

Sodium-glucose cotransporter 2 inhibitors with insulin in type 2 diabetes: Clinical perspectives

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ABSTRACT

The treatment of type 2 diabetes is a challenging problem. Most subjects with type 2 diabetes have progression of beta cell failure necessitating the addition of multiple antidiabetic agents and eventually use of insulin. Intensification of insulin leads to weight gain and increased risk of hypoglycemia. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a class of antihyperglycemic agents which act by blocking the SGLT2 in the proximal tubule of the kidney. They have potential benefits in terms of weight loss and reduction of blood pressure in addition to improvements in glycemic control. Further, one of the SGLT2 inhibitors, empagliflozin has proven benefits in reducing adverse cardiovascular (CV) outcomes in a CV outcome trial. Adding SGLT2 inhibitors to insulin in subjects with type 2 diabetes produced favorable effects on glycemic control without the weight gain and hypoglycemic risks associated with insulin therapy. The general risks of increased genital mycotic infections, urinary tract infections, volume, and osmosis-related adverse effects in these subjects were similar to the pooled data of individual SGLT2 inhibitors. There are subsets of subjects with type 2 diabetes who may have insulin deficiency, beta cell autoimmunity, or is prone to diabetic ketoacidosis. In these subjects, SGLT2 inhibitors should be used with caution to prevent the rare risks of ketoacidosis.

Key words: Canagliflozin, dapagliflozin, empagliflozin, sodium glucose cotransporter 2, type 2 diabetes

INTRODUCTION

Diabetes and its associated complications account for significant healthcare costs in both developing and developed countries.^[1-3] The control of hyperglycemia forms the cornerstone in managing diabetes. United Kingdom Prospective Diabetes Study (UKPDS) has shown that improving blood sugars in subjects with type 2 diabetes early in the course of disease can result in a reduction in onset of retinopathy, microalbuminuria, and neuropathy.^[4] Follow-up of the subjects in UKPDS

after 10 years have shown a distinct improvement in outcomes such as mortality, microvascular disease, and macrovascular disease in subjects who were intensively controlled.^[5] Various classes of oral antidiabetic agents, insulin, and glucagon-like peptide 1 (GLP-1) agonists form the armamentarium against hyperglycemia. Despite the availability of these agents, the overall control of hyperglycemia remains suboptimal in both developed and developing countries.^[6,7]

Sodium-glucose cotransporter 2 (SGLT2) inhibitors form a new class of agents that act on the kidney by competitively blocking the SGLT2 channels. These agents are approved by the Food and Drug Administration (FDA) to be used as monotherapy or in combination with metformin, sulfonylurea (SU), pioglitazone, or insulin. The American

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Diabetes Association practice guidelines have added SGLT2 inhibitors as the first add-on to metformin alongside other drugs such as SU, dipeptyl peptidase 4 (DPP4) inhibitors, thiazolidinedione, and basal insulin.^[8] SGLT2 inhibitors also find a place as a second add-on drug after two of the other drugs are used.^[8] As more drugs are added, the complexity of diabetes regimes also increases.

Most patients with type 2 diabetes have progressive worsening of beta cell function that necessitates the addition of insulin as the duration of disease increases.^[9] The UKPDS reported that over a 6-year period, ~53% of patients who were randomized to receive sulfonylureas needed additional insulin therapy.^[10] Once insulin is introduced, there are limited recommendations on how the oral diabetes agents be used. Studies have shown that insulin in combination with oral antidiabetic medications such as SU, metformin, and pioglitazone leads to reduced insulin dosage.^[11] Metformin may counteract the increased weight gain associated with insulin when used in combination.^[12] It is recommended that the SU be discontinued when the basal insulin doses increase and when prandial insulin is started.^[13] SUs can cause weight gain and increase the risk of hypoglycemia when used in association with insulin.^[11,14] The combination of thiazolidinedione with insulin is associated with weight gain, edema, and increased risk of congestive heart failure.^[14,15] Incretin-based therapies, GLP-1 receptor agonists, and DPP4 inhibitors can be combined with insulin with favorable effects on glycemic control, weight loss, and insulin dose.^[16] SGLT2 blockers have favorable properties, which make it a near-ideal agent for using with insulin: oral administration, substantial hemoglobin A1c (HbA1c) lowering, weight loss, and reduction in systolic blood pressure. Since EMPA-REG OUTCOME, the cardiovascular (CV) outcome trial of empagliflozin proved superiority over standard treatment in subjects with high CV risk, the use of this class of drugs in high CV risk subjects will be an area of interest.^[17] This review focus of the use of insulin along with SGLT2 inhibitors in subjects with type 2 diabetes.

