DR. ARTI DHAR (Orcid ID : 0000-0003-1892-6875)

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SGLT1 Inhibition Boon or Bane for Diabetes Associated Cardiomyopathy

Running title: SGLT and cardiac perturbations.

Jaspreet **Kalra**[a], Suresh Babu **Mangali** [a], Deepika **Dasari**[a], Audesh **Bhat**[b], Srashti **Goel**[a], Indu **Dhar**[c], Dharamrajan **Sriram**[a], Arti **Dhar**[a,*]

[a]Department of Pharmacy, Birla Institute of Technology and Sciences (BITS) Pilani, Hyderabad Campus, Jawahar Nagar, Shameerpet, Hyderabad, Andhra Pradesh 500078, India.

[b]Centre for Molecular Biology, Central University of Jammu, India

[c]Department of Clinical Science, University of Bergen, Norway

***Author for correspondence:**
Arti Dhar

Department of Pharmacy, Birla Institute of Technology and Sciences Pilani, Hyderabad, Jawahar Nagar, Shameerpet, Hyderabad, Andhra Pradesh 500078, India

Tel. 04066303647 / +919505563087

E-mail:artidhar@hyderabad.bits-pilani.ac.in,

dhar.arti@gmail.com

ABSTRACT

Chronic hyperglycaemia is a peculiar feature of diabetes mellitus (DM). Sequential metabolic abnormalities accompanying glucotoxicity are some of its implications. Glucotoxicity most likely corresponds to the vascular intricacy and metabolic alterations, such as increased oxidation of free fatty acids and reduced glucose oxidation. More than half of those with diabetes also develop cardiac abnormalities due to unknown causes, posing a major threat to the currently available marketed preparations which are being used for treating these cardiac complications. Even though impairment in cardiac functioning is the principal cause of death in individuals with type 2 diabetes (T2D), reducing plasma glucose levels has little effect on cardiovascular disease (CVD) risk. *In vitro* and *in vivo* studies have demonstrated that inhibitors of sodium glucose transporter (SGLT) represent a putative therapeutic intervention for these pathological conditions. Several clinical trials have reported the efficacy of SGLT inhibitors as a novel and potent anti-diabetic agent which along with its anti-hyperglycaemic activity possesses the potential of effectively treating its associated cardiac abnormalities. Thus, hereby, the present review highlights the role of SGLT inhibitors as a successful drug candidate for correcting the shifts in deregulation of cardiac energy substrate metabolism together with its role in treating diabetes related cardiac perturbations.

Keywords: Sodium glucose co-transporter (SGLT); Diabetes mellitus; Diabetic cardiomyopathy.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterised by progressive hyperglycaemia and sequential metabolic abnormalities accompanying glucotoxicity [1]. Hyperglycaemia in type1 diabetes (T1D) pertains to the absolute loss of pancreatic β cells, whereas in T2D, hyperglycaemia is an indicative of an insulin resistant state together with the abnormalities in an insulin production and its secretion, including various endocrinopathies contributing in this heterogeneous disorder [2]. An insulin resistant state in T2D is followed by a concomitant hyperglycaemia, hypertension, dyslipidemia, pro-thrombotic factors, and pro-inflammatory state. All of these factors are interrelated in the pathogenesis of cardiac complications and are considered as a significant paramount for an increased risk of cardiac abnormalities [1,2]. Glucotoxicity most likely corresponds to the vascular intricacy attending DM. Micro-vascular diseases are stratified by the changes in vessel size, development of diabetes associated nephropathy, neuropathy, retinopathy and onset of premature macro-vascular or cardiovascular (CV) complications [1].

On an average, 450 million people were affected by diabetes in year 2015 and this number has been projected to escalate to 642 million by the end of year 2040. Countries with low national per capita income/developing countries are at increased risk of having CV mortality due to diabetes related cardiac abnormalities [3]. Multiple trials including Diabetes Control and Complications Trial Research Group and UK Prospective Diabetes Study (UKPDS) came to an agreement that micro-vascular changes can be improved by monitoring the glycaemic control [4,5]. However, macro-vascular changes convey a potential risk for the progression of cardiac abnormalities [1]. Obese/overweight individuals or individuals with concomitant hyperglycaemia, hypertension, dyslipidemia, pathogenic and pro-inflammatory state are highly susceptible to cardiac complications [6,7]. In view of multiple CV risk factors

beyond hyperglycaemia that are commonly presentable in majority of the T2D patients, a multi-factorial approach for combating these CV risk contributors needs to be highlighted. Currently available drugs for the treatment of diabetes are potent glucose lowering agents, capable of improving accompanying cardio-metabolic abnormalities but their chronic use for sustained glycaemic control, limits their efficacy [8]. Recently, up-regulation of SGLT has been implicated in causing glucose dysregulation and alterations in cardiac energy substrate metabolism in diabetic patients [9-12]. In hyperglycaemic conditions, glucose transport through SGLT is also associated with the activation of NADPH oxidase (NOX2), production of reactive oxygen species (ROS), and cell death of cardiomyocytes (13,14).

Currently, much attention has been laid on the role of SGLT1/SGLT2 inhibitors for improving glycaemic control by reducing intestinal and renal absorption of glucose and by promoting excretion of glucose in urine [15]. SGLT1 is expressed in heart tissue of several species including various other organs. Increased cardiac glucose uptake and SGLT1 expression has been reported in diabetic cardiomyopathy [16]. Therefore, aforementioned facts clearly indicate that inhibition of SGLT could be the newer therapeutic strategy for the management of diabetes and its associated cardiomyopathy. The present review discusses about the newer therapeutic approach aimed at improving hyperglycaemia associated complications by altering the function of sodium glucose transporters (SGLT) in heart and kidney.

