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Review Article

SGLT 2 Inhibitors: Review of Systemic Effects and Safety

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Abstract

Sodium glucose transporter 2 (SGLT2) inhibitors are a new group of drugs for the treatment of type 2 diabetes. They act by inhibiting SGLT2 located in the proximal convoluted tubule (PCT) of the kidney and prevent the reabsorption of filtered glucose into the blood stream. They are effective in lowering blood glucose and glycated haemoglobin (HbA1c) when used as monotherapy or add on to other oral antidiabetic agents. SGLT2 inhibitors effectively reduced mortality and duration of hospitalization in diabetic patients with cardiovascular diseases in both the CANVAS and EMPA REG OUTCOME trials. A reduced requirement for renal replacement therapy and improved kidney function were also observed. Other systemic effects of these drugs include weight reduction, increased haematocrit and reduced hepatic fat deposition. The safety profile of SGLT2 inhibitors is generally encouraging but the observation of increased amputation risk in patients treated with the drugs has raised a major concern. In addition, euglycemic diabetic ketoacidosis, bone demineralization and fracture, electrolyte imbalance and acute kidney injury are important safety issues being evaluated in therapy with the drugs. Hypoglycemia is not a common side effect but can occur when used in conjunction with other antidiabetic medications. Nevertheless, they are very well tolerated in the vast majority of type 2 diabetes (T2DM) patients.

Keywords: *Sodium Glucose Transporter 2 (SGLT2); Proximal Convoluted Tubule (PCT); Type 2 Diabetes (T2DM)*

Introduction

Current estimates indicate that over 425 million individuals have diabetes and the number is expected to grow. Thus, making it an enormous epidemic which requires focused strategies in terms of research, advocacy and clinical management to reduce the disease burden. The available management options include lifestyle modification and pharmacotherapy. The classes of medications currently used to treat diabetes include biguanides, sulfonylureas, incretin mimetics, glitazones as well as insulin. SGLT2 inhibitors are a novel group of medications developed for the treatment of T2DM. Besides the blood glucose lowering effect, a special feature of this class of drugs is cardiovascular protection. This was abundantly illustrated in the CANVAS and EMPA REG OUTCOME trials. This has generated the momentum for exploration of the mechanisms behind this crucial advantage and possibly discovering other areas of therapeutic efficacy. The advent of this class of drugs is considered by some as a new era in the treatment of diabetes. The aim of this article is to summarize the systemic impact and safety information of SGLT2 inhibitors pharmacotherapy.

Historical timelines

- 1853: Phlorizin was isolated from the bark of apple trees by French chemists [1,2] in search for medicines for the treatment of fever.

- 1886: Von Mering discovered that phlorizin could cause increased excretion of glucose in the urine of dogs [3]. He later teamed up with Oskar Minkowski to discover the pancreatic origin of diabetes.
- 1933: Chasis., *et al*. tested phlorizin in humans and observed that it inhibits renal glucose reabsorption and increased urinary glucose excretion [4].
- 1960: Robert K Crane discovered sodium glucose co-transporter. He proved that influx of ion (Na^+) and a substrate (Glu) could be coupled by combining the same reversible carrier in the cell membrane of the intestinal cells.
- 1999: T 1095, an oral inhibitor of renal sodium-glucose co-transporter was developed [2]. The drug is metabolized to an active form T 1095A. It decreased blood glucose levels and increased urinary glucose excretion [2]. However, it also inhibited SGLT1 which was a major setback.
- 2007/2008: Sergifloxin [5] and remogliflozin [6] were developed. They had poor pharmacokinetic stability and incomplete selectivity for SGLT2.
- Nov. 2012: The committee for medicinal products for human use of the European Medicines Agency (EMA) gave the marketing authorization for dapagliflozin in the EU [7]. It was later approved by the US FDA in January 2014.
- March 2013: The FDA approved canagliflozin [8], becoming the first SGLT2 inhibitor to be marketed for the treatment of diabetes in the US.

