Metabolic effects of SGLT-2 inhibitors beyond increased glucosuria: A review of the clinical evidence

A. J. Scheen a,b,*, N. Paquot a,c

aDivision of Diabetes, Nutrition and Metabolic Disorders, Department of Medicine, CHU Liège, University of Liège, Liège, Belgium
bClinical Pharmacology Unit, CHU Liège, Center for Interdisciplinary Research on Medicines (CIRM), University of Liège, Liège, Belgium
cDiabetology and Nutrition, GIGA I3, University of Liège, Liège, Belgium

Abstract

Sodium-glucose cotransporter type 2 (SGLT-2) inhibitors (canagliflozin, dapagliflozin, empagliflozin) are new glucose-lowering agents that exert their therapeutic activity independently of insulin by facilitating glucose excretion through the kidneys. However, this simple renal mechanism that results in sustained glucose urinary loss leads to more complex indirect metabolic effects. First, by reduction of chronic hyperglycaemia and attenuation of glucose toxicity, SGLT-2 inhibitors can improve both insulin secretion by beta cells and peripheral-tissue insulin sensitivity. In the case of canagliflozin, because of low-potency SGLT1 inhibition, a non-renal (intestinal) effect may also be considered, which may contribute to better control of postprandial hyperglycaemia, although this contribution remains to be better analyzed in humans. Second, chronic glucose loss most probably leads to compensatory mechanisms. One of them, although not well evidenced in humans, might involve an increase in energy intake, an effect that may limit weight loss in the long run. Another could be an increase in endogenous glucose production, most probably driven by increased glucagon secretion, which may somewhat attenuate the glucose-lowering effect. Nevertheless, despite these compensatory mechanisms and most probably because of the positive effects of the reduction in glucotoxicity, SGLT-2 inhibitors exert clinically relevant glucose-lowering activity while promoting weight loss, a unique dual effect among oral antidiabetic agents. Furthermore, the combination of SGLT-2 inhibitors with other drugs that either have anorectic effects (such as incretin-based therapies) or reduce hepatic glucose output (like metformin) and, thus, may dampen these two compensatory mechanisms appears appealing for the management of type 2 diabetes mellitus.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a disease characterized by persistent and progressive deterioration of glucose tolerance. Both insulin resistance and impaired insulin secretion contribute to the development of T2DM [1]. Intense research has identified a number of genetic variants that may predispose to insulin resistance and impaired beta-cell function. However, such a predisposition can be precipitated and worsened by toxic effects of hyperglycaemia (glucose toxicity or glucotoxicity) and elevated levels of free fatty acids (lipotoxicity) [2,3]. Obesity, especially increased visceral adipose tissue, plays a major role in the pathophysiology of the disease [4], and paves the way to new therapies able to combat the dual burden of obesity and T2DM [5].

In the late 1980s, studies performed with phlorizin in 90% pancreatectomized diabetic rats provided proof of concept for the efficacy of sodium-glucose cotransporter type 2 (SGLT-2) inhibition in reducing the deleterious effects of glucotoxicity. In this insulinopenic T2DM model, chronic phlorizin administration induced sustained glucosuria, and normalized both fasting and fed plasma glucose levels with complete reversal of insulin resistance [6] and correction of defects in both first- and second-phase insulin secretion [7]. When phlorizin was withdrawn from these animals, hyperglycaemia, insulin resistance and impaired insulin secretion returned. Because phlorizin is poorly absorbed from the gastrointestinal tract and inhibits both the SGLT-2 and SGLT1 transporters, it has not been developed commercially for the treatment of T2DM. More recently, however, selective SGLT-2 inhibitors have been successfully developed to produce glucosuria and reduce plasma glucose concentrations without adverse gastrointestinal effects. These new oral antidiabetic agents have the potential to improve glycaemic control while avoiding hypoglycaemia and
to promote weight loss [8]. Some of these SGLT-2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) are already available in a number of countries, and are increasingly being used mainly in combination therapies with other antidiabetic agents for the management of hyperglycaemia in T2DM [9,10].