SEARCH STRATEGY

A PubMed search was conducted using the search terms SGLT2 blockers [title], canagliflozin [title], dapagliflozin [title], empagliflozin [title] to identify the published studies on SGLT2 blockers in type 2 diabetes. In addition, these references were supplemented by publications identified from the similar search option in PubMed, bibliographies of selected articles from the PubMed search including review articles and known references. These articles were scrutinized and the publications considered relevant to the topic were included

in the review. Abstracts presented in conferences were searched from Google Scholar. None of these were included in the review as the data were seemed to be overlapping with published studies. Studies <3 months duration and those in languages other than English were not used in the review.

SODIUM GLUCOSE COTRANSPORTERS

SGLT2 is a high-capacity and low-affinity glucose transporter that is expressed in the luminal membranes of the proximal renal tubules and is responsible for 90% of glucose reabsorption from S1 and S2 segment of the proximal convoluted tubule. The rest 10% of the glucose absorption happens in the S3 segment of proximal convoluted tubule and is taken care of by SGLT1.^[18,19] In renal cells isolated from subjects with type 2 diabetes, there is an enhanced expression of SGLT2 and GLUT2.^[20] Blocking SGLT2 would reduce the renal threshold for glucose (RTG) in the kidney thereby causing osmotic diuresis.^[19] However, despite SGLT2 transporters being responsible for 90% of glucose reabsorption, SGLT2 inhibitors inhibit only 30–50% of the glucose absorption in diabetic subjects. This is a result of residual SGLT2 activity and SGLT1 compensation.^[21,22] SGLT2 inhibitors, by the inherent nature of the target of action, are independent of insulin secretion and insulin resistance. This would make them theoretically attractive to be used at any stage of diabetes.

SODIUM GLUCOSE COTRANSPORTER 2 INHIBITORS

The FDA has approved 3 SGLT2 inhibitors for use in adults with type 2 diabetes: Canagliflozin (Invokana, Janssen), dapagliflozin (Farxiga, AstraZeneca), and empagliflozin (Jardiance, Boehringer Ingelheim). Approved fixed-dose combination products include canagliflozin/metformin (Invokamet, Janssen), extended-release dapagliflozin/metformin (Xigduo XR, AstraZeneca), and empagliflozin/linagliptin (Glyxambi, Boehringer Ingelheim) and empagliflozin/metformin (Synjardy, Boehringer Ingelheim). Ipragliflozin, luseogliflozin, and tofogliflozin has been approved in Japan for subjects with type 2 diabetes.^[23]

SGLT2 inhibitors have various advantages as oral antidiabetic agents: effective glucose lowering, low risk of hypoglycaemia as monotherapy and when used with Pioglitazone, DPP-4 inhibitors or Metformin, reduction in visceral fat, long durability of action, weight loss, and reduction of systolic blood pressure.^[18] In a meta-analysis of SGLT2 inhibitors including studies up

to 52 weeks, SGLT2 inhibitors produce improvements in HbA1c compared to placebo (−0.66%) and active comparators (mean difference −0.06%). SGLT2 inhibitors reduce body weight (mean difference −1.8 kg) and systolic blood pressure (mean difference −4.45 mm Hg).^[24] The risk of hypoglycemia was similar to that of metformin and DPP 4 inhibitors but less than that of SU.^[24]

DIFFERENCE BETWEEN AGENTS

The SGLT2 inhibitors in clinical practice have structural similarity. Despite being highly selective inhibitors of SGLT2, these agents also inhibit SGLT1 to a minor extent. Among these molecules, empagliflozin has the highest selectivity for SGLT2 over SGLT1 (>2500-fold), followed by tofogliflozin (>1875-fold), dapagliflozin (1200-fold), ipragliflozin (550-fold), and canagliflozin (250-fold).^[19] In a double-blind, randomized, 2-period crossover study, canagliflozin 300 mg had a higher urinary glucose excretion and lower 24 h mean RTG compared to dapagliflozin 10 mg. Further 300 mg canagliflozin reduced and delayed the postprandial glucose excursion compared to dapagliflozin 10 mg.^[25] The potential role of action of SGLT1 inhibition in the intestine in addition to SGLT2 inhibition in the kidney by canagliflozin 300 mg is instrumental in producing these effects on postprandial sugars.^[26] These drugs have differences in drug interaction profile and pharmacokinetic profiles.^[18]

STUDIES OF SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS WITH INSULIN

Being a drug active at any stage of diabetes and its advantages in reducing weight, it is logical to consider it as an add-on therapy to insulin. Use of SGLT2 inhibitor with insulin combination can fall under three broad categories:

- A subject with type 2 diabetes on oral antidiabetic drugs (OAD) including SGLT2 inhibitors getting initiated on basal/basal–bolus or premixed insulin
- A subject with type 2 diabetes with insulin initiated on SGLT2 inhibitors
- A subject with type 1 diabetes mellitus on insulin getting initiated on SGLT2 inhibitors.