MECHANISMS INVOLVED IN DIABETES INDUCED CARDIAC COMPLICATIONS

Chronic diabetes is a cluster of numerous cardiac abnormalities such as cardiac dysfunction, ischemia/reperfusion (I/R) injury, cardiomyopathy and microangiopathy [17,18]. Alterations in lipid profile, pancreatic insulin insufficiency, increased glycaemic index and sedentary lifestyle are the major contributors involved in diabetes-related cardiac abnormalities but still

the precise mechanism and pathways involved in the development and worsening of cardiac dysfunction in hyperglycaemic subjects are not clearly understood [19]. However, ROS generation and alterations in cardiac energy substrate metabolism could be the probable mechanisms responsible for diabetes induced cardiac abnormalities.

The reactive oxygen species (ROS) theory

Hyperglycaemic condition is well correlated with oxidative damage and insulin resistance, which occurs through oxidative phosphorylation (OXPHOS) of glucose in mitochondria. OXPHOS of glucose is related with the generation of free radicals such as nitrite, hydroxyl ions and superoxide anion [20]. Oxidative damage occurs at cellular level causing direct damage to proteins and mitoDNA causing modulations in normal physiological processes [21, 22]. For instance, elevated oxidative load is linked with the down-regulation of nitric oxide level causing impairment in the functioning of endothelium, ultimately heading towards vascular dysfunction and CV abnormalities [23-25]. Role of oxidative stress in modulating various intracellular signalling pathways has been well recognized [26]. In insulin resistant state, translocation of glucose transporter 1 (GLUT1) from intracellular compartments towards the plasma membrane is significantly decreased. However, under the same condition, SGLT1 gets expressed in the sarcolemma membrane where it co-localizes with the sodium potassium ATPase. An age-dependent increase in the cardiac SGLT1 expression is reported in mice models, although the underlying mechanism behind this increase is still unknown. SGLT1 up-regulation is also related with the glucotoxicity and insulin resistant state in T2D (27). Figure 1 gives a brief idea about the role of SGLT1 inhibitors in the mechanism of diabetes induced CV complications.

Cardiac energy substrate metabolism

Insulin sensitive/ insulin resistant mechanism are necessary for proper cardiac functioning. Studies carried out by Belke et al., in cardiomyocyte selective insulin receptor knockout mice demonstrates that proper insulin signalling is of utmost relevance for maintenance and maturation of contractile phenotype of cardiomyocytes. Results of their study indicates that in cardiomyocytes derived from insulin signalling deficient mice there exists a shift in cardiac energy substrate metabolism which can be characterized by decreased fatty acid oxidation and elevated glucoxidation [28]. The observed shift in substrate metabolism is paradoxically the reversed change as evident in diabetes, where fatty acids are major cardiac fuel compared to glucose [29]. Insulin-dependent glucose uptake at cellular level is primarily carried out by glucose transporters, which facilitates the transport of glucose from intracellular compartment to the cell membrane [30]. However, SGLT are another class of transporters which are involved in the renal, intestinal and cardiac absorption of glucose [31].

RENAL AND INTESTINAL GLUCOSE ABSORPTION: ROLE OF SODIUM GLUCOSE TRANSPORTERS

Approximately 160-180 g of glucose is filtered on the daily basis by glomeruli of kidneys in normo-glycaemic individuals. Most of the filtered glucose is reabsorbed by the proximal tubules [14, 32-35], however in diabetic condition, amount of filtered glucose exceeds the maximal threshold for renal glucose absorption such that the excess glucose is excreted out in urine [36-38]. Between the early 1980's and 1995, transport studies carried out on membrane vesicles and gene expression studies in isolated proximal tubules of rat and rabbit revealed that most of the glucose uptake is mediated by the two SGLT namely *(i)* high affinity/low capacity SGLT1 (SLC5A1) (K0.5 of 0.4mM for glucose and 3 mM for sodium) and *(ii)* low affinity/high capacity SGLT2 (SLC5A2) (K0.5 of about 2·0 mM for glucose and about 0·1 mM for sodium) [34, 38-40]. These transporters have the characteristic property of

accumulating glucose within the cells. SGLT are capable of initiating several intracellular events as sodium glucose co-transport is coupled with the membrane depolarization. SGLT1 also act as a rate limiting factor for glucose absorption [34,40,41]. Among both the SGLT isoforms, SGLT2 is responsible for the maximum renal glucose absorption (approximately 90%) in the segment 1 (S1) region of the proximal tubule while the SGLT1 facilitates the absorption of intestinal glucose, contributing only 10% of the total renal glucose absorption in the S3 segment of distal proximal tubule. SGLT2 inhibitors exert its anti-hyperglycaemic activity through increased renal excretion of glucose in urine posing a minimal risk for hypoglycaemia. Increased volume depletion due to elevated glycosuria also helps in reducing blood pressure and promoting weight loss [39].

SGLT1transporter is predominantly expressed in gut, heart and lungs. SGLT1 is the principal transporter present in the enterocytes lining intestinal villi, these transporters account for maximal glucose absorption in the intestine. Transport of glucose across the brush border of apical membrane is driven by electrogenic gradient established by sodium potassium ATPase pump [42,43]. Mutations in the SGLT1 genes (SLC5A1) or defects in SGLT1 trafficking are responsible for causing glucose galactose malabsorption, an autosomal recessive disease characterised by severe diarrhoea and dehydration [39,44]. mRNA expression analyses have conferred its localization in several other organs as well, such as brain, skeletal muscle, lung, gall bladder, trachea, liver, uterus, testis, colon, rectum, brain, blood vessels, stomach, mesenteric adipose tissue, breast, pancreatic alpha-cells including heart. Table 1 enlists the different organs where SGLT1 is expressed in humans and rats [34, 43, 45-47]. Expression of SGLT1 has also been reported in rats and humans myocyte and sarcolemma of heart. In diabetes, improved capacity of cardiac glucose uptake by SGLT1 directly relates to its increased expression and activity in the myocyte and sarcolemma

playing a significant role in sustained hyperglycaemia and worsening of cardiac functions [48-49]. Figure 1 gives the brief representation of the role of SGLT inhibitors in progression of diabetic cardiomyopathy.