SGLT-2 inhibitors may also exert endocrine and metabolic effects beyond their glucuretic action. Although the mechanism of action of dapagliflozin is not directly linked to either insulin secretion or insulin sensitivity, reduction of plasma glucose by dapagliflozin via induction of urinary glucose excretion (UGE) could improve muscle insulin sensitivity and possibly also preserve beta-cell function via correction of glucotoxicity [11,12]. Recently, however, paradoxical insights into whole-body metabolic adaptations following SGLT-2 inhibition have been described in humans [13]. They imply increased endogenous glucose production (EGP) and most probably increased energy intake, both effects that may limit the glucose-lowering efficacy and weight-reducing effects of SGLT-2 inhibitors.

The present review provides an updated evaluation of the effects of SGLT-2 inhibitors beyond increased glucosuria in patients with T2DM. The pharmacokinetic and toxicological properties of these compounds have been reviewed elsewhere [10], as well as the clinical efficacy of the various compounds of this novel pharmacological class in the management of T2DM: canagliflozin [14]; dapagliflozin [15]; empagliflozin [16]; and ipragliflozin [17]. However, this review is more particularly focused on the indirect effects resulting from decreased glucotoxicity on insulin secretion and insulin sensitivity, and on the possible compensatory mechanisms linked to sustained glucose (energy) loss through urine (Fig. 1).

2. Methods

To identify the relevant studies, a literature search of MEDLINE was performed from January 2010 to August 2014, using the terms ‘SGLT-2 inhibitor’, ‘canagliflozin’, ‘dapagliflozin’ and ‘empagliflozin’ in combination with ‘weight loss’, ‘energy intake’, ‘insulin secretion’, ‘insulin sensitivity’ and ‘glucotoxicity’. No language restrictions were imposed. Reference lists of original studies, narrative reviews and previous systematic reviews were also carefully examined.

3. Results

3.1. Effects resulting from decreased glucotoxicity

3.1.1. Effects on insulin secretion

Normalization of the plasma glucose profile by phlorizin treatment in diabetic rats completely corrected beta-cell abnormalities [7]. These results indicate that chronic hyperglycaemia can lead to a defect in in-vivo insulin secretion, which is reversible when normoglycaemia is restored [18–19]. Sustained glucose-lowering with dapagliflozin in a rat model of T2DM prevented the continued decline in functional adaptation of pancreatic beta cells [20]. Reduction of glucotoxicity may also improve insulin secretion in patients with T2DM [18,19]. This hypothesis has been tested with the most widely investigated SGLT-2 inhibitors.

Over 12 weeks, numerical reductions from baseline in glycated haemoglobin (HbA1c), fasting plasma glucose and body weight were observed with dapagliflozin 5 mg once daily (–0.38%, –0.39 mmol/L and –1.58%, respectively) vs slight numerical increases with placebo (0.03%, 0.26 mmol/L and 0.62%, respectively) in patients with T2DM. Insulin secretion was determined from the acute insulin response to glucose (AIRg) during the first 10 min of a frequently sampled intravenous glucose tolerance test. A change from baseline in the adjusted mean AIRg of 15.39 mU/l min was observed with dapagliflozin at week 12 vs –12.73 mU/l min with placebo (p=0.0598) [21].

Another recent study evaluated patients with T2DM at baseline, after a single dose and following 4-week treatment with empagliflozin (25 mg). Beta-cell function was assessed by the relationship between insulin secretion rates and concomitant
plasma glucose concentrations (beta-cell glucose sensitivity) during a meal test [22]. After a single first dose of 25-mg empagliflozin in patients with T2DM (acute study), glucose sensitivity was improved ($p<0.0001$) and total insulin output was decreased, whereas potentiation and rate sensitivity did not change. The glucagon-like peptide (GLP)-1 response to the meal was enhanced. After 4 weeks of treatment (chronic study), 25-mg empagliflozin caused fasting and after-meal glucosuria that was similar in quantity and time course to those of the acute study. Compared with the baseline study, HbA$_1c$ and fasting and mean glucose levels after meal ingestion were all significantly decreased. Beta-cell glucose sensitivity was enhanced to a similar extent as in the acute study ($p<0.0001$) but, again, neither potentiation nor rate sensitivity differed. The GLP-1 response still appeared somewhat enhanced (though not significantly) [22]. Nevertheless, beta-cell glucose sensitivity is an index of beta-cell function that is independent of insulin sensitivity, which suggests that the improvement observed in the study was not related to any concomitant effect of the SGLT-2 inhibitor on insulin sensitivity.