There are studies of all FDA-approved SGLT2 inhibitors with insulin.^[27-32] All these studies are in subjects of type 2 diabetes getting initiated on SGLT2 inhibitors or subjects with type 1 diabetes on insulin getting initiated on these agents.^[33] These studies are of variable duration, with a variable number of patients and with various types of insulin regimes. Table 1 gives the design of these studies with type 2 diabetes. In most of these studies, insulin doses were kept constant over a period of 12–18 weeks. In studies of empagliflozin, a treat to target model has

Table 1: Design of studies using SGLT2 inhibitors with insulin in type 2 diabetes

Author/year Molecule	Design of study
Neal <i>et al.</i> , 2015 ^[29] 52 weeks Canagliflozin	This was part of insulin sub study of CANVAS, the cardiovascular outcome trial of canagliflozin. Insulin doses were held constant for 18 weeks. Thereafter dose adjustment at the discretion of investigator. Rescue criteria were applied during the first 18 weeks. FPG 270 mg/dL (0-6 weeks), >240 mg/dL (6-12 weeks), >200 mg/dL (12-18 weeks)
Wilding <i>et al.</i> , 2009 ^[32] 12 weeks Dapagliflozin	Randomized double blind, 3 arm, parallel group, placebo controlled, 1:1:1 assignment to placebo, 10 mg dapagliflozin, and 20 mg dapagliflozin. Dose of OAD was held constant and dose of insulin was reduced 50% from baseline. Further dose reduction after start of study was allowed only for hypoglycemic episodes and investigator decision. Doses of insulin were allowed to be increased only based on rescue criteria
Wilding <i>et al.</i> , 2012 ^[27] 48 weeks Dapagliflozin	24 weeks placebo controlled trial followed by 24 weeks extension period. Further continued into an extension protocol mentioned in reference 28. 1:1:1 randomization into placebo, dapagliflozin 2.5 mg, 5 mg, and 10 mg. No modification in insulin or other OAD doses. Insulin kept constant (within 10%) unless the patient has hypoglycemic episodes or the blood sugars satisfy the following criteria: FPG >240 mg/dL (0-12 weeks), >220 mg/dL (12-24 weeks), >180 mg/dL (25-48 weeks) or HbA1c >8% (25-48 weeks). Doses reduced only if >2 readings <80 mg/dL in the first 7 days and <70 mg/dL after the first 7 days
Wilding <i>et al.</i> , 2014 ^[28] 104 weeks Dapagliflozin	This is the 104 weeks extension of the trial given above (reference 27). Following 48 weeks of the above study, subjects in 5 mg group were switched to the 10 mg group (called 5/10 mg group). Insulin was kept constant. Up titration of insulin was permitted between weeks 52 and 65 if HbA1c >7.5% and between weeks 78 and 104 if HbA1c >7%. Dose reduction of insulin only if 2 monitored values <70 mg/dL
Rosenstock <i>et al.</i> , 2014 ^[31] 52 weeks Empagliflozin	Randomized, double blind, placebo controlled parallel group study. 1:1:1 randomization to placebo, empagliflozin 10 mg, and empagliflozin 25 mg. For first 18 weeks, the doses of insulin to remain constant (within 10%). 19-40 weeks are treated to target with FBS <100 mg/dL and preprandial sugars <140 mg/dL, and 41-52 weeks the doses to remain within 10% of the week 40 dose. Rescue criteria for 1-12 weeks (FPG >240 mg/dL), 13-24 weeks (FPG >200 mg/dL) and 24-52 weeks (FPG >180 mg/dL) or HbA1c >8%. Dose reduction permitted for safety reasons
Rosenstock <i>et al.</i> , 2015 ^[30] 78 weeks Empagliflozin	Randomized, double-blind, placebo-controlled parallel group study. 1:1:1 randomization to placebo, empagliflozin 10 mg, and empagliflozin 25 mg. For first 18 weeks, the doses of insulin to remain constant. 19-78 weeks are treated to target with FPGs <110 mg/dL. Rescue criteria for 1-12 weeks (FPG >240 mg/dL), 13-24 weeks (FPG >200 mg/dL) and 24-52 weeks (FPG >180 mg/dL) or HbA1c >8%. Dose reduction permitted for safety reasons

CANVAS: Canagliflozin Cardiovascular Assessment Study, FPG: Fasting plasma glucose, OAD: Oral antidiabetic drug, HbA1c: Hemoglobin A1c, FBS: Fasting blood sugar, SGLT2: Sodium glucose cotransporter 2

been used during a part of the study although it was investigator decision based.^[30,31] The salient features of baseline characteristics and results of these trials are given in Tables 2 and 3.

