Review Article

Sodium Glucose Co-transporter-2 Inhibitor: Benefits beyond Glycemic Control

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Abstract

Type 2 diabetes mellitus (T2DM) is a family of metabolic disorders characterized by hyperglycemia as a consequence of abnormalities in insulin secretion and insulin sensitivity. It affects hundreds of millions of people worldwide and leads to increased morbidity, compromised quality of life, higher mortality sodium glucose co-transporter 2 (SGLT2) inhibitors, a new class of oral antidiabetic drugs, have garnered considerable attention in the recent past and are considered potential first-line candidates for the management of T2DM. This review outlines the evidence-based therapeutic efficacy, safety, limitations, and advantages of SGLT2 inhibitors in the management of T2DM. SGLT2 inhibitors work by preventing the kidneys from reabsorbing glucose back into the blood, leading to increase in excretion of glucose through urine, thereby lowering hyperglycemia. Treatment with SGLT2 inhibitors improves A1C levels, reduces blood pressure and body weight, and is overall well tolerated by patients with T2DM. However, additional data on long-term cardiovascular safety are still needed. Characteristic adverse events include mild genital - urinary tract infection more commonly seen in women than in men, but serious infection is uncommon. Their use should be exercised with extra caution in patients suffering from renal impairment. Further, advancing to dual/triple combinational therapies with SGLT2 inhibitors and existing oral antidiabetic options may prove to be a breakthrough in the management of T2DM.

Keywords: Efficacy, hyperglycemia, safety, sodium glucose co-transporter Type 2 inhibitors, Type 2 diabetes mellitus

Introduction

Diabetes is one of the major noncommunicable diseases which have almost reached epidemic disease proportions. At present, including diagnosed and undiagnosed, it affects 4.2 billion people worldwide and the numbers are expected to reach 6.2 billion by 2040; the number of diabetes patients in India is estimated at 69.2 million.[1]

A large community study conducted by the Indian Council of Medical Research reported the prevalence of diabetes and prediabetes in Tamil Nadu (diabetes: 10.4%, 4.8 million; prediabetes: 8.3%, 3.9 million), Maharashtra (diabetes: 8.4%, 6 million; prediabetes: 12.8%, 9.2 million), Jharkhand (diabetes: 5.3%, 0.96 million; prediabetes: 8.1%, 1.5 million), and Chandigarh (diabetes: 13.6%, 0.12 million; prediabetes: 14.6%, 0.13 million).[2] The study revealed that diabetes has a startup age of 25–34 years in the country and decline age of 65 years, along with high prevalence in urban areas compared with rural areas in the country.

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In India, the financial burden of health care is usually borne by individuals, with the government contributing only one-third of total health expense and out-of-pocket payments representing about 58% of total health spend in 2012.[3] It has been speculated that by 2025, most diabetic people will be in 45–64 years age group in developing countries, so the income earning ability will be decreased by that age group and a greater economic burden will be posed on government funding.[4] Hence, to strengthen the Indian health-care system, government has to plan serious health-care coverage by 2022 for the management of diabetes and its complications.

Recently, in an Indian study, 368 hospitalized diabetic patients who were divided into different groups based on the type

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of complications, the cost of treatment was analyzed. The average cost of hospitalization for diabetic patients with foot complications was 19,020 INR; for patients with the presence of two complications was 17,633 INR; for patients with chronic kidney disease was 12,690 INR; for patients with cardiovascular (CV) complications was 13,135 INR; for patients with retinal complications was 13,922 INR; and for patients without any complications was 4493 INR.[5] Another Indian study with 556 diabetic patients reported median expenditure in 2005 as 8930 INR with range of 893–284,821 INR.[6]

Unmet Needs from Current Antidiabetic Agents

The standard treatment strategy for diabetes management involves pharmacotherapy along with exercise and diet restructuring with the chief aim of hyperglycemia control and reduction in other comorbid factors, especially dyslipidemia, hypertension, hypercoagulability, and obesity.[7,8]

The American Diabetes Association (ADA) recommends metformin in combination with one or more oral antidiabetic agents for routine use to help patients maintain the blood sugar levels.[9] The drugs for the management of Type 2 diabetes (T2D) include biguanides, sulfonylureas (SUs), alpha-glucosidase inhibitors, thiazolidinediones, and dipeptidyl peptidase-4 inhibitors (DPP4i). The mechanism of action of most of these drugs includes maintenance of normal glucose levels, increasing insulin release, decreasing insulin resistance, and controlling the intestinal absorption of glucose.[10,11] All these drugs are effective at the beginning, but the treatment effect declines with time and is ineffective in long term because the beta cell dysfunction progressively increases and this requires combination therapy and insulin.[12] Common side effects associated with the use of conventional oral antidiabetic drugs (OADs) include hypoglycemia, weight gain, edema, and CV adverse effects.[12-14] The sustained glycemic control over the period is not available with most of other antidiabetic agents which could be due to natural progression of disease, self-monitoring for glucose, and the administration by use of injections.[12,15] These Type 2 sodium glucose co-transporter (SGLT2) inhibitors act by inhibiting the reabsorption of glucose in kidneys, a mechanism which is independent of insulin pathway and therefore not affected by the decline in beta cell function, and are in the process of evaluation by many pharmaceutical research organizations.[11,16,17]

Role of Sodium Glucose Co-transporter-2 Inhibitors – Rationale and Mechanism of Action

The mechanism of conventional antihyperglycemic agents focuses majorly on controlling glucose levels in blood by working on the insulin secretion, insulin resistance, beta cell functions, or carbohydrate metabolism. Drugs of the class SGLT2 inhibitors have a unique mechanism of action which is independent of the beta cell function and insulin resistance. Since these drugs do not depend on beta cell function and hence can be prescribed at any stage of diabetes. Apart from the basic function of antihyperglycemia, these drugs also work on the metabolic components of diabetes including hypertension, dyslipidemia, and obesity. This makes them the preferred drug in patients with these coexisting conditions.

In healthy human beings, the kidneys maintain the glucose homeostasis by gluconeogenesis and reabsorbing glucose from glomerular filtrate in blood circulation.[18,19] The entire blood volume is filtered by kidneys about 50 times/day for an average healthy adult with daily filtration rate of 160–180 g of glucose.[20] This filtered glucose is absorbed back completely in the kidneys through its proximal tubules, thus making urine glucose free, and this is made possible by sodium-dependent transmembrane proteins' family called SGLTs.[21] The glucose reabsorption process involves two members of the SGLT family, namely, SGLT1 and SGLT2. SGLT1 is a low-capacity high-affinity transporter and is responsible for reabsorption of 10% of glucose, while SGLT2 is high-capacity low-affinity transporter and reabsorbs 90% of glucose.[22-29] However, in T2D mellitus (T2DM), due to upregulation of SGLT2 and SGLT1 co-transporter, more glucose reabsorption takes place in renal tubule of kidneys; this leads to the increase in T_{max} levels from normal level which is 350 mg/min up to 420 mg/min. This increase in T_{max} further resulted in increased renal threshold from 180 mg/dl up to 250 mg/dl.[30] The SGLT2 inhibitor agents inhibit SGLT2 in kidney and thus leading to increase in urinary glucose excretion and reduction in blood glucose. In India, currently approved SGLT2 inhibitor compounds are canagliflozin, dapagliflozin, and empagliflozin.