3.1.2. Effects on insulin sensitivity

Correction of hyperglycaemia by phlorizin, with no changes in insulin levels, normalizes insulin sensitivity in partially pancreatectomized rats [6]. These results provide the first in-vivo evidence that hyperglycaemia per se can lead to the development of insulin resistance [18,19]. Normalization of blood glucose in diabetic rats with phlorizin treatment reverses insulin-resistant glucose transport in adipose cells without restoring glucose transporter gene expression, which suggests changes in glucose transporter functional activity [23]. In Zucker diabetic fatty (ZDF) rats, dapagliflozin treatment for 2 weeks significantly lowered fasting and fed glucose levels and resulted in a significant increase in glucose utilization rate [24]. Similar effects in humans with T2DM have also been reported with the more recently developed SGLT-2 inhibitors.

In a randomized double-blind, placebo-controlled, parallel-group study that assessed the effects of dapagliflozin 5 mg on insulin sensitivity and secretion (data on insulin secretion already presented above) in subjects with T2DM, insulin sensitivity was assessed by measuring the glucose disappearance rate during the last 40 min of a 5-h hyperinsulinemic-euglycemic clamp [21]. At week 12, an adjusted mean increase from baseline in glucose disappearance rate was observed with dapagliflozin (7.98%) vs a decrease with placebo (−9.99%; between-group difference: $p=0.0059$). Thus, in patients with T2DM and inadequate glycaemic control, dapagliflozin treatment improved insulin sensitivity in the setting of reductions in HbA$_1c$ and body weight [21]. Similar findings were reported in a shorter, 2-week study. Dapagliflozin treatment induced glucosuria and markedly lowered fasting plasma glucose. Insulin-mediated tissue glucose disposal increased by approximately 18% after 2 weeks of dapagliflozin treatment, whereas placebo-treated subjects saw no changes in insulin sensitivity ($p<0.05$ vs baseline and vs placebo) [25].

A large group of 66 patients with T2DM was evaluated both at baseline after a single 25-mg dose of empagliflozin and following 4-week treatment (25 mg once daily). At each time point, patients received a mixed meal coupled with dual-tracer glucose administration and indirect calorimetry [22]. Tissue glucose disposal (median: 75 g [interquartile ratio (IQR): 16 g] was reduced (70 g [IQR: 21 g] vs 93 g [IQR: 18 g]; $p<0.0001$) due to a decrease in both glucose oxidation and non-oxidative glucose disposal, with a concomitant rise in lipid oxidation after chronic administration (all $p<0.01$). However, insulin sensitivity [indirectly assessed as the ratio of mean glucose metabolic clearance rate (MCR) to mean insulin concentration during meal absorption] was improved after empagliflozin administration. The increase was significant in the acute study (from 8.2 [5.8] to 9.1 [6.7] mL • kg fat free mass (FFM) $^{-1}$ • min$^{-1}$ • nM$^{-1}$; $p=0.0226$), but only a numerical increase was observed in the chronic study (from 8.2 [5.8] to 8.6 [8.0] mL • kg FFM$^{-1}$ • min$^{-1}$ • nM$^{-1}$; NS). It is noteworthy, however, that chronic dosing shifted substrate utilization from carbohydrate to lipid. Yet, despite these not very convincing data, the authors concluded that, in patients with T2DM, empagliflozin-induced glucosuria improved insulin sensitivity, thereby lowering fasting and postprandial glycaemia [22].

Taken all together, these data indicate that reducing plasma glucose with an agent that works specifically on the kidney to induce glucosuria improves muscle insulin sensitivity, findings that support the concept of glucose toxicity that was largely developed in the late 1980s and early 1990s [18,19].

3.1.3. Effects on postprandial hyperglycaemia

Substantial reductions in 1- and 2-h postprandial glucose levels after a standard mixed-meal tolerance test were observed with canagliflozin 100 mg and 300 mg compared with placebo in patients with T2DM treated with diet and exercise; differences in least-squares mean changes for 2-h postprandial glucose were −2.7 and −3.6 mmol/L, respectively ($p<0.001$ for both 100-mg and 300-mg doses). Such reductions were almost 50% greater than those observed in the same study for fasting plasma glucose concentrations (−2.0 mmol/L and −2.4 mmol/L, respectively) [26].

