(Review Article)

Review on sodium glucose co-transporter-2 inhibitors for treatment of type-2 diabetes mellitus

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Abstract

Sodium glucose transporter-2 inhibitors (SGLT2-i) are a class of medicine that have been recently acknowledged and approved for management of Type-2 Diabetes Mellitus (T2DM). They have distinct encouraging extra-pancreatic glucuretic role that has been clinically applied for blood sugar management. Reports have been published for multiple side effects including ketoacidosis & ketonuria induced by SGLT2-i. This endeavor delves into the pharmacokinetics of SGLT-i agents, deliberates the utility of these drugs and suggests steps to maximize the safe use of these agents including their diverse beneficial effects.

Keywords: Canagliflozin; Dapagliflozin; Empagliflozin; Ketoacidosis; Ketonuria; T2DM

1. Introduction

Type-2 diabetes mellitus (T2DM), a metabolic disorder is characterized by hyperglycemia consequent to the defective insulin secretion, insulin action or both (1). With rising pervasiveness globally, type-2 diabetes mellitus is considered as a major public health concern neither restricted to ethnicity nor economic conditions prevailing both in developing and developed nations and has also been designated as 'public health priority' by the international scientific community (2).

International Diabetes Federation estimated global prevalence of diabetes to be 9.3% (463 million) in 2019, expected rising to 10.2% by 2030 and 10.9% by 2045 (3). Diabetes is one of the most agile and perilous health threats of the 21st century, with number of adult diabetics having more than tripled over the past 20 years. Considering the current upsurge, by 2030 a projected 578.4 million, and by 2045, 700.2 million adults aged 20–79 years, will be surviving with diabetes. Currently China is spearheading with 116.4 million diabetics followed by India 77 million and US 31 million people living with diabetes (3).

Type-2 diabetes mellitus is a chronic progressive disease needing multiple medications in order to control blood glucose levels. Sodium-glucose cotransporter-2 (SGLT2) inhibitors are the latest and novel class of hypoglycemic agents that received FDA approval in recent past. SGLT2 inhibitors function through a unique mechanism of reducing renal tubular glucose re-absorption, producing a reduction in blood glucose without stimulating insulin release.

Other benefits may include favorable effects on blood pressure and weight. Several studies documented that approximately 30-70% of patients could not attain target glycemic control in spite of standard conventional management (4, 5). Uncontrolled T2DM may lead to macro-vascular & micro-vascular pathological changes including cardiovascular (CV) complications causing unwanted death and disability (6). The risk of stroke and coronary artery

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disease (CAD) also doubles in overweight/obese T2DM patients (7).Therefore, a comprehensive concept of treatment strategy encompassing attainment of glycemic targets, attenuation of diabetic macro & micro-vascular pathological changes by reduction of body weight, blood pressure (BP) and lipid levels appears essential in the management of T2DM (8). SGLT2 inhibitors ensure glycemic control inducing weight loss without hypoglycemia thereby; help reduce BP with micro & macro-vascular adversities preventing precipitation of cardiovascular & cerebrovascular morbidities (9).

This endeavor makes an effort to highlight clinical application & benefits noted over the past few years including the safety concerns for SGLT2 inhibitors.

2. Physiological Characteristics of SGLT Inhibition

Glucosuria has been studied over many years using the botanical glucoside, phlorizin since its discovery in 1935 (10). Later, phlorizin was observed to be a non-specific inhibitor of SGLT proteins and several similar types of SGLT proteins have since been noted. These proteins work through non-insulin dependent pathway. Inhibition of SGLT results in changes that significantly improve hyperglycemic conditions, therefore initiated a newer concept in diabetes management (11,12).