Efficacy Comparison of Sodium Glucose Co-transporter-2 Inhibitors with Other Antihyperglycemic Agents

Canagliflozin was the first approved molecule from USFDA and has been evaluated in a number of studies for the clinical efficacy of antihyperglycemia. A recently published meta-analysis (n = 10) of canagliflozin in T2DM patients (n = 6701) reported significant absolute reductions in hemoglobin A1c (HbA1c) levels when used as monotherapy (weighted mean difference [WMD] - 1.08%, 95% confidence interval [CI]: −1.25 to −0.90, $P < 0.00001$), as add-on treatment (WMD - 0.73%, 95% CI: −0.84 to −0.61, $P < 0.00001$), and in comparison to other antihyperglycemic agents (WMD - 0.21%, 95% CI: −0.33 to −0.08, $P = 0.001$).[31]

Dapagliflozin was the second molecule approved by FDA. In a report with results from two randomized controlled trials (RCTs) to compare dapagliflozin plus metformin, dapagliflozin alone, and metformin alone, the HbA1c reductions were −2.05 for dapagliflozin + metformin, −1.19 for dapagliflozin, and −1.35 for metformin ($P < 0.0001$) (Study 1); −1.98 for dapagliflozin + metformin, −1.45 for dapagliflozin, and −1.44

for metformin ($P < 0.0001$) (Study 2); and combination therapy was statistically superior to monotherapy in reduction of fasting plasma glucose (FPG) ($P < 0.0001$ for both studies).[32] In another 52-week trial, the T2DM patients received dapagliflozin ($n = 406$) or glipizide ($n = 408$) uptitrated over 18 weeks, the HbA1c reduction with dapagliflozin was similar to that with glipizide (−0.52%).[33]

Empagliflozin has been recently approved by FDA for antidiabetic indication. In a meta-analysis of empagliflozin, the mean changes in HbA1c were −0.62% (95% CI: −0.68 to −0.57%) for empagliflozin 10 mg and −0.66% (95% CI: −0.76 to −0.57%) for empagliflozin 25 mg.[34] In a Phase III trial, adjusted mean differences in change from baseline HbA1c at week 24 for empagliflozin 10 mg compared with placebo were −0.74% (95% CI: −0.88 to −0.59; $P < 0.0001$), for empagliflozin 25 mg were −0.85% (−0.99 to −0.71; $P < 0.0001$).[35] In an RCT, the changes from baseline in HbA1c at week 90 for empagliflozin were −0.34 to −0.63% (−3.7 to −6.9 mmol/mol).[36] Intercomparison of SGLT2 inhibitors is shown in Figure 1.

Extra-glycemic Effects of Sodium Glucose Co-transporter 2 Inhibitors

Effect on blood pressure

Hypertension is a common comorbid condition in diabetes and vice versa. Diabetes and hypertension coexist in approximately 40%–60% of patients with T2DM.[37] SGLT2 inhibitors show decline in systolic blood pressure (SBP) along with the antihyperglycemic effect. Hence, this class of drugs has the benefits of antihypertensives in addition to the basic action of antidiabetic.

Canagliflozin has been shown to reduce elevated blood pressure (BP) in number of recently published literature.[38-42]

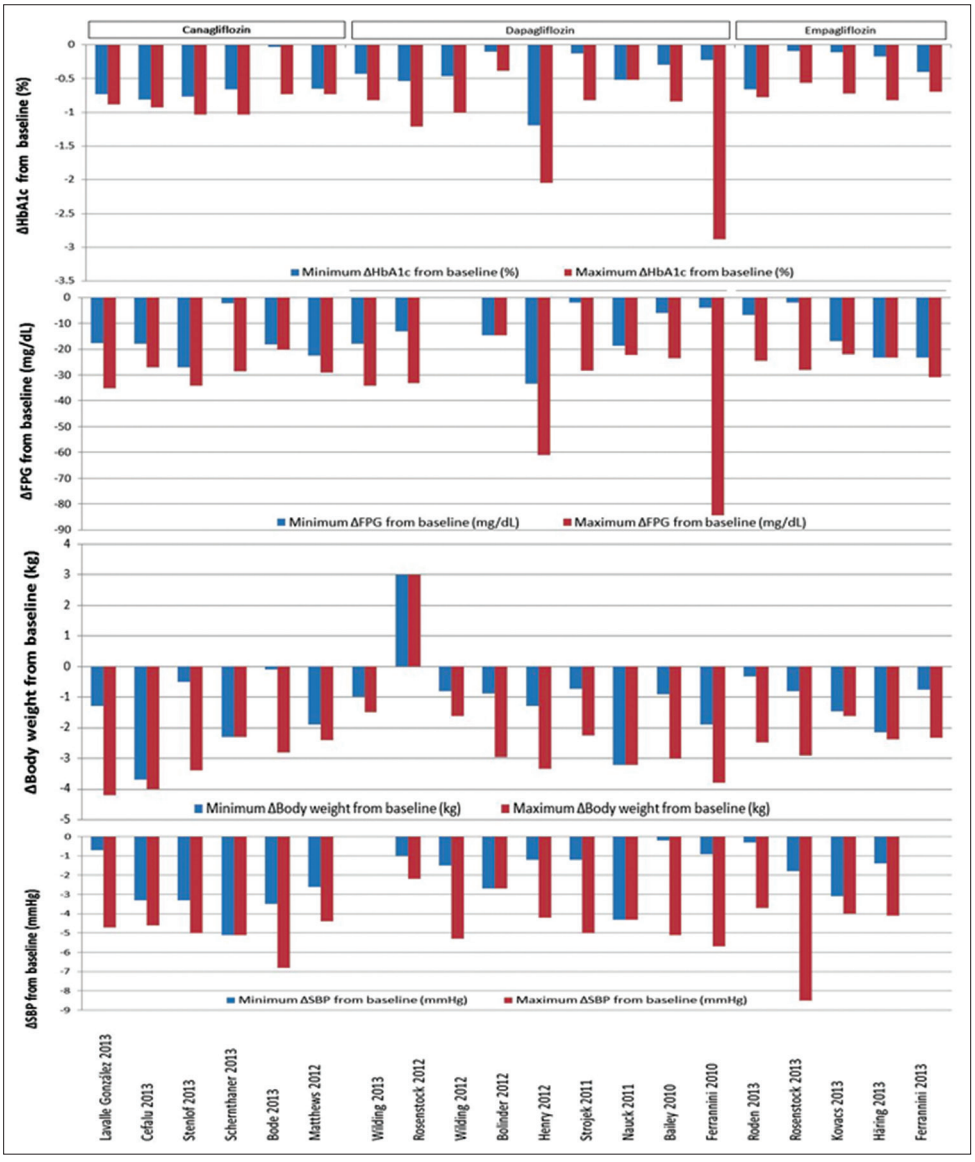

Figure 1: Sodium glucose co-transporter 2-inhibitors available and intercomparison

