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Review

Promise, peril, and possible new treatment options incurred by sodium glucose co-transporter 2 (SGLT2) inhibitors: A precise review up to 2018

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ABSTRACT

The sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitors) are newly introduced adjuvant antidiabetic medications that block the reabsorption of glucose in the area of proximal tubule of the kidney. In this review, we pointed out all the beneficial (promises) and unwanted (perils) effects of SGLT2 inhibitors recorded in the groups with diabetes mellitus and animal models for developing risk benefit idea. After reviewing sufficient literature we also put forward the diseases those can be the novel indications of SGLT2 inhibitors. Review also revealed that besides Type 2 diabetes (T2D), SGLT2 inhibitors are likely to be used for the treatment of heart failure (HF), nonalcoholic steatohepatitis (NASH), chronic kidney disease (CKD), hypertension, obesity etc. SGLT2 inhibitors mitigate numerous complications that may worsen the intensity of diabetes mellitus. Most of the benefits resulted from the use of SGLT2 inhibitors modify the quality of life of person with diabetes towards improvement. But there is also controversy that SGLT2 inhibitors elicit several unwanted effects like cancer, bone fracture, amputation risk etc. However, the standardization of this drugs class for the treatment of new indication can be ensured after thorough investigation with a view to generating sufficient data for better understanding.

1. Introduction

Common symptoms of diabetes were first observed more than 3500 years ago. Aretaeus of Cappadocia recorded excessive urination, thirst, and wasting of the flesh and limbs into the urine, this disorder was named diabetes which means “a flowing through” (Diamant and Morsink, 2013). T2D afflicts more than 380 million people throughout the world which is considered as a prominent cause of terminal stage kidney disease. It also endangers cardiovascular disease by aggravating relevant risk factors. It is also presumed that a number of patients with diabetes will die from cardiovascular disease (Gallo et al., 2015). In T2D glucotoxicity results in apoptosis of β-cells which in turn diminishes β-cell mass thus the disease is responsible for reduced gene transcription, biosynthesis, and supply of insulin (Chao and Henry, 2010). Currently used agents for the treatment of diabetes possess numerous side effects that conceal the benefits from blood glucose lowering effects. For instance, gastrointestinal upset is a common side effect of metformin, glucagonlike peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 inhibitors are likely to be associated with nausea and vomiting. Thiazolidinediones (glitazones) cause edema and weight gain. Sulphonylurea exacerbates myocardial infarction and heart failure. Sulphonylurea or insulin may promote hypoglycemia and weight gain (Gallo et al., 2015; Chao and Henry, 2010). The concept of SGLT2 inhibitors developed when French chemists separate phlorizin in 1835 from the root bark of the apple tree. This agent caused glycosuria, normalized both fasting and postprandial glucose level, phlorizin also restored the insulin resistance activity to normal. But the agent was not further proceeded due to its propensity for poor intestinal absorption and prompt β-glucosidase degradation (Chao and Henry, 2010). Recently marketed SGLT2 inhibitors have additional advantages over conventional agents for treating the condition of T2D. SGLT2 inhibitors manifested weight loss, renoprotective effects, cardiovascular risk reduction, and blood pressure reduction etc (Avogaro et al., 2018). In contrast, study reported that SGLT2 inhibitors may have a link to genital infection, cancer, ketoacidosis, acute kidney injury, electrolyte disorders, lipid metabolism abnormalities, skin reactions, amputation risk, and bone fractures (Filippas-Ntekouan et al., 2018).

In this review, we tried to put together all the favorable and unfavorable effects of SGLT2 inhibitors from the up to date published studies. In addition, we also tried to surmise the attribute of SGLT2 inhibitors that can be extrapolated as future treatment options for morbidities other than diabetes.

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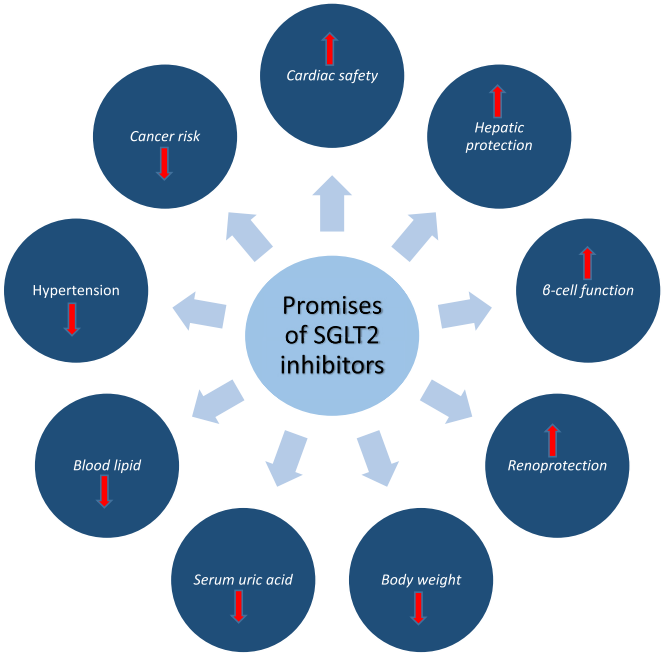

Fig. 1. Schematic presentation showing all the favorable effects of SGLT2 inhibitors ↑ and ↓ signs indicate the increase and decrease of the mentioned term or state respectively.

2. Search methodology

We confined our study search between 2009 and November 2018 with a view to congregating updated information from studies of last decade. Nonetheless, relatively most recent published works were used to set up the manuscript. We emphasized on using the information from various renowned journals like Nature family journals, The lancet, The New England journal of medicine and rest of the journals are indexed in either PubMed, Scopus, Sci, Sci Expended or Medline. Primarily, we used google scholar site for selecting articles according to the order of relevance, secondarily, sci-hub site was used for downloading the selected articles. Keywords used for searching articles by google scholar were SGLT2 inhibitors, SGLT2 inhibitors latest update, SGLT2 inhibitors and cancer etc. We also looked into the references of downloaded articles to import the pertinent information of interest.