Out of common variants of SGLT proteins (SGLT 1&2), SGLT1 showed low competence nonspecific transporter of glucose having functional expression both in the small intestines as well as the proximal tubule of the kidneys (12, 13). Use of SGLT1 inhibitors may lead to unwanted gastrointestinal derangement and severe diarrhea (12). SGLT1 inhibitors cause less than 10% of filtered glucose reabsorption in the proximal convoluted tubule of the kidneys (13). The function of SGLT1 inhibitor in control of hyperglycemia has been under study; interestingly the same may have likely beneficial effect being dual inhibitor in intestine as well as renal proximal tubules.
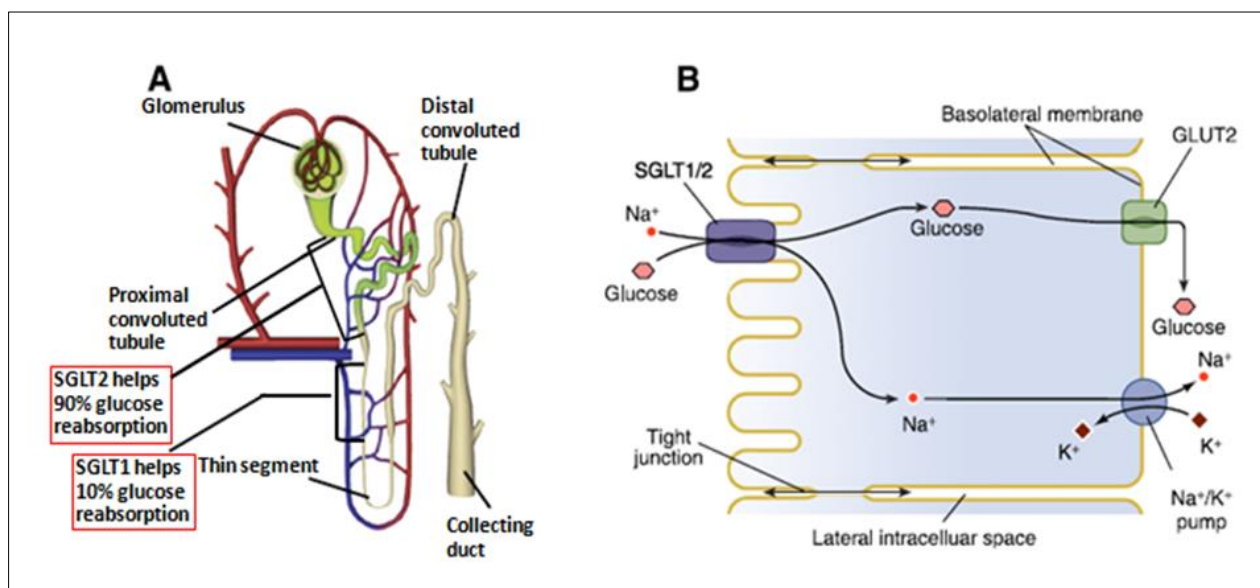

Figure 1 Glucose reabsorption from the proximal tubule. A: Anatomical arrangement of a kidney nephron with its blood supply. B: A model for glucose reabsorption across epithelium of proximal tubule. Na+ electrochemical potential gradient provides energy source and transport across the epithelium occurs in two steps. Glucose is transported across the apical membrane by SGLT1 and SGLT2. SGLT2 is predominantly located in PCT. Glucose Transporter-2 (GLUT2) is the major glucose transporter across baso-lateral membrane. (14)

SGLT2 proteins are functionally operational in the renal proximal convoluted tubule (RPCT) (Fig-1). These transporters facilitate reabsorption of around 90% of filtered glucose in RPCT and therefore, its inhibitions constitute a newer avenue for treatment T2DM (12,13, 15)Physiological renal threshold for reabsorption of glucose in RPCT corresponds to serum glucose level of 180 mg/dL. In T2DM patients, this threshold may be increased and the SGLT2 functionality enhanced causing intensification of hyperglycaemic condition (16). Selective SGLT2 inhibitors help lower the renal threshold for glucose significantly to level of 40 to 120 mg/dL (17). However, patients with Familial Renal Glucosuria (FRG) lack in functional SGLT2 proteins and thereby manifest glucosuria even in euglycemic conditions. FRG patients rarely present hypotension or hypoglycaemia signifying safety of short and long term use of SGLT2 inhibitors (18, 19).

2.1. Contemporary SGLT2 inhibitors in current use

Discovery of phlorizin in 1935, stood as a starting point for development of modern gliflozin group of SGLT2 inhibitors, that included canagliflozin (Invokana), dapagliflozin (Farxiga) and empagliflozin (Jardiance) for the treatment of T2DM (20).Food and Drug Administration (FDA) also approved these SGLT2 inhibitors for treatment of T2DM for clinical application (19). In addition, research activities being undertaken to detect other similar medicines that may prove beneficial for T2DM management in the near future. Of the three FDA approved drugs, empagliflozin has the highest specific selectivity for SGLT2 compared to SGLT1, while canagliflozin bears the least (19). Four combinations currently used in clinical practice are canagliflozin/metformin (Invokamet®), dapagliflozin/metformin (Xigduo XR®), empagliflozin/metformin (Synjardy®) and empagliflozin/linagliptin (Glyxambi®) (19).

2.2. Pharmacological attributes of SGLT2 inhibitors

Table - 1 depicts the US-FDA approval, common pharmacological attributes, dosage and contraindications of SGLT2 inhibitors (21, 22, 23, 24).