POTENTIAL BENEFITS OF SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITOR + INSULIN COMBINATION

The benefits of combining insulin with SGLT2 inhibitors in subjects with type 2 diabetes have been explored in different studies.

Improvements in glycaemic parameters

In these studies of add-on SGLT2 inhibitors to insulin regimes, there was a reduction in HbA1c. From a baseline HbA1c of 8.3–8.5%, there was a reduction of 0.2–0.7% over the study periods ranging from 12 weeks to 104 weeks. Although not compared head on, the maximum reduction was achieved with canagliflozin 300 mg. The reduction of HbA1c was by 0.73% (95% confidence interval [CI]: 0.63–0.83) at 52 weeks.^[29] In keeping with the same, the fasting plasma glucose reduction was also more in canagliflozin study.^[29] Postprandial sugars were not mentioned in all studies [Table 2]. The action of canagliflozin on SGLT1 in the intestine in addition to the SGLT2 inhibition in kidney can be a reason for this enhanced reduction.^[26] The trend of greater reduction

in HbA1c with canagliflozin 300 mg compared to other SGLT2 inhibitors is evident also in meta-analysis data.^[24]

Improvements in weight

There was a placebo-subtracted weight loss of 2.39–3.5 kg in patients using SGLT2 inhibitors compared to placebo [Table 3]. This weight loss was achieved despite a higher proportion of patients reaching a target HbA1c and with a reduction of total daily dose of insulin. This data would not give the true change in insulin doses and improvement in glycaemic control as none of these trials were designed in treat to target mode throughout the duration of the study.

Weight loss in uncontrolled diabetes is due to glycosuria.^[11] Weight gain is one of the potential disadvantages of insulin therapy. Higher insulin dose along with higher baseline HbA1c and lower body mass index at baseline were factors associated with higher weight gain in subjects on insulin.^[34,35] Agents such as thiazolidinedione and SU used in association with insulin leads to weight gain. Using a combination of SGLT2 inhibitors and insulin would help nullify this challenge of weight gain. The body weight loss is due to calorie loss secondary to glycosuria and negative energy balance. Visceral fat loss in preference to subcutaneous fat loss was demonstrated by dual energy absorptiometry, computed tomography imaging, or magnetic resonance imaging in studies of SGLT2 inhibitors.^[36] This would help

Table 2: Salient features of trials of SGLT2 with insulin

Molecule Author Duration of study	Number of subjects	Mean age of subjects	Mean duration of diabetes (years)	Baseline HbA1c (%)	Change in HbA1c in both groups (%)	Change in FPG and PPG versus placebo (mg/dL)
Canagliflozin (C) Neal <i>et al.</i> , 2015 ^[29] 52 weeks*	Placebo: 690 C100: 692 C300: 690	Median age Placebo: 63 C100: 62 C300: 63	Placebo: 16 C100: 16.4 C300: 16.3	Placebo: 8.3 C100: 8.3 C300: 8.3	C100: -0.58 C300: -0.73	FPG (C100): -19.8 FPG (C300): -27 PPG: No data
Dapagliflozin (D) Wilding <i>et al.</i> , 2014 ^[28] 104 weeks**	Placebo: 193 D2.5: 202 D5/10*: 211 D10: 194	Placebo: 58.8 D2.5: 59.8 D5/10: 59.3 D10: 59.3	Placebo: 13.5 D2.5: 13.5 D5/10: 13.1 D10: 14.2	Placebo: 8.46 D2.5: 8.47 D5/10: 8.61 D10: 8.58	D2.5: -0.21 D5/10: -0.39 D10: -0.35	FPG D2.5: -2.52 D5/10: -16.02 D10: -5.58
Dapagliflozin (D) Wilding <i>et al.</i> , 2009 ^[32] 12 weeks	Placebo: 23 D10: 24 D20: 24	Placebo: 58.4 D10: 55.7 D20: 56.1	Placebo: 13.8 D10: 11.8 D20: 11.3	Placebo: 8.4 D10: 8.4 D20: 8.5	D10: -0.70 D20: -0.78	FPG D10: -15.4 D20: -27.4 PPG D10: -53.0 D20: -60.6
Empagliflozin (E) Rosenstock <i>et al.</i> , 2014 ^[31] 78 weeks	Placebo: 170 E10: 169 E25: 155	Placebo: 58.1 E10: 58.6 E25: 59.9	Around 90 % had duration > 5 years	Placebo: 8.2 E10: 8.3 E25: 8.3	E10: -0.5 E25: -0.6	FPG E10: -12.9 E25: -18.0 PPG: Data not available
Empagliflozin (E) Rosenstock <i>et al.</i> , 2015 ^[30] 52 weeks	Placebo: 188 E10: 186 E25: 189	Placebo: 55.3 E10: 56.7 E25: 58.0	Around 70 % had duration > 10 years and 20 % had duration > 5 years	Placebo: 8.33 E10: 8.39 E25: 8.29	E10: -0.38 E25: -0.46	FPG E10: -12.42 E25: -14.22 PPG: Data not available

