease in extracellular fluid and plasma volumes. The natriuretic effect of SGLT2 inhibition dissipates after 2-3 days and sodium and fluid balance is re-established, albeit with a ~7% reduction in plasma volume[13]. This modest reduction in extracellular fluid volume most likely accounts for the 5-6 mmHg decrease in systolic and 1-2 mmHg decrease in diastolic blood pressure observed within 1-2 weeks of initiating therapy. Over a period of 6-12 months, weight loss, alterations in the renin– angiotensin–aldosterone system, reduced plasma uric acid levels, decreased proteinuria, and other factors are also likely contribute to the sustained reduction in blood pressure[14].

The modest reduction in plasma volume following initiation of SGLT inhibitor therapy is associated with a small decline in glomerular filtration rate (GFR) of ~4-5 ml/min per 1.73m^2, which tends to return to baseline within 6-12 months of initiating therapy. A growing body of evidence suggests that SGLT2 inhibition might afford renal protection and prevent the development of diabetic nephropathy[15].

Prevention of Cardiovascular Disease :

EMPA-REG OUTCOME study showed that empagliflozin reduced the composite primary cardiovascular end point among patients with T2DM and a previous cardiovascular event or angiographically documented diffuse coronary artery disease, by 14%[3]. This study was not designed to examine the mechanisms responsible for the cardiovascular benefit achieved with SGLT2 inhibition. However, haemodynamic factors, including reductions in blood pressure (after load), intravascular volume (preload), and aortic stiffness are likely to have contributed[3]. The failure of heart rate to increase despite intravascular volume depletion suggests a potential role for reduced sympathetic nervous system activity. Of considerable interest is the ketone hypothesis, by which a switch from glucose to fat oxidation in the liver increases the plasma concentration of ketones that are preferentially taken up and oxidized as a fuel by the myocardium. Improved glycaemic control is unlikely to explain the cardio-protective effect of empagliflozin as the reduction in HbA1c was very modest (-0.25%) and as any beneficial cardiovascular effect of improved glycaemic control takes up to 10 years to manifest, whereas the reductions in cardiovascular mortality and hospitalization for heart failure with SGLT2 inhibition were observed within 3 months. A number of other mechanisms (decreased plasma uric acid level, reduced inflammation and oxidative stress, activation of the angiotensin II receptor type 2 (AT2) , improved insulin sensitivity, and diminished albuminuria) have been suggested to explain the cardio-pro-

tective effective of empagliflozin but hard evidence to support any of these possibilities is lacking[16].

Pragmatic use of SGLT-2 Inhibitors : The Metabolic Fulcrum :

Individuals can be categorized into three categories based on their metabolic state. The healthy individuals, considered to be "eubolic," with appropriate balance between catabolism and anabolism have a normal Insulin Glucagon Ratio (IGR). Subjects with hyperinsulinemia (insulin resistance) have a high IGR and can be termed "maladaptively anabolic." In such patients, obesity, high BP, dyslipidemia, and insulin resistance are observed. "Catabolic" patients have a low IGR with increased gluconeogenesis and glycogenolysis, demonstrate asthenia, weight loss, cachexia, and malnutrition, and are characterized as insulin deficient. Using an IGR-based metabolic-fulcrum, a metabolic "triage" or classification of diabetes patients can be created to help inform treatment[17]. A fall in IGR due to increase in glucagon and reduction in insulin levels is observed with SGLT2i treatment. For maladaptive anabolism, therefore, SGLT2i are the preferred choice of treatment. However, they can also be used in "eubolic" patients[17].

Use of SGLT-2 inhibitors requires adequate fluid intake to prevent volume depletion. Cautious use is recommended in frail elderly patients with concomitant use of diuretics. Also, it requires maintenance of perineal hygiene to prevent genital tract infections (GTI), and is to be avoided in patients with history of recurrent GTI (>4/year) or history of recent upper urinary tract infection (UTI). During an episode of severe UTI, temporary discontinuation is recommended[17]. Contra-indications of use are listed in Table 2.

Adverse effects :

Major adverse effects of this class of drugs include[16] (Table 3).

Conclusion :

The number of patients with T2DM continues to grow in India and across the world. Cardiovascular disease is a significant cause of morbidity and mortality in these patients. SGLT-2 inhibitors add to the armamentarium of drugs that can be used to manage hyperglycemia, with the advantage of reduction in cardiovascular mortality in those at high risk. However, much is still not known regarding long term use of these drugs and research to answer many pertinent questions is in progress. Nevertheless, their use in rationally selected patients brings about favourable cardiovascular and renal effects apart from effectively reducing HbA1c.

Table 2 — *Contraindications of SGLT-2 inhibitors*

1.	History of recurrent genital tract infections (>4/year)
2.	History of recent upper urinary tract infection
3.	Estimated glomerular filtration rate <45 mL/min/1.73 m^2
4.	Patients with extreme insulinopenia or type-1 diabetes
5.	Patients on fluid/carbohydrate restricted diet
6.	Decompensated medical/surgical illness
7.	Pregnancy and lactation
8.	Children

Table 3 — *Major adverse effects of this class of drugs include*

1. Genital mycotic infections.
2. Adverse effects related to reduced intravascular volume –orthostatic hypotension, increase in BUN and transient decrease in eGFR.
3. Hyperkalaemia- with canagliflozin but not with other SGLT2 inhibitors.
4. Hypoglycaemia when SGLT2 inhibitors used with sulfonylureas or insulin.
5. Rare cases of ketoacidosis in situations known to be associated with diabetic ketoacidosis.
6. Increase in bladder cancer reported with dapagliflozin but the number of cases is very small and causality unproven.
7. Bone fractures with canagliflozin; however, causality remains unclear.
8. Toe amputations with canagliflozin; but the number of cases is very small and explanation not available.

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