Table 1 FDA approval, pharmacological attributes and dosage for SGLT2 inhibitors

	Canagliflozin [a]	Dapagliflozin [b]	Empagliflozin [c]
US-FDA approval [d]	March 2013	January 2014	August 2014
Dosage (range)	100 – 300 mg daily	5 – 10 mg daily	10 – 25 mg daily
Absorption (Time to peak in plasma)	1 to 2 hr	2 hr	1.5 hr
Protein binding (%)	99 mainly to albumin	91	86.2
Excretion	Faeces > urine	Urine > faeces	Urine > faeces
Half-life (hours)	10.6–13.1	12.9 (10 mg dose)	12.4
Drug–drug interaction	-Efficacy enhances with- alpha lipoic acid, heparin guanethidine, MAO inhibitors, salicylates	-Efficacy enhances with- alpha lipoic acid, MAO inhibitors, salicylates, SSRIs quinolone antibiotics,	-Efficacy enhances with- alpha lipoic acid, MAO inhibitors, salicylates, SSRIs quinolone antibiotics,
	-Efficacy declines with- carbamazepine, efavirenz, phenytoin, rifampicin, ritonavir	-Efficacy declines with- rifampicin, diuretics, NSAIDs	-Efficacy declines with- rifampicin, diuretics, NSAIDs
Contraindications	History of serious hypersensitivity, severe renal impairment, ESRD		
Dose adjustment in renal impairment	-eGFR ≥ 60 mL/min /1.73 m^2	-eGFR ≥ 45 mL/min/ 1.73 m^2	-eGFR ≥ 45 mL/min/1.73 m^2:
	no dose adjustment	no dose adjustment	no dose adjustment
	-eGFR 45–60 mL/ min/1.73 m^2	-eGFR45 < mL/min/ 1.73 m^2	-eGFR < 45 mL/min/1.73 m^2
	100 mg once daily (maximum)	not recommended	not recommended

a - Reported by Sarnoski-Brocavich S (19); b - Reported by Kasichayanula S (20); c - Reported by Ndefo UA (21); d - Reported by Public Citizen (22);e - Abbreviations US-FDA - US Food and Drug Administration, MAO – Mono-amine oxidase, SSRI- Selective serotonin reuptake inhibitor, NSAID: Non-steroidal anti-inflammatory drugs, eGFR - estimated glomerular filtration rate, ESRD - end stage renal disease

2.3. Clinical application of SGLT2 inhibitors

SGLT2 inhibitors appear useful alternative for obese hypertensive clientele needing weight loss and antihypertensive benefits. High risk of hypoglycemia in certain patients may help them with a metformin-SGLT2 inhibitor combination as the risk of hypoglycemia with SGLT2 inhibitors is considerably small as against insulin and sulfonylurea (17).
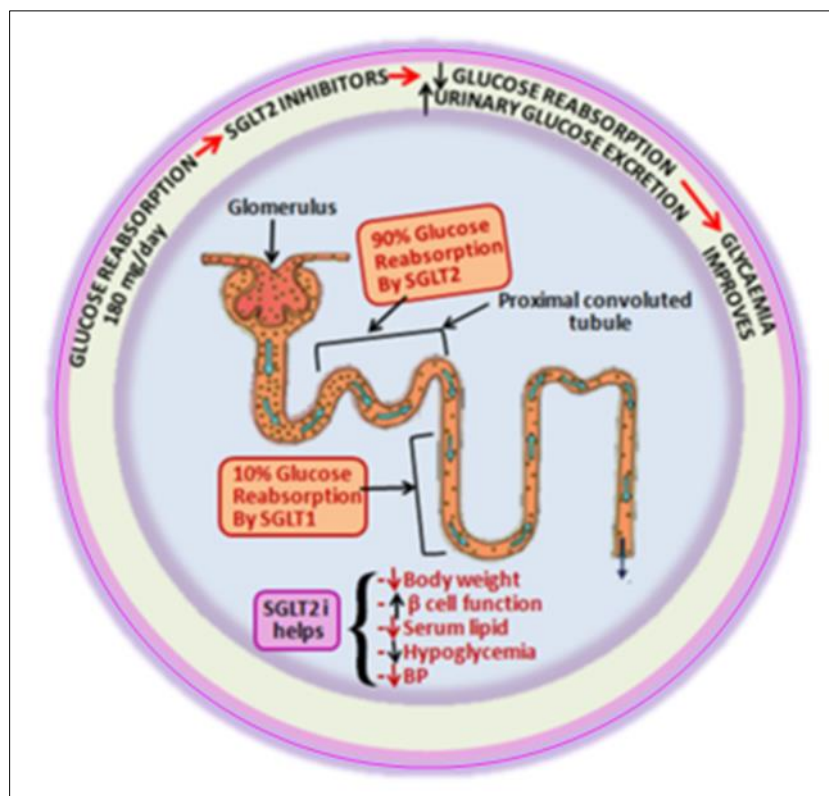
Figure 2 Action of SGLT2 inhibitor (SGLT2 i) in the renal tubule ensuing certain metabolic & clinical benefits