When evaluated in a Phase III study, canagliflozin resulted in reductions of SBP by −1.4 mmHg with 100 mg and −3.9 mmHg with 300 mg dose.[43] The antihypertensive effects of dapagliflozin were also documented in a number of studies.[44-47] In comparison to glipizide, this molecule has shown a SBP reduction by −3.9 mmHg (95% CI: −6.1, −1.7).[48] When evaluated in another RCT, the drug produced SBP reductions by −3.3 mmHg (95% CI: −6.8, +0.2) at week 12.[49] In a recent study with 252 diabetic patients, the dapagliflozin 10 mg dose reduced SBP and diastolic BP by −6.83 mmHg and −2.53 mmHg at week 1 and by −6.73 mmHg and −2.91 mmHg at week 2, respectively.[50] The third and latest molecule from SGLT2 inhibitors class, empagliflozin has shown favorable effects on the BP.[34,51] After a 12-week treatment, the drug has shown reduction in SBP by 4–5 mmHg in a clinical study.[52] Another study reported that after 24 weeks of treatment with 10 and 25 mg doses of empagliflozin, the placebo-corrected SBP reduction was 2–5 mmHg.[17]

Effect on body weight

Patients receiving SGLT2 inhibitors consistently experience weight reduction. Meta-analysis had shown that in comparison to other antidiabetic agents, SGLT2 inhibitors reduced the body weight with a mean difference of 1.8 kg (95% CI: −3.5, −0.1).[53] As per European Medicines Agency assessment report, an approximately 2–3 kg reduction in body weight was noted in the majority of Phase III dapagliflozin studies.[54] Early reduction of weight may represent fluid loss because of osmotic diuretic effect of these agents, whereas over consecutive weeks, increasing weight loss is most probably due to caloric loss as revealed by dual-energy X-ray absorptiometry. The glucose excreted in the urine as a result of SGLT2 inhibition equals to about 200–300 calories each day.[55] Further 2–3 kg weight loss has been demonstrated in a 12-week trials of dapagliflozin,[55] canagliflozin,[56] and empagliflozin as well as in a 52-week trial of dapagliflozin when used as an add on to metformin therapy.[57,58] Long-term trials of up to 2 years with dapagliflozin as add on to metformin therapy and also with glipizide demonstrate sustained weight loss.[55] Dapagliflozin has also demonstrated a significant reduction in waist circumference which would be consistent with fat mass reduction.[55] For Phase III canagliflozin studies, change in body weight was seen consistent from baseline measurements in comparison to placebo-controlled groups.[59] With empagliflozin monotherapy, the mean change in body weight after 24 weeks was lesser in comparison to mean change in body weight with empagliflozin plus metformin therapy as measured from baseline measurement (−1.9 kg for 10 mg group and −2.1 kg for 25 mg group; −2.1 kg for 10 mg group and −2.5 kg for 25 mg group, respectively).[35] Further long-term clinical trials of SGLT2 inhibitors are required to fully understand the weight loss changes and to define their stability with body composition assessments. Small increases in high-density lipoprotein-cholesterol (HDL-C) (1.8%–4.4% dapagliflozin vs. 0.4% placebo) and small reductions in triglycerides (TGs) (–2.4% to –6.2% dapagliflozin vs. 2.1% placebo) are also possibly due to the weight reduction achieved with these compounds.[60]

Effect on beta cell function

The primary pathophysiological component which contributes to hyperglycemia in T2DM is the decline in beta cell function which ultimately leads to reduction in insulin secretion and reduction in conversion of proinsulin to insulin. This decline in beta cell function contributes toward the progression of diabetes to a stage which would demand insulin regimens for the disease management. This situation arises when the beta cells are not improved with pharmacotherapy due to apoptosis of beta cell and the antihyperglycemics fail to achieve their goals. SGLT2 inhibitors have established their positive effects on beta cell function. Merovci *et al*. provided conclusive evidence that treatment with dapagliflozin improves ß-cell function in T2DM by correcting hyperglycemia since dapagliflozin primarily acts on kidneys with no direct action on ß-cell function.[61] The study showed that during the oral glucose tolerance test, dapagliflozin significantly lowered FPG levels (by 33 mg/dL), 2-h plasma glucose (by 73 mg/dL), and mean plasma glucose levels (by 60 mg/dL) which resulted in more than two-fold increase in ß-cell function.[61] Similar findings were also proved by the same group earlier in experimental studies with rodents.[62] Moreover, previous studies have also shown that a 2-week treatment with dapagliflozin also leads to improvement in insulin sensitivity along with hyperglycemia. Therefore, these studies conclude that the glucotoxic effect of hyperglycemia on ß-cell function in T2DM is reversible.[63]

Effect on lipid metabolism

The lipid metabolism is negatively impacted by diabetes and its associated comorbidities. This change in lipid metabolism further gives rise to CV disease (CVD) complications and other associated complications. Many of the antidiabetic drugs enhance this changed lipid metabolism function in body and further degrade it toward the negative end. SGLT2 inhibitors act toward improving the lipid metabolism of patients. SGLT2 inhibitor treatment is associated with small increases in low-density lipoprotein-cholesterol (LDL-C) and HDL-C. However, studies have shown that SGLT2 inhibitors significantly increased HDL-C levels with no significant change of TG and LDL-C levels.[64,65] Further, EMPA-REG OUTCOME trial[66] demonstrated small increase in both LDLC and HDL-C. Long-term data of more than 2 years have shown that increase in LDL-C with dapagliflozin, canagliflozin, and empagliflozin was ~5, 3, and 6 mg/dL, respectively. For HDL-C increase with dapagliflozin, canagliflozin, and empagliflozin was ~1, 0.6, and 3.5 mg/dL, respectively.[67-69] However, there is no change in LDL/HDL-C ratio. Further with 10 mg of dapagliflozin, percentage change in lipids from baseline at 24 weeks was shown in Figure 2 in comparison to placebo group.