Canagliflozin, besides its action on SGLT-2, is also a low-potency SGLT1 inhibitor, which may differentiate it from other SGLT-2 inhibitors. One study has tested the hypothesis that intestinal canagliflozin levels post-dose are sufficiently high to transiently inhibit intestinal SGLT1. Indeed, canagliflozin lowered postprandial glucose and insulin by delaying intestinal glucose absorption while increasing UGE [27]. This additional effect may contribute to better control of postprandial glucose excursions in patients with T2DM, and might at least partly explain why treatment with canagliflozin for 6 to 12 months improved model-based measures of beta-cell function in patients with T2DM in three separate phase-III studies [28]: (study 1) canagliflozin 100 mg and 300 mg were compared with placebo as monotherapy for 26 weeks;
SGLT1, contributes to glucose-lowering with canagliflozin (beyond UGE), possibly through inhibition of intestinal glucose transport by blockade of SGLT1 by high intraluminal concentrations of canagliflozin in the upper gastrointestinal tract after drug ingestion, but before drug absorption [31]. Thus, these findings suggest that a non-renal mechanism is the transient inhibition of gut glucose transport by blockade of SGLT1 when given prior to a meal. One plausible explanation for a non-renal mechanism of glucose-lowering with the higher excursions seen with canagliflozin 300 mg is consistent with an SGLT-2 inhibitor like canagliflozin exerts a positive effect on insulin secretion comparable to that observed with sitagliptin, a DPP-4 inhibitor classically considered an insulin secretagogue, is remarkable. It suggests that canagliflozin may exert clinically relevant direct or indirect positive effects on beta-cell function. Taking also into account the observed weight loss with canagliflozin (which concomitantly could be contributing to the reduced insulin resistance), this observation may explain why canagliflozin 300 mg exerts a significantly greater reduction in HbA1c than sitagliptin 100 mg in T2DM patients insufficiently controlled by either metformin alone [30] or a combination of metformin and sulphonylurea [29].

A recent study evaluated renal and non-renal effects of two doses of canagliflozin (150 mg and 300 mg) on postprandial plasma glucose excursions in patients with T2DM inadequately controlled with metformin [31]. The total postprandial area under the plasma concentration-time curve from 0 to 2 h (AUC0–2h) was reduced in all canagliflozin-treated groups, with 300 mg providing a significantly greater reduction compared with placebo: −15.7% [95% CI: −19.1% to −12.1%]; p<0.001. A less marked reduction in total postprandial plasma glucose AUC0–2h was observed when the dose of canagliflozin was reduced from 300 mg to 150 mg. As UGE was generally comparable during the mixed-meal tolerance tests across all active-treatment periods, the difference in incremental glucose excursions seen with canagliflozin 300 mg is consistent with a non-renal mechanism of glucose-lowering with the higher dose when given prior to a meal. One plausible explanation for such a non-renal mechanism is the transient inhibition of gut glucose transport by blockade of SGLT1 by high intraluminal concentrations of canagliflozin in the upper gastrointestinal tract after drug ingestion, but before drug absorption [31]. Thus, these findings suggest that a non-renal mechanism (beyond UGE), possibly through inhibition of intestinal SGLT1, contributes to glucose-lowering with canagliflozin 300 mg, but not 150 mg. However, these conclusions are drawn from indirect comparisons and need to be confirmed in further, more detailed, studies [31].

An additional piece of information supporting a significant role of SGLT1 inhibition in overall glucose metabolism is provided by the recent results obtained with LX4211, a dual SGLT1/SGLT-2 inhibitor [32]. Distinct SGLT1 effects on GLP-1, peptide YY, glucose and insulin that were separate from SGLT-2-mediated effects were observed in healthy subjects. These results suggest that SGLT1 inhibition may be clinically meaningful in the management of T2DM [33]. It would also be of interest to have head-to-head studies comparing the effects of canagliflozin (an SGLT-2 inhibitor with modest effects on SGLT1) with those of dapagliflozin (a more specific SGLT-2 inhibitor) on insulin secretion, postprandial hyperglycaemia and HbA1c levels in patients with T2DM.