3. Promises

All promises of SGLT2 inhibitors are outlined in Fig. 1.

3.1. Antihypertensive effect

Study reported that twenty-seven randomized controlled trials (RCTs) were conducted involving 12,960 participants to evaluate the effect of SGLT2 inhibitors on hypertension. This study suggested that SGLT2 inhibitors markedly decreased both systolic blood pressure (mean difference, −4.0 mm Hg; 95% confidence interval) and diastolic blood pressure (mean difference, −1.6 mm Hg; 95% confidence interval) from baseline (Baker et al., 2014). It is assumed that SGLT2 inhibitors may cause mild osmotic diuresis, this results in increased urine output backed by diminished reabsorption of water in the kidney (Basile, 2013). Study also reported that SGLT2 inhibitors displayed a steadfast small reduction in blood pressure (BP). In patients with diabetes, co-transportation of sodium and glucose results in decreased natriuresis due to enhanced glucose reabsorption in the milieu of the proximal tubule. Therefore, it is explored that SGLT2 inhibitions cause a direct natriuretic effect which results in reduced blood pressure (Garcia-Ropero et al., 2018). Another study reported, the sodium-hydrogen exchanger (NHE3 isoform) is explicitly abundant in the renal apical surface, which causes for the maximum sodium reuptake following filtration in the glomerulus. SGLT2 inhibitors have been shown to inhibit NHE3 to turn natriuretic effects (Packer, 2017).

3.2. Weight loss

Study reported that the 2.5% weight reduction is achieved with SGLT2 inhibitors in the intensive treatment arm when compared to control group. Clinical trials conducted on T2D also revealed significant weight reduction with SGLT2 inhibitors, it showed 1.7 kg or 2.4% reduction of weight compared with placebo. Significant weight reduction is demonstrated during the first week of the treatment with SGLT2 inhibitors that may be associated with osmotic diuresis (Van Bommel et al., 2017; Lambers Heerspink et al., 2013). Loss of glucose facilitated by SGLT2 inhibitors is also responsible for the reduction of weight loss (Cefalu and Riddle, 2015). Dual-energy X-ray absorptiometry postulated that the weight reduction was primarily associated with diminution of fat of the body other than fluid or lean tissue loss (Bolinder et al., 2014; Madaan et al., 2016).

3.3. Cardiac safety

The EMPA-REG OUTCOME was assumed to be the first trial to disseminate cardiovascular safety about empagliflozin. This trial demonstrated that empagliflozin possessed a notable reduction in all-cause mortality, mortality due to cardiac disease, and heart failure hospitalizations compared with placebo (Scheen, 2016a; Zinman et al., 2015; Fitchett et al., 2016). The CANVAS program conducted with canagliflozin also revealed a similar cardiovascular benefit to the EMPA-REG OUTCOME trial but patients, in this case, demonstrated lesser cardiovascular (CV) risk than those treated with placebo. A meta-analysis trial conducted with dapagliflozin on 9339 patients demonstrated multifactorial benefits on CV risk factors (Avogaro et al., 2018; Sonesson et al., 2016; Neal et al., 2017).

3.4. Renoprotective effect

The EMPA-REG OUTCOME trial attributed that empagliflozin decreased the advancement of the renal disease. 44% significant risk reduction was conceded for doubling serum creatinine level on the other hand 55% significant risk reduction was achieved for want of kidney-replacement treatment in the empagliflozin treated group when compared with group of placebo. Patients treated with empagliflozin group also manifested lower risk of occurring microalbuminuria (Garcia-Ropero et al., 2018; Wanner et al., 2016). The CANVAS program showed associated benefit possibly derived from the use of canagliflozin against the advancement of albuminuria (hazard ratio, 0.73; 95% CI, 0.67 to 0.79) and the combined effect of a continuous 40% decrease in the calculated glomerular filtration rate, the necessity for kidney-replacement therapy, or death from kidney related causes (hazard ratio, 0.60; 95% CI, 0.47 to 0.77). The cross-over trial that adopted post hoc analysis reported that dapagliflozin contributed to decrease in albuminuria by 44% (95% CI, 30.3%–54.8%) (Garcia-Ropero et al., 2018).

3.5. Improvement of pancreatic β-cell function

A 4-week pilot study investigated β-cell function after the therapy conducted with a SGLT2 inhibitor, ipragliflozin in Japanese individuals predisposed with T2D. The disposition index elevated meaningfully both at 4 weeks ($p < 0.001$) and 5 weeks ($p = 0.008$) compared to baseline. Study concluded that disposition index derived from an oral glucose tolerance test (OGTT) was significantly developed after treatment for four-weeks with ipragliflozin in Japanese people enduring T2D. Study also reported that the uplift of β-cell performance achieved by a single starting dose equivalent to that achieved after 28-day

chronic treatment (Takahara et al., 2015). Deletion of SGLT2 in hyperglycemic *db/db* mice resulted in improved function of pancreatic β-cell. It contributed to 60% rise in β-cell mass and reduction in β-cell death (Jurczak et al., 2011).