Low incidence of hypoglycemia

Hypoglycemia events were generally low with SGLT2 inhibitor treatment, except for those groups who receive SU

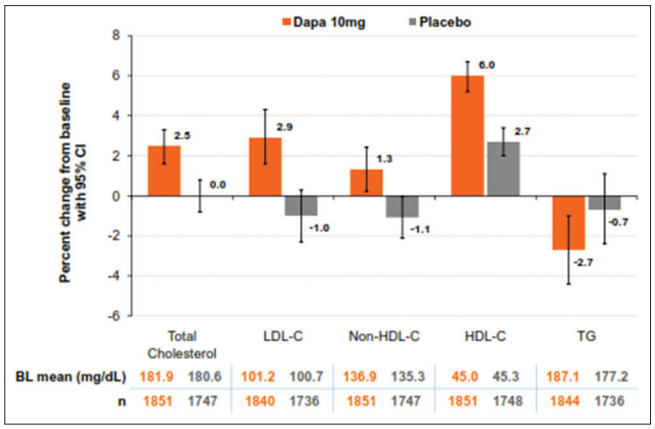

Figure 2: Change in lipids from baseline at 24 weeks

or insulin as add-on therapy. Meta-analysis of dapagliflozin and canagliflozin trials concluded that hypoglycemic risk was similar to that of other agents.[70] With dapagliflozin monotherapy, there was no major episodes of hypoglycemia but along with SU or insulin risk of hypoglycemic events were increased.[71] Similar findings were seen with canagliflozin, with a low risk of hypoglycemia when canagliflozin taken as monotherapy, and an increased incidence of hypoglycemia when canagliflozin was used in combination with insulin or SU.[72] This information suggests using lower dose of insulin or insulin secretagogue when used with both canagliflozin and dapagliflozin to reduce the risk of hypoglycemia.[53,73] Similarly with empagliflozin monotherapy, the rate of hypoglycemia was also low and was comparable to placebo.[35] Empagliflozin along with metformin and SU, incidence of definite hypoglycemia was greater for empagliflozin versus placebo, but not any of these events required assistance.[74] However, when empagliflozin was added to basal insulin, no increased risk of hypoglycemia was reported.[75]

Role in Cardiovascular Risk Reduction

Several CV safety trials have been done so far with different classes of antidiabetic agents, but this is for the first time that this class of molecule has shown CV benefit in diabetic patients with established CVD.[66,76] There are several mechanisms such as intensive glycemic benefit, weight loss, reduction of BP, fluid loss, and reduction of serum uric acid that are responsible for the CV benefit with this class of molecules. Till now, this class has shown CV benefit only with established CV T2DM patient.[66] Hence, what will be an effect in T2D patient at risk of developing CV event, some ongoing study will throw some light for this class.[77,78]

Safety Concerns for Sodium Glucose Co-transporter 2 Inhibitors

Urinary tract infections (UTIs)

It has been established that treatment with SGLT2 inhibitors leads to glycosuria along with decrease in blood glucose levels.[79] Data suggest that glycosuria is one of the major risk factors for the occurrence of UTI events.[80] Other possible confounding factors include history of recurrent UTIs, studies show that patients with a history of recurrent UTIs were experienced more UTI events during the SGLT2 inhibitors treatment.[80] Therefore, further studies or trials were required to better understand the link between the glycosuria and these infections. Small increase in incidence of UTI has been documented in patients treated with 5 or 10 mg dapagliflozin similar tends is also there with Dapagliflozin in recently published trial Declare Timi.[78,81] The rate of clinical diagnosis of UTI is generally more common in women than in men, and mostly, events were mild to moderate in intensity which usually resolved with one course of standard antimicrobial treatment.[81] There are hardly any studies which discontinue dapagliflozin treatment due to occurrence of UTI event which means that events were clinically manageable and with initial course of standard therapy, the rate of recurrence is minimal.[81]

Mycotic infections

Genital infections such as vulvovaginitis and balantis are two well-known complications of T2DM.[82] As discussed above, insufficient glycemic control results in glycosuria as well as hyperglycemia which are main culprits for increased incidence of these genital infections in diabetic population. Hyperglycemia interferes with host defense mechanism which is further linked to vulvovaginal candidiasis.[83] Glycosuria is also known to be associated with increased incidence of candidal infection.[84] Studies have shown that increased adherence of bacteria and yeast to uroepithelial and vaginal epithelial cells make the environment favorable for the growth of commensal organisms.[4] Since SGLT2 inhibitors are known to induce glycosuria, the potential relation between glycosuria and genital infections raises the question on the safety issues of SGLT2 inhibitor treatment. However, studies have demonstrated that though SGLT2 inhibitor treatment was associated with genital infections in T2DM patients, the intensity of these infections was mild to moderate and was treated with standard antimicrobial agents. The infection rarely led to the discontinuation of the dapagliflozin therapy.

Euglycemic diabetic ketoacidosis

Recently, FDA and European Medicines Evaluation Agency have raised warnings against SGLT2 inhibitors use as they may add to the risk of diabetic ketoacidosis (DKA) in both types of diabetes.[85] Increased glycosuria with SGLT2 inhibitors leads to normalization of glycemia; thus in such patient, the presence of low serum insulin level leads to enhanced lipolysis that contributes toward production of ketones which possibly contribute to the development of DKA with normoglycemic state, so-called euglycemic DKA.[86] Apart from single case reports of SGLT2 inhibitors linked DKA, 9 patients with 13 episodes of euglycemic DKA have been recently observed with normal levels of blood glucose.[85] Further from March 2013 to May 2015, FDA identified 73 cases of ketoacidosis reported from FDA Adverse Event (AE) Reporting System database reported with the use of SGLT2

inhibitors (canagliflozin [*n* = 48], dapagliflozin [*n* = 21], and empagliflozin [*n* = 4]). Forty-four cases out of 73 reported no less than one diagnostic criteria indicative of ketoacidosis, which include high anion gap metabolic acidosis, ketonemia, or reduced serum bicarbonate. In 40 cases, blood glucose levels ranged from 90 to 1366 mg/dL (median 211 mg/dL) and two cases reported mild hyperglycemia. The median time between the initiation or increase in dose of SGLT2 inhibitor to the onset of any reported ketoacidosis was 43 days (range 1 day to 1 year). Concurrent events were also reported in majority of the cases (53/73) associated with ketoacidosis, the most common were dehydration, infection, and changes in insulin dose. However, no trend demonstrates the relationship between the dose of SGLT2 inhibitor and the risk of ketoacidosis. Further, possible risk factors identified in the 73 cases for developing ketoacidosis due to SGLT2 inhibitor includes infection, low carbohydrate diet or an overall reduction of caloric intake, reduction in dose or discontinuation of exogenous insulin, discontinuation of an oral insulin secretagogue, and alcohol use.[87]