There are subtle differences in the eGFR thresholds for the commonly used 3 SGLT2 inhibitors however they need to be avoided in patients with renal insufficiency having estimated GFR < 45 mL/min/1.73m^2 (9). By lowering renal threshold for glucose excretion, SGLT-2 inhibitors diminishes glucose reabsorption at RPCT independently of insulin action and are therefore suitable for patients with long-standing diabetes even with impaired β-cell function (24). However, the distinctive glycosuric mechanism depends on the glomerular filtration rate so that in patients with chronic kidney disease having estimated GFR < 45 ml/min/1:73m^2, SGLT-2 inhibitors do not increase the urinary glucose excretion and, therefore, are not recommended (25).

3. Merits of SGLT2 inhibitors

3.1. Glycemic control

A meta-analysis of 2014 documented that 24-week fall in HbA1c with SGLT2 inhibitors was higher in patients with a lesser mean age, shorter duration of diabetes and an elevated baseline BMI with raised HbA1c & fasting glucose (26). Albeit reference 22, drop in body weight against the placebo attained its maximum around 24 weeks and retained up to 52 weeks.

When compared with other oral anti-diabetic agents, SGLT2 inhibitors exhibited a comparable ability in glycemic control aside additional metabolic advantages. In a randomized, double-blind trial in a group of 1,450 study subjects, HbA1c fell by − 0.65% with canagliflozin 100 mg, by − 0.74% with canagliflozin 300 mg and by − 0.55% with glimepiride 6-8 mg over a 104 week period (27). SGLT2 inhibitors demonstrated added enhancement in glucose control when combined with other anti-diabetic agents. Dapagliflozin add-on to subjects receiving metformin, confirmed a drop in HbA1c by −0·30% (95% CI −0·44 to −0·16) in the placebo group, against −0·67% (−0·81 to −0·53, p=0·0002) , −0·70% (−0·85 to −0·56, p<0·0001) & −0·84% (−0·98 to −0·70, p<0·0001) in the group of patients taking 2.5 mg, 5 mg and 10 mg dapagliflozin respectively over 24 weeks (28). On extended dapagliflozin add-on trial at 102 week, fall in HbA1c was -0.02% (95% CI: -0.20 to 0.23) for placebo as compared to -0.48% (CI: -0.68 to -0.29), -0.58% (CI: -0.77 to -0.39) & -0.78% (CI: -0.97 to -0.60) for dapagliflozin 2.5 mg, 5 mg and 10 mg respectively. The declines in HbA1c with dapagliflozin were dose dependent and statistically significant (29).

In T2DM patients inadequately managed with basal insulin, Rosenstock and others could demonstrate in a 78 week randomized, double-blind, placebo-controlled study that empagliflozin remarkably reduced HbA1c by −0.5±0.1% and −0.6±0.1% with 10 & 25 mg doses respectively, (both p<0.001) (30).Furthermore, while the placebo set of subjects required to increase their basal insulin dose by 5.5±1.6 units, the empagliflozin 10 mg assembly of patients could even do with lowering their dose by 1.2 ± 1.5 units and the empagliflozin 25 mg group needed to cut down their dose by 0.5 ± 1.6 units showing that SGLT2 inhibitors help reduce insulin dose requisites thereby moderate insulin-induced weight gain (30). In a sub-study of subjects getting ≥ 20 units/day of insulin at baseline in the Canagliflozin Cardio-vascular Assessment Study (CANVAS), HbA1c fell by − 0.62% and −0.73% in the Canagliflozin 100 mg and 300 mg group respectively versus placebo at 18 weeks. Improved level of HbA1c continued to remain same till 52 weeks along with significant declines in fasting plasma glucose, body weight and blood pressure (31). Table-2 portrays several RCTs that recounted a fall in Hb1Ac and other glycemic parameters with SGLT2 inhibitors as a second-line agent as compared to other anti-diabetic drugs. (32-36).