Glucose transport in the kidney

Glucose is transported in the kidney by two groups of transport proteins i.e. the sodium glucose co-transporters 1 & 2 (SGLT 1 & 2) and glucose transporters 1 & 2 (GLUT 1 & 2) [9]. While the SGLTs transport glucose from the lumen into the interstitium against a concentration gradient, the GLUTs transport glucose into the blood stream via facilitated diffusion [10]. GLUTs are a group of transporters with about 14 different types and are extensively distributed in various organs e.g. liver, muscle, brain and pancreas [9]. GLUT 2 is located in the basolateral membrane of the S_1 (and S_2) segment of the proximal convoluted tubule (PCT) while GLUT 1 is located in the S_3 segment. This arrangement corresponds with the location of the SGLTs i.e. SGLT 2 in the initial segment and SGLT 1 in the later portion of the PCT. Glucose is transported into the blood stream with most of the transport occurring in S_1 [11].

Six SGLTs have been identified. Although, SGLT1 and SGLT2 are best characterized [10]. SGLT1 is extensively distributed in the small intestine [12] were it is involved in glucose reabsorption. It is also present in the tracheal, brain, prostrate and heart [13]. SGLT2 is encoded by the gene SLC5A2 localized to chromosome 16p11.2 [14]. It has 59% homology with SGLT1. SGLT2 is described as low affinity/high capacity transporter and its location in the earlier part of the PCT ensures that maximum glucose is reabsorbed early. SGLT1 which is described as a high affinity/low capacity transporter is located in the S_3 segment where it reabsorbs residual glucose that escapes the initial segment [15]. About 180g of glucose is filtered daily by the glomerulus and 90% is reabsorbed in the S_1/S_2 segment [13]. An increased expression of SGLT2 mRNA is observed in the kidneys of animal models with diabetes and this is linked to the development of diabetic kidney disease [16]. HNF 1α (hepatocyte nuclear factor 1α), a transcription factor that is mutated in MODY type 3 is thought to control the expression of SGLT2 [16]. Mutation of the gene coding for SGLT2 is associated with familial renal glycosuria which causes polyuria, enuresis and growth delay [17]. Severe cases can present with dehydration and ketosis during starvation or pregnancy.

Mechanism of action

They inhibit SGLT2 located in the PCT thereby preventing the reabsorption of filtered glucose in the tubular lumen [12]. The unabsorbed glucose is excreted via the urine causing glycosuria and osmotic diuresis. Calorie loss and intravascular volume reduction thus

become a physiological plausibility by the virtue of this mechanism, conferring a clinical advantage on these drugs. The mechanism of action does not interfere with insulin secretion [18], practically attenuating the tendency towards hypoglycaemia. The pharmacological actions of SGLT2 inhibitors are predicated upon the optimal functioning of the filtration and reabsorption properties of the kidneys. A defect in either e.g. in moderate to severe kidney disease compromises the anticipated clinical efficacy [19,20]. This inhibition of sodium and glucose transport is thought to interfere with the reabsorption of other electrolytes like calcium and phosphate which are the main constituents of the bone [21]. Thus, raising questions about the potential effect on bone metabolism. The selectivity for SGLT2 is not uniform across class. Canagliflozin is noted to exert some inhibitory effects on SGLT1 [22]. The drugs have excellent bioavailability after oral administration and long enough half-life to permit once daily dosing [23]. They are metabolized in the liver mainly via glucuronidation [24] to inactive metabolites.