3.2. Effects resulting from compensatory mechanisms

3.2.1. Effects on food intake

SGLT-2 inhibitors are the only oral glucose-lowering agents that also promote significant weight loss [34]. Metformin is generally associated with only mild weight reduction, while alpha-glucosidase and DPP-4 inhibitors are weight-neutral, and sulphonylureas and thiazolidinediones result in weight gain [5]. Dapagliflozin induced weight loss predominantly by reducing fat mass, and visceral and subcutaneous adipose tissues, in patients with T2DM inadequately controlled with metformin. These observations, initially made after 24 weeks [35], have also been confirmed after 104 weeks of dapagliflozin therapy [36]. In a 52-week trial comparing canagliflozin with glimepiride [37], a body composition substudy using dual-energy X-ray absorptiometry (DXA) scans showed that, in the canagliflozin 100-mg and 300-mg treatment groups, roughly two-thirds of the reduction in body weight was from fat mass and a third from lean body mass, whereas the increase in body weight with glimepiride included both fat and lean body mass. Analysis of abdominal fat in the canagliflozin groups using computed tomography (CT) imaging showed a slightly greater reduction in visceral adipose tissue than in subcutaneous adipose tissue [37]. Closely similar results were reported with empagliflozin compared with glimepiride in T2DM patients. When used as an add-on to metformin, treatment with empagliflozin 25 mg once daily led to significant reductions in trunk fat, limb fat, abdominal visceral adipose tissue and subcutaneous adipose tissue at week 52, with further reductions at week 104, compared with glimepiride [38].

Weight loss associated with SGLT-2 inhibitors may result from energy loss through UGE, increased energy expenditures and/or reduced energy intakes. Sustained increased UGE has been consistently reported with each of the SGLT-2 inhibitors, and a daily waste of 60–80 g of glucose may certainly contribute to weight reduction [10]. However, in a 52-week
phase-III study, the canagliflozin-associated sustained UGE increases led to an initial period of weight loss followed by a plateau, during which a lower equilibrium body weight was maintained. Such a plateau in body weight is thought to be due to sustained increases in energy intakes that match the caloric loss due to UGE, with only minimal changes predicted in energy expenditures [39]. After a single 25-mg dose of empagliflozin, resting energy expenditures and meal-induced thermogenesis were superimposable on baseline values in patients with T2DM. Similarly, after chronic administration of empagliflozin 25 mg for 28 weeks, resting energy expenditure rates and those after meal ingestion remained unchanged [22], yet indirect calorimetry measurements showed a shift in substrate utilization from carbohydrate to lipid [22]. However, energy intake has yet to be carefully evaluated after SGLT-2 inhibition in humans. A recent study showed that the GLP-1 response to a mixed meal was increased after empagliflozin after both a single dose of 25 mg and chronic 4-week administration [22]. Knowing the anorectic effect of GLP-1, this GLP-1 potentiation may contribute to somewhat dampen appetite, although experimental data in rodents have suggested that the persistent UGE induced by dapagliflozin was accompanied by compensatory hyperphagia [40]. These animal observations are in agreement with findings in humans, showing less weight loss than predicted by the recurrent waste of calories through sustained increased glucosuria. Data from 86 T2DM subjects who received empagliflozin 25 mg/day for 90 weeks were retrospectively analyzed (data only available in abstract form). The relation of calorie-to-weight changes was estimated using a mathematical model to simulate the time course of weight loss for a given change in caloric balance. At week 90, weight loss averaged –3.2±4.2 kg while, over the 90 weeks, UGE averaged 54±15 g/day. The observed weight loss corresponded to a caloric deficit of –78±103 kcal/day. On the other hand, the observed caloric loss (–71±59 kcal/day) predicted a weight loss of –8.7±2.4 kg over the 90 weeks. Thus, patients lost only 38±53 % of the weight loss predicted by their glucosuria. As previous studies have shown that empagliflozin does not affect either resting or meal-induced energy expenditure, patients most likely increased their energy intakes (by an estimated 138±116 kcal/day) [22]. The conclusion was that chronic glucosuria elicits an adaptive increase in energy intake, particularly in leaner patients with preserved renal function. This conclusion has been supported by the results with empagliflozin 25 mg daily in a single-arm open-label proof-of-concept trial in patients with type 1 diabetes [41]. After 8 weeks, mean HbA1c decreased from 8.0±0.9 % to 7.6±0.9 % (p<0.0001), and daily insulin doses from 54.7±20.4 to 45.8±18.8 units/day (p<0.0001). UGE increased markedly from 18.9±19.1 to 33.5±61.1 g/24 h (p<0.0001) while body weight decreased only from 72.6±12.7 to 70.0±12.3 kg (p<0.0001). In the study, despite stable prandial insulin, carbohydrate intake increased from 177±121 to 229±160 g/24 h (p=0.0007) [41].