Bone mass density reduction

Both Type 1 diabetes and T2D are known to have impact on skeletal health of patients, the mechanism by which these two conditions impact on bone structures may be different.[88] Patients with Type 1 diabetes exhibit lower bone mineral density, whereas patients with T2D exhibit higher bone mineral density than nondiabetics.[89] Nevertheless, studies have shown that these patients are at higher risk of osteoporotic fracture[90] because of additional factors that alter bone quality and may add to the greater fracture risk, especially in T2D.[91] Various factors that add on to the higher risk of fractures with diabetes include increased number of risk of falls,[92] faster bone density loss,[93] metabolic changes,[94] oxidative stress,[95] and direct effect of antihyperglycemic medications. SGLT2 inhibitors which were approved for the treatment of T2D have limited data on effect of bony structure. Studies have demonstrated that dapagliflozin did not mark any significant change in bone mineral density both in men and women (post menopause) with T2D.[96] However, a recent study has also shown that large section of T2D patients of moderate renal failure (estimated glomerular filtration rate (eGFR) – 30–60 ml/min per 1.73 m^2) experienced fractures while on dapagliflozin (13 fractures in 168 patients) versus placebo (0 fracture in 84 patients) in 104 weeks. Currently in India dapagliflozin is licensed to used up to eGFR 45 ml/min per 1.73 m^2 and above.[50,97] Further, pooled analyses of clinical trials have observed more frequency of upper limb fractures with canagliflozin use as compared with placebo.[98] During early course of therapy, orthostatic hypotension and dehydration were linked with SGLT2 inhibitors, which possibly resulted in increase in falls in elderly patients.[99] However, long-term effect of SGLT2 inhibitors on skeletal structure still needs further assessment.[100]

Hypovolemia

In Phase III studies of SGLT2 inhibitors, small increase in Hb and hematocrit was constantly seen. Small reduction in fluid volume, approximately 400 ml of water loss, was reported due to osmotic diuresis by SGLT2 inhibitors.[30] In addition to this, small increase in reticulocyte count, erythropoietin, and red cell mass was also reported in a 12-week study with dapagliflozin,[49] suggesting that changes in hematopoiesis due to SGLT2 inhibitors may contribute to changes in Hb and hematocrit.

Electrolyte imbalance

Dapagliflozin does not cause any change in mean concentration of serum sodium, potassium, bicarbonate, calcium, or chloride ions at week 24 and up to 102 weeks as seen from baseline levels. However, there was small change seen in the levels of mean serum inorganic phosphorus levels from baseline measure.[68] Use of SGLT2 inhibitor is associated with decreases in levels of serum uric acid.[101] Hyperuricemia is known to be associated with an increased risk of gout, kidney stones, and CVD.

Future of Sodium Glucose Co-transporter 2 Inhibitors

As the pathogenesis of T2DM is multifaceted and involves several metabolic defects, the use of combination therapies with agents having different mechanisms of action has the potential to cause additional benefits.[11] In addition, combination therapies may possess the potential to counter the undesirable effects produced by the individual agents.

Combination of sodium glucose co-transporter 2 inhibitors and gliptins

In T2DM, many pathophysiological defects cannot be corrected by any of single group of antidiabetic agent. Therefore, sometimes, combination of antidiabetic agents is required to manage the pathophysiological condition over time. A number of studies found combination of SGLT2 inhibitors plus DPP4i to be an effective approach to treat hyperglycemia in T2DM. Recently, studies have shown that glycosuria caused by SGLT2 inhibitors is associated with an increase in the rate of hepatic endogenous glucose production (EGP) which may compensate its glucose lowering potential by ~50%.[63,102] While SGLT2 inhibitors have been associated with increase in glucagon, decrease in insulin, and increase in EGP, DPP4i acts exactly opposite to SGLT2 inhibitors; it lowers glucagon, increases insulin, and lowers EGP. DPP4i is an OAD agent that has no effect on weight, bone-lipid-friendly and has well-known cardiac safety with minimal hypoglycemic potential. Further, combination therapy of SGLT2 inhibitors and DPP4i reduced HbA1c significantly better than the either therapy alone and also without inducing further hypoglycemia. In addition, significantly higher fraction of patients attained target HbA1c <7% with combination therapy as compared to either therapy alone. Although weight loss was also significant with combination therapy compared to DPP4i, no significant difference was noted versus SGLT2 inhibitors therapy. In case of BP measurement, no significant difference was noted

compared to SGLT2 inhibitors. Furthermore, few studies also reported decreased rate of genitourinary infections with combination therapy as compared to SGLT2 inhibitors alone. Therefore, combination of SGLT2 inhibitors plus DPP4i, with or without background metformin therapy, is a safe and effective option to treat T2DM. Besides, numerous studies with DPP4i and SGLT2 inhibitors are also presently undergoing, which can further explicate our understanding of combining incretin-based therapies to SGLT2 inhibitors.

Current Clinical Practice Recommendations

Considering all risks and benefits of this class of agents, one of the most of the important guidelines such as ADA has placed this class as one of the 1st line agent as an add on to metformin along with other recommended antidiabetic agents.[103] Another important guideline, American Association of Clinical Endocrinology has placed SGLT2 inhibitor after metformin but ahead of all other oral antidiabetic agents in T2D management algorithm within 3 years of launching of this class globally.[4]

Conclusion

The introduction of SGLT2 inhibitors has set an example in diabetes management. SGLT2 inhibitors are the class of drugs which act with a mechanism different from that of traditional antidiabetics. Glycosuria, previously considered a symptom of poor glycemic control, is nowadays being used to lower blood glucose levels. Increased glycosuria with use of SGLT2 inhibitors improves glycemia and results in caloric loss and modest weight loss, small decline in BP, a low occurrence of hypoglycemia and improved beta cell functions in diabetic patients. Thus, SGLT2 inhibitor acts like a polypill. Further weight loss is a unique and important characteristic of these compounds and by the end of the treatment period, weight loss up to 3 kg can be achieved by SGLT2 inhibitors. An additional observation with SGLT2 inhibitors is the diuretic effect. Urinary losses include mainly glucose and very small amount of sodium but that will not cause any electrolyte imbalance. This surely provides the root for the antihypertensive effect seen with SGLT2 inhibitors and is most likely accountable for the good CV profile reported for this class. Studies have shown the CV benefits with SGLT2 inhibitors in CV benefit trials, but still this will require further authentication with long-term trials. SGLT2 inhibitors were found to be useful antihyperglycemic drugs, either alone or in combination with other oral agents and insulin, not associated with hypoglycemia. The SGLT2 inhibitors are generally well tolerated. However, these drugs had some concerns regarding the increase in number, serious side effects such as acute kidney injury and euglycemic DKA as reported in USFDA adverse effect reporting system.[104,105] Genital (mycotic) tract infections is one of the most common AE seen with these drugs. Usually not severe and easily treated, they should not be a reason for treatment discontinuation. Hence, considering all these benefits of this class, which is beyond glycemic control, this class of antidiabetic agent is becoming popular in day-to-day clinical practice as monotherapy or add on to other antidiabetic agents.

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Conflicts of interest

There are no conflicts of interest.