*Patients receiving dapagliflozin 5 mg were switched to 10 mg at 48 weeks, **Data at 104 weeks, *Data expressed for 52 weeks FPG: Fasting plasma glucose, PPG: Postprandial glucose, SGLT2: Sodium glucose cotransporter 2, HbA1c: Hemoglobin A1c

Table 3: Salient features of trials of SGLT2 with insulin in type 2 diabetes showing insulin regimes, change in insulin doses, weight, blood pressure, and renal parameters

Molecule Author Duration of study	Regime of insulin	Mean insulin dose/day	Change in TDD of insulin	Weight change (placebo corrected) (in kg)	Change in blood pressure (placebo corrected mm Hg)	Change in ACR (mg/g)	Change in eGFR (mL/min/ 1.73 kg/m ²) (change from baseline)
Canagliflozin (C) Neal et al., 2015 ^[29] 52 weeks	Basal plus bolus/basal Alone/ bolus alone	Placebo: 58 C100: 60 C300: 60	Placebo: +4.4 C100: -2 C300: -4.3	C100: -2.8 C300: -3.5	C100: -3.1/-1.2 C300: -6.2/-2.4	C100: -9.6 C300: -9.5 (placebo corrected change)	C100: -2.6 C300: -3.2
Dapagliflozin (D) Wilding et al., 2014 ^[28] 104 weeks	Basal plus bolus/basal Alone/ bolus alone	Placebo: 74.0 D2.5: 79.9 D5/10: 77.1 D10: 78.0	Placebo: 18.3 D2.5: 4.1 D5/10: 1.6 D10: -0.8	D2.5: -2.81 D5/10: -2.86 D10: -3.33	D5/10: -2.1/-1.6 D10: -7.0/-2.7	Placebo: -1.6 D2.5: -13.3 D5/10: 0.7 D10: -5 (change from baseline)	Placebo: 1.4 D2.5: -1.5 D5/10: 1.6 D10: -0.9
Dapagliflozin (D) Wilding et al., 2009 ^[32] 12 weeks	Data not available	Placebo: 54.1 D10: 52.4 D20: 54.5	Placebo: 1.7 D10: -1.4 D20: -0.8	D10: -2.6 D20: -2.4	D10: -7.2/-1.2 D20: -6.1/-3.9	No data on ACR	Placebo: -0.58 D10: -0.84 D20: 1.45
Empagliflozin (E) Rosenstock et al., 2014 ^[31] 78 weeks	Basal	Placebo: 47.8 E10: 45.13 E25: 48.43	Placebo: 5.5 E10: -1.2 E25: -0.5	E10: -2.9 E25: -2.7	E10: -4.2/-2.6 E25: -2.6/-1.2	No data on ACR	Placebo: -6.3 E10: -4.8 E25: -5.7
Empagliflozin (E) Rosenstock et al., 2015 ^[30] 52 weeks	Basal plus bolus	Placebo: 93.1 E10: 89.9 E25: 92.9	Placebo: 10.2 E10: 1.3 E25: -1.1	E10: -2.39 E25: -2.48	E10: -0.6/-0.7 E25: -0.9/-1.9	No data on ACR	Placebo: -2.0 E10: -1.6 E25: -1.6

TDD: Total daily dose, ACR: Albumin-creatinine ratio, eGFR: Estimated glomerular filtration rate, SGLT2: Sodium glucose cotransporter 2

improve insulin sensitivity and would likely translate into CV benefits of these agents.^[36]

Improvements in blood pressure

Use of SGLT2 inhibitors is associated with a reduction in systolic blood pressure and diastolic blood pressure. This advantage of SGLT2 blockers was seen also in studies along with insulin. The mean reductions in blood pressure compared to placebo were higher in subjects receiving SGLT2 inhibitors [Table 3]. These were numerically higher than the pooled data of all SGLT2 inhibitors.^[19,24] The reduction in blood pressure is due to a combination of osmotic diuresis, natriuresis, weight loss, and possible effects of improved endothelial nitric oxide release due to better glycemic control.^[36,37] Since these agents produce natriuresis, it would likely counteract the sodium retention properties of insulin.^[38]