DIABETIC CARDIOMYOPATHY AND SGLT1

The term diabetic cardiomyopathy was coined by Rubler et al. in 1972. Clinically, it is defined as the structural and functional changes of myocardium occurring in diabetic individuals even in the absence of coronary artery disease and hypertension [51]. Compared to the healthy individuals, individuals with diabetic cardiomyopathy are more vulnerable towards the increased risk of heart failure. Numerous reports suggest that ROS has been implicated in the progression and development of diabetic cardiomyopathy. ROS deteriorates the normal cardiac functioning by causing direct damage to proteins, initiating programmed cell death and altering several signal transduction pathways [50,52].

Association of high glucose and activation NOX2 was clearly demonstrated by Balteau and his colleagues in their *in-vitro* study conducted on primary cultured rat cardiomyocytes. High glucose (HG 21mM)-treated cultured rat cardiomyocytes exhibited increased expression of NOX2. Results of their study further reports that activation of NOX2 is related with the activation of Rac1GTP secondary pathway. Evidently, Rac1GTP activation is connected with the enhanced production of ROS and cell death through translocation of p47phox from cytoplasm to the plasma membrane. However, ROS production was significantly reduced in HG treated primary cultured rat cardiomyocytes co-incubated along with 1mM phlorizin. In conclusion, they proposed that the inhibition of SGLT1 in heart could be one of the probable mechanisms behind the reduced generation of ROS as it is the only isoform of SGLT transporter to be expressed in the heart [50].

Moreover, similar kinds of results were also obtained in an *in vitro* experiment conducted on neonatal ventricular myocytes, where co-incubation of HG (30mM) for 24 hrs in insulin (10nM) pre-treated neonatal ventricular myocytes resulted in glycogen deposition. Increased expression of glycogen specific autophagy proteins has been reported in hearts of streptozotocin treated diabetic rats [53]. Evidently, increased glycogen accumulation has also been noticed in db/db diabetic mice [54]. Mutations in the PRKAG2 gene are one of the chief contributors in glycogen storage cardiomyopathy in human subjects [55]. An *in vivo* study, carried out on double transgenic mice, has reported that the transgenic knockdown of cardiac SGLT1 is associated with the attenuation of PRKAG2 gene mutation related cardiomyopathy. Double transgenic mouse (TG) (TGT400N/TGSGLT1-DOWN) was used in their experimental study, which was reproduced by allowing the transgenic mice (TG) over expressing human T400N mutant PRKAG2 cDNA (TGT400N) to cross over with the TG mice exhibiting particular knock down of cardiomyocyte selective RNA of SGLT1 (TGSGLT1-DOWN). Data obtained from their study reveals that cardiac mass and glycogen accumulation was significantly reduced in TGT400N/TGSGLT1-DOWN mice indicating the potential role of SGLT1 in PRKAG2 gene related mutation. Salient findings obtained from their histopathological and echocardiographic studies further elucidate that TGT400N/TGSGLT1-DOWN mice were also capable of restoring structural and functional abnormalities and exerts beneficial effects on left ventricular function in comparison to the TG mice expressing SGLT1 *i.e.* (TGSGLT1-ON) (56).

DRUG CANDIDATES FOR SGLT INHIBITION

In 1835, a dihydrochalcone glucoside, phlorizin (Fig 2.a) was isolated from the bark of apple tree, due to its bitter taste it was used as an antipyretic in patients suffering from malaria. In 1886, Joseph Von Mering reported that phlorizin administration can cause transient

glycosuria and later on it was established that phlorizin related effects are mediated through SGLT [57]. In early the 1970s, it was discovered that phlorizin acts on the renal proximal tubules playing an important role in restoring insulin sensitivity, and regulates glycaemic levels [58-62]. Phlorizin is a non-selective inhibitor of SGLT, but its poor pharmacokinetic profile and gastrointestinal side effects has limited its clinical utility [61,62]. Chemically, phlorizin is derived from an O-glycoside which undergoes rapid hydrolysis by the action of intestinal glycosidase [63]. Rapid hydrolysis of phlorizin has led to the development of novel phlorizin based analogues. These analogues are categorized by the type of glycoside from which they are derived *(i)* compounds derived from O-glycosides and *(ii)* those which are derived from C-glycoside (64). Table 2 presents the list of O and C glycosides. Compounds derived from C-glycoside hold better pharmacokinetic properties as they are resistant to the action of intestinal glycosidase. Currently, a majority of C-glycosides are under clinical trials while few got approved for their use in United States and Europe as an add-on therapy with marketed anti-hyperglycaemic agent [65]. Table 3 represents the list of recommended SGLT inhibitors approved by Diabetes Canada which are used in combination with marketed anti-hyperglycaemic agents and table 4 presents the pharmacokinetic profile of the prominent SGLT inhibitors which are derived from C-glycosides.

Presently, few SGLT2 inhibitors are approved for their commercial use in Europe, Canada, Japan and United States for treating T2DM [66]. Although available preparations are listed under inhibitors for SGLT2 but still they all possess varying degree of selectivity for SGLT1. For example, empagliflozin is 27,000 times more specific for SGLT2 in comparison to SGLT1 with a inhibitory concentration of IC50 = 3.1 nM (SGLT2), IC50 = 8,300 nM (SGLT1), similarly dapagliflozin, and canagliflozin are also highly specific for SGLT2 compared to SGLT1. Inhibitory concentration of dapagliflozin for both the SGLT is IC50 = 1.2 nM (SGLT2), IC50 = 1,400 nM (SGLT1) and specificity of canagliflozin for SGLT2 is

achieved at maximal IC50 of 4.2 nM, however for attaining similar degree of inhibition for SGLT1 greater amount of inhibitor is required having an IC50 of 663 nM (67). Canagliflozin at a dose of 300 mg (more than the marketed dose) inhibits intestinal glucose absorption through inhibition of SGLT1 and stimulates the secretion of enteroendocrine cell (EEC) hormone in normoglycaemic adults (68).

