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Efficacy and Safety of SGLT2 Inhibitors in Patients with Type 1 Diabetes: A Meta-analysis of Randomized Controlled Trials

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Objective To assess the efficiency and safety of a novel sodium-glucose co-transporter 2 (SGLT2) inhibitor—SGLT2 inhibitors, in combination with insulin for type 1 diabetes mellitus (T1DM).

Methods We searched Medline, Embase, and the Cochrane Collaboration Library to identify the eligible studies published between January 2010 and July 2016 without restriction of language. The Food and Drug Administration (FDA) data and ClinicalTrials (<http://www.clinicaltrials.gov>) were also searched. The included studies met the following criteria: randomized controlled trials; T1DM patients aged between 18 and 65 years old; patients were treated with insulin plus SGLT2 inhibitors for more than 2 weeks; patients' glycosylated hemoglobin (HbA1c) levels were between 7% and 12%. The SGLT2 inhibitors group was treated with SGLT2 inhibitors plus insulin, and the placebo group received placebo plus insulin treatment. The outcomes should include one of the following items: fasting blood glucose, HbA1c, glycosuria, or adverse effects. Data were analyzed by two physicians independently. The risk of bias was evaluated by using the Cochrane Collaboration's Risk of Bias tool and heterogeneity among studies was assessed using Chi-square test. Random effect model was used to analyze the treatment effects with Revman 5.3.

Results Three trials including 178 patients were enrolled. As compared to the placebo group, SGLT2 inhibitor absolutely decreased fasting blood glucose [mean differences (*MD*) -2.47 mmol/L, 95% confidence interval (*CI*) -3.65 to -1.28 , $P < 0.001$] and insulin dosage (standardized *MD* -0.75 U, 95% *CI* -1.17 to -0.33 , $P < 0.001$). SGLT2 inhibitors could also increase the excretion of urine glucose (*MD* 131.09 g/24 h,

95%CI 91.79 to 170.39, $P<0.001$). There were no significant differences in the incidences of hyperglycemia [odds ratio (OR) 1.82, 95%CI 0.63 to 5.29, $P=0.27$], urinary tract infection (OR 0.95, 95%CI 0.19 to 4.85, $P=0.95$), genital tract infection (OR 0.27, 95%CI 0.01 to 7.19, $P=0.43$), and diabetic ketoacidosis (OR 6.03, 95%CI 0.27 to 135.99, $P=0.26$) between the two groups.

Conclusion SGLT2 inhibitors combined with insulin might be an efficient and safe treatment modality for T1DM patients.

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EARLY initiation of basal insulin has been applied not only for type 1 diabetes mellitus (DM) but also type 2 DM, but this kind of therapy will increase the risk of weight gain and the event of hypoglycemia. For type 2 DM, various oral drugs such as metformin, sulphonylureas, α -glucosidase inhibitor, dipeptidyl peptidase-4 inhibitors (DDP-4 inhibitor), glucagon-like peptide-1 receptor agonist and thiazolidi-nedione combined with insulin were prescribed for patients with lower insulin resistance and blood glucose level.¹ Sodium-glucose co-transporter 2 (SGLT2) inhibitors, a new class of oral anti-hyperglycemic agents available to treat type 2 DM, were approved by Food and Drug Administration (FDA) in March 2013. Dapagniflozin, enpagliflozin, and capagniflozin are the three major SGLT2 inhibitors to be used in type 2 DM therapy. SGLT2 expressing in the proximal renal tubules accounts for about 90% of glucose reabsorption from tubular fluid, thus inhibiting SGLT2 expression can block glucose reabsorption by the kidney, and then increasing glucose excretion, finally lowering blood glucose levels of diabetes patients.² Therefore, it is regarded SGLT2 inhibitors regulate blood glucose through non-insulin dependent mechanism. Previous studies indicated that SGLT2 inhibitors could lower glycemic level either as a mono-therapy or combined with insulin and other anti-hyperglycemic drugs.^{1, 3} However, SGLT2 inhibitors have not yet been approved for use in type 1 DM treatment.

Several large randomized trials are undergoing in order to elucidate the potentials of SGLT2 inhibitors as add-on therapy to insulin for patients with type 1 diabetes. Here, the efficiency and safety of SGLT2 inhibitors combined with insulin for type 1 diabetes patients were investigated by doing a meta-analysis of randomized controlled trials.