Cardiovascular benefits

The favorable CV risk profile created by the use of SGLT2 inhibitor would favor positive CV outcomes; improved glycemia, reduced weight, reduced blood pressure, reduced uric acid, reduced visceral fat, and its ill effects.^[36] These favorable effects were reflected in the dedicated CV outcome trial of empagliflozin – EMPA-REG OUTCOME trial.^[17] A similar improvement in CV risk profile was seen in studies with SGLT2 inhibitor-insulin combination also [Tables 2 and 3]. There are ongoing CV outcome trials of other SGLT2 inhibitors: Dapagliflozin

Effect on Cardiovascular Events (DECLARE TIMI 58), Canagliflozin Cardiovascular Assessment Study (CANVAS) and CV outcomes following treatment with ertugliflozin in participants with type 2 diabetes mellitus and established vascular disease.^[19]

In EMPA-REG OUTCOME trial, around 48% of subjects in all arms were on insulin although a separate analysis of this population is not available till date. The hazard ratio for primary composite outcome in this subgroup of insulin users was 0.93 (95% CI: 0.75–1.13) compared to 0.61 (0.44–0.85) among insulin nonusers.^[17]

Renal outcomes

SGLT2 inhibitors being a predominantly renal acting molecule, the renal outcomes are of interest. The possible effects on tubule glomerular feedback and improvement of renal disease progression are being pursued. In the trials of SGLT2 inhibitors with insulin, significant improvements in albumin: creatinine ratio (ACR) was seen with dapagliflozin and canagliflozin [Table 3].^[27,29] Patients transitioning from normoalbuminuria or microalbuminuria at baseline to microalbuminuria or macroalbuminuria in the course of the study was less in subjects on SGLT2 inhibitors.^[28] The effects of SGLT2 inhibitors on reducing the ACR is mediated via the reduced sodium transport in the proximal tubule which leads to increased sodium delivery to the juxtaglomerular apparatus. This leads to a reduction in the glomerular pressure and reduction of glomerular

hyperfiltration. This is hypothesized to be responsible for renoprotection by the activation of tubuloglomerular feedback.^[39-41] Further renal protection may be provided by an improvement in glycemic control, reduction in weight and blood pressure. However, during the course of these studies, there was a minor reduction in creatinine clearance in arms using SGLT2 inhibitors compared to placebo which stabilized in the course of the study and returned to baseline after treatment discontinuation.^[27,29,31] This early drop in estimated glomerular filtration rate (eGFR) with SGLT2 inhibitors is attributed to modest diuretic effect and increased tubuloglomerular feedback, with resultant afferent arteriolar vasoconstriction. Whether these early changes in GFR or changes in ACR translate to improved long term renal outcomes are not known.^[40,42] Long-term trials like CANVAS-R and CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) will give data on renal outcomes of using SGLT2 inhibitors beyond standard of care.

CONCERNS WHILE USING SODIUM-GLUCOSE COTRANSPORTER 2 AND INSULIN COMBINATION THERAPY

Adding an oral agent to an insulin regime comes with its own share of adverse effects. Weight gain associated with the use of pioglitazone and SU with insulin and risk of hypoglycemia with SU are some of the drawbacks of insulin-OAD combinations. Concerns with the addition of SGLT2 blockers to insulin are related to various adverse effects.

Genital infections and urinary tract infections

In trials of SGLT2 inhibitors, there is a mildly increased risk of urinary tract infections (UTIs) and moderately increased the risk for genital mycotic infections (GMI). In the meta-analysis of SGLT2 inhibitors versus placebo or comparators, there was an increased incidence of UTIs (odds ratio [OR] 1.34; 95% CI 1.03–1.74).^[24] These events were mild to moderate in intensity and were more common in females than males, whereas pyelonephritis was uncommon.^[24]

Moreover, treatment with SGLT2 inhibitors was associated with a marked increase of GMI (OR vs. placebo 3.50; 95% CI 2.46–2.99).^[24] The commonly reported events were vulvovaginal mycotic infections in females and balanitis in males; however, none of them was classified as serious.^[24] In studies of SGLT2 inhibitors with insulin, a similar increase in the risk of UTI and GMI has been found [Table 4]. Subjects with type 2 diabetes who are insulin users are generally older and more likely to have autonomic neuropathy involving bladder which predisposes them to UTI.^[43] However, the risk of vulvovaginitis is lower in postmenopausal women in the absence of risk factors

such as uncontrolled diabetes and hormone replacement therapy.^[44] The incidence of GMI and UTI in subjects with SGLT2 inhibitor with insulin combination was similar to the overall pooled data of canagliflozin, dapagliflozin, and empagliflozin.^[24]