EFFICACY OF SGLT1 INHIBITORS IN PRECLINICAL AND CLINICAL STUDIES

Sotagliflizon, a dual inhibitor of SGLT (SGLT1/SGLT2) possess a greater potency towards the inhibition of SGLT2. Per-oral (p.o) administration of sotaglifloizn significantly attenuates the increase in plasma glucose levels in T2D subjects maintained at high glucose diet [69, 70]. Administration of sotagliflozin in T2D patients is coupled with the increased secretion of glucagon like peptide 1 (GLP-1) indicating its potent glucose lowering action with no reports of gastrointestinal side effects [70].

At present, numerous clinical trials are being carried out on SGLT for the development of selective SGLT1 inhibitors [71-73]. Mizagliflozin (DSP-3235) and KGA-2727 are two selective SGLT1 inhibitors which are under clinical trials; (Fig.2.b and Fig.2.c) [74]. Several lines of evidence indicate that the maximal glycaemic control can be achieved by administration of target specific pharmacologically active novel molecules [75,76]. For evaluating the role of SGLT1 inhibitor (KGA-2727), Shibazaki et al have investigated the effects of acute/chronic administration of KGA-2727 in Zucker fatty diabetic (ZDF) rats (a model for T2D) and in streptozotocin treated rats (a model for T1D) [77]. Administration of single dose of KGA 2727 in both the animal models caused significant reduction in intestinal glucose absorption and plasma glucose levels as demonstrated by oral glucose tolerance test (OGTT). Chronic administration of KGA 2727 in ZDF rats fed on normal pellet diet and/or

rats kept on fasting, caused significant reduction in blood glucose with an increase in GLP-1 secretion although plasma glucose levels were reported to be decreased as demonstrated by OGTT. Improvement in structural abnormalities and morphological changes in pancreatic β-cells were also observed in ZFD rats [77]. Dobbin and his colleagues reported that oral application of SGLT1 inhibitors prior to high glucose diet has significantly reduced the elevated blood glucose level [72]. Contrarily, when compared with the chronic treatment of sotagliflozin, chronic administration of KGA 2727 to ZFD rats has resulted in significantly increased levels of plasma insulin in OGTT. According to their study reduced excursions of blood glucose by SGLT1 inhibitors after uptake of glucose-rich food are due to the inhibition of glucose absorption. The effects of SGLT1 inhibitors on secretion of gastrointestinal hormones may be dependent on the composition of the ingested food. The effects may change during progression of the T2D [77]. Thus, SGLT1 inhibition represents a promising therapeutic strategy aimed at correcting diabetic complications through the inhibition of cardiac glucose uptake in myocytes.

[Figure 2.a to 2.f]

SGLT INHIBITORS UNDER CARDIOVASCULAR TRIALS

Several gliflozins such as empagliflozin, canagliflozin, dapagliflozin (Fig.2.d, Fig.2.e, Fig.2.f) are known to possess positive outcome on CV mortality. EMPA REG clinical trial for empagliflozin has reported 14% reduction in total incidences of non-fatal myocardial infarction and stroke in empagliflozin treated patients. Empagliflozin also caused a 35% reduction in hospitalization rate for heart failure although frequency for hospitalization of unstable angina cases remains unaltered. In secondary outcomes, remarkable decline of 38% has been observed in CV mortality rates and moreover deaths due to other causes have witnessed a decline of 32%. Minimal decrease in blood sugar levels were also documented

between empagliflozin and placebo groups (7.8% vs. 8.2%) [78,79]. Despite of its listed beneficial effects, none of the changes have been observed in case of myocardial infarction (MI) and stroke in patients treated with empagliflozin compared to placebo. The exact mechanism of action behind the protective effect of SGLT inhibitors on CV function is still unknown. However, according to some reports obtained effects of SGLT inhibitors are related with the overall improvement in hemodynamic and renal functions [80, 81]. Some studies claim that modulation in cardiac energy substrate metabolism is the acting mechanistic pathway for SGLT [81]. Numerous trials are under pipeline on the major drug candidates of this class such as canagliflozin and dapagliflozin for evaluating its effect on CV function [82,83].

Canagliflozin Cardiovascular Assessment Study (CANVAS) was a randomized, placebo controlled single blinded, parallel study. A total of 10,142 T2D patients were enrolled in the presented study with (n = 5,795) in canagliflozin arm and (n = 4,347) in placebo arm. Patients were treated daily with 100 mg and 300 mg daily doses of canagliflozin. T2D patients of ≥30 years of age having history of atherosclerotic cardiac disease and are highly susceptible for CV risk were recruited in this study. Another age group of patients having ≥50 years of age with high-density lipoprotein cholesterol concentration (<38.7 mg/dl) were considered suitable for the CANVAS. In canagliflozin arm incidence of MI, stroke and CV mortality has been reported in 26.9 patients out of 1,000 patients compared to the 31.5 patients out of 1,000 patients in placebo arm. Albuminuria levels were also found to be reduced in 89.4 patients compared to the 128.7 patients out of 1,000 participants, p value < 0.05 was considered as statistically significant. Results obtained from the CANVAS trial have shown beneficial effects on T2D patients presentable with a history of CVD [83]. Hence, it can be interpreted that canagliflozin could be one of the best suitable drugs for treating T2D and for combating associated CV complications. Similarly, various

clinical trials are also being carried out on dapagliflozin for evaluating the risk benefit ratio for its use in T2D subject which are prone to CV risk [84].

Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI158) (ClinicalTrials.gov Identifier: NCT01730534) [84]. Based on the findings of this trial, the use of dapagliflozin at 5 mg and 10 mg doses has been approved by European Medical agency (EMA), Food drug administration (FDA), and Pharmaceuticals and Medical Devices Agency. Japan (PMDA). Dapagliflozin Effect on Symptoms and Biomarkers in Diabetes Patients with Heart Failure (DEFINE-HF) (ClinicalTrials.gov Identifier: NCT02653482) [85], presently participants are being enrolled for this study, it is sponsored by Saint Luke's Health System. In addition to this, Effect of Dapagliflozin on the Incidence of Worsening Heart Failure (DAPA-HF) is another study to be conducted for dapagliflozin. DAPA-HF is sponsored by AstraZeneca (ClinicalTrials.gov Identifier: NCT03036124) [86]. Above mentioned are the major clinical trials for assessing the efficacy of dapagliflozin against CV disease events [84-87]. Results from CANVAS, DECLARE and EMPA REG in future will help the scientists and health care providers to conclude that whether the positive CV outcomes achieved are confined only to the empagliflozin drug of this class or they are associated with the class effect. Table 5 briefly explains the current status of gliflozins.

POTENTIAL SIDE EFFECTS OF INHIBITION OR DOWN REGULATION OF SGLT1/SGLT2

Potential side effects in the small intestine and kidney

Glucose galactose malabsorption is often linked with the use of SGLT1 inhibitors acting in the small intestine. Gastrointestinal side effects can be minimized by using reversible SGLT1 inhibitors which partially blocks SGLT1 and by prescribing suitable dosage that could be given in the presence of food containing small quantities of glucose and galactose. It has been

reported that RS1 protein, encoding RSC1A1 gene causes upregulation of SGLT1 at post-transcriptional level and RS1derived peptides containing motifs of hRS1 such as QCP, QSP possess the ability to cause inhibition of SGLT1 expression at post-transcriptional level at low glucose concentrations. Regardless of this information, further studies on RS1 peptides are still needed to be carried out to investigate its role in selective inhibition of SGLT1. Moreover with use of these peptides, side effects of glucose and galactose malabsorption were also not observed [88]. In case of enteric inflammation caused due to bacterial infection, up-regulation of SGLT1 is known to impart protective effect. Possible mechanism behind the observed effects could be associated with the increased uptake, followed by subsequent increase in glucose and galactose concentrations in the small intestine [89-91]. Evidently, SGLT1 also plays an important role in ameliorating the gastrointestinal mucositis when treated with the cytostatic agents. Interestingly, gastrointestinal mucositis was also found to be inhibited in wild type mice expressing SGLT++ on treatment with glucose analog BLF501, however no inhibition was observed in SGLT—knockdown mice [92].

Genital mycotic infections (GMI)

Data obtained from several clinical studies have presented the increased risk of GMIs and urinary tract infections (UTIs) linked with the use of SGLT inhibitors [93-100]. Increased incidence of GMIs and UTIs has been reported with the use of dapagliflozin and canagliflozin in female population when compared to male population [101-102]. In one study, investigators have found that four month chronic treatment of canagliflozin has presented the risk of GMI in 10.4% female and 4.2 % male patients compared to the dummy medication (3.2% males and 0.6% females) [103].

Majority of the GMI cases (99% approx) can be treated with the marketed antifungal drugs. The chances of getting affected by UTI are approximately 5 % in all the subjects who are on glifozin therapy. Recent meta-analysis conducted on gliflozins presented an increased risk of 42% for UTIs with a confidence interval of 1.06 to 1.90, whereas risk for GMIs is predominant in females with an occurrence rate of 5 to 10%. [104]. A higher occurrence rate of UTIs and GMIs in gliflozin users is attributed to the consistent and marked glycosuria which promotes the growth of pathogenic microbes. Interestingly, inhibition of SGLT1 is known to exert immunological effect playing an essential role in prevention and protection of sepsis in gut [86]. The Canagliflozin trial, having both male and female participants, has indicated that the male subjects are at greater vulnerability of developing genital infections such as balanitis/balanoposthitis [97,105], while the females were more prone to candidiasis infection such as vulvo-vaginal candidiasis, vulvitis, vulvovaginal mycotic infection, vulvo-vaginitis [101, 105-111]. Higher rates of UTIs (2.9% to 13.3%) compared to placebo/dummy medication have also been noted in the T2D patients taking one or more medication from standard treatment regimen such as pioglitazone or sitagliptin, irrespective of the use of any of the inhibitor of SGLT, less than 1% cases are linked with the concurrent organ damage or withdrawal of drug therapy [101, 105-107, 109, 111]. Most of the GMIs and UTIs occur within the first year of a start of the drug therapy, with a relapse rate of less than 3 %. A newer meta-analysis for dapagliflozin, comprising data obtained from 12 randomized placebo controlled trials was carried out to assess the vulnerability of UTIs, with their most common forms such as dysuria or cystitis. The collected data was represented in the form of percentage, but this study fails to provide the mean statistical differences existing between the specific groups. Three doses of dapagliflozin 2.5 mg, 5 mg, and 10 mg with n =814, n=1145 and n=1193 patients and n=1393 patients in placebo arm were used in the study [112]. Higher incidence of UTIs approximately 7.3% and 6.5% have been reported in 5mg and 10mg

dapagliflozin dose groups compared to the placebo arm with an incidence rate of 4.2% and 4.5% in case of 2.5mg dose of dapagliflozin. For clinical assessment of UTIs, urine samples were collected from all the patients who have been found symptomatic for the occurrence of UTIs. Routine culture of urine samples was performed to determine the vulnerability of UTIs in dapagliflozin treated patients, patients treated with 5 mg and 10 mg doses of dapagliflozin represents the more positive trend for getting affected by UTIs [101, 112]. Treatment with canagliflozin has not shown any significant differences in the mean percentage risk for bacterial infections affecting the lower urinary tract. Evidently, 8.7% females are at increased susceptibility of having lower urinary tract bacterial infections, compared to placebo with a percentage risk of 7.7% [113]. However, comparatively lower rate of incidence has been observed in male subjects (1.4%) compared to placebo (0.6%) [114]. Further, reported UTIs are not fatal and can be treated with the marketed antibiotics.