MATERIALS AND METHODS

Search strategy

We searched Medline, Embase, and the Cochrane Collaboration Library to identify the studies reported from January 2010 to July 2016, without restriction of country, race, language or publication year. The Food and Drug

Administration (FDA) data and ClinicalTrials (<http://www.clinicaltrials.gov>) were also searched. The following terms were used: "sodium-glucose co-transporter 2 inhibitor", "SGLT2 inhibitor", "sotagliflozin", "canagliflozin", "dapagliflozin", "tofogliflozin", "Invokana", "enpagniflozin", "JNJ28431754", "Farxiga", "Jardiance", "T1DM", and "Type 1 diabetes". These terms were adjusted to comply with the rules of each database.

Inclusion criteria and exclusion criteria

Inclusion criteria were: (1) Randomized or quasi-randomized controlled trials. (2) Patients who were diagnosed with type 1 DM according to the WHO diagnostic criteria⁴ aged between 18 and 65 years old, with glycosylated hemoglobin (HbA1c) level between 7% and 12%. (3) Studies compared the efficiency and safety of SGLT2 inhibitors plus insulin vs. placebo plus insulin irrespective of the dose and the type of SGLT2 inhibitor and insulin. The insulin therapy could be multiple daily injections consisting of long-acting (basal) plus short-acting insulin or continuous subcutaneous insulin infusion pump. (4) The route of insulin administration for the placebo patients was the same as the experimental patients. (5) The primary outcomes were one of the following items: fasting blood glucose (FBG), HbA1C, urine glucose, or adverse reactions.

Exclusion criteria were: (1) case report, case review and non-randomized controlled trials; (2) studies in which SGLT2 inhibitors were used as mono-therapy in the experimental group; (3) studies in which the placebo group did not receive therapy or placebo.

Selection of eligible studies and data collection

First, randomised or quasi-randomised controlled trials were identified through screening title or abstract (if necessary). Further, eligible studies that satisfied the inclusion and exclusion criteria were included by two reviewers (Yingying Yang and Shi Chen) independently through reviewing abstract or full text (if necessary). Discrepancies were resolved by discussion between the two reviewers and unresolved disagreement was referred to a third reviewer (Huijuan Zhu).

Our final outcomes include one of the following items:

FBG, HbA1c, glycosuria, or adverse effects (hypoglycemia, diabetic ketoacidosis, urinary infection and reproductive tract infection). The definition of hypoglycemia referred to blood glucose <4 mmol/L according to the WHO diagnosis criteria,⁴ other outcomes were considered and diagnosed by professional physicians with patients' symptoms. Similarly, all outcome data were analyzed by two authors (Yingying Yang and Shi Chen), the questions that they disagree were discussed together with another reviewer (Huijuan Zhu).

Assessment of bias risk

Two reviewers (Yingying Yang and Shi Chen) independently used the Cochrane Collaboration's Risk of Bias tool (Review Manager Software Version 5.3) to assess risk of bias, based on the following aspects: random sequence generation, allocation concealment, blinding, incomplete data regarding outcome, selective reporting, and other bias (e.g., groups comparable at baseline, funder, and incomplete information).

Statistical analysis

All outcomes comparisons were performed by using the RevMan 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). For continuous data, mean difference (MD) and 95% confidence intervals (CIs) were calculated to evaluate the influence of SGLT2 inhibitors on the outcomes. When different scales were used, the standardized MD (SMD) was calculated. For discontinuous data, odds ratio (OR) and 95% CIs were used

to estimate the safety of SGLT2 inhibitors. When standard deviation (SD) was not given, an e-mail will be sent to corresponding authors to get further information. When necessary, the value of SD was calculated from CI or standard error as described in the Cochrane Handbook.

Heterogeneity among studies was assessed using Chi-square test and I^2 statistics, and random-effect model was adopted regardless of I^2 . A P value of <0.05 was considered as statistically significant.

RESULTS

Characteristics of the included studies

We identified 13 reports. Of them, 10 studies including 7 studied on type 2 diabetes, 1 case report, 1 non-RCT, and 1 study with intervention duration less than 2 weeks were eliminated. Finally, 3 eligible studies (178 participants) were included.⁵⁻⁷ Two studies were IIa pilot trial; two were multi-center studies. Table 1 shows the characteristics of the 3 included studies. All studies had relatively a low risk of bias (Table 2).

Efficiency of SGLT2 inhibitor

There was no significant heterogeneity among 3 studies ($P=0.28$, $I^2=20\%$). The meta-analysis using the random effects model showed that SGLT2 inhibitors could absolutely reduce FBG compared with placebo (MD -2.47 mmol/L, 95% CI -3.65 to -1.28 , $P<0.0001$) (Fig. 1).