Systemic effects

Blood glucose

Data from multiple interventional studies have convincingly demonstrated the effectiveness of SGLT2 inhibitors in glycemic control. The results of these trials have shown a significant reduction in blood glucose and HBA1c whether as monotherapy or combined with other antidiabetic drugs in treatment of T2DM. In the Canagliflozin Treatment and Trial Analysis (CANTATA), the drug was evaluated as a monotherapy and add on therapy with the outcome determined after 26 and 52 weeks. In a randomized double blind placebo controlled trial involving 584 patients, HbA1c was reduced by 0.77 and 1.03 percentage points at the end of 26 weeks after administration of 100 mg and 300 mg dose respectively [25]. The mean reduction in blood glucose was 27 mg/dl and 35 mg/dl respectively [25]. In the placebo group HbA1c was increased by 0.14%. When used as add on to metformin and pioglitazone the mean percentage points reduction in HbA1c was 0.89, 1.03 and 0.26 for 100 mg, 300 mg and placebo respectively from a baseline of 7.9% [26]. In clinical trials with dapagliflozin a reduction in FPG of 25 mg/dl was recorded after 24 weeks of treatment from a baseline of 160 mg/dl. From a baseline of 10.1 - 12.0% dapagliflozin therapy reduced HbA1c by 2.88 and 2.66% using 5 mg and 10 mg dose respectively [27]. When used as add on to metformin in poorly controlled T2DM the placebo subtracted reduction in HbA1c was 0.4% and 0.54% with 5 mg and 10 mg dose respectively after 24 weeks [28]. Hypoglycemia is not commonly encountered during treatment with SGLT2 inhibitors primarily because they do not interfere with insulin secretion. Most reported cases of hypoglycaemia occurred in patients who were already on other antidiabetic drugs [12]. In the CANTATA study only 3.6% and 3.0% of patients on canagliflozin 100 mg and 300 mg respectively had hypoglycaemia with no report of severe cases [25]. In comparison with Glimepiride, the number of patients who experienced hypoglycemic symptoms while on treatment with Canagliflozin 100 mg or 300 mg was significantly lower [29].

Cardiovascular

Diuresis: The osmotic diuresis induced by these drugs is a function of both glycosuria and natriuresis. Although, clinically significant hyponatremia is not a commonly encountered adverse effect [30,31]. The accompanying reduction in intravascular volume is associated with a host of potentially protective cardiovascular effects e.g. reduction of preload and volume overload [32], decrease myocardial oxygen demand [33] and improved contractility, reduced systolic and diastolic blood pressure [33,34] and reduced arterial wall stiffness [35] and ventricular wall tension. These effects make them ideal for diabetic patients with heart failure. It is essential to appreciate the notable disparities between the diuretic effect of SGLT2 inhibitors and conventional diuretics. Loop and thiazide diuretics cause reflex sympathetic activation in response to volume depletion and this is often accompanied by tachycardia. Also, hyperglycemia and hyperuricemia are recognized metabolic alterations associated these diuretics. Conversely, SGLT2 inhibitors are not associated with any of the above [36]. The diuretic effect is considered the major mechanism behind the blood pressure lowering feature [30,31,36]. In addition, the inhibition of RAAS due to increased delivery of sodium to the juxtaglomerular apparatus enhances tubuloglomerular feedback [37] causing afferent arteriolar vasoconstriction and decrease glomerular hyperfiltration.

Cardiac metabolism and energetics: The energy utilized by cardiac myocytes is derived from mitochondria oxidative metabolism with major contribution from fatty acids and glucose [38]. Although, fatty acids predominantly supply the fuel for oxidative phosphorylation [39], this may be altered in certain physiologic or disease conditions. For example, glucose is preferentially utilized in the presence of increased cardiac workload [39,40]. Myocardial fatty acid deposition occurs in T2DM particularly in association with obesity and this cardiac steatosis is considered independent of other cardiac conditions like Coronary artery disease [37,41]. Lipid deposition in the heart may cause excessive reliance on FAs for oxidative metabolism precipitating lipotoxicity, production of reactive oxygen species, cardiac myocyte apoptosis etc [37,39].