Effects on bone biomarkers and fracture

Higher incidence of bone fractures have been prevalent in T2D subjects, however the possible causes of bone fractures, changes in bone mineral density and bone biomarkers remains poorly understood. These incidences are further strengthened by the concomitant use of other anti-diabetic agents such as thiazolidinediones which are commonly used for treating T2D [115]. Hence, assessing the risk benefit ratio and effect of SGLT on bone mineral density and biomarkers is of considerable importance. Clinical studies have reported significant increase in beta-CTx (17.1% to 24.9%), a known bone resorption marker with a modest decrease in procollagen type 1 N-terminal propeptide (P1 NP) (−5.7% to −6.9%), an important marker for bone formation in the canagliflozin treated group [116, 117]. Similar kind of modifications in bone density markers were also observed in the patients taking pioglitazone as a drug therapy. Pioglitazone treatment resulted in 16.8% increase in beta-CTx

with no changes in P1 NP [115]. Despite several changes in bone biomarkers, none of the incidence has been reported for bone fracture in gliflozin users [114]. Several evidences elucidate that pioglitazone use is linked with the greater risk (5.1%) of bone fractures compared to placebo (2.5%). However, the use of canagliflozin for treating T2D possess an advantage over pioglitazone as its use is associated with negligible bone demineralization as illustrated by Dual-energy X-ray absorptiometry (DEXA) [117]. Another study assessed that the use of canagliflozin is linked with an overall increase of up to 2.5% and 2.3% bone fracture incidence at 100 mg and 300 mg dose compared to placebo [118]. According to European medical agency (EMA), no incidence of dapagliflozin induced bone demineralization has been reported in elderly patients or in renal compromised patients (≥60 to <90 mL/min/1.73 m2), although some cases of bone fractures have been related well with the use of dapagliflozin in renal compromised patients with an average risk of 4.8% and 9.4% in 5 mg and 10 mg treated individuals (EMA [homepage on the Internet] Forxiga (Dapagliflozin) [119,120]. A phase III, randomized, double-blind, placebo controlled, 102-week (24-weeks for multicentred study and 78 weeks of extended patient blind study) study demonstrates the zero percent change in bone biomarkers when compared with placebo. It also recommends the use of dapagliflozin as a safer add-on therapy to metformin for treating T2D. Moreover, similar results were also reported for canagliflozin use. However, canagliflozin was administered only for a limited period of 26 weeks [121].

In case of emapagliflozin minimal number of evidences has been reported for bone fracture compared to placebo, with no effects on bone mineral density even after the chronic treatment of two years [122,123].

Malignancies

Studies on clinical subjects have indicated that SGLT1 plays an important role in mediating glucose uptake in cancerous cells. However, the precise mechanism by which it contributes to carcinogenesis is poorly understood [124]. Recently, it has been reported that inhibition of SGLT1 directly exerts deteriorating effects on the treatment of cancer. Increased risk of bladder and breast cancer has been observed in dapagliflozin trial. Data obtained from meta-analysis of dapagliflozin indicates the increased risk of bladder and breast cancer when compared with the placebo [119,121,124]. According to the reports published by FDA, 10/6045 bladder cancer cases were noted in dapagliflozin group and 1/3512 in control group, with an overall occurrence rate of 6.11% [118]. The underlying mechanism behind the increased risk of cancer growth with the use of dapagliflozin could be based on the following assumptions *(i)* increased excretion of glucose in urine, promoting proliferation of malignant cells and *(ii)* urinary tract infections associated with the use of SGLT, as there continuous use may cause irritation in bladder epithelium [125]. Further use of dapagliflozin alone and in combination with pioglitazone is contraindicated in the patients having history of bladder cancer [94,126].

CONCLUSION

Enhanced glycosuria offers a promising therapeutic approach for treating hyperglycaemia and its related cardiovascular complications. Efficacy of SGLT inhibitors for treating diabetes has been proven clinically, it has been elucidated that SGLT inhibitors can also be used for treating obesity. Further, reports suggest that it can be used in conjunction with other available anti-diabetic agents and insulin to enhance its efficacy. Recent reports suggest that oral application of SGLT inhibitors also helps in reducing blood pressure and promotes weight loss. Moreover, reduction in plasma glucose level may directly relate with the

improvement in glomerular function and damage, results from chronic studies are still awaited. To date, very few data is available, concerned with the use of dual SGLT1/SGLT2 inhibitors and much more safety data from clinical trials is still awaited for proving its protective role in diabetes related cardiovascular complications and for the development of specific SGLT1 inhibitors.

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DISCLOSURES

There are no conflicts of interest.

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FIGURE LEGENDS

Figure.1. Role of SGLT inhibitors in progression of diabetic cardiomyopathy. In addition to free fatty acids glucose acts as a cardiac fuel and is involved in energy production. Under normal conditions basal glucose uptake was regulated by glucose transporter 1 (GLUT1), whereas glucose transporter 4 (GLUT4) is responsible for insulin induced glucose uptake. *Both GLUT1 and GLUT4 belong to the major class of facilitative transporters.* It has been suggested that under diabetic condition, GLUT4 expression is getting significantly reduced however this decrease is compensated by the upregulation of sodium glucose transporter 1 (SGLT1) which is possibly involved in impairment of cardiac energy substrate metabolism playing a chief role in cardiac damage. Along with this, SGLT1 upregulation has also been correlated well with the glycogen accumulation, activation of NADPH oxidase (NOX2) and production of reactive oxygen species (ROS).

Figure.2. Chemical structures for SGLT1/2 inhibitors (approved/under clinical trials).

Table 1 Localization and expression of SGLT1 in human and rat under diabetic condition.