Thus, combining SGLT-2 inhibition with strategies to maintain energy intakes or to curb appetite is expected to be associated with greater weight loss [5,42]. The combination of an SGLT-2 inhibitor, such as canagliflozin, and an incretin mimetic/analgoue, such as liraglutide, results in improved glycaemic control accompanied by significant weight loss [43]. This combination needs to be studied in prospective randomized controlled trials, as the effect of each component of this combination appears to be synergistically magnified by the addition of the partnered drug [5].

### 3.2.2. Effects on hepatic glucose production

In ZDF rats, dapagliflozin treatment for 2 weeks significantly lowered glucose levels and resulted in a significant reduction in EGP accompanied by (as already discussed) a significant increase in muscle glucose utilization rate [24]. Glucotoxicity targets hepatic glucokinase in ZDF rats, a model of T2DM associated with obesity [44]. However, recent data in humans reported a paradoxical increase in EGP following SGLT-2 inhibition that induces glucosuria, an effect probably explained by a significant increase in glucagon secretion [13]. Increased basal EGP has also been reported in patients with T2DM treated with dapagliflozin [25], empagliflozin [22] and ipragliflozin (Table 1) [45]. Each of these three studies evaluated the inhibition of basal EGP using a dynamic test, a hyperinsulinaemic clamp, a mixed meal and an oral glucose tolerance test (OGTT), respectively. Whereas the suppression of EGP was similar with dapagliflozin and placebo during the hyperinsulinaemic clamp [25], the inhibition was significantly less pronounced with empagliflozin and ipragliflozin than without these SGLT-2 inhibitors during more physiological tests, a mixed meal [22] and an OGTT, respectively [45].

EGP before (baseline) and 2 weeks after treatment with dapagliflozin was measured by the euglycaemic-hyperinsulinaemic clamp technique in men with T2DM (Table 1) [25]. At baseline, EGP was 2.0±0.1 mg/kg/min and 2.1±0.1 mg/kg/min in the placebo-treated and dapagliflozin-treated groups (NS), respectively, and EGP was suppressed to 0.32±0.10 mg/kg/min and 0.34±0.10 mg/kg/min (NS), respectively, during the insulin clamp. During the insulin clamp performed on day 14, basal EGP was 2.11±0.10 mg/kg/min and 2.55±0.20 mg/kg/min in the placebo- and dapagliflozin-treated groups (p<0.05), respectively, while EGP was suppressed to 0.35±0.11 mg/kg/min and 0.22±0.10 mg/kg/min during the insulin clamp. Thus, glucosuria induction following SGLT-2 inhibition is associated with a paradoxical increase in EGP [25].

In the above-mentioned study where 66 patients with T2DM were evaluated during a mixed meal coupled with dual-tracer glucose administration at baseline after a single dose (25 mg) and 4 weeks of treatment with empagliflozin (25 mg/day), both the single-dose and chronic empagliflozin treatment caused glucosuria during fasting and after meal ingestion (Table 1) [22]. After 3 h of fasting, EGP was increased by 25%, while glycaemia was 0.9±0.7 mmol/L lower (p<0.0001 vs baseline). After meal ingestion, glucose and insulin AUC (area under the plasma concentration curve) decreased, whereas the glucagon response increased (all
Table 1

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Drug</th>
<th>Reference</th>
<th>Treatment</th>
<th>EG (μmol/kg/min)</th>
<th>FPG (mmol/L)</th>
<th>UGE (g/per)</th>
<th>Duration (days)</th>
<th>Before SGLT-2 inhibitor</th>
<th>After SGLT-2 inhibitor</th>
</tr>
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<tbody>
<tr>
<td>Ferrannini et al., 2014 [22]</td>
<td>IPRA</td>
<td>100 mg</td>
<td>RCT, parallel</td>
<td>66 ± 31</td>
<td>8.7 ± 1.6</td>
<td>37 ± 14</td>
<td>3</td>
<td>12 ± 8</td>
<td>8.7 ± 1.6</td>
</tr>
<tr>
<td>Smulders et al., 2013 [45]</td>
<td>IPRA</td>
<td>100 mg</td>
<td>RCT, parallel</td>
<td>66 ± 31</td>
<td>8.7 ± 1.6</td>
<td>37 ± 14</td>
<td>3</td>
<td>12 ± 8</td>
<td>8.7 ± 1.6</td>
</tr>
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Results are expressed as means ± SD or as medians [interquartile range]:
- Intravenous glucose injection (IVG, intravenous glucose clamp);
- Mixed meal;
- Oral glucose tolerance test (OGTT).