References

1. Anderson JH Jr., Brunelle RL, Koivisto VA, Trautmann ME, Vignati L, DiMarchi R. Improved mealtime treatment of diabetes mellitus using an insulin analogue. Multicenter Insulin Lispro Study Group. Clin Ther 1997;19:62-72.
2. Anjana RM, Pradeepa R, Deepa M, Datta M, Sudha V, Unnikrishnan R, *et al.* Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: Phase I results of the Indian Council of Medical Research-INdia DIABetes (ICMR-INDIAB) study. Diabetologia 2011;54:3022-7.
3. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: A pooled analysis of 751 population-based studies with 4.4 million participants. Lancet 2016;387:1513-30.
4. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, *et al.* Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm-2016 executive summary. Endocr Pract 2016;22:84-113.
5. Kumpatla S, Kothandan H, Tharkar S, Viswanathan V. The costs of treating long-term diabetic complications in a developing country: A study from India. J Assoc Physicians India 2013;61:102-9.
6. Ramachandran A, Ramachandran S, Snehalatha C, Augustine C, Murugesan N, Viswanathan V, *et al.* Increasing expenditure on health care incurred by diabetic subjects in a developing country: A study from India. Diabetes Care 2007;30:252-6.
7. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, *et al.* Medical management of hyperglycaemia in type 2 diabetes mellitus: A consensus algorithm for the initiation and adjustment of therapy: A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2009;52:17-30.
8. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, *et al.* Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. BMJ 2000;321:405-12.
9. American Diabetes Association 8. Pharmacologic approaches to glycemic treatment. Diabetes Care 2017;40 Suppl 1:S64-74.
10. Bell DS. Type 2 diabetes mellitus: What is the optimal treatment regimen? Am J Med 2004;116 Suppl 5A:23S-9S.
11. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, *et al.* Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2006;29:1963-72.
12. Bhartia M, Tahrani AA, Barnett AH. SGLT-2 inhibitors in development for type 2 diabetes treatment. Rev Diabet Stud 2011;8:348-54.
13. Mitchell BD, Vietri J, Zagar A, Curtis B, Reaney M. Hypoglycaemic events in patients with type 2 diabetes in the United Kingdom: Associations with patient-reported outcomes and self-reported HbA1c. BMC Endocr Disord 2013;13:59.
14. Aronson R. The role of comfort and discomfort in insulin therapy. Diabetes Technol Ther 2012;14:741-7.
15. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes

mellitus: Progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA 1999;281:2005-12.
16. Jabbour SA, Goldstein BJ. Sodium glucose co-transporter 2 inhibitors: Blocking renal tubular reabsorption of glucose to improve glycaemic control in patients with diabetes. Int J Clin Pract 2008;62:1279-84.
17. Bays H. Sodium Glucose Co-transporter Type 2 (SGLT2) inhibitors: Targeting the kidney to improve glycemic control in diabetes mellitus. Diabetes Ther 2013;4:195-220.
18. Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: Therapeutic implications. Diabet Med 2010;27:136-42.
19. Mather A, Pollock C. Glucose handling by the kidney. Kidney Int Suppl 2011;79:S1-6.
20. Abdul-Ghani MA, DeFronzo RA, Norton L. Novel hypothesis to explain why SGLT2 inhibitors inhibit only 30-50% of filtered glucose load in humans. Diabetes 2013;62:3324-8.
21. Tahrani AA, Barnett AH, Bailey CJ. SGLT inhibitors in management of diabetes. Lancet Diabetes Endocrinol 2013;1:140-51.
22. Wright EM, Loo DD, Hirayama BA. Biology of human sodium glucose transporters. Physiol Rev 2011;91:733-94.
23. Kanai Y, Lee WS, You G, Brown D, Hediger MA. The human kidney low affinity Na+/glucose cotransporter SGLT2. Delineation of the major renal reabsorptive mechanism for D-glucose. J Clin Invest 1994;93:397-404.
24. Vallon V, Platt KA, Cunard R, Schroth J, Whaley J, Thomson SC, *et al.* SGLT2 mediates glucose reabsorption in the early proximal tubule. J Am Soc Nephrol 2011;22:104-12.
25. Wright EM. Renal Na(+)-glucose cotransporters. Am J Physiol Renal Physiol 2001;280:F10-8.
26. You G, Lee WS, Barros EJ, Kanai Y, Huo TL, Khawaja S, *et al.* Molecular characteristics of Na(+)-coupled glucose transporters in adult and embryonic rat kidney. J Biol Chem 1995;270:29365-71.
27. Tahrani AA, Barnett AH. Dapagliflozin: A sodium glucose cotransporter 2 inhibitor in development for type 2 diabetes. Diabetes Ther 2010;1:45-56.
28. Gerich JE, Bastien A. Development of the sodium-glucose co-transporter 2 inhibitor dapagliflozin for the treatment of patients with type 2 diabetes mellitus. Expert Rev Clin Pharmacol 2011;4:669-83.
29. Abdul-Ghani MA, DeFronzo RA. Inhibition of renal glucose reabsorption: A novel strategy for achieving glucose control in type 2 diabetes mellitus. Endocr Pract 2008;14:782-90.
30. Rajeev SP, Cuthbertson DJ, Wilding JP. Energy balance and metabolic changes with sodium-glucose co-transporter 2 inhibition. Diabetes Obes Metab 2016;18:125-34.
31. Yang XP, Lai D, Zhong XY, Shen HP, Huang YL. Efficacy and safety of canagliflozin in subjects with type 2 diabetes: Systematic review and meta-analysis. Eur J Clin Pharmacol 2014;70:1149-58.
32. Henry RR, Murray AV, Marmolejo MH, Hennicken D, Ptaszynska A, List JF. Dapagliflozin, metformin XR, or both: Initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. Int J Clin Pract 2012;66:446-56.
33. Nauck M, del Prato S, Meier JJ, Durán-García S, Rohwedder K, Elze M, *et al.* Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin. Dtsch Med Wochenschr 2013;138 Suppl 1:S6-15.
34. Liakos A, Karagiannis T, Athanasiadou E, Sarigianni M, Mainou M, Papatheodorou K, *et al.* Efficacy and safety of empagliflozin for type 2 diabetes: A systematic review and meta-analysis. Diabetes Obes Metab 2014;16:984-93.
35. Roden M, Weng J, Eilbracht J, Delafont B, Kim G, Woerle HJ, *et al.* Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol 2013;1:208-19.
36. Ferrannini E, Berk A, Hantel S, Pinnetti S, Hach T, Woerle HJ, *et al.* Long-term safety and efficacy of empagliflozin, sitagliptin, and metformin: An active-controlled, parallel-group, randomized, 78-week open-label extension study in patients with type 2 diabetes. Diabetes Care 2013;36:4015-21.
37. Jagadesan S, Harish R, Miranda P, Unnikrishnan R, Anjana RM, Mohan V. Prevalence of overweight and obesity among school children and adolescents in Chennai. Indian Pediatr 2014;51:544-9.
38. Yale JF, Bakris G, Cariou B, Nieto J, David-Neto E, Yue D, *et al.* Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes mellitus and chronic kidney disease. Diabetes Obes Metab 2014;16:1016-27.
39. Sha S, Polidori D, Heise T, Natarajan J, Farrell K, Wang SS, *et al.* Effect of the sodium glucose co-transporter 2 inhibitor canagliflozin on plasma volume in patients with type 2 diabetes mellitus. Diabetes Obes Metab 2014;16:1087-95.
40. Sinclair A, Bode B, Harris S, Vijapurkar U, Mayer C, Fung A, *et al.* Efficacy and safety of canagliflozin compared with placebo in older patients with type 2 diabetes mellitus: A pooled analysis of clinical studies. BMC Endocr Disord 2014;14:37.
41. Ji L, Han P, Liu Y, Yang G, Dieu Van NK, Vijapurkar U, *et al.* Canagliflozin in Asian patients with type 2 diabetes on metformin alone or metformin in combination with sulphonylurea. Diabetes Obes Metab 2015;17:23-31.
42. Forst T, Guthrie R, Goldenberg R, Yee J, Vijapurkar U, Meininger G, *et al.* Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes on background metformin and pioglitazone. Diabetes Obes Metab 2014;16:467-77.
43. Stenlöf K, Cefalu WT, Kim KA, Jodar E, Alba M, Edwards R, *et al.* Long-term efficacy and safety of canagliflozin monotherapy in patients with type 2 diabetes inadequately controlled with diet and exercise: Findings from the 52-week CANTATA-M study. Curr Med Res Opin 2014;30:163-75.
44. Strojek K, Yoon KH, Hruba V, Sugg J, Langkilde AM, Parikh S. Dapagliflozin added to glimepiride in patients with type 2 diabetes mellitus sustains glycemic control and weight loss over 48 weeks: A randomized, double-blind, parallel-group, placebo-controlled trial. Diabetes Ther 2014;5:267-83.
45. Paisley AN, Yadav R, Younis N, Rao-Balakrishna P, Soran H. Dapagliflozin: A review on efficacy, clinical effectiveness and safety. Expert Opin Investig Drugs 2013;22:131-40.
46. Whaley JM, Tirmenstein M, Reilly TP, Poucher SM, Saye J, Parikh S, *et al.* Targeting the kidney and glucose excretion with dapagliflozin: Preclinical and clinical evidence for SGLT2 inhibition as a new option for treatment of type 2 diabetes mellitus. Diabetes Metab Syndr Obes 2012;5:135-48.
47. Katsiki N, Papanas N, Mikhailidis DP. Dapagliflozin: More than just another oral glucose-lowering agent? Expert Opin Investig Drugs 2010;19:1581-9.
48. Nauck MA, Del Prato S, Durán-García S, Rohwedder K, Langkilde AM, Sugg J, *et al.* Durability of glycaemic efficacy over 2 years with dapagliflozin versus glipizide as add-on therapies in patients whose type 2 diabetes mellitus is inadequately controlled with metformin. Diabetes Obes Metab 2014;16:1111-20.
49. Lambers Heerspink HJ, de Zeeuw D, Wie L, Leslie B, List J. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. Diabetes Obes Metab 2013;15:853-62.
50. Kohan DE, Fioretto P, Tang W, List JF. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. Kidney Int 2014;85:962-71.
51. Häring HU, Merker L, Seewaldt-Becker E, Weimer M, Meinicke T, Broedl UC, *et al.* Empagliflozin as add-on to metformin in patients with type 2 diabetes: A 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care 2014;37:1650-9.
52. Neumiller JJ. Empagliflozin: A new sodium-glucose co-transporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes. Drugs Context 2014;3:212262.
53. Bolinder J, Ljunggren Ö, Johansson L, Wilding J, Langkilde AM, Sjöström CD, *et al.* 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 2014;16:159-69.
54. Smyth S, Heron A. Diabetes and obesity: The twin epidemics. Nat Med 2006;12:75-80.