We found no significant heterogeneity among studies

Table 1. Characteristic of the 3 eligible studies

Studies	Participates			Intervention		FBG (mmol/L)	Insulin(n)		Duration
	<i>n</i>	Age (yrs, range)	BMI (kg/m ²)	SGLT2 inhibitors	Placebo		Multiple daily injections	Continuous subcutaneous insulin infusion pump	
Henry <i>et al</i> ⁶	70	18-65	24.8	Dapagliflozin 10 mg	Placebo	8.6	37	33	2 weeks
Pieber <i>et al</i> ⁶	75	18-65	25.7	Empagliflozin 25 mg	Placebo	9.8	75	0	4 weeks
Sands <i>et al</i> ⁷	33	18-55	26.6	Sotagliflozin 400 mg	Placebo	9.16	11	22	29 days

BMI: body mass index; FBG: fasting blood glucose; SGLT2: sodium-glucose co-transporter 2.

Table 2. Summary of bias risk of the 3 eligible studies

Studies	Method of allocation	Allocation concealment	Blinding	Data integrity	Selective reporting	Other source of bias	Risk of bias
Henry <i>et al</i> ⁶	Yes	No	Yes	Yes	*	No	Low
Pieber <i>et al</i> ⁶	Yes	Yes	Yes	*	No	*	Low
Sands <i>et al</i> ⁷	Yes	Yes	Yes	*	No	No	Low

*: unclear risk of bias.

($P=0.57$, $I^2=0$). Meta-analysis using the random effects model revealed that SGLT2 inhibitors could significantly decrease insulin dose compared with placebo ($SMD -0.75$ U, 95%CI -1.17 to -0.33 , $P<0.001$) (Fig. 2).

There was no significant heterogeneity among studies ($P=0.45$, $I^2=0$). The meta-analysis using the random effects model showed that SGLT2 inhibitors combined with insulin could significantly increase urine glucose compared

with placebo (MD 131.09 g/24h, 95%CI 91.79 to 170.39, $P<0.00001$) (Fig. 3).

Side effects of SGLT2 inhibitor

There was no significant difference in hypoglycemia accident between the SGLT2 inhibitor group and the placebo group (OR 1.82, 95%CI 0.63 to 5.29, $P=0.27$; Fig. 4). Hypoglycemia occurred in 1 patient in Pieber *et al's* study.⁶

Figure 1. Forest plot of FBG in the SGLT2 inhibitor *versus* the placebo groups.

SD: standard deviation; IV: inverse variance; CI: confidence interval.

Figure 2. Forest plot of insulin dose in the SGLT2 inhibitor *versus* the placebo groups.

Figure 3. Forest plot of urine glucose in the SGLT2 inhibitor *versus* the placebo groups.

Figure 4. Forest plot of hypoglycemia in the SGLT2 inhibitor *versus* the placebo groups.

There was no heterogeneity among 3 studies ($P=0.57$, $I^2=0$). No significant difference occurred in urinary tract infection incidence between the SGLT2 inhibitor group and placebo group (OR 0.95, 95% CI 0.19 to 4.85, $P=0.95$) (Fig. 5).

Two studies including 55 participates recorded the risk of genital tract infection. Two studies with 61 participates reported the risk of DM ketoacidosis. But our data revealed that SGLT2 inhibitor did not increase the risk of genital tract infection (OR 0.27, 95% CI 0.01 to 7.19, $P=0.43$) and DM ketoacidosis (OR 6.03, 95% CI 0.27 to 135.99, $P=0.26$) when compared with the placebo group.

DISCUSSION

Insulin therapy plays a crucial part in type 1 DM. Many patients have achieved normal HbA1C by the replacement therapy of insulin. However, insulin will lead to increased weight and a sequence of microvascular complications. Previous research showed that even large doses of insulin could not improve the insulin resistance in obese patients with type 1 diabetes. Instead, this insulin therapy could increase the occurrence of hypoglycemia.⁸ Therefore, SGLT2 inhibitors are rendered as a promising addition to the current therapeutic options in type 1 DM. It decreases blood glucose by reabsorption of glucose from tubular fluid without insulin.⁹