Table 2 RCTs depicting glycemic efficacy of SGLT2i against non-SGLT2i as add-on to metformin

Authors	No. of subjects (n)	Added SGLT inhibitor	Comparator Study period	Glycaemic efficacy
Leiter et al. (32)	1450	A: CANA 100 mg or 300 mg daily	B: GLIM 6–8 mg/daily 104 weeks	A1C~ Reduction from baseline (A vs. B)~ - 0.65 or - 0.74% vs. - 0.55% FPG ~Reduction from baseline (A vs. B)~ - 1.1 or- 1.3 mmol/l vs. - 0.6 mmol/l Achievement of target A1C<7% (A vs. B) ~ 42.5% or 50.2% vs. 43.9%
Del Prato et al. (33)	814	A: DAPA 2.5, 5 or 10 mg	B: GLIP 5, 10 or 20 mg 208 weeks	A1C ~ Reduction from baseline (A vs. B)~ - 0.10 vs. + 0.20% FPG ~ Reduction from baseline (A vs. B)~ - 0.7 vs. - 0.2 mmol/l A1C coefficient of failure (A vs. B) ~ 0.19 vs. 0.61 (P = 0.0001)
Ridderstråle et al. (34)	1449	A: EMPA 25 mg daily	B: GLIM 1–4 mg daily 104 weeks	A1C ~ Reduction from baseline (A vs. B) ~- 0.66 vs. - 0.55% (P<0.0001 for non-inferiority) FPG ~ Reduction from baseline (A relative to B)~ - 0.85 or - 0.17 mmol/l (P<0.0001)
Rosenstock et al.(35)	355	A: DAPA 10 mg daily	B: SAXA 5 mg daily 102 weeks	A1C~ Reduction from baseline (A vs. B)~ - 1.20% vs. - 0.88% FPG ~ Reduction from baseline (A vs. B)~ - 32 mg/dl & - 14 mg/dl PPG~ Reduction from baseline (A vs. B)~ - 70 mg/dl & - 36 mg/dl Achievement of target A1C<7% (A vs. B) ~ 22% & 18%
DeFronzo et al.(36)	413	A: EMPA 10 or 25 mg daily	B: LINA 5 mg daily 52 weeks	A1C ~ Reduction from baseline (A vs. B)~ - 0.66 or - 0.62% vs. - 0.70% FPG ~ Reduction from baseline (A vs. B)~ - 18.8 mg/dl or - 20.8 vs. - 13.1 mg/dl Achievement of target A1C <7% (A vs. B)~ 32.6 or 28.0% vs. 36.1%

Abbreviations

- SGLT2i – SGLT2 inhibitor,
- A1C – HbA1c ,
- FPG – fasting plasma glucose
- CANA – canagliflozin,
- GLIM - glimepiride,
- DAPA – dapagliflozin,
- GLIP – glipizide,
- EMPA – empagliflozin,
- SAXA – saxagliptin,
- LINA – linagliptin,
- PPG – postprandial glucose

3.2. Control of BP

Table 3 RCTs depicting changes in body weight & systolic BP with SGLT2 inhibitor as add-on to metformin in T2DM patients

Authors	No. of subjects (n)	Added SGLT inhibitor	Comparator Study period	Change in Body weight	Change in SBP
Haring et al. (39)	637	A: EMPA 10 mg or 25 mg daily	B: Placebo 24 weeks	- 2.08 or -2.46 kg against - 0.45 kg (both P<0.001)	- 4.5 or - 5.2 mm Hg against - 0.4 mm Hg (both P<0.001)
Leiter et al. (32)	1450	A: CANA 100 mg or 300 mg daily	B: GLIM 6–8 mg/daily 104 weeks	- 3.6 or - 3.6 kg against + 0.8 kg	- 2.0 or - 3.1 mm Hg against - 1.7 mm Hg
Del Prato et al. (33)	814	A: DAPA 2.5, 5 or 10 mg	B: GLIP 5, 10 or 20 mg 208 weeks	- 3.65 kg vs. + 0.73 kg	- 3.69 mmHg vs.- 0.02 mm Hg
Ridderstråle et al. (34)	1449	A: EMPA 25 mg daily	B: GLIM 1–4 mg daily 104 weeks	Difference– 4.5 kg (P<0.0001)	- 3.1 mmHg vs. + 2.5 mm Hg.(P<0.0001)
Rosenstock et al. (35)	355	A: DAPA 10 mg daily	B: SAXA 5 mg daily 102 weeks	- 2.4 kg vs. 0.0 kg	- 3.5 mmHg vs. 0.0 mmHg

EMPA – empagliflozin ,CANA-canagliflozin, GLIM- glimepiride, DAPA-dapagliflozin, DAPA – dapagliflozin, GLIP – glipizide,SAXA – saxagliptin, LINA – linagliptin