55. List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. Diabetes Care 2009;32:650-7.
56. Rosenstock J, Arbit D, Usiskin K, Capuano G, Canovatchel W. Canagliflozin, an inhibitor ofsodium glucose co-transporter 2(SGLT2), improves glycemic controland lowers body weight in subjectswith type 2 diabetes (T2D) onmetformin (abstract 77-OR). Diabetes 2010;59 Suppl 1:A21.
57. Ferrannini E, Muscelli E, Frascerra S, *et al*. Metabolic response to sodium-glucose co-transporter 2 inhibition in type-2 diabetic patients. J Clin Invest. 2014;124:499–508.
58. Nauck MA, Prato SD, Meier JJ, Durán-García S, Rohwedder K, Elze M, *et al.* Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial; Diabetes Care 2011;34:2015-22.
59. Hsia DS, Grove O, Cefalu WT. An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus. Curr Opin Endocrinol Diabetes Obes 2017;24:73-79.
60. Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: A randomised, double-blind, placebo-controlled trial. Lancet 2010;375:2223-33.
61. Merovci A, Mari A, Solis C, Xiong J, Daniele G, Chavez-Velazquez A, *et al.* Dapagliflozin lowers plasma glucose concentration and improves ß-cell function. J Clin Endocrinol Metab 2015;100:1927-32.
62. Rossetti L, Shulman GI, Zawalich W, DeFronzo RA. Effect of chronic hyperglycemia on *in vivo* insulin secretion in partially pancreatectomized rats. J Clin Invest 1987;80:1037-44.
63. Merovci A, Solis-Herrera C, Daniele G, Eldor R, Fiorentino TV, Tripathy D, *et al.* Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. J Clin Invest 2014;124:509-14.
64. Matthaei S, Bowering K, Rohwedder K, Sugg J, Parikh S, Johnsson E; Study Group. Durability and tolerability of dapagliflozin over 52 weeks as add-on to metformin and sulphonylurea in type 2 diabetes. Diabetes Obes Metab 2015;17:1075-84.
65. Monami M, Nardini C, Mannucci E. Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes: A meta-analysis of randomized clinical trials. Diabetes Obes Metab 2014;16:457-66.
66. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, *et al.* Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.
67. Tanizawa Y, Kaku K, Araki E, Tobe K, Terauchi Y, Utsunomiya K, *et al.* Long-term safety and efficacy of tofogliflozin, a selective inhibitor of sodium-glucose cotransporter 2, as monotherapy or in combination with other oral antidiabetic agents in Japanese patients with type 2 diabetes mellitus: Multicenter, open-label, randomized controlled trials. Expert Opin Pharmacother 2014;15:749-66.
68. Poole RM, Dungo RT. Ipragliflozin: First global approval. Drugs 2014;74:611-7.
69. Syed SH, Gosavi S, Shami W, Bustamante M, Farah Z, Teleb M, *et al.* A review of sodium glucose co-transporter 2 inhibitors canagliflozin, dapagliflozin and empagliflozin. Cardiovasc Hematol Agents Med Chem 2015;13:105-12.
70. Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, *et al.* Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: A systematic review and meta-analysis. Ann Intern Med 2013;159:262-74.
71. Wilding JP, Woo V, Soler NG, Pahor A, Sugg J, Rohwedder K, *et al.* Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: A randomized trial. Ann Intern Med 2012;156:405-15.
72. Wilding JP, Charpentier G, Hollander P, González-Gálvez G, Mathieu C, Vercruysse F, *et al.* Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea: A randomised trial. Int J Clin Pract 2013;67:1267-82.
73. Abstracts of the th EASD (European Association for the Study of Diabetes) Annual Meeting. September 23-27, 2013. Barcelona, Spain. Diabetologia 2013;56 Suppl 1:1-566.
74. Häring HU, Merker L, Seewaldt-Becker E, Weimer M, Meinicke T, Woerle HJ, *et al.* Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: A 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care 2013;36:3396-404.
75. Rosenstock J, Jelaska A, Zeller C, Kim G, Broedl UC, Woerle HJ. Impact of empagliflozin added on to basal insulin in type 2 diabetes inadequately controlled on basal insulin: A 78-week randomized, double-blind, placebo-controlled trial; Diabetes Obes Metab. 2015;17:936-48.
76. Kumar R, Kerins DM, Walther T. Cardiovascular safety of anti-diabetic drugs. Eur Heart J Cardiovasc Pharmacother 2016;2:32-43.
77. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, *et al.* Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017.
78. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, *et al.* Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2018.
79. Johnsson KM, Ptaszynska A, Schmitz B, Sugg J, Parikh SJ, List JF. Vulvovaginitis and balanitis in patients with diabetes treated with dapagliflozin. J Diabetes Complications 2013;27:479-84.
80. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: A randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care 2010;33:2217-24.
81. Johnsson KM, Ptaszynska A, Schmitz B, Sugg J, Parikh SJ, List JF. Urinary tract infections in patients with diabetes treated with dapagliflozin. J Diabetes Complications 2013;27:473-8.
82. Goswami R, Dadhwal V, Tejaswi S, Datta K, Paul A, Haricharan RN, *et al.* Species-specific prevalence of vaginal candidiasis among patients with diabetes mellitus and its relation to their glycaemic status. J Infect 2000;41:162-6.
83. Rayfield EJ, Ault MJ, Keusch GT, Brothers MJ, Nechemias C, Smith H. Infection and diabetes: The case for glucose control. Am J Med 1982;72:439-50.
84. Donders GG. Lower genital tract infections in diabetic women. Curr Infect Dis Rep 2002;4:536-9.
85. Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic diabetic ketoacidosis: A potential complication of treatment with sodium-glucose cotransporter 2 inhibition. Diabetes Care 2015;38:1687-93.
86. Taylor SI, Blau JE, Rother KI. SGLT2 Inhibitors may predispose to ketoacidosis. J Clin Endocrinol Metab 2015;100:2849-52.
87. Raz I, Riddle MC, Rosenstock J, Buse JB, Inzucchi SE, Home PD, *et al.* Personalized management of hyperglycemia in type 2 diabetes: Reflections from a Diabetes Care Editors' Expert Forum. Diabetes Care 2013;36:1779-88.
88. Hamann C, Kirschner S, Günther KP, Hofbauer LC. Bone, sweet bone – Osteoporotic fractures in diabetes mellitus. Nat Rev Endocrinol 2012;8:297-305.
89. Vestergaard P, Rejnmark L, Mosekilde L. Relative fracture risk in patients with diabetes mellitus, and the impact of insulin and oral antidiabetic medication on relative fracture risk. Diabetologia 2005;48:1292-9.
90. Giangregorio LM, Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, *et al.* FRAX underestimates fracture risk in patients with diabetes. J Bone Miner Res 2012;27:301-8.
91. Leslie WD, Rubin MR, Schwartz AV, Kanis JA. Type 2 diabetes and bone. J Bone Miner Res 2012;27:2231-7.
92. Schwartz AV, Hillier TA, Sellmeyer DE, Resnick HE, Gregg E, Ensrud KE, *et al.* Older women with diabetes have a higher risk of falls: A prospective study. Diabetes Care 2002;25:1749-54.
93. Schwartz AV, Ewing SK, Porzig AM, McCulloch CE, Resnick HE, Hillier TA, *et al.* Diabetes and change in bone mineral density at the hip, calcaneus, spine, and radius in older women. Front Endocrinol (Lausanne) 2013;4:62.
94. de Paula FJ, Horowitz MC, Rosen CJ. Novel insights into the relationship between diabetes and osteoporosis. Diabetes Metab Res Rev 2010;26:622-30.
95. Hamada Y, Fujii H, Fukagawa M. Role of oxidative stress in diabetic bone disorder. Bone 2009;45 Suppl 1:S35-8.
96. Ljunggren Ö, Bolinder J, Johansson L, Wilding J, Langkilde AM, Sjöström CD, *et al.* Dapagliflozin has no effect on markers of bone formation and resorption or bone mineral density in patients with