In our understanding of diabetes, ketone bodies are the major culprit behind diabetic ketoacidosis (DKA). A hyperglycemic emergency which occurs in TIDM and to a lesser extent in T2DM. However, evolving knowledge of the molecular interaction between SGLT2 inhibitors and cardiac myocytes suggests that β-hydroxybutyrate could play a significant role in cardioprotection [42,43]. This paradox is explained by the observation that SGLT2 inhibitors promote the preferential utilization of β-hydroxybutyrate termed a "superfuel" by cardiac myocytes which is considered more economical and beneficial than fatty acids or glucose particularly in the presence of cardiac pathology e.g. heart failure [37]. The speculated benefits of this phenomenon include preventing the generation of toxic intermediates associated with fatty acid oxidation [44], improved cardiac mitochondria oxidative metabolism, lower myocardial oxygen consumption, enhanced antioxidants [45] effects which maintain mitochondria stability and overall improvement in cardiac function. This is the basis of thrifty substrate hypothesis postulated by Ferannini., *et al*. and Mudaliar., *et al* [39].

Cardiac Na^+ homeostasis: Na^+ homeostasis is a physiological requirement for myocardial functioning [46] and this ionic equilibrium is altered in diabetic hearts. Cardiac Na^+ transport is tightly connected to myocyte calcium handling which is key to contraction-relaxation dynamics [35]. Multiple ionic channels exist in the heart that regulate Na^+ and Ca^{2+} homeostasis among which are Na^+/Ca^{2+} exchanger (NCX), Na^+/H^+ exchanger (NHE) and Na^+/K^+ pump [35]. Activation of NHE is associated with cytosolic accumulation of Na^+ and Ca^{2+} in heart failure [32]. Over expression of SGLT1 in the hearts of diabetic patients with heart failure has equally been documented and this has been linked to Na overload [47]. Findings from animal studies have indicated that empagliflozin modulates NHE activity and decreases myocyte Na^+ and Ca^{2+} concentration while increasing mitochondria Ca^{2+} concentration [48]. This helps in improving mitochondria energetics and reduce oxidative stress.

Others: Experiment in animal models have demonstrated that SGLT2 inhibitors suppress collagen synthesis via the activation of M_2 macrophages and by the inhibition of myofibroblast differentiation [49]. In addition, canagliflozin inhibited TGF-β_1 induced fibroblast activation [50]. These effects are associated with reduced extracellular matrix deposition and cardiac fibrosis which is partly responsible for cardiac remodelling in heart failure. It has also been suggested that canagliflozin could exert some anti-inflammatory effects based on the observation that it increases serum levels of adiponectin and decreases both leptin and IL-6 [51].

Serum lipids: The lipid profile picture in patients treated with SGLT2 inhibitors is somewhat inconsistent. However, both LDL and HDL were elevated in patients receiving empagliflozin in the EMPA-REG OUTCOME Trial [52]. This is possibly due to hemoconcentration [53]. Similar findings have been reported for dapagliflozin [37]. The clinical significance of this is currently unclear.

Canagliflozin cardiovascular assessment study (CANVAS)

A randomized double blind placebo controlled trial conducted in 667 centres across 30 countries. 10,142 participants were randomized into canagliflozin 100 mg, 300 mg and placebo groups [54]. The primary outcome was a composite of death from cardiovascular causes, non-fatal myocardial infarction and non-fatal stroke. The mean duration of diabetes was 13.5 years and 65.6% of participants had history of CVDs. The incidence of cardiovascular deaths, stroke and MI was 2.6 per 1000 patients' years in the canagliflozin treatment arm and 31.5 per 1000 patients' years in the placebo group [54]. The secondary outcomes were death from any cause, death from cardiovascular causes, progression to albuminuria and the composite death from cardiovascular causes and hospitalization from heart failure. The trial revealed a lower risk of cardiovascular events in patients treated with canagliflozin but increased risk of amputation [54].