Localization	Species	Expression under diabetic condition	Reference
Heart	Rat (capillaries), human	Up-regulated in both	(123,124)
Small intestine	Rat , human	Up-regulated in both	(123, 125)
Kidney	Rat , human	Up-regulated in rat	(47, 128)
Trachea	Human	Unknown	(46)
Pancreatic alpha cells	Human	Unknown	(4)
Liver	Human	Unknown	(43)
Lung	Human	Unknown	(43)
Brain (ventromedial hypothalamus)	Rat, human	Unchanged in rat, unkonwn in case of humans	(129,130)
Mesenteric adipose Tissue	Human	Unknown	(45)
Skeletal muscle	Rat	Unknown	(131)
Prostate	Human	Unknown	(45)
Cervix	Human	Unknown	(45)
Salivary glands	Rat	Unknown	(129, 132)

Table 2 SGLT inhibitors derived from O glycosides and C glycosides. ** SGLT1 selective.*

O-glycosides	**Drawback**	**Reference**
T-1095	Extensive hepatic metabolism of its active metabolite, increased glucosuria	(133)
Sergliflozin	Unfavourable efficacy, pharmacokinetic instability, rapid hydrolysis by β-glucosidases	(134)
Remogliflozin	Unfavourable efficacy, pharmacokinetic instability, rapid hydrolysis by β-glucosidases	(135)
AVE2268	Pharmacokinetic instability	(137)
C-glycosides	**Drawback**	**Reference**
Dapaglifozin (BMS-512148)	Urinary tract infections, painful micturition	(137)
Empagliflozin (BI 10773)	Intravascular volume contraction, hypotension in patients	(139)

	with compromised renal function.	
Canagliflozin (TA-7284, JNJ-28431754)	Urinary tract infections	(140)
Tofogliflozin (CSG-452 (R-7201, RG-7201)	Urinary tract infections	(141)
Ipragliflozin (ASP-1941)	Urinary tract infections	(141)
Luseogliflozin (TS-071)	Urinary tract infections	(141)
Ertugliflozin (PF-04971729)	Urinary tract infections	(140)
Sotagliflozin (LX-4211)	Urinary tract infections	(142)
*Mizagliflozin (DSP-3235)	None reported yet	(143)
ISIS-SGLT2Rx (ISIS-388626)		NCT00836225
KGA-2727*	Abdominal pain, flatulence	(139)

Table 3 SGLT inhibitors as add on therapy agents with other anti-hyperglycaemic conditions.

SGLT inhibitor and its trade name	Min dose	Max dose	Metformin is contraindicated	Add on to MET, SU/ Add on to MET+ SU	Add on to insulin (+/- MET)
Dapagliflozin (Forgixa®, Fargixa®)	5 mg	10 mg	Yes	Yes	Yes
Empagliflozin (Jardiance®)	10 mg	25 mg	Yes	Yes and also with PIO	Yes
Canagliflozin (Invokana®)	100 mg	300 mg	Yes	Yes	Yes

Abbreviations: MET: metformin, SU: sulfonylurease, PIO: pioglitazone

Table.4. Pharmacokinetic profile of the prominent SGLT inhibitors which are derived from C-glycosides.

Drug / trade name	Dose (mg/kg)	Cmax* (µM)	IC50 for SGLT1 (nm)	IC50 for SGLT (µm)	Ratio IC50SGLT1/ Cmax	Reference
Dapagliflozin	10,20	0.5, 0.7	1391-1400	1.4	2.8, 2.0	(136-140, 143-145,143-149)
Empagliflozin	5, 25	0.2, 0.6	8300	8.3	41.5, 13.8	
Canagliflozin	100, 300	2.5, 7.8	684-710	0.7	0.3, 0.1	

SGLT inhibitor	Development phase	Dose (mg/kg)	Registered cardiovascular trial
Empagliflozin	Approved by European medicine agency (2014/05), Food drug administration (2014/08)	10, 25	(EMPA-REG-OUTCOMETM) (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients NCT01131676
Canagliflozin	Approved by European medicine agency (2013/11), Food drug administration	100, 300	CANVAS (Canagliflozin Cardiovascular Assessment Study)

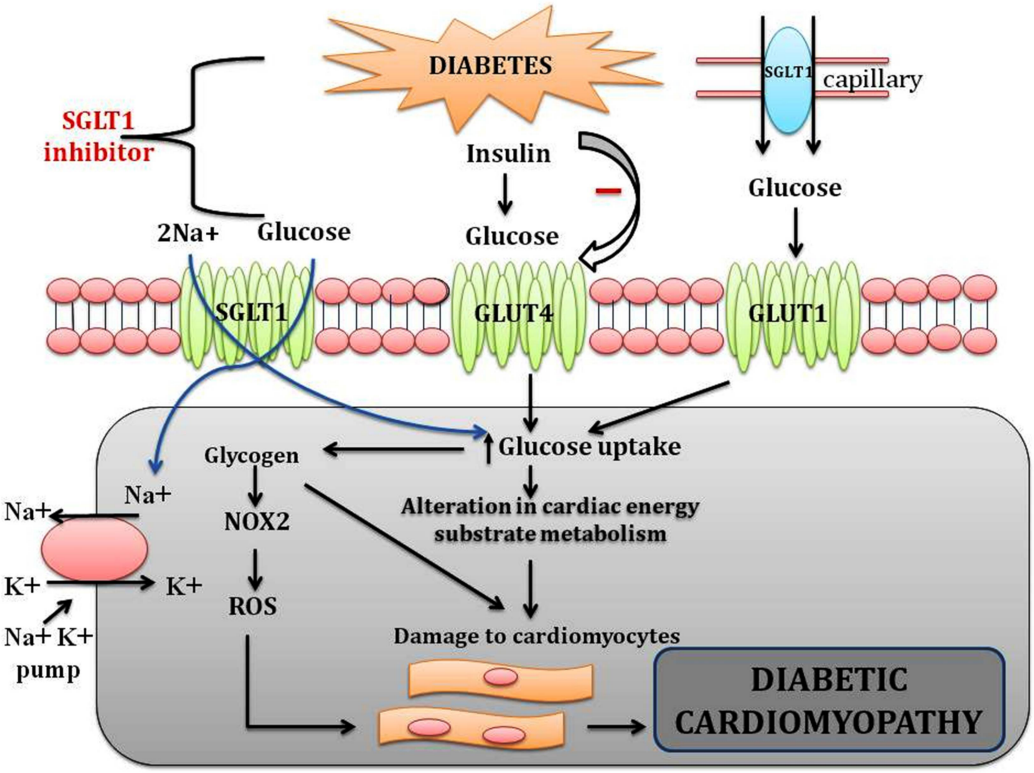
	(2013/03),		NCT01032629
Dapagliflozin	Approved by European medicine agency (2012/11), Food drug administration (2014/01), PMDA (2014/03)	5, 10 mg	DECLARE TIMI58 (Dapagliflozin Effect on Cardiovascular Events) NCT01730534
Luseogliflozin	Approved by PMDA (2014/03)	2.5, 5	NCT02528019
Tofogliflozin	Approved by PMDA (2014/3)	20	Not applicable
Ipragliflozin	Approved by PMDA (2014/01)	25, 50	Not applicable
GSK-1614235	Phase I	1, 5, 20 (0.25 to 40)	NCT01607385
BI44847	Phase I	100, 400, 800	Not applicable
LX4211	Phase II		NCT01742208
EGT0001474	Phase I	25, 75, 150	NCT00924053
ISIS-SGLT2Rx	Phase I	50, 100, 200, 400	NCT00836225
EGT0001442	Phase II	20	NCT01377844