Most of the studies in the recent past with SGLT2 inhibitors documented significant fall in BP, with greater declining effect in systolic (1.66 to 6.9mmHg) than diastolic (0.88 to 3.5mmHg) pressure (17). It appears gratifying to mention that similar grades of fall in blood pressures have been observed in people with eGFR of 45 mL/min/1.73 m2 as those with 85 mL/min/1.73 m2; and patients didn't develop hyponatremia as many patients generally manifest with diuretics (37). The fall of BP in initial stage has been attributed to the diuretic effect resulting in volume depletion. However, longer-term effects may be attributable to inhibition of the renin-angiotensin system and weight loss. A meta-analysis of RCTs conducted in the recent past evaluated the efficacy of SGLT2 inhibitors on 24 hour ambulatory BP. SGLT2 inhibitor significantly reduced 24-h ambulatory systolic & diastolic BP by - 3.76 mm Hg (95% CI - 4.23 to - 2.34) and - 1.83 mm Hg (95% CI - 2.35 to - 1.31), respectively (38). Table-3 represents recently conducted RCTs that depicted a

significant fall in systolic BP with SGLT2 inhibitors as a second-line agent as compared to other anti-diabetic drugs (32-36, 39).

3.3. Reduction of body weight

Decrease in body weight helps reduction of diabetes related complications and excels the quality of life & wellbeing of the subject. Certain benefits accrued by drop in body weight in T2DM patients are illustrated in Fig.2. A recent meta-analysis of RCTs in 2017 annotated that around 5% weight loss had positive favorable effects on HbA1C, lipids and BP in T2DM patients (40). An incisive post-hoc analysis of 'Look AHEAD trial' documented that T2DM patients who had at least 10% drop of body weight during 52 weeks trial, experienced a 21% lower risk of fatal and non-fatal CV incidents {adjusted hazard ratio (AHR) 0.79, P = 0.034} and a 24% lesser risk of other CV episodes (AHR 0.76, P = 0.003) in comparison to the subjects with static or increasing body weight (41).

The Look AHEAD trial also confirmed that drop in body weight reduced several micro-vascular complications in T2DM patients (42). Furthermore, a reduction of body weight ensures better glycemic control, insulin sensitivity & β cell function with decrease in insulin resistance in T2DM patients (43). Therefore, weight reduction appears inescapable in T2DM patients to control unwanted mortality and morbidity arising out of diabetic complications. SGLT2 inhibitors have a noteworthy effect on body weight decline, which takes place principally due to loss of abdominal fat mass rather than lean mass from other parts of the body (44). Bolinder et al in a double-blind RCT, noted that the addition of SGLT2 inhibitor in T2DM patients uncontrolled with metformin, reduced body weight by 4.54 kg, waist circumference by 5.0 cm and fat mass by 2.80 kg over 102 weeks (45). Table-3 embodies certain current RCTs that rendered a significant fall in body weight with SGLT2 inhibitors as a second-line add-on against other anti-diabetic drugs (32-36, 39).

3.4. Control of lipid levels

SGLT2 inhibitors cause a small rise in high-density lipoprotein cholesterol (HDL-C) in addition to low-density lipoprotein cholesterol (LDL-C) besides a drop in triglyceride levels (48). Study involving meta-analyses of RCTs in recent past noted that treatment with SGLT2 inhibitor was associated with a small rise in HDL-C in T2DM patients without any significant changes in LDL-C and triglyceride (26, 49). In a double-blind RCT, add-on SGLT2 inhibitor in uncontrolled T2DM patients with metformin documented an increase in HDL-C and decline in triglycerides in comparison to placebo (28). Over and above, SGLT2 inhibitor induced a significant accretion in HDL-C and LDL-C levels after 24 weeks as against DPP4i (dipeptidyl peptidase-4 inhibitor) (50).

3.5. Cardiovascular protection

Cardiovascular disease (CVD) constitutes the preponderant precipitator of mortality and morbidity among diabetics around the world (51). The literature marked hypertension and diabetes as the significant risk factors for CVD. Furthermore, metabolic abnormalities related to lipid conform to pivotal role in the evolution of CVD. Evidence substantiates that SGLT2 inhibitors ensure CV benefits to T2DM patients through multi-directional pathway (52). Some of the possible & probable routes that might influence the CV benefits of SGLT2 inhibitors are represented in Fig 3. An explicit review and meta-analysis consolidating data from many RCTs observed that SGLT2 inhibitors cut down the risk of major adverse CV events (MACE) (RR 0.84; P = 0.006), CV death (RR 0.63; P\0.0001), heart failure (RR 0.65; P = 0.002), and death from any cause (RR 0.71; P\0.0001), in comparison to the control group (52).

An astute meta-analysis conducted in 2016, revealed that SGLT2 inhibitors along with their multifaceted metabolic and clinical benefits were associated with minimal risk for MACE in various subgroup populations (53). Furthermore to support in this course, certain insightful pooled analyses of RCTs (54, 55) aside the prime CANVAS trial (56) advocated that SGLT2 inhibitors are allied with a lesser occurrence of CV mortality and morbidity in contrast to placebo in high-risk CV patients.

Further adding up, illustrative world-based data from the CVD-REAL study (57), UK THIN database study (58) and Swedish national registries (59) exemplified that treatment with SGLT2 inhibitor was associated with a lower risk of CV event, mortality and morbidity in comparison with other anti-diabetic drugs in T2DM patients. The CVD-REAL study covered 309,056 patients from six countries (US, Norway, Denmark, Sweden, Germany and the UK); and those were lately put on either SGLT2 inhibitor or other anti-diabetic drugs. Against other anti-diabetic agents, patients treated with SGLT2 inhibitors manifested with lower rates of heart failure hospitalization (HHF) (hazard ratio [HR] 0.61; 95% CI 0.51–0.73; P <0.001); death (HR 0.49; 95% CI 0.41–0.57; P < 0.001), and HHF or death (HR 0.54; 95% CI 0.48–0.60, P < 0.001) without remarkable heterogeneity by country of origin (57).
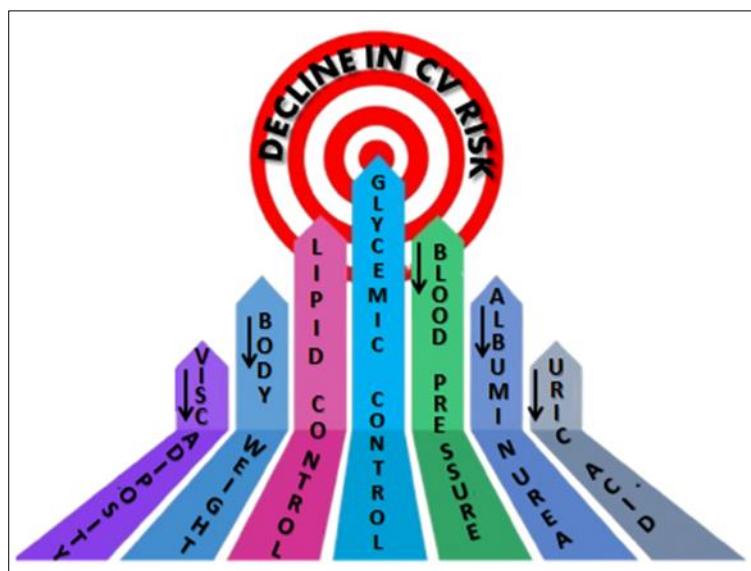
Figure 3 Possible pathways that result in CV benefits

3.6. Reno-protective Effect

SGLT2 inhibitors also exhibit a reno-protective effect in patients with T2DM. SGLT2 inhibitors help stabilize estimated glomerular filtration rate (eGFR), followed by progressive recovery and improvement of renal function (60). Certain distinguished RCTs (CANVAS & EMPA-REG OUTCOME) divulged that SGLT2 inhibitors helped delay progression of kidney disease, reduced albuminuria and stabilized eGFR with minimal clinically significant renal adverse events in high-risk groups (56, 61). In addition, a collective review of 12 RCTs revealed that SGLT2 inhibitors didn't manifest any enhanced risk of acute reno-toxicity or worsening of renal function in T2DM patients having normal or mildly impaired renal function (62). Moreover, as compared to glimepiride, canagliflozin slowed down the progression of renal disease over 104 weeks, and might have rendered reno-protective effects independently of its glycemic effects in T2DM patients (63).

3.7. Improved insulin sensitivity and β-cell function

Supporting data suggests that SGLT2 inhibitors augment insulin sensitivity and β cell function in the background of HbA1C and body-weight reduction in T2DM patients (64, 65). SGLT2 inhibitors may possibly benefit insulin-resistant patients due to their proven advantage for enhancing insulin sensitivity allied to weight reduction. RCTs of recent past documented that SGLT2 inhibitors not only boosted insulin sensitivity as compared to placebo (P = 0.0059) as well helped cut down insulin resistance (p < 0.001) significantly in patients with T2DM (64, 66).

3.8. Adverse effects of SGLT2 inhibitors

3.8.1. Genital infection

The common adverse effect of SGLT2 inhibitors emerges to be genital infections that amplified to four times in clinical trials (26). Noticeable levels of glucose in the urine can usher the precipitation of mycotic infections, as found in patients who had high grade of hyperglycemia with glycosuria. Osmotic diuresis actuated by glycosuria resulting from SGLT2 inhibition, results in volume depletion. This is usually manifested by accelerated urinary frequency, thirst and infrequently orthostatic hypotension. Precipitating factors for volume depletion could be age >75 years, GFR <60 mL/min/1.73m^2 and use of loop diuretics (17). Incidences of genital mycotic infections, urinary tract infections, and osmotic diuresis–related adverse events were higher in clinical trials but were generally mild to moderate in intensity and led to few discontinuations (67, 68).

3.8.2. Ketoacidosis in SGLT2 inhibitors users

Absolute insulin deficiency leads to reduced glucose utilization with increased lipolysis; increased free fatty acids (FFAs) in the liver along with high glucagon secretion promoting FFA oxidation and production of ketone bodies thereby generating diabetic ketoacidosis (DKA) (69). DKA generally manifests with hyperglycemia (glucose >250 mg/dL), glycosuria and hyperketonemia. Euglycemic DKA (euDKA) that's observed during use of SGLT inhibitors entails a different pathway. SGLT2 inhibition induces a rapid increase in urinary glucose excretion, ranging 50–100 g/day

resulting in decline in plasma glucose by 20–25 mg/dL ensuing fall in plasma insulin level (by ~10 pmol/L fasting and ~60 pmol/L post-meal) stimulating compensatory increase in glucagon levels (69). Importantly, renal glucose clearance (the ratio of glycosuria to prevailing glycemia) is twice as much with euDKA compared to DKA (69).

Thus, in SGLT2-treated T2DM patients with euDKA, the reduced insulin-to-glucagon ratio stimulates lipolysis increasing FFA delivery to the liver resulting in mild stimulation of ketogenesis. If insulin deficiency is intense as seen in T1DM or carbohydrate is severely restricted, the mild ketosis may turn in to ketoacidosis. Generally speaking, euDKA is patho-physiologically analogous to DKA except for the circumstance of SGLT2-induced glycosuria that lowers plasma glucose levels and influences development of ketogenesis (69). These lower levels of glucose make diagnosis of euDKA more difficult and may lead to delayed treatment (27).

Use of SGLT-2 inhibitors seems to be associated with euDKA and ketosis, consequent to the noninsulin-dependent glucose clearance, hyper-glucagonemia and volume depletion.

However, in an elegant clarification on the topic, Rosenstock and Ferrannini commented on this potential complication of euDKA related to SGLT2 inhibition as most predictable, detectable and preventable safety issues so that the balance of benefits and risks favor the use of SGLT2 inhibitors among the uncontrolled diabetics, who are in dire need of add-on therapy (69).

It was observed that DKA and similar events related to SGLT2 inhibitors occurred at a low frequency in over 17,000 subjects evaluated in the canagliflozin T2DM clinical programs. The incidence was consistent with limited existing observational data in the general population with type 2 diabetes (70).

3.8.3. Fractures

Use of SGLT2 inhibitors (Canagliflozin) has been related to the higher risk of bone fractures because of decreased bone mineral density. Canagliflozin was associated with a higher fracture incidence in an interim analysis of the CANagliflozin Cardio Vascular Assessment Study (CANVAS) in patients with a history or high risk of cardiovascular disease; the incidence of fracture extremities per 100 patient-years of 1.6, 1.6, and 1.1 with Canagliflozin 100 and 300 mg and placebo was observed (71).

Fractures and bony injuries came up as early as 12 weeks after initiation of treatment with SGLT2 inhibitors and were generally due to trauma involving the extremities (71). Decreases in total hip Bone Mineral Density (BMD) were seen with Canagliflozin 100 and 300 mg versus placebo after 102 weeks were -1.7%, -2.1%, -0.8%; compared to normal age-related bone loss of -0.5 to -1.0% per year (71). In post-hoc analysis, change in body-weight appeared to explain about 40% of the observed difference in total hip BMD between the pooled canagliflozin group and the placebo group (72).

4. Conclusion

SGLT2 inhibitors are the novel class of oral anti-hyperglycemic agents currently available to treat patients with type 2 diabetes mellitus. The unique mode of action makes this class of medicine a fascinating choice for patients throughout the natural course of history of type 2 diabetes mellitus under close & continuous supervision. Although there are a wide range of side effects including recently identified incidence of ketoacidosis related to SGLT2 inhibitor use, this class may be a good option in the carefully selected patient. Protracted cardio-vascular safety trials are in progress and will ultimately justify the sustainability of this class of medication in the treatment T2DM clients in the long run.

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