3.6. Reduction of serum uric acid (SUA)

Study reported that SGLT2 inhibitors abate the serum uric acid (SUA) level. To expatiate the process involved in reduction, SUA and the urinary excretion rate of uric acid (UE_{UA}) were examined following the oral route ingestion of luseogliflozin, a SGLT2 inhibitor, to healthy subjects. Analysis revealed a decrease in SUA, and a negative connection was noticed between the SUA level and the UE_{UA}. Study suggested that SUA declined as a result of the rise in the UE_{UA} (Chino et al., 2014). Hyperuricaemia contributed to the development of gout, stones in the kidney and cardiovascular disease. The post hoc investigation of pooled data derived from phase III studies that linked four placebo-controlled groups explored the effect of SGLT2 inhibitor canagliflozin on SUA levels in patients predisposed with T2DM and in a subset of patients suffering from hyperuricaemia. At week 26, canagliflozin 100 and 300 mg demonstrated a ~13% recrease in serum uric acid compared with placebo. Majority of patients in the hyperuricaemic group achieved a serum uric acid level of < 360 μmol/l (~6 mg/dl) with both canagliflozin 100 mg (23.5%) and 300 mg (32.4%) compared with placebo (3.1%) (Davies et al., 2015). Tofogliflozin, a sodium glucose co-transporter 2 inhibitor significantly decreased SUA level in patients with moderate HbA1c levels (Ouchi et al., 2018).

3.7. Lipid lowering effect

Canagliflozin caused a mean 8% increment in plasma levels of low-density lipoprotein (LDL) cholesterol compared with placebo. However, this negative role was compensated by other beneficial lipid lowering effects, such as raise in high-density lipoprotein (HDL) cholesterol and reduction in triglycerides (TG) (Scheen, 2016b). Treatment with dapagliflozin also contributed to increase in total cholesterol and HDL-cholesterol and a reduction in triglycerides (Basile, 2013). SGLT2 inhibitors revealed a small increase in plasma LDL and HDL cholesterol and a decreased in plasma TG. The ratio between LDL and HDL was found unchanged. The mechanism that SGLT2 inhibitors deploy for contributing to these changes in lipid is not clearly understood (Abdul-Ghani et al., 2016).

3.8. Amelioration of hepatic diseases

Study demonstrated that the luseogliflozin, a SGLT2 inhibitor ameliorated the conditions aggravated by the development of non-alcoholic steatohepatitis (NASH). Treatment with luseogliflozin attenuated hepatic weight enhancement with lipid accumulation and increase in serum alanine aminotransferase in mice pretreated with nicotinamide and streptozotocin (NA/STZ) (Qiang et al., 2015). The effect of ipragliflozin was evaluated on choline-deficient L-amino acid-defined (CDAA) induced NAFLD in mice, the rats showed hepatic triglyceride (TG) accumulation, mild inflammation and fibrosis five weeks after feeding. Ipragliflozin was found to exert preventive activity on liver fibrosis which was evident by a noticeable decrease in fibrosis score and content of hydroxyproline. Study concluded that ipragliflozin obstructed the fibrosis and hepatic TG accumulation in CDAA-diet rats (Hayashizaki-Someya et al., 2015). An eight-week treatment with canagliflozin attenuated hepatic steatosis in Western diet fed melanocortin 4 receptor-deficient (WD-fed MC4R-KO) mice. But the same treatment after 20 weeks resulted in the devolution of fibrotic liver in WD-fed MC4R-KO mice. After a year the treatment with canagliflozin significantly lessened the count of abnormal liver growth in WD-fed MC4R-KO mice (Shiba et al., 2018). Canagliflozin has been found to decrease serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP) and γ-glutamyl transferase (Leiter et al., 2016).

3.9. Effectiveness in cancer

Canagliflozin was found to obstruct proliferation of cells and clonogenic survival in prostate and lung cancers. It was effective when used alone or combined with ionizing radiation and chemotherapeutic agent (Villani et al., 2016).

4. Perils

This part cited all the potential unwanted effects resulted from the use of SGLT2 inhibitors in various scientific studies.

4.1. Ketoacidosis

Study reported that euglycemic ketoacidosis might occur frequently in individuals with diabetes and received treatment with SGLT2 inhibitors. 13 occurrence of ketoacidosis were linked to mild hyperglycemia or normoglycemia in nine subjects who received treatment with the SGLT2 inhibitor canagliflozin. Seven among these nine subjects, who displayed 11 incidences of ketoacidosis, had type 1 diabetes mellitus (Peters et al., 2015). Study also revealed two cases of euglycemic ketoacidosis in subjects with T2D and who were receiving treatment with the SGLT2 inhibitor dapagliflozin (Hine et al., 2015). Depending on 28 reported cases of ketoacidosis in July 2015 in Japan, manufacturers revealed the postmarketing reports concerning adverse events of six SGLT2 inhibitors (ipragliflozin, dapagliflozin, luseogliflozin, tofogliflozin, canagliflozin, and empagliflozin) during their tenure in the market (Ogawa and Sakaguchi, 2016). Ketoacidosis in diabetes is likely to occur in various conditions like T2D, during retardation of insulin dose, severe acute illness, dehydration, surgery, extensive exercise, low-carbohydrate diets, or excessive alcohol intake etc (Goldenberg et al., 2016).

4.2. Risk of cancer

A meta-analysis consists of 46 randomized controlled trials (RCTs) reported 80- cancer cases among 34,569 individuals with T2D. Study also stated that SGLT2 inhibitors were not associated with overall cancer risk during study period. SGLT2 inhibitors might increase the risk of cancer in obese patients with BMI $\geq 30\ kg/m^2$. It was reported that empagliflozin might increase the bladder cancer risk, although it was not clearly confirmed (Tang et al., 2017). The carcinogenic potency of canagliflozin can be attributed by the presence of testicular tumors, pheochromocytomas and renal tubular tumors in rat models (De Jonghe et al., 2014).

4.3. Risk of infection

Systematic review along with meta-analysis assessed the impact of SGLT2 inhibitors upon genital infections and urinary tract infections (UTIs) in T2D patients. In 77 randomized controlled trials (RCTs) there was no significant deviation in UTIs between SGLT2 inhibitors and control, risk ratio (RR) 1.05, (95% CI, 0.98 to 1.12) but SGLT2 inhibitors showed the increased risk of genital infections, (RR 3.30, 95% CI, 2.74 to 3.99) (Liu et al., 2017).

4.4. Bone fractures

SGLT2 inhibitors have the potential to change calcium and phosphate homeostasis and thereby increase bone fracture risk (Scheen, 2016b). A pooled analysis reported that there was a roughly 30% increase in bone fractures among patients received canagliflozin in eight clinical trials conducted for 68 weeks. 9.4% and 6.0% incidences of

bone fracture were accompanied by treatment of 10 mg and 5 mg dapagliflozin respectively after 104 weeks of follow-up (Taylor et al., 2015).

4.5. Hypoglycemia

Hypoglycemia is manifested when SGLT2 inhibitors are administered along with sulfonylureas but is not likely to occur with metformin or insulin. Hypoglycemia is not an event of SGLT2 inhibitors as a drug class (Filippas-Ntekouan et al., 2018). But empagliflozin may induce hypoglycemia if combined with sulfonylurea or insulin (Reddy and Inzucchi, 2016).

4.6. Electrolyte imbalance

SGLT2 inhibitors contributed to small rise in serum concentrations of magnesium, potassium and phosphorus. Recently published CANVAS trial suggested that small increase in serum phosphorus may have contribution for the reduction of bone density and thereby bone fracture. Nonetheless, recent meta-analyses did not relate the impact of SGLT2 inhibitors to bone fractures (Filippatos et al., 2018).

4.7. Risk of amputations

The CANVAS trial programme showed that canagliflozin unlike dapagliflozin or empagliflozin increased the risk of amputations by two times. Among 66 adverse event reports analyzed by FDA up to March 31, 2017, canagliflozin was responsible for the 57 or 86% adverse events (Fadini and Avogaro, 2017). Among affected patients 71% showed the amputation risks at toe or metatarsal levels. This risk was higher in patients with predisposition of peripheral vascular disease or in individuals who carried history of an antecedent amputation (Neal et al., 2017). Studies clarified that the fact of amputation is related to the use of canagliflozin only. The process of pathogenicity is not clearly understood. So it should not be considered as the class effect of SGLT2 inhibitors (Monami et al., 2017).

4.8. Acute kidney injury (AKI)

FDA received 100 reports about acute kidney injury (AKI) cases as of October 2015 those were found to have link to the use of SGLT2 inhibitors. Majority of patients recovered from AKI, 11 of them developed chronic kidney disease and four became deceased. It is suggested to withstand the use of these medicaments in patients who are dehydrated, receiving treatment with NSAIDs or radiocontrast agents. The mechanism involved in the process of renal injury with SGLT2 inhibition is not clearly understood. However, increase in uric acid in urine both by crystal-dependent and crystal-independent mechanisms and activation of the gene that encodes aldose reductase are indicated (Hahn et al., 2016). Although one recent study reported that there is there is no evidence for an enhanced risk of AKI with the use of SGLT2 inhibitors. In addition, canagliflozin and dapagliflozin, is likely to be hazardous for the high-risk population and AKI is not related to any inherent nephrotoxicity of SGLT2 inhibitors (Nadkarni et al., 2017).

4.9. Skin related events

Serious generalized rash, erythema, urticarial, eczema drug eruption were likely to be seen within 2 weeks of SGLT2 inhibitors administration. Animal study suggested that ipragliflozin possessed higher risk for skin reaction, it might be due to excessive accumulation of ipragliflozin and its metabolites in skin (Yabe et al., 2015). A case report revealed the development of severe pruritus during the treatment accompanying canagliflozin. Inception of treatment with pioglitazone/metformin fixed combination and cessation of canagliflozin helped remission of pruritus (Vasapollo et al., 2018).

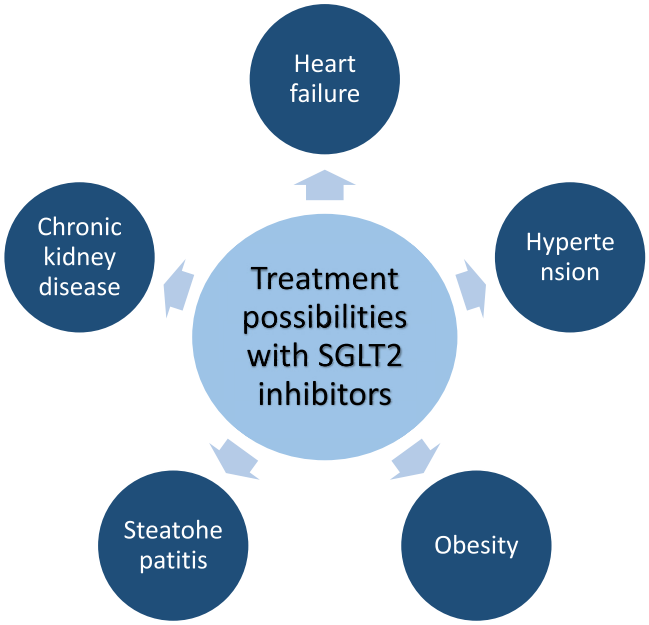

Fig. 2. Schematic presentation showing new treatment possibilities with SGLT2 inhibitors.

5. New treatment possibilities

Fig. 2 represents the new treatment possibilities with SGLT2 inhibitors.

5.1. Treatment of heart failure (HF)

The number of agents those lower glucose in plasma for treating patients with coexistence of diabetes and heart failure are very narrow. Glucose lowering medications with favorable impact on heart failure are elusive rather few may have noxious impact on the condition (Fitchett et al., 2016). SGLT2 inhibitor empagliflozin could reduce the CVD risk by providing hemodynamic effects than metabolic effects. Primary major cardiac events like CV death, nonfatal heart attack and nonfatal stroke were minimized by 14% with the treatment of empagliflozin. Empagliflozin also contributed to 35% reduction in hospitalization due to heart failure. It can be an opportunity to assess the drug in individuals with reduced left ventricle (LV) function or congestive heart failure (CHF) with or without diabetes (Abdul-Ghani et al., 2016). Currently EMPATROPISM trial is evaluating the efficacy as well as safety concern of empagliflozin in individuals without diabetes. If the result becomes promising, it can be considered for the treatment of heart failure independent of diabetes (Garcia-Ropero et al., 2018). SGLT 2 inhibitors cause very lower level of hypoglycemia, it can benefit the patients with heart failure (HF) in the absence of diabetes because they lessen plasma volume expansion, ameliorate natriuretic and diuretic processes and shift cardiac metabolism towards favorable effects (Martens et al., 2017).

5.2. Treatment of hypertension

Study data suggests that SGLT2 inhibitors possess remarkable reduction in blood pressure, although the actual mechanism is not clearly elucidated (Maliha and Townsend, 2015). Although SGLT2 inhibitors have not been approved for hypertension, these agents may help achieve BP goal within 7–10 mm Hg (Oliva and Bakris, 2014).

A 12 week study demonstrated that 25 mg dose of empagliflozin contributed to the 24 h reduction of systolic and diastolic BP, 4/2 mm Hg than placebo. There are many possible mechanisms adopted by SGLT2 inhibitors to cause antihypertensive effects e.g. osmotic diuresis,

mild natriuresis, weight loss and nitric oxide release (Majewski and Bakris, 2015). Studies consistently showed that canagliflozin had positive effects on BP including one study that revealed improvement in hypertensive condition irrespective of the presence or absence of other antihypertensive medicaments like ARB, ACE inhibitor, and/or diuretics (Townsend et al., 2016). Ongoing researches related the mechanism of SGLT2 inhibitors with the pathophysiology of nephropathy in patients with diabetes and diabetes-related hypertension, they also allude for the novel drug target for the treatment of hypertensive conditions (Martens et al., 2017).

5.3. Treatment of chronic kidney disease (CKD)

Chronic kidney disease (CKD) is generally based on the estimation of the glomerular filtration rate (eGFR) and is being diagnosed by a reduction of GFR by 40% for more than 3 months. Study on people with T2D and CKD with SGLT2 inhibitor canagliflozin showed an acute reduction in eGFR with subsequent eGFR stabilization. This effect was related to the significant and dose-dependant reduction in albuminuria (Breyer and Susztak, 2016). SGLT2 inhibitors are effective in mitigating renal hyperfiltration and consequently restrict the progression of chronic kidney disease (CKD). In addition, SGLT2 inhibitors reduce intraglomerular pressure, hypertension and uric acid levels which are potentially beneficial for patients with CKD without diabetes (Zanoli et al., 2015).

5.4. Treatment of nonalcoholic steatohepatitis (NASH)

Nonalcoholic steatohepatitis (NASH) has been a global burden. Amylin liver NASH model (AMLN) mice represent various features of human NASH like steatosis, inflammation, liver fibrosis, obesity and insulin resistance. Ipragliflozin, a SGLT2 inhibitor improved pathogenic condition by reducing insulin resistance and lipotoxicity (Honda et al., 2016). Empagliflozin alone or in combination with linagliptin intervenes the development of NASH and possesses anti-steatotic and anti-inflammatory effects (Jojima et al., 2016). Study clearly demonstrated that SGLT2 inhibitors including luseogliflozin showed favorable effects on NASH accompanying diabetes mellitus. This study concluded that the therapeutic benefit of SGLT2 inhibitors may be exploited for the treatment of NASH in human suffering from T2D (Qiang et al., 2015).

5.5. Treatment of obesity

SGLT2 inhibitors, enhance glycosuria by inhibiting glucose reabsorption in the renal proximal tubule. Consequently they accelerate urinary glucose excretion and ameliorate hyperglycemic condition. These drugs have the ability to reduce 300–400 kcals energy per day (Kusminski et al., 2016). Chronic administration of dapagliflozin in mice dose-dependently increased the hyperphagia but reduced the body weight by 4% at highest dose compared with control. But if the hyperphagia was prevented it could result in 9% weight reduction (Devenny et al., 2012).

6. Discussion and conclusion

Risk and benefit estimation and evaluation are very important for any novel drug class. Because it is indicative to the safety concern that ultimately plays role for the acceptance and consequently establishment of novel drugs by conventional health care setting. Ideally SGLT2 inhibitors are a type of medications that are designed to barrier uncontrolled glucose reabsorption in the proximal convoluted tube of the kidney. SGLT2 inhibitors offers a number of clinically meaningful benefits (pleiotropic effects) in patients with T2D. An ideal medicament for diabetes mellitus should sustain the blood glucose level within the normal body range at the same time it should attenuate the group of hazards that a patient with diabetes pass through in real life. Various studies have cleared that SGLT2 inhibitors have favorable effects on CV and renal system in individuals with T2D. At the same time, there are also some drawbacks that exist with the use of these novel drugs. On the other hand, any individual severe effect of any of these molecules cannot be considered as a class or core effect. In fact, all members of SGLT2 inhibitors generally do not possess identical form of effects under similar study conditions. Alongside any specific SGLT2 inhibitor that has undesirable effect in any particular state may produce favorable effect in another state. The fact of bone fracture is more pronounced with the treatment of canagliflozin and dapagliflozin and canagliflozin also aggravate the risk of amputation. On the other side the CANVAS program and EMPA-REG OUTCOME trial have expressed that canagliflozin has favorable CV effects. Likewise EMPA-REG OUTCOME trial also revealed that empagliflozin contributed to favorable effects on CV outcome. But empagliflozin may have link to the bladder cancer progression although the issue is not clearly elucidated.

Each of the SGLT2 inhibitors has their individual advantages and disadvantages and drug from this class should be selected for any individual depending on various adjoining factors related to patients with diabetes e.g. status of complications other than diabetes, physiological status, sex etc. As per literature review seemingly SGLT2 inhibitors have the propensity for developing new treatment options for ailments beyond diabetes including heart failure, chronic kidney disease, steatohepatitis, hypertension and obesity. It is critical to conjecture the impact of SGLT2 inhibitors on the course of cancer and gout due to lack of suitable data. In addition, the issue of cancer is yet to be solved because study resulted in ambivalent outcome in different cases. Link of SGLT2 inhibitors to cancer can be defined after conducting studies for long period of time involving large sample size. Moreover, hyperuricemia may contribute to the development of gout but there are many other factors e.g. obesity, sex, age, family history, diet etc. those may have strong relationship for the development of gout. Perhaps there are more other options that may effectively target gout. Besides, almost 70% uric acid is excreted into urine and the excretion of uric acid is primarily rely on the performance or function of the kidney. However, rigorous and in depth investigations are essential to support and ascertain the use of SGLT2 inhibitors in any of the above mentioned novel indications.

Conflicts of interest

No conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.obmed.2019.100099.

References

Abdul-Ghani, M., Del Prato, S., Chilton, R., et al., 2016. SGLT2 inhibitors and cardiovascular risk: lessons learned from the EMPA-REG OUTCOME study. Diabetes Care 39, 717–725. https://doi.org/10.2337/dc16-0041.

Avogaro, A., Delgado, E., Lingvay, I., 2018. When metformin is not enough: pros and cons of SGLT2 and DPP-4 inhibitors as a second line therapy. Diabetes Metab. Res. Rev. 34, e2981. https://doi.org/10.1002/dmrr.2981.

Baker, W.L., Smyth, L.R., Riche, D.M., et al., 2014. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: a systematic review and meta-analysis. J. Am. Soc. Hypertens. 8, 262–275. https://doi.org/10.1016/j.jash.2014.01.007.

Basile, J.N., 2013. The potential of sodium glucose cotransporter 2 (SGLT2) inhibitors to reduce cardiovascular risk in patients with type 2 diabetes (T2DM). J. Diabet. Complicat. 27, 280–286. https://doi.org/10.1016/j.jdiacomp.2012.12.004.

Bolinder, J., Ljunggren, Ö., Johansson, L., et al., 2014. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. Diabetes Obes. Metab. 16,