Source of information: homepages of the FDA, EMA, PMDA, (148-153) (www.clinicaltrials.gov). Abbreviations: PMDA, Pharmaceuticals and Medical Devices Agency. Japan.

SGLT inhibitor	Development phase	Dose (mg/kg)	Registered cardiovascular trial
Empagliflozin	Approved by European medicine agency (2014/05), Food drug administration (2014/08)	10, 25	(EMPA-REG-OUTCOMETM) (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients NCT01131676
Canagliflozin	Approved by European medicine agency (2013/11), Food drug administration (2013/03),	100, 300	CANVAS (Canagliflozin Cardiovascular Assessment Study) NCT01032629
Dapagliflozin	Approved by European medicine agency (2012/11), Food drug administration (2014/01), PMDA (2014/03)	5, 10 mg	DECLARE TIMI58 (Dapagliflozin Effect on Cardiovascular Events) NCT01730534
Luseogliflozin	Approved by PMDA (2014/03)	2.5, 5	NCT02528019
Tofogliflozin	Approved by PMDA (2014/3)	20	Not applicable
Ipragliflozin	Approved by PMDA (2014/01)	25, 50	Not applicable
GSK-1614235	Phase I	1, 5, 20 (0.25 to 40)	NCT01607385
BI44847	Phase I	100, 400, 800	Not applicable
LX4211	Phase II		NCT01742208
EGT0001474	Phase I	25, 75, 150	NCT00924053
ISIS-SGLT2Rx	Phase I	50, 100, 200,	NCT00836225

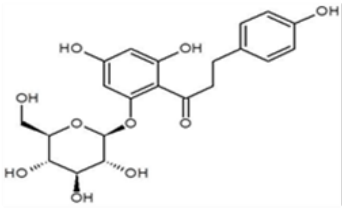
		400	
EGT0001442	Phase II	20	NCT01377844

Table 5. Current status of gliflozins.

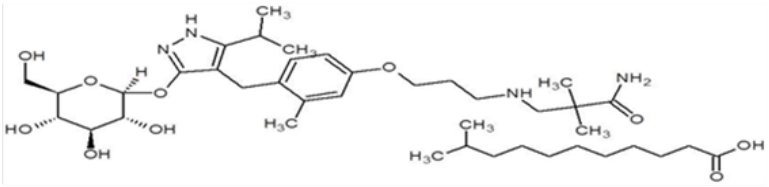


fcp_12516_f1.jpg

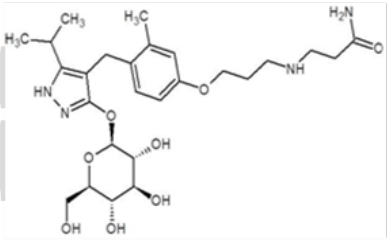
Figure 2



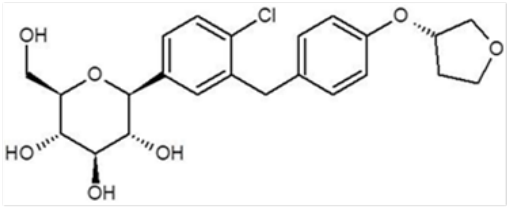
2.a. Phlorizin



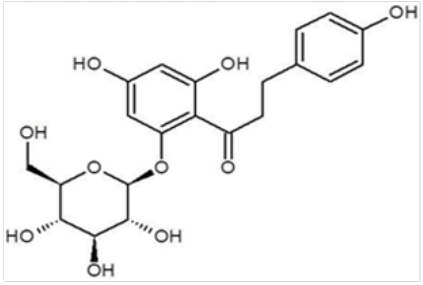
2.b. DSP-3235



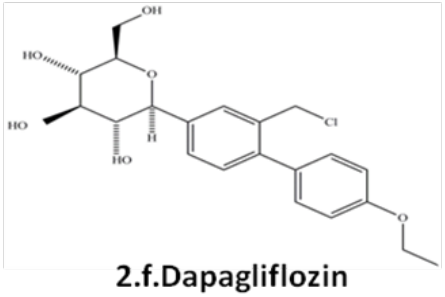
2.c. KGA-2727



2.d.Empagliflozin



2.e.Canagliflozin



2.f.Dapagliflozin