inadequately controlled type 2 diabetes mellitus on metformin. Diabetes Obes Metab 2012;14:990-9.
97. Forxiga India Specific Prescription Information, Version 6; May, 2016.
98. Sonesson C, Johansson PA, Johnsson E, Gause-Nilsson I. Cardiovascular effects of dapagliflozin in patients with type 2 diabetes and different risk categories: A meta-analysis. Cardiovasc Diabetol 2016;15:37.
99. Scheen AJ. Pharmacodynamics, efficacy and safety of sodium-glucose co-transporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. Drugs 2015;75:33-59.
100. Taylor SI, Blau JE, Rother KI. Possible adverse effects of SGLT2 inhibitors on bone. Lancet Diabetes Endocrinol 2015;3:8-10.
101. Gilbert RE. Sodium-glucose linked transporter-2 inhibitors: Potential for renoprotection beyond blood glucose lowering? Kidney Int 2014;86:693-700.
102. Ferrannini E, Muscelli E, Frascerra S, Baldi S, Mari A, Heise T, *et al.* Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. J Clin Invest 2014;124:499-508.
103. American Diabetes Association. Pharmacologic approaches to glycemic treatment: Standards of medical care in diabetes-2018. Diabetes Care 2018;41:S73-85.
104. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA Strengthens Kidney Warnings for Diabetes Medicines Canagliflozin (Invokana, Invokamet) and Dapagliflozin (Farxiga, Xigduo XR); 2016. Available from: https://www.fda.gov/Drugs/DrugSafety/ucm505860.htm. [Last accessed on 2018 Nov 30].
105. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA warns that SGLT2 Inhibitors for Diabetes May Result in a Serious Condition of Too Much Acid in the Blood. U.S. Food and Drug Administration; 2015. Available from: https://www.fda.gov/downloads/Drugs/DrugSafety/UCM446954.pdf [Last accessed on 2018 Nov 30].