In the current systematic review, we evaluated the efficiency and safety of SGLT2 inhibitor usage as an add-on insulin therapy in type 1 DM. Three studies were included in our research, and Cochrane risk bias tool was used to evaluate the risk of bias. As a result, the three studies evaluated had a low risk of bias, thus increasing the reliability of the results. Four limitations merit consideration. Firstly, total sample size in our included studies was small, therefore, it may increase the incidence of random error and more study will have to be replicated with a larger sample size. Secondly, during the process of data extraction,

one study did not give the data we needed, so we have not performed sensitivity analyses that may influence the veracity and objectivity of the result. Thirdly, durations of studies included in this meta-analysis were short, study periods were insufficient and longer duration of observation is necessary to understand the long-term benefits and risks of SGLT2 inhibitors in type 1 DM. Finally, all studies we included were in English and published the positive result which may lead to systematic error.¹⁰

Compared to placebo, SGLT2 inhibitors significantly lowered FBG levels, which were consistent with the results reported in previous meta-analyses (MD -2.47 mmol/L, 95% CI -3.65 to -1.28, $P<0.05$). It also showed that FBG in most of patients treated by SGLT2 inhibitors plus insulin was <7.0 mmol/L. It has been demonstrated that many vascular diseases were related to high level of FBG and controlling glucose could slow the progression of long-term complications.¹¹ This glycemic control was achieved without an increase in the daily mean insulin requirement that will result in weight gain and insulin resistance ($P=0.57$, $I^2=0$, SMD -0.75 U, 95% CI -1.17 to -0.33, $P<0.001$), indicating that SGLT2 inhibitors can also decrease the complications in type 1 DM. Moreover, we found SGLT2 inhibitors greatly increased the urine glucose extraction ($P=0.45$, $I^2=0$; MD 131.09 g/24 h, 95% CI 91.79 to 170.39, $P<0.001$) as other research reported.¹² A meta-analysis has shown that SGLT2 inhibitor could achieve the lowest odds of hypoglycemia as combination therapy with metformin in patients with type 2 DM.¹³ The effect of reducing hypoglycemia events was also proved in a limited number of studies.¹⁴ There was no difference in event of hypoglycemia between two groups (OR 1.82, 95% CI 0.63 to 5.29, $P=0.27$). Even though prior studies have shown that urinary tract infection was connected with SGLT2 inhibitors.¹⁵ Our meta-analysis demonstrated that urinary tract infection had a small increase in the SGLT2 group but with no statistical significance (OR 0.95, 95% CI 0.19 to 4.85, $P=0.95$). Only one case of urinary tract infection

Figure 5. Forest plot of urinary tract infection in the SGLT2 inhibitor *versus* the placebo groups.

happened in the 2.5 mg group of Pieber *et al*'s study (not the highest dose).⁶ In our meta-analysis, the risk of genital tract infection with SGLT2 inhibitor was similar to that of placebo (*OR* 0.27, 95%*CI* 0.01 to 7.19, *P*=0.43). This needs to be stressed that an incident of genital tract infection was observed in both 1 mg and 5 mg group of Henry *et al* study.⁵ However, our meta-analysis showed that the rate of DM ketoacidosis in the SGLT2 inhibitor treatment group was not significantly different from that of the control group (*OR* 6.03, 95%*CI* 0.27 to 135.99, *P*=0.26). FDA warned that SGLT2 inhibitor has potential risks of DM ketoacidosis in type 2 DM in 2015.¹⁶ But American Association of Clinical Endocrinologists of American College of Endocrinology (AACE) claimed that it's still unclear if SGLT2 inhibitors will lead to DM ketoacidosis recently, because most of SGLT2 related DM ketoacidosis easily occurred in patients who were insulin deficient. That may be the reason why some researches show that SGLT2 inhibitor will cause DM ketoacidosis in patients with type 1 DM who indeed lack insulin. We suggest that DM ketoacidosis should be considered if patients presented with the symptoms like abdominal pain, vomiting and nausea during a SGLT2 inhibitors use.¹⁷

In summary, SGLT2 inhibitors were effective and safe for type 1 DM as an add-on therapy of insulin. It improved FBG remarkably in type 1 DM without increasing the risks of hypoglycemia, urinary tract infection, genital tract infection and DM ketoacidosis. Even though there were adverse events occurred in each SGLT2 inhibitor group, but it was hard to prove that these events were related to the use of SGLT2 inhibitor. Our meta-analysis indicated that SGLT2 inhibitor will be promising for the application in type 1 DM, but more large, multi-center trials will be needed to clarify the efficacy and safety of SGLT2 inhibitors combined with insulin in subjects with type 1 diabetes.

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