Some outcomes from the CANVAS trial:

- Mean systolic blood pressure difference of -3.93 mmhg between canagliflozin and placebo group
- Mean diastolic blood pressure difference of -1.39 mmhg between both groups
- Mean body weight difference of -1.60 kg between both groups
- HbA1c difference mean of 0.58%
- Decrease hospitalization for heart failure in canagliflozin group
- Decrease all-cause mortality in the canagliflozin group
- Higher levels of HDL and LDL cholesterol in the canagliflozin group
- Increased incidence of amputation in canagliflozin group.

EMPA-REG outcome trial

Empagliflozin 10 mg and 25 mg were compared with placebo to evaluate the impact on cardiovascular outcomes and mortality. The determinants of the primary outcome were similar to the CANVAS trial and occurred in 10.5% of patients in the empagliflozin arm versus 12.1% in the placebo group. The empagliflozin group had lower cardiovascular deaths (3.7% vs 5.9%), hospitalization for heart failure (2.7% vs 4.1%) and death from any cause (5.7% vs 8.3%) [52].

Renal effects

The principal site of action of SGLT2 inhibitors is the kidney which underscores the critical importance of adequate renal function in patients taking these agents. The multitude of effects they have on the kidneys are mediated via various pathways:

(a) **Tubuloglomerular feedback:** TGF is a renal mechanism that regulates glomerular filtration on the basis of Na^+ and Cl^- concentration in the fluid delivered to the distal tubule [55]. Central to this regulation is the juxtaglomerular apparatus [56] which is located in the hilium and made of vascular and tubular components [57]. It consists of (i) Macula dense cells found in the distal tubule and they sense tubular fluid concentration [58] and send appropriate signals for the control of GFR and renal blood flow. (ii) Juxtaglomerular or granular cells in the afferent arterial wall which synthesizes and secretes renin [57]. (iii) Mesangial cells located between both [59].

TGF operates through a negative feedback in which an increase or decrease in the concentration of Na^+, K^+ or Cl^- sensed by the macula dense via Na-K-2CL co-transporter (NKCC2) triggers a compensatory alteration in GFR by adjusting vascular tone [55]. Hence, it balances tubular reabsorption with GFR.

SGLT2 inhibitors prevent the reabsorption of filtered Na^+ at the PCT thereby allowing increased load of sodium to be delivered to the distal tubules which is sensed by the macula dense. This results in an increased adenosine production which mediates afferent arteriolar vasoconstriction leading to reduced renal blood flow and glomerular filtration [56]. In diabetic kidneys, hyperglycemia causes increased reabsorption of glucose in the PCT [11,60].

(b) **RAAS:** It is a major pathogenetic pathway [62,63] in diabetic kidney disease. The relationship between RAAS and SGLT2 inhibitors is still being explored. Although, some studies have revealed an initial increase in RAAS activity [64,65], the long

term consequence of this finding is still unclear. Moreover, some authors [66,67] have suggested that a synergistic renoprotection could be achieved with the combined therapy of SGLT2 inhibition and RAAS blockade.

(c) **Others:** SGLT2 inhibitors reduce renal oxidative stress, production of growth factors and inflammatory markers [68,69]. They also reduce the activation of Advanced glycation end-products (AGEs) and RAGE [69].

The initiation of SGLT2 inhibitors therapy is often associated with transient decline in GFR before return to baseline [70]. These observation is thought to be due to hemodynamic adaptations and not necessarily a pathological process. The renal outcome from the CANVAS trial were encouraging and included reduced progression to albuminuria, regression of albuminuria and 40% improvement in GFR [54]. Additional findings were decreased need for renal replacement therapy and reduced incidence of death from renal causes. In the EMPAREG OUTCOME study, progression to macroalbuminuria occurred in 11.2% of the empagliflozin group compared to 16.2% in those receiving placebo [71]. Doubling of serum creatinine occurred in 1.5% in the empagliflozin group and 2.6% in the placebo group. Also, the empagliflozin group recorded a significantly lower incidence of renal replacement therapy [71].