Volume depletion

SGLT2 inhibitors act by excreting glucose and thereby an extra volume of fluids by osmotic diuresis. Studies have shown that there is an extra 375 ml of urine/day excreted with dapagliflozin 10 mg/day.^[19] Volume depletion-related adverse effects were captured in trials of SGLT2 inhibitors: reduced blood pressure, dehydration, postural dizziness, orthostatic hypotension, orthostatic intolerance, syncope, and reduced urine output.^[45] In a pooled analysis, volume depletion-related adverse events occurred in 2.3% and 3.4% of canagliflozin 100 mg and 300 mg groups, respectively, versus 1.5% in the comparator groups.^[46] Risk factors for these events were more in subjects with age ≥ 75 years, eGFR < 60 ml/min/1.73 m², and use of loop diuretics.^[46]

Subjects with type 2 diabetes using insulin tend to be older, more likely to have reduced eGFR, CV disease, and autonomic neuropathy with altered baroreceptor reflex mechanisms.^[47] The insulin substudy of CANVAS recruited subjects at high CV risk. The subjects in this study had a mean age of 63 years and mean duration of diabetes of 16 years. In this study, 40% of patients had peripheral neuropathy although the prevalence of autonomic neuropathy was not mentioned.^[29] Adverse effects such as postural hypotension and dizziness were more in the canagliflozin groups although the risk was similar to a pooled group data of canagliflozin.^[19,24] Similarly, there was no increased risk of volume depletion-related adverse effects in the EMPA-REG OUTCOME study, which had older patients and those with high CV risk.^[17]

The comparison data of volume related adverse effects of each of the SGLT2 inhibitors is given in Table 4. The overall incidence of volume-related adverse effects with SGLT2 inhibitor-insulin combination were similar to that of their data in the pooled analysis [Table 4].^[19]

Osmotic diuresis-related adverse effects

SGLT2 inhibitors produce osmotic diuresis due to glycosuria. The common osmotic diuresis-related adverse effects reported were pollakiuria, nocturia, micturition frequency, and thirst related (increased thirst, dry mouth, polydipsia, throat dry, or tongue dry).^[45] In studies with insulin, osmotic diuresis-related adverse were more common in subjects on SGLT2 inhibitors compared to those on placebo although these were comparable to the pooled dataset [Table 4].

Table 4: Adverse effects of use of SGLT2 inhibitors with insulin: A comparison of pooled data of SGLT2 inhibitors with SGLT2 + insulin data

Molecule	UTI (%)		GMI (%)		Volume AE (%)	Hypoglycemia (%)
	Upper	Lower	Male	Female		
Neal et al., 2015 ^[29]						
52 weeks						
Placebo	1	5	2	3	2	48
C100	1	5	8	18	4	59
C300	0	6	12	13	6	57
Wilding et al., 2009 ^[32]						
12 weeks						
Placebo	0		4.3		Pollakiuria 17.4	13
D10	0		0		8.3	29.2
D20	4.2		20.8		12.5	25.0
Wilding et al., 2014 ^[28]						
104 weeks						
Placebo	5.6		3.0		Pollakiuria 1.5	61.9
D2.5	8.4		7.4		3.0	69.3
D5/10	13.2		12.7		3.3	61.3
D10	13.8		14.3		5.1	60.7
Rosenstock et al., 2014 ^[31]						
52 weeks						
Placebo	15.4		1.6		Not mentioned	59.0
E10 mg	15.6		4.3			52.2
E25 mg	15.3		9.5			58.2
Rosenstock et al., 2015 ^[30]						
78 weeks						
Placebo	9		2		Not mentioned	33
E10 mg	15		8			33
E25 mg	12		5			35

UTI: Urinary tract infection, GMI: Genital mycotic infection, C: Canagliflozin, D: Dapagliflozin, E: Empagliflozin, SGLT2: Sodium glucose cotransporter 2, OR: Odds ratio, AE: Adverse event

Hypoglycemia

The risk of hypoglycemia with SGLT2 inhibitors is similar to that of placebo when used as monotherapy or in association with metformin or DPP4 inhibitors.^[19,24] In use with Insulin and SU, they may potentiate the risk of hypoglycemia.^[24] In most trials of the use of SGLT2 inhibitors with insulin, the overall risk of hypoglycemia was similar in patients on the combination compared to patients using insulin alone. During the insulin constant phase in these trials, more hypoglycemia episodes were reported the SGLT2 inhibitor arm than in the placebo arm in keeping with the improvements in glycemetic control.^[27,30-32]

Possible risk of diabetic ketoacidosis

In May 2015, FDA warned that treatment with SGLT2 inhibitors may increase the risk of ketoacidosis based on 20 cases reported in the FDA Adverse Event Reporting System (FAERS). One-third of these cases was in off-label use in type 1 diabetes.^[48] A total of 101 cases of diabetic ketoacidosis in patients treated with SGLT2 inhibitors for type 2 diabetes had been reported worldwide in EudraVigilance as of May 19, 2015.^[49] Data from the FAERS, EudraVigilance, canagliflozin development program, and published case series show that there is disproportionately high representation of subjects with type 1 diabetes

subjects, subjects with beta cell autoimmunity and those using insulin among those developing ketoacidosis with the use of SGLT2 inhibitors. In most of these cases, a precipitating event was also recognized.^[48-51]

The compromised beta cell function present in certain subgroups of type 2 diabetes subjects may make them at high risk of ketoacidosis. This includes patients with longer duration of diabetes, those with beta cell autoimmunity (e.g. latent autoimmune diabetes in adults) and patients with ketosis-prone type 2 diabetes.^[52] In subjects in UKPDS study, among subjects clinically diagnosed as type 2 diabetes, 11.6% have autoantibodies to various beta cell antigens.^[53] They were likely to require insulin earlier than subjects who are antibody negative.

Various mechanisms have been postulated to be associated with diabetic ketoacidosis in subjects using SGLT2 inhibitors. In subjects with type 2 diabetes on SGLT2 inhibitors, there is a significant loss of urinary glucose, which will reduce blood glucose and lead to loss of glucose stimuli to insulin (resulting in lower insulin levels) and increased glucagon concentration, partly driven by the loss of paracrine inhibition by insulin. The lower insulin: glucose ratio would increase gluconeogenesis in the liver and

lipolysis in adipose tissue. This releases free fatty acids and leads to subsequent ketogenesis in the liver.^[54] In subjects with type 1 diabetes, reduction of insulin while adding SGLT2 inhibitors would lead to lipolysis and subsequent ketogenesis in the liver. Since blood sugars would be normal in this scenario due to increased urinary loss of sugars, the ketoacidosis would be euglycemic. Increased glucagon levels associated with SGLT 2 inhibitors leading to hepatic ketogenesis and reduced renal clearance of ketone bodies may contribute to ketogenesis.^[54,55]

Clinicians using the insulin-SGLT2 inhibitor combinations should be aware of these potential mechanisms leading on to ketoacidosis. Since the blood sugars may remain normal in these subjects due to urinary loss of sugar, and urinary ketones may not be significantly elevated due to reduced urinary clearance of ketones, the diagnosis of this “euglycemic diabetic ketoacidosis” may be delayed. Demonstrating ketonemia and metabolic acidosis even in the face of reasonably normal blood sugars in an unwell patient will form the key to diagnosis. In conditions such as sepsis, surgical stress, intensive care, dehydration, starvation, vomiting, and trauma, there is a tendency for ketogenesis due to increase in counter-regulatory hormones. Subjects should be advised to withhold SGLT2 inhibitors during these scenarios, check blood sugars and serum ketones and refrain from reducing the dose of insulin drastically. They should be educated to inform the health care team if the situation is not under control. In the scenario of elective surgery, stopping of SGLT2 inhibitor well in advance would be warranted as the effects of these drugs may remain beyond the duration of action.^[55]

Cost considerations

Adding SGLT2 inhibitors to insulin therapy will escalate the cost of therapy. However, the added benefits of HbA1c reduction, blood pressure reduction, weight reduction, potential favorable effects on renal disease progression, and reduction in insulin dose should be weighed against the cost of therapy. As an add-on therapy to insulin, dapagliflozin was proven to be cost effective in the Dutch population.^[56] The implications of the superiority of empagliflozin in reducing mortality and CV events in EMPA-REG OUTCOME trial underscores the need to study the cost effectiveness of SGLT2 inhibitor-insulin combination therapy.^[17]

SGLT2 inhibitors have mild effects in elevating both low-density lipoprotein (LDL) and high-density lipoprotein (HDL) while maintaining an unaltered LDL:HDL ratio.^[36] Most trials of SGLT2 inhibitors with insulin gave limited information of this parameter.

CONCLUSION

The use of SGLT2 inhibitors in type 2 diabetes subjects on insulin has major advantages in terms of dose reduction of insulin, reducing HbA1c and blood sugars, reduction of weight, and reduction of blood pressures. Currently, SGLT2 inhibitors are approved for use in this setting. However, the associated problems with this combination should be kept in mind. There is a moderately increased risk of GMI and possible a mild increase in UTI. Further, being older subjects, there is a higher risk of compromised renal function and a higher risk of volume related and osmotic diuresis-related in these subjects although clinical trials have not shown these risks conclusively. In younger patients who progress on to early requirement for insulin, there is a potential risk of underlying beta cell autoimmunity and thereby the risk of ketoacidosis in situations which predispose patients to the same. It would be wise to understand the beta cell status of these patients and their endogenous insulin reserve before initiating SGLT2 inhibitors. Patient and provider education would form the key to the judicious use of this combination.

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Conflicts of interest

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