159–169. https://doi.org/10.1111/dom.12189.
Breyer, M.D., Susztak, K., 2016. The next generation of therapeutics for chronic kidney disease. Nat. Rev. Drug Discov. 15, 568. https://doi.org/10.1038/nrd.2016.67.
Cefalu, W.T., Riddle, M.C., 2015. SGLT2 inhibitors: the latest "new kids on the block"!. Diabetes Care 38, 352–354. https://doi.org/10.2337/dc14-3048.
Chao, E.C., Henry, R.R., 2010. SGLT2 inhibition—a novel strategy for diabetes treatment. Nat. Rev. Drug Discov. 9, 551. https://doi.org/10.1038/nrd3180.
Chino, Y., Samukawa, Y., Sakai, S., et al., 2014. SGLT2 inhibitor lowers serum uric acid through alteration of uric acid transport activity in renal tubule by increased glycosuria. Biopharm Drug Dispos. 35, 391–404. https://doi.org/10.1002/bdd.1909.
Davies, M.J., Trujillo, A., Vijapurkar, U., et al., 2015. Effect of canagliflozin on serum uric acid in patients with type 2 diabetes mellitus. Diabetes Obes. Metab. 17, 426–429. https://doi.org/10.1111/dom.12439.
De Jonghe, S., Proctor, J., Vinken, P., et al., 2014. Carcinogenicity in rats of the SGLT2 inhibitor canagliflozin. Chem. Biol. Interact. 224, 1–2. https://doi.org/10.1016/j.cbi.2014.09.018.
Devenny, J.J., Godonis, H.E., Harvey, S.J., et al., 2012. Weight loss induced by chronic dapagliflozin treatment is attenuated by compensatory hyperphagia in diet-induced obese (DIO) rats. Obesity 20, 1645–1652. https://doi.org/10.1038/oby.2012.59.
Diamant, M., Morsink, L.M., 2013. SGLT2 inhibitors for diabetes: turning symptoms into therapy. Lancet 382, 917–918. https://doi.org/10.1016/S0140-6736(13)60902-2.
Fadini, G.P., Avogaro, A., 2017. SGLT2 inhibitors and amputations in the US FDA adverse event reporting system. Lancet Diabetes Endocrinol. 5, 680–681. https://doi.org/10.1016/S2213-8587(17)30257-7.
Filippas-Ntekouan, S., Filippatos, T.D., Elisaf, M.S., 2018. SGLT2 inhibitors: are they safe? Postgrad. Med. 130, 72–82. https://doi.org/10.1080/00325481.2018.1394152.
Filippatos, T.D., Tsimihodimos, V., Liamis, G., et al., 2018. SGLT2 inhibitors-induced electrolyte abnormalities: an analysis of the associated mechanisms. Diabetes Metab. Syndr. 12, 59–63. https://doi.org/10.1016/j.dsx.2017.08.003.
Fitchett, D., Zinman, B., Wanner, C., et al., 2016. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. Eur. Heart J. 37, 1526–1534. https://doi.org/10.1093/eurheartj/ehv728.
Gallo, L.A., Wright, E.M., Vallon, V., 2015. Probing SGLT2 as a therapeutic target for diabetes: basic physiology and consequences. Diabetes Vasc. Dis. Res. 12, 78–89. https://doi.org/10.1177/1479164114561992.
Garcia-Ropero, A., Badimon, J.J., Santos-Gallego, C.G., 2018. The pharmacokinetics and pharmacodynamics of SGLT2 inhibitors for type 2 diabetes mellitus: the latest developments. Expert Opin. Drug Metabol. Toxicol. 14, 1287–1302. https://doi.org/10.1080/17425255.2018.1551877.
Goldenberg, R.M., Berard, L.D., Cheng, A.Y., et al., 2016. SGLT2 inhibitor–associated diabetic ketoacidosis: clinical review and recommendations for prevention and diagnosis. Clin. Ther. 38, 2654–2664. https://doi.org/10.1016/j.clinthera.2016.11.002.
Hahn, K., Ejaz, A.A., Kanbay, M., et al., 2016. Acute kidney injury from SGLT2 inhibitors: potential mechanisms. Nat. Rev. Nephrol. 12, 711. https://doi.org/10.1038/nrneph.2016.159.
Hayashizaki-Someya, Y., Kurosaki, E., Takasu, T., et al., 2015. Ipragliflozin, an SGLT2 inhibitor, exhibits a prophylactic effect on hepatic steatosis and fibrosis induced by choline-deficient l-amino acid-defined diet in rats. Eur. J. Pharmacol. 754, 19–24. https://doi.org/10.1016/j.ejphar.2015.02.009.
Hine, J., Paterson, H., Abrol, E., et al., 2015. SGLT inhibition and euglycaemic diabetic ketoacidosis. Lancet Diabetes Endocrinol. 3, 503–504. https://doi.org/10.1016/S2213-8587(15)00204-1.
Honda, Y., Imajo, K., Kato, T., et al., 2016. The selective SGLT2 inhibitor ipragliflozin has a therapeutic effect on nonalcoholic steatohepatitis in mice. PLoS One 11, e0146337. https://doi.org/10.1371/journal.pone.0146337.
Jojima, T., Tomotsune, T., Iijima, T., et al., 2016. Empagliflozin (an SGLT2 inhibitor), alone or in combination with linagliptin (a DPP-4 inhibitor), prevents steatohepatitis in a novel mouse model of non-alcoholic steatohepatitis and diabetes. Diabetol. Metab. Syndrome 8, 45. https://doi.org/10.1186/s13098-016-0169-x.
Jurczak, M.J., Lee, H.Y., Birkenfeld, A.L., et al., 2011. SGLT2 deletion improves glucose homeostasis and preserves pancreatic β-cell function. Diabetes 60, 890–898. https://doi.org/10.2337/db10-1328.
Kusminski, C.M., Bickel, P.E., Scherer, P.E., 2016. Targeting adipose tissue in the treatment of obesity-associated diabetes. Nat. Rev. Drug Discov. 15, 639. https://doi.org/10.1038/nrd.2016.75.
Lambers Heerspink, H.J., De Zeeuw, D., Wie, L., et al., 2013. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. Diabetes Obes. Metab. 15, 853–862. https://doi.org/10.1111/dom.12127.
Leiter, L.A., Forst, T., Polidori, D., et al., 2016. Effect of canagliflozin on liver function tests in patients with type 2 diabetes. Diabetes Metab. 42, 25–32. https://doi.org/10.1016/j.diabet.2015.10.003.
Liu, J., Li, L., Li, S., et al., 2017. Effects of SGLT2 inhibitors on UTIs and genital infections in type 2 diabetes mellitus: a systematic review and meta-analysis. Sci. Rep. 7, 2824. https://doi.org/10.1038/s41598-017-02733-w.
Madaan, T., Akhtar, M., Najmi, A.K., 2016. Sodium glucose CoTransporter 2 (SGLT2) inhibitors: current status and future perspective. Eur. J. Pharm. Sci. 93, 244–252. https://doi.org/10.1016/j.ejps.2016.08.025.
Majewski, C., Bakris, G.L., 2015. Blood pressure reduction: an added benefit of sodium–glucose cotransporter 2 inhibitors in patients with type 2 diabetes. Diabetes Care 38, 429–430. https://doi.org/10.2337/dc14-1596.