Weight loss

The weight loss triggered by SGLT2 inhibitors is in principle an extension of the diuretic effect. The underlying mechanisms are glycosuria which depletes potential calories for storage and increased fluid loss via urine. Ferrannini., *et al*. (2015) discovered that therapy with these drugs could lead to major weight loss [72]. In a cohort of 86 T2DM patients treated with empagliflozin for 90 weeks, the recorded weight loss was 3.2 ± 4.2 kg. The predicted weight loss through glycosuria was 11.3 ± 3.1 [72]. The difference is believed to be due to compensatory increase in caloric intake. In the CANTATA study canagliflozin 100 mg and 300 mg resulted in significant weight loss (-3.7% and -4.2% vs -1.2%) [11].

Fatty liver disease

Emerging evidence has indicated that SGLT2 inhibitors could have a promising role in the treatment of non-alcoholic fatty liver disease (NAFLD), a condition common to both T2DM and obesity. The spectrum of abnormalities in this condition include fat deposition, chronic inflammation, fibrosis with altered liver enzymes. Initial results have suggested that SGLT2 inhibitors could have a positive impact on these parameters. Empagliflozin has been reported to decrease lipid accumulation in the livers of high fat diet fed mice with reduction in total cholesterol, triglycerides and non-esterified fatty acids [73]. These findings were associated with a decrease in plasma AST and ALT. In experiment with high fat diet induced and leptin deficient (ob/ob) mice, ipragliflozin significantly reduced liver weight and improved hepatic steatosis in addition to suppressing the expression of lipogenic genes [74]. In an uncontrolled, small sample, pilot study, serum levels of AST, ALT and GGT decreased progressively with the administration of dapagliflozin 5 mg for 24 weeks in T2DM patients with non-alcoholic steatohepatitis (NASH) [75]. The level of serum ferritin, hs-CRP and NAFIC scores were also reduced. Also, results from E-LIFT trials in which the effects of empagliflozin on liver fat was examined by MRI derived proton density fat fraction (MRI-PDFF) revealed that empagliflozin significantly reduced liver fat and improved ALT [76]. Several other studies are available attesting to the potential effectiveness of SGLT2 inhibitors in the management of NAFLD [77] and this phenomenon appears to be a class action rather than individual drug property.

Hematocrit

Patients treated with SGLT2 inhibitors have been observed to have increased haematocrit [37]. In general, diuretic drugs are associated with hemoconcentration and SGLT2 inhibitors are not exceptional to this rule. Although, the predominant mechanism by which this occurs is still been evaluated, diuretic effect and increased erythropoietin production are currently believed to be the most important. Divergent views exist as to how the increased erythropoietin production occurs. Sano., *et al*. hypothesized that the dysfunction of adja-

cent neural crest derived fibroblasts is responsible for reduced EPO production in diabetes and by reducing the workload of the proximal tubules, SGLT2 inhibitors allow the restoration of tubulointerstitial function and increased EPO production by the neural crest derived fibroblasts [78]. Heyman., *et al*. proposed a counter model [79] in which the intensified hypoxia at the renal corticomedullary junction induced by SGLT2 inhibitors offers a more evidence based explanation for the increased EPO production and reticulocytosis. Results from future studies are likely to modify the direction of this unfolding debate and possibly resolve the issues surrounding the consequences of the observable rise in haematocrit.

Safety and adverse events

- **Lower limb amputation:** In May 2017 the FDA issued a safety communication confirming the increased risk of leg and foot amputation in patients treated with canagliflozin [80]. This was apparently based on findings from the CANVAS study which revealed a twofold occurrence of amputation in the canagliflozin group [54]. The precise mechanism by which this occurs is still yet to be ascertained, although diuretic related intravascular contraction has been suggested. Several other studies have not associated lower limb amputations with other drugs [81,82] in this class while some studies have not found increased frequency of amputation in patients treated with canagliflozin [83]. Nevertheless, caution should be exercised when used in patients at risk for lower limb amputation e.g. those with diabetic foot ulcer, previous amputation, peripheral vascular disease or diabetic neuropathy [84].