Effects of sodium-glucose cotransporter-2 (SGLT-2) inhibitors on urinary glucose excretion (UGE), fasting plasma glucose (FPG) and basal endogenous glucose production (EGP) in patients with type 2 diabetes mellitus (T2DM).


4. Conclusion

Although the primary mechanism of action of SGLT-2 inhibitors appears to be relatively simple and independent of insulin, complex secondary effects have recently been observed. The increased inhibition of basal EGP during dynamic tests (duration 8.7 ± 1.6 days) with SGLT-2 inhibitors appears to be relatively simple and independent of other effects such as increased plasma insulin levels resulting in basal EGP inhibition. A dose of 10 mg (DAPA) and 25 mg (EMPA) canagliflozin was sufficient to reduce EGP by 0.68 ± 1.5 μmol/min/kg and 0.91 ± 1.4 μmol/min/kg, respectively (p < 0.05 vs placebo). However, the lower insulin response can be explained by lower glucose levels which remain the main drivers of insulin secretion. In patients treated with SGLT-2 inhibitors, the prehepatic insulin/glucagon molar concentration ratio was significantly decreased compared with baseline in both the fasting state and post-prandial phase. These differences were already apparent after a single 25-mg dose of empagliflozin and persisted after chronic administration for 28 days (p < 0.0001) [22]. The lower insulin response can be easily explained by lower glucose levels which remain the main drivers of insulin secretion. Multiple factors could be contributing to the relative hyperglucagonaemia, although the precise underlying mechanisms remain unclear [22]. One explanation might be the lower insulin levels because of the well-known paracrine feedback loop between beta and alpha cells. Another intriguing recently proposed mechanism is that inhibition of SGLT-2 activity might directly induce glucagon secretion by alpha cells [47].

An increase in EGP was also reported with ipragliflozin. Both healthy subjects and patients with T2DM received ipragliflozin 100 mg or placebo once daily for 6 days in a two-period crossover design. During each period, an OGTT with a double-tracer methodology was performed at baseline and on day 6 (data published only in abstract form) [45]. Baseline EGP increased significantly (p < 0.05) after ipragliflozin compared with placebo in both healthy subjects and T2DM patients (+0.68 ± 1.5 and +0.91 ± 1.4 μmol/min/kg, respectively; Table 1). After an oral glucose load, the OGTT-related EGP decrease was less with ipragliflozin than with placebo (p < 0.01) in both healthy subjects and T2DM patients.

No detailed study has investigated the effects of canagliflozin on glucose turnover, especially its effects on EGP. Because of the unique effect of canagliflozin on SGLT1 cotransporters (see above section on ‘Effects on insulin secretion’), it would be of interest to investigate whether canagliflozin may have differential effects on EGP in the fasting state and postprandial phase compared with other SGLT-2 inhibitors.
reported that should be taken into account in any complete evaluation of this novel pharmacological class for the management of T2DM. Because of the reduction in hyperglycaemia and correction of the so-called glucotoxicity, both insulin secretion and peripheral insulin sensitivity may be improved, thereby reinforcing the glucose-lowering activity of the drugs. Furthermore, the potential contribution of the low-potency inhibition of SGLT1 exerted by canagliflozin in the gut to control of postprandial hyperglycaemia in T2DM patients deserves further investigation. However, increased UGE may also trigger compensatory mechanisms that may limit weight loss while avoiding hypoglycaemia. These mechanisms are most likely similar to those involved in individuals with a mutation of SGLT-2 that leads to familial renal glucosuria. Indeed, such subjects maintain normal body weight and normal plasma glucose levels despite sustained, lifelong glucosuria. Nevertheless, despite these compensatory mechanisms (increased food intakes and increased EGP), patients with T2DM treated by SGLT-2 inhibitors show improvements in fasting and postprandial plasma glucose levels as well as weight reduction, two main objectives in the management of T2DM. Combining SGLT-2 inhibitors with strategies to inhibit EGP and to limit energy intakes may magnify the success of the therapy in overweight/obese patients with T2DM.

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