Maliha, G., Townsend, R.R., 2015. SGLT2 inhibitors: their potential reduction in blood pressure. J. Am. Soc. Hypertens. 9, 48–53. https://doi.org/10.1016/j.jash.2014.11.001.
Martens, P., Mathieu, C., Verbrugge, F.H., 2017. Promise of SGLT2 inhibitors in heart failure: diabetes and beyond. Curr. Treat. Options Cardiovasc. Med. 19, 23. https://doi.org/10.1007/s11936-017-0522-x.
Monami, M., Zannoni, S., Nreu, B., et al., 2017. Toe amputations with SGLT-2 inhibitors: data from randomized clinical trials. Acta Diabetol. 54, 411–413. https://doi.org/10.1007/s00592-016-0928-z.
Nadkarni, G.N., Ferrandino, R., Chang, A., et al., 2017. Acute kidney injury in patients on SGLT2 inhibitors: a propensity-matched analysis. Diabetes Care 40, 1479–1485. https://doi.org/10.2337/dc17-1011.
Neal, B., Perkovic, V., Mahaffey, K.W., et al., 2017. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N. Engl. J. Med. 377, 644–657. https://doi.org/10.1056/NEJMoa1611925.
Ogawa, W., Sakaguchi, K., 2016. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors. J. Diabetes Investig. 7, 135–138. https://doi.org/10.1111/jdi.12401.
Oliva, R.V., Bakris, G.L., 2014. Blood pressure effects of sodium–glucose co-transport 2 (SGLT2) inhibitors. J. Am. Soc. Hypertens. 8, 330–339. https://doi.org/10.1016/j.jash.2014.02.003.
Ouchi, M., Oba, K., Kaku, K., et al., 2018. Uric acid lowering in relation to HbA1c reductions with the SGLT2 inhibitor tofogliflozin. Diabetes Obes. Metab. 20, 1061–1065. https://doi.org/10.1111/dom.13170.
Packer, M., 2017. Activation and inhibition of sodium-hydrogen exchanger is a mechanism that links the pathophysiology and treatment of diabetes mellitus with that of heart failure. Circulation 136, 1548–1559. https://doi.org/10.1161/CIRCULATIONAHA.117.030418.
Peters, A.L., Buschur, E.O., Buse, J.B., et al., 2015. Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium-glucose cotransporter 2 inhibition. Diabetes Care 38, 1687–1693. https://doi.org/10.2337/dc15-0843.
Qiang, S., Nakatsu, Y., Seno, Y., et al., 2015. Treatment with the SGLT2 inhibitor luseogliflozin improves nonalcoholic steatohepatitis in a rodent model with diabetes mellitus. Diabetol. Metab. Syndrome 7, 104. https://doi.org/10.1186/s13098-015-0102-8.
Reddy, R.M., Inzucchi, S.E., 2016. SGLT2 inhibitors in the management of type 2 diabetes. Endocrine 53, 364–372. https://doi.org/10.1007/s12020-016-0943-4.
Scheen, A.J., 2016a. Effects of reducing blood pressure on cardiovascular outcomes and mortality in patients with type 2 diabetes: focus on SGLT2 inhibitors and EMPA-REG OUTCOME. Diabetes Res. Clin. Pract. 121, 204–214. https://doi.org/10.1016/j.diabres.2016.09.016.
Scheen, A.J., 2016b. SGLT2 inhibitors: benefit/risk balance. Curr. Diabetes Rep. 16, 92. https://doi.org/10.1007/s11892-016-0789-4.
Shiba, K., Tsuchiya, K., Komiya, C., et al., 2018. Canagliflozin, an SGLT2 inhibitor, attenuates the development of hepatocellular carcinoma in a mouse model of human NASH. Sci. Rep. 8, 2362. https://doi.org/10.1038/s41598-018-19658-7.
Sonesson, C., Johansson, P.A., Johnsson, E., et al., 2016. Cardiovascular effects of dapagliflozin in patients with type 2 diabetes and different risk categories: a meta-analysis. Cardiovasc. Diabetol. 15, 37. https://doi.org/10.1186/s12933-016-0356-y.
Takahara, M., Shiraiwa, T., Matsuoka, T.A., et al., 2015. Ameliorated pancreatic β cell dysfunction in type 2 diabetic patients treated with a sodium-glucose cotransporter 2 inhibitor ipragliflozin. Endocr. J. 62, 77–86. https://doi.org/10.1507/endocrj.EJ14-0335.
Tang, H., Dai, Q., Shi, W., et al., 2017. SGLT2 inhibitors and risk of cancer in type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. Diabetologia 60, 1862–1872. https://doi.org/10.1007/s00125-017-4370-8.
Taylor, S.I., Blau, J.E., Rother, K.I., 2015. Possible adverse effects of SGLT2 inhibitors on bone. Lancet Diabetes Endocrinol. 3, 8–10. https://doi.org/10.1016/S2213-8587(14)70227-X.
Townsend, R.R., Machin, I., Ren, J., et al., 2016. Reductions in mean 24-hour ambulatory blood pressure after 6-week Treatment with canagliflozin in patients with type 2 diabetes mellitus and hypertension. J. Clin. Hypertens. 18, 43–52. https://doi.org/10.1111/jch.12747.
Van Bommel, E.J., Muskiet, M.H., Tonneijck, L., et al., 2017. SGLT2 inhibition in the diabetic kidney—from mechanisms to clinical outcome. Clin. J. Am. Soc. Nephrol. 12, 700–710. https://doi.org/10.2215/CJN.06080616.
Vasapollo, P., Cione, E., Luciani, F., et al., 2018. Generalized intense pruritus during canagliflozin treatment: is it an adverse drug reaction? Curr. Drug Saf. 13, 38–40. https://doi.org/10.2174/1574886311666160405110515.
Villani, L.A., Smith, B.K., Marcinko, K., et al., 2016. The diabetes medication Canagliflozin reduces cancer cell proliferation by inhibiting mitochondrial complex-I supported respiration. Mol. Metab. 5, 1048–1056. https://doi.org/10.1016/j.molmet.2016.08.014.
Wanner, C., Inzucchi, S.E., Lachin, J.M., et al., 2016. Empagliflozin and progression of kidney disease in type 2 diabetes. N. Engl. J. Med. 375, 323–334. https://doi.org/10.1056/NEJMoa1515920.
Yabe, D., Nishikino, R., Kaneko, M., et al., 2015. Short-term impacts of sodium/glucose co-transporter 2 inhibitors in Japanese clinical practice: considerations for their appropriate use to avoid serious adverse events. Expert Opin. Drug Saf. 14, 795–800. https://doi.org/10.1517/14740338.2015.1034105.
Zanoli, L., Granata, A., Lentini, P., et al., 2015. Sodium-glucose linked transporter-2 inhibitors in chronic kidney disease. Sci. World J. 2015, 317507. https://doi.org/10.1155/2015/317507.
Zinman, B., Wanner, C., Lachin, J.M., et al., 2015. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N. Engl. J. Med. 373, 2117–2128. https://doi.org/10.1056/NEJMoa1504720.