- **Urinary tract infection:** Increased frequency of urinary tract [85,86] and genital infections have been associated with the use of SGLT2 inhibitors and this is not surprising considering the glycosuria [87] they induce. However, results from recent trials have questioned the relationship between dosage of SGLT2 inhibitors and the occurrence UTIs. A meta-analysis of randomized controlled trials by Donan., *et al*. revealed that current evidence does not support a dose response relationship between SGLT2 inhibitors and UTI except for Dapagliflozin [88].

- **Necrotizing fasciitis of the perineum (Fournier's gangrene):** A rare but serious infection of the genitalia was recently observed in patients treated with SGLT2 inhibitors. The FDA identified 12 cases between March 2013 to May 2018 in patients who were taking SGLT2 inhibitors [89].

- **Diabetic ketoacidosis:** SGLT2 inhibitors are associated rarely with cases of ketoacidosis in the presence of normal or mildly elevated blood glucose i.e. euglycemic DKA [90]. Reported cases of euDKA mostly occurred on the background of intercurrent illness, reduced insulin dosage, reduced oral intake and history of alcohol consumption [90]. Depletion of body glucose is associated with reduced insulin secretion (not insulin sensitivity) as glucose is the most potent stimulus for insulin secretion. This is accompanied by increased levels of serum glucagon [91] which is capable of stimulating intermediary metabolism in the counter-regulatory direction with ensuing ketosis.

- **Bone fracture**: The FDA warning for canagliflozin also included increased risk for bone fracture and decreased bone mineral density [92]. Patients treated with canagliflozin in the CANVAS [54] trial had a higher incidence of bone fracture compared to placebo. Canagliflozin administration was found to increase serum phosphate as well as parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF-23) levels while decreasing serum 1,25 dihydrovitamin D [93]. These changes are thought to increase bone resorption and possible predispose to fractures.

- **Renal impairment:** Initial reports have indicated that SGLT2 inhibitors might be associated with acute kidney injury (AKI) considering the intravascular volume depletion they produce. From March 2013 to October 2015 101 cases of AKI were reported to the FDA with about half of the cases starting within one month of commencing treatment and most of them improved after discontinuation of the drug [94]. On the contrary, both the CANVAS and EMPA-REG OUTCOME studies recorded a reduced incidence of renal replacement therapy and death from renal causes in patients taking SGLT2 inhibitors [52,54]. Hence, more

studies focusing specifically on SGLT2 inhibitors associated AKI are required because of this seemingly contradictory findings and the fact that the reported cases above were not matched with control.

- **Others:** The osmotic diuretic effect might be associated with polyuria, polydipsia, dehydration and hypotension [95]. These symptoms are more pronounced in the elderly, chronic kidney disease and those on diuretics [96]. It has equally been suggested that elevated serum potassium [97,98] could result from treatment with these drugs but with current evidence this seems unlikely except in cases of renal impairment or when used in conjunction with drugs that cause hyperkalemia [99,100]. Some authors have also raised a concern about bladder cancer particularly with dapagliflozin [101,102]. Some cases of associated skin disorders have also been reported [103].

Conclusion

Clinical experience with SGLT2 inhibitors is still evolving even if accumulated data so far predicts a bright future for the drugs in the treatment of T2DM. They are also being studied for use in selected patients with type I diabetes. The cardiovascular protection they offer is currently unmatched by any other class of anti-diabetic drugs. Their weight reducing property and low tendency to cause hypoglycaemia are added advantages in treatment of diabetes. Interventional studies have showed that these drugs are safe and very well tolerated with only rare reports of major adverse events. Drug safety could further be enhanced by using the drugs with caution or avoiding them in patients at risk of adverse events. Further research is obviously required to improve our understanding of certain equivocal issues surrounding the observed adverse events.

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