Efficacy and safety of SGLT-2i in overweight/obese, non-diabetic individuals: a meta-analysis of randomized controlled trials

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Abstract

Introduction: Sodium-glucose cotransporter 2 inhibitor (SGLT-2i) has been shown to decrease blood glucose levels in type 2 diabetes mellitus (T2DM) patients and potentially yield additional benefits in weight loss. This meta-analysis aimed to investigate the efficacy and safety of giving SGLT-2i to overweight/obese, non-diabetic individuals.

Material and methods: The search was underpinned by PubMed, Cochrane Central Register of Controlled Trials, Web of Science, and Springer to identify English-language papers on randomized controlled trials (RCTs) on the use of SGLT-2i in overweight/obese, non-diabetic individuals published in and before March 2021, to study its effectiveness and safety. Results were evaluated by weighted mean difference (WMD), standardized mean difference (SMD), risk ratio (RR), and 95% confidence interval (CI).

Results: We reviewed 13 papers and compared the SGLT-2i group with the control group (other drugs and placebo) and found that SGLT-2i reduced weight (WMD = –1.33, p = 0.002) and waist circumference (WMD = –1.94, p = 0.03) in overweight/obese, non-diabetic individuals. The use of SGLT-2i is more effective than other interventions in terms of weight loss ≥ 5% (RR = 2.04, p < 0.001), but not in terms of weight loss ≥ 10% (RR = 1.83, p = 0.22). In addition, there were no significant changes in other metabolic parameters, like fasting plasma glucose (FPG), lipids, blood pressure, etc. SGLT-2i increased the risk of infections in urinary tract (RR = 1.91, p = 0.009) and reproductive system (RR = 4.09, p < 0.001).

Conclusions: SGLT-2i is a promising candidate to reduce weight and waist circumference to a limited extent in overweight/obese, non-diabetic individuals. Generally, it is safe and effective. However, it potentially increased the risk of urogenital infections, which cannot be ignored. **(Endokrynol Pol 2022; 73 (1): 71–80)**

Key words: SGLT-2i; overweight; obese; weight reduction; non-diabetic; meta-analysis

Introduction

With the rapid development of social economy, the way of people's life and diet have undergone great changes. Overweight [body mass index (BMI) ≥ 25 kg/m²] and obesity (BMI ≥ 30kg/m²) have become a seriously public health problem [1]. Currently, approximately 1.9 billion adults around the world are overweight or obese [2]. Alarmingly, an elevated BMI is associated with increased risk of various kinds of chronic diseases, including cardiovascular disease, diabetes, cancers, etc. [3].

At present, non-surgical treatments for obesity, such as lifestyle intervention and dietary restrictions, need strict self-control of the patients and the processes are painful and arduous [4]. Hence, achieving an ideal weight or maintaining long-term weight loss process may be difficult from an individual's perspective. Obesity control guidelines recommend lifestyle interventions and medication for the overweight population [5]. So far, only four kinds of anti-obesity drugs (orlistat, phentermine/topiramate, naltrexone/bupropion, and liraglutide/semaglutide) have been approved by the US Food and Drug Administration for sustained weight management [5, 6]. The effectiveness of orlistat, phentermine/topiramate, and naltrexone/bupropion is limited, the safety is unknown, and the use cycle is long. According to the limited data available, some glucagon-like peptide 1 receptor agonists (liraglutide/semaglutide) can lead to good weight loss and have high safety [6]. At present, more efforts are being made to seek new anti-obesity drugs with higher efficacy and more assured safety.

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Sodium-glucose cotransporter 2 inhibitor (SGLT-2i) is a class of drugs registered, according to the product characteristics, for the treatment of not only type 2 diabetes mellitus (T2DM) but also for people without carbohydrate disorders presenting heart failure and/or chronic kidney disease. Furthermore, T2DM patients treated with SGLT-2i have shown significant weight loss compared to those with placebo [7]. Therefore, some randomized controlled trials (RCTs) are designed to apply SGLT-2i to overweight/obese, non-diabetic individuals in order to reduce body weight with protection in cardiac and renal function. Some results have been obtained, but the conclusions have not been widely accepted due to the limited sample sizes. In order to enhance the credibility of the conclusions and further explore the safety and effectiveness of SGLT-2i, especially in terms of weight of the overweight/obese with non-diabetic individuals, this meta-analysis was performed.

Material and methods

Literature search

This meta-analysis was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [8]. Two researchers conducted a comprehensive, systematic search from the PubMed, Cochrane Central Register of Controlled Trials, Web of Science, and Springer databases. English literature documenting data was retrieved, published in March 2021 and before, on RCTs of the use of SGLT-2i in overweight/obese, non-diabetic individuals, to study the efficacy and safety of SGLT-2i in weight loss and other aspects in this population. The retrieval formula is as follows: (dapagliflozin OR canagliflozin OR empagliflozin OR ipragliflozin OR tofogliflozin OR ertugliflozin OR luseogliflozin OR bexagliflozin OR sotagliflozin OR janagliflozin OR sergliflozin OR licogliflozin OR remogliflozin OR sodium-glucose cotransporter 2 inhibitors OR sodium-glucose cotransporter 2 inhibitor OR SGLT-2i) AND (obesity OR corpulence OR fat OR overweight OR overload weight). We identified the included studies by browsing titles and abstracts, viewing full texts and supplementary materials.

Study selection and quality assessment

Inclusion criteria for this meta-analysis were as follows: (1) the overweight/obese, non-diabetic individuals were included in RCTs with SGLT-2i being used as monotherapy or as a supplement of non-surgical treatment in the intervention group; (2) vital parameters: changes in body weight, waist circumference, and metabolic indicators, including but not limited to fasting plasma glucose (FPG), blood pressure, lipids, and adverse effects were recorded in RCTs; (3) follow-up time ≥ 8 weeks. Exclusion criteria: (1) non-English language; (2) data unavailable; (3) duplicate reports. When the article was updated, the most recent or most complete article was selected.

Based on the above inclusion criteria, the two researchers independently evaluated the eligible studies, further discussed the parts causing disagreement, or asked a third researcher to review the controversial articles. The Cochrane Collaboration's tool was applied to accomplish quality assessment of the included studies and the risk of bias by reviewing and judging in terms of sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and lack of other bias.

Data extraction

Data extracted from the studies included the following: (1) basic study characteristics, such as author, publication year, region, Clinical Trials.gov identifier, inclusion criteria, follow-up time, drugs and dose, or other interventions in the experimental group and control group; (2) outcomes, including weight-related changes; waist circumference changes; and metabolism-related indicators, such as FPG, blood pressure, lipids, etc.; (3) detailed data on adverse events occurred in the experimental and control groups. The data not available in the papers, including full texts and supplementary materials, will be supplemented by excerpting study results in Clinical Trials.gov (if it is registered). Data extraction was done independently by two researchers and reviewed by a third researcher.

Statistical analysis

Review Manager 5.3 statistical analysis software was used for this analysis. The weighted mean difference (WMD) or standardized mean difference (SMD) and 95% confidence interval (CI) were calculated to assess continuous variables. Risk ratio (RR) and 95% CI were calculated to evaluate dichotomous variables. Due to the different types of SGLT-2i included in the study and the diversity of intervention measures in the control group, we applied a random effects model for analysis. $p \leq 0.05$ was statistically significant. Publication bias was appraised via a funnel plot.

Results

Search results and study characteristics

A total of 3271 papers were identified: 3270 papers were searched from the database through the retrieval formula, and 1 paper was identified by other sources. 796 papers were left after deletion of duplicates. 771 articles were successively deleted by reviewing the titles and abstracts. After revision of 25 full texts, 12 were excluded, including 1 without available data, 5 duplicate studies, 5 with a study population of diabetic patients, and 1 with a follow-up time that was less than 8 weeks. Finally, a total of 13 studies were included for this meta-analysis [9–21] (Fig. 1).

The included studies were published from 2014 to 2021 and the range of their follow-up time was 8–48 weeks. All the included participants were overweight/obese (baseline BMI ≥ 25 kg/m²), non-diabetic individuals. The experimental group was given SGLT-2i as an intervention, including canagliflozin, licogliflozin, dapagliflozin, empagliflozin, remogliflozin, and sergliflozin. The interventions that were applied to the control group included placebo, metformin, phentermine, exercise, and no intervention. These RCTs were conducted in different countries: 5 in the United States, 1 in the United States and Puerto Rico, 2 in the United Kingdom, 1 in Denmark, 1 in Mexico, 1 in Iran, 1 in Japan, and 1 multi-country, multicentre study (Tab. 1).

Risk of bias assessment

Due to incomplete information, the risk of sequence generation in 5 studies was unclear, and the risk in 8 studies was low. In terms of allocation concealment,
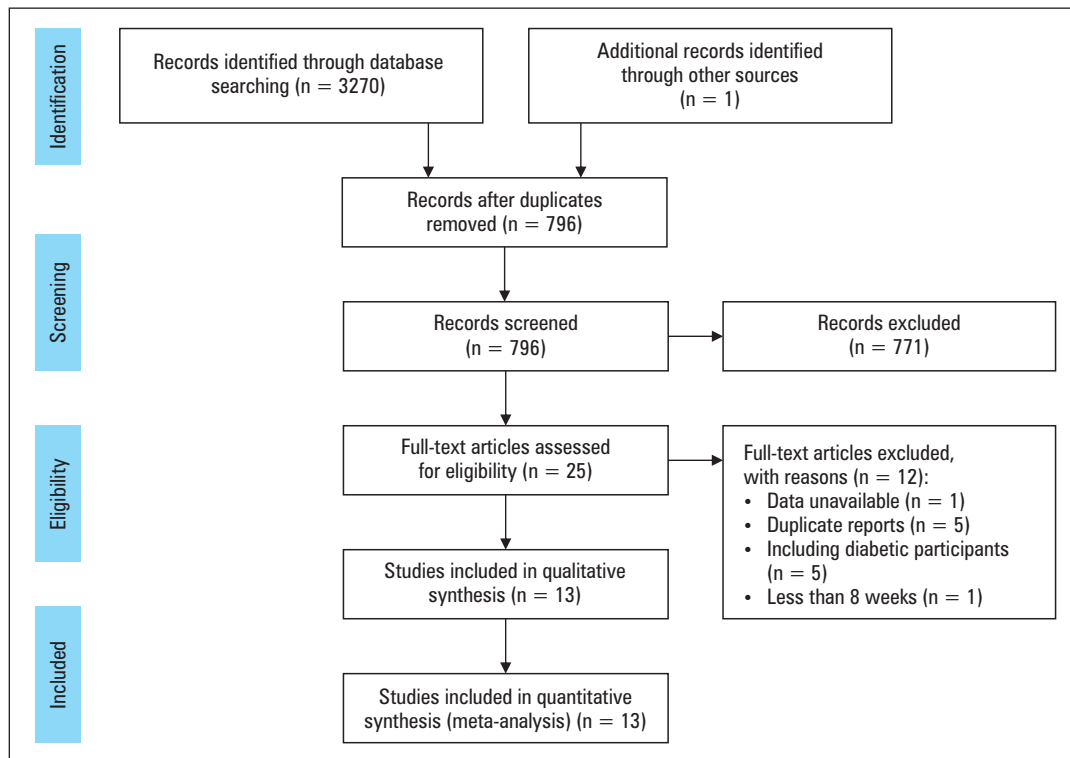
Figure 1. *A schematic flow for selecting the articles included in this meta-analysis*

7 studies were in low risk and 6 studies were unclear. As for blinding, 2 trials possessed high risk of bias, 1 was unclear, and the remaining 10 studies were low. In most studies, both incomplete outcome data and selective outcome reporting assessments were of low risk of bias, and only 1 study was unable to clearly determine the selective outcome reporting. In the aspect of lack of other bias, it was difficult to obtain accurate evaluations for all studies, some of which were thus judged as unclear (Supplementary File — Tab. 1).

Efficacy outcomes on weight and waist circumference

An analysis involving 648 participants showed that SGLT-2i significantly reduces body weight compared with the control group (WMD = –1.33, 95% CI = –2.17 to –0.50, p = 0.002) (Fig. 2A). Also, 3 studies indicated that SGLT-2i significantly reduces weight percentage (WMD = –1.52, 95% CI = –2.04 to –1.00, p < 0.001) (Fig. 2b).

Two studies with 540 participants involved revealed that SGLT-2i reduces waist circumference in overweight/obese, non-diabetic individuals (WMD = –1.94, 95% CI = –3.73 to –0.14, p = 0.03) (Fig. 3A). In addition, the percentage reduction in waist circumference in 103 subjects also indicated significant benefit of using SGLT-2i (WMD = –3.00, 95% CI = –5.48 to –0.52, p = 0.02) (Fig. 3B).

Furthermore, 345 of the 1645 participants in 5 studies experienced a ≥ 5% weight decrease. 208 out of the 743 participants in the SGLT-2i intervention group, and 137 of the 902 patients in the control group had weight loss ≥ 5%. In short, SGLT-2i is significantly advantageous in weight decrease (≥ 5%) (RR = 2.04, 95% CI = 1.51 to 2.76, p < 0.001) (Fig. 4). Whereas, when weight loss was ≥ 10%, there was no significant difference between SGLT-2i and the control group (RR = 1.83, 95% CI = 0.70 to 4.76, p = 0.22) when looking at the combined data of 12 weeks and 26 weeks from these 2 studies (Fig. 5).

Other metabolic conditions

In terms of blood glucose, data of 5 studies showed no significant effect of SGLT-2i on FPG (SMD = –0.33, p = 0.27) in overweight/obese, non-diabetic individuals. Similarly, for blood pressure we found that, comparing with the controlled group, SGLT-2i was not correlated with systolic blood pressure (SBP) (WMD = 1.86, p = 0.39) or diastolic blood pressure (DBP) (WMD = 0.13, p = 0.92). As for lipid-wise parameters, SGLT-2i was shown to have no significant effect on high-density lipoprotein cholesterol (HDL-C) (SMD = 0.03, p = 0.86), low-density lipoprotein cholesterol (LDL-C) (SMD = –0.07, p = 0.73), total cholesterol (TC) (SMD = –0.03, p = 0.87), and triglyceride (TG) (SMD = –0.07, p = 0.69). We also found that alanine aminotransferase (ALT) (WMD = 1.86, p = 0.39), aspar-

Table 1. *Characteristics of all the studies included in the meta-analysis*

Author	Year	Country	Clinical Trials.gov Identifier	Follow-up time [weeks]	Drug Experiment	Drug Control	Inclusion criteria
Bays	2014	United States and Puerto Rico	NCT00650806	12	Canagliflozin 50/100/300 mg	Placebo	18–65-year-olds with BMI ≥ 30 and < 50 kg/m² or ≥ 27 and < 50 kg/m² in the presence of controlled hypertension and/or treated or untreated dyslipidaemia; serum creatinine ≤ 1.5 mg/dL for men and ≤ 1.4 mg/dL for women; FPG < 7.0 mmol/L
Bays	2020	Multicentre	NCT03100058	24	Licogliflozin 2.5/10/50/150 mg	Placebo	18–75-year-olds with BMI ≥ 30 kg/m² or ≥ 27 kg/m² combined with at least one obesity complication
					Licogliflozin 2.5/5/25/50 mg	Placebo	
				24–48	Licogliflozin 25/35 mg	Placebo	
Elkind-Hirsch	2020	United States	NCT02338193	24	Dapagliflozin 5 mg + Metformin XR 1000 mg	Metformin XR 1000mg	18–45-year-old females with BMI > 25 kg/m²; GDM during recent (within 12 months) pregnancy; no DM
					Dapagliflozin 10 mg	Metformin 1700 mg	
Faerch	2021	Denmark	NCT02695810	26	Dapagliflozin 10 mg	Exercise / No intervention	30–70-year-olds with BMI ≥ 25 kg/m²; prediabetes HbA_{1c} 39–47 mmol/mol [5.7–6.4%]
Hollander	2017	United States	NCT02243202	26	Canagliflozin 300 mg + Phentermine 15 mg	Phentermine 15 mg	18–65-year-olds with BMI ≥ 30 and < 50 kg/m² or ≥ 27 and < 50 kg/m² with comorbidities of hypertension and/or dyslipidaemia; stable dose of antihypertensive or lipid-modifying medications for ≥ 4 weeks before screening; no DM
					Canagliflozin 300 mg	Placebo	
Javed	2019	United Kingdom	NCT03008551	12	Empagliflozin 25 mg	Metformin 1500 mg	18–45-year-olds with BMI ≥ 25 kg/m²; PCOS based on Rotterdam criteria; irregular periods and biochemical hyperandrogenaemia
Napolitano	2014	United Kingdom	NA	8	Remogliflozin etabonate 250 mg	Placebo	18–55-year-olds with BMI 30–40 kg/m²; no T2DM
					Sergliflozin etabonate 1000 mg		
Neeland	2020	United States	NCT02833415	12	Empagliflozin 10 mg	Placebo	≥ 18 years old with BMI ≥ 30 kg/m²; no T2DM; be able to undergo a neck-to-knee magnetic resonance imaging scan for body fat assessment
Newman	2019	United States	NCT02371187	12	Dapagliflozin 10 mg + Exercise	Placebo + Exercise	18–50-year-olds with BMI 25–45 kg/m²; sedentary lifestyle; willing to perform endurance exercise; no T2DM
Ramirez-Rodriguez	2020	Mexico	NCT02700334	12	Dapagliflozin 10 mg	Placebo	30–60-year-olds with prediabetes based on American Diabetes Association criteria and without pharmacological treatment
Ryan	2020	United States	NCT03180489	12	Dapagliflozin 10 mg + dietary counselling	Placebo + dietary counselling	18–65-year-olds with BMI ≥ 27.5 kg/m²; limited exercise participation
Taheri	2020	Iran	IRCT20190122 042450N1	24	Empagliflozin 10 mg	Placebo	20–65-year-olds with NAFLD; no T2DM
Yokote	2020	Japan	NCT03320941	12	Licogliflozin 2.5/10/25/50 mg	Placebo	20–75-year-olds with BMI ≥ 25 kg/m² combined with at least two obesity-related comorbidities or BMI ≥ 35 kg/m² with at least one obesity-related comorbidity; waist circumference at umbilical level, ≥ 85 cm for men and ≥ 90 cm for women; visceral fat area ≥ 100 cm²

NA — not available; BMI — body mass index; FPG — fasting plasma glucose; DM — diabetes mellitus; GDM — gestational diabetes mellitus; T2DM — type 2 diabetes mellitus; XR — extended release; PCOS — polycystic ovary syndrome; NAFLD — non-alcoholic fatty liver disease
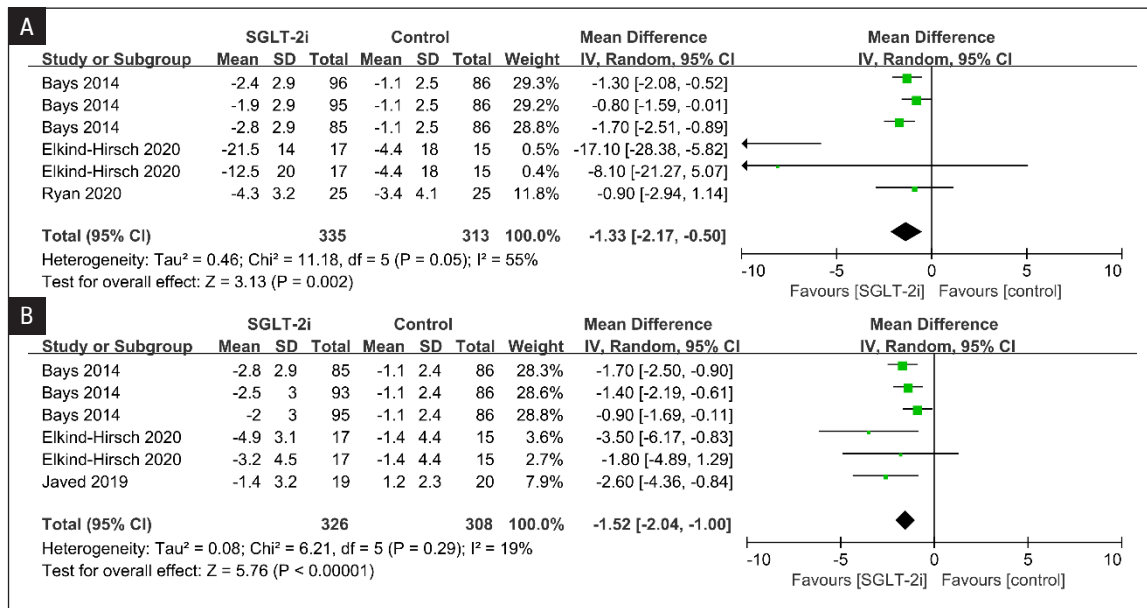
Figure 2. *Effect on body weight of SGLT-2i compared to controls: weight change (kg) (A) and weight change (%) (B)*
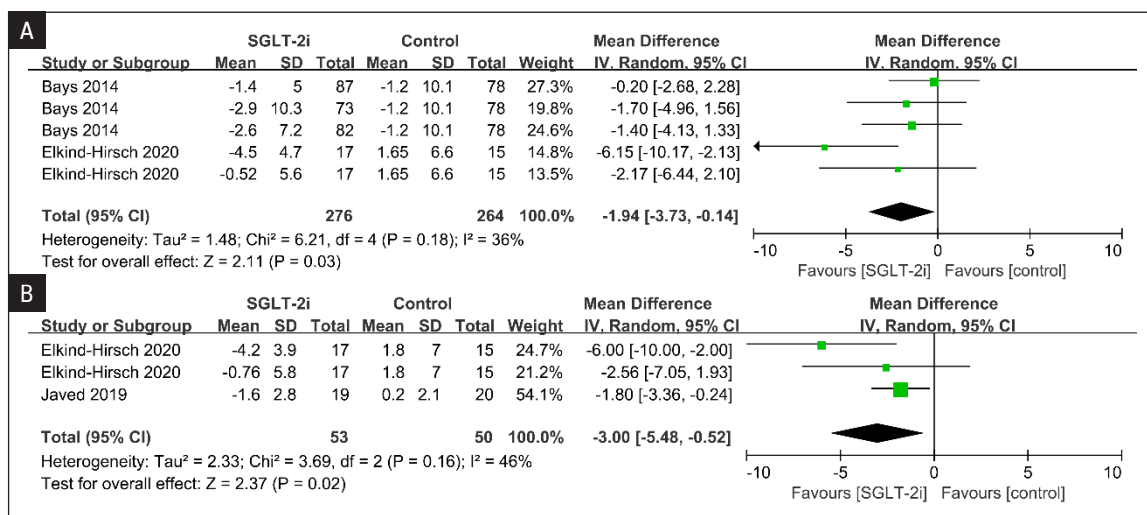

Figure 3. *Effect on waist circumference of SGLT-2i compared to controls: waist circumference change (cm) (A), waist circumference change (%) (B)*

tate aminotransferase (AST) (WMD = 1.84, p = 0.29), and homeostasis model assessment-insulin resistance (HOMA-IR) (WMD = 0.12, p = 0.58) showed no difference between groups with and without intervention involving SGLT-2i (Tab. 2).

Safety outcomes

Analysis of any adverse events results of 8 studies, with 1671 participants involved, showed that SGLT-2i did not significantly increase the risk of total adverse events (RR = 1.09, 95% CI = 0.99 to 1.21, p = 0.08). However, it is worth noting that SGLT-2i has a risk of inducing infection. After analysing data from 6 RCTs,

we reached a conclusion that SGLT-2i would increase the incidence of urinary tract infection (RR = 1.91, 95% CI = 1.17 to 3.11, p = 0.009), and 4 studies with 1327 participants demonstrated that SGLT-2i significantly raised the infectious risk in the reproductive system (RR = 4.09, 95% CI = 2.31 to 7.26, p < 0.001). In addition, an analysis of 4 studies with 1208 participants illustrated that SGLT-2i potentially played a role in relieving diarrhoea (RR = 0.48, 95% CI = 0.26 to 0.88, p = 0.02).

Analysis of other safety outcomes showed no significant effects of SGLT-2i in overweight/obese, non-diabetic individuals, including nausea, constipation, dizziness,
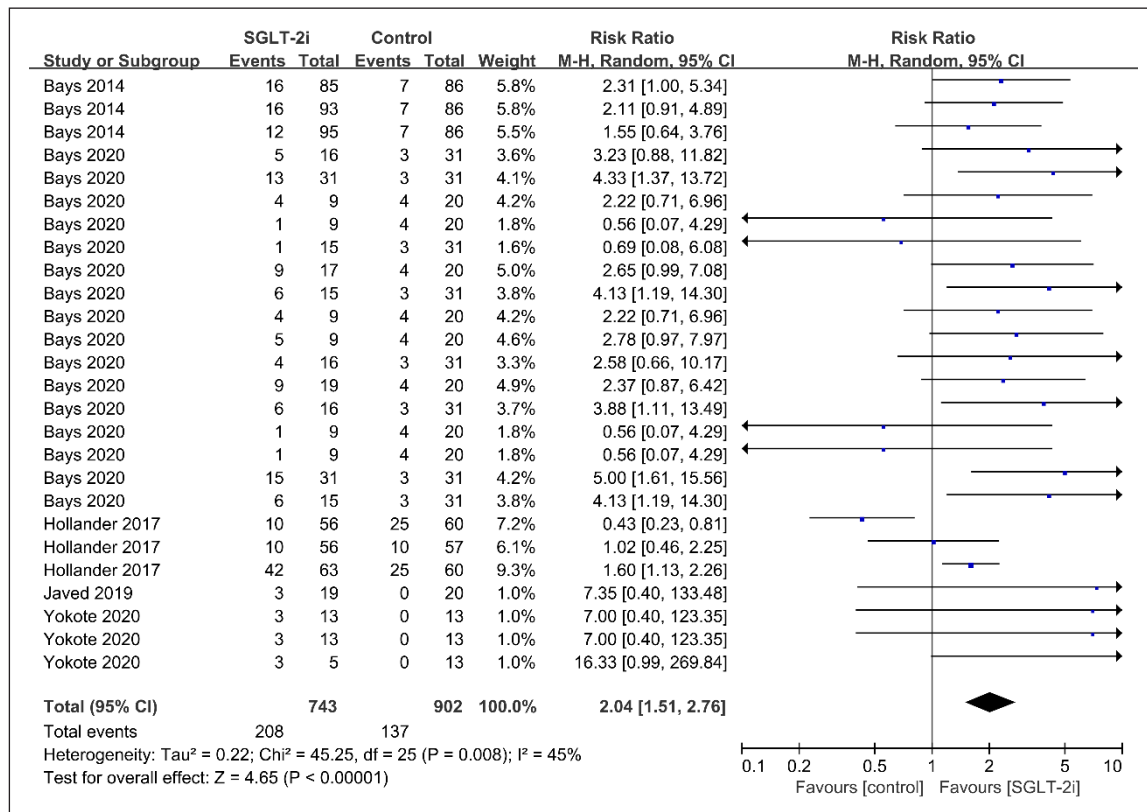
Figure 4. *A forest plot of SGLT-2i compared to controls regarding weight decrease ≥ 5%*
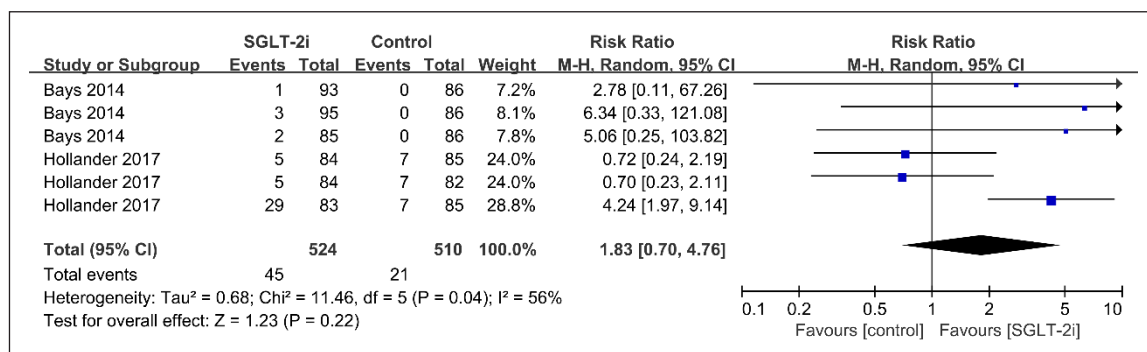

Figure 5. *A forest plot of SGLT-2i compared to controls regarding weight decrease ≥ 10%*

headache, arthralgia, and allergy, compared with the control group (Tab. 3).

Publication bias
The results of publication bias test for the included studies gave a roughly symmetric funnel plot. There was no significant publication bias in this study.

Discussion

In a previous meta-analysis, SGLT-2i, used as an anti-hyperglycaemic agent, was investigated regarding its association with weight loss in T2DM patients com-

pared with placebo [7]. Our meta-analysis evaluated the efficacy and safety of SGLT-2i in the overweight/obese with non-diabetic individuals by reviewing 13 RCTs with a follow-up duration of ≥ 8 weeks.

According to the results of our study, SGLT-2i is potentially more effective than the control group in terms of reducing waist circumference and body weight loss ≥ 5% in overweight/obese, non-diabetic individuals. A retrospective cohort study showed that adding SGLT-2i in the metformin treatment for T2DM patients is significantly advantageous in weight loss ≥ 3%, the number of people accounted for 53.6% (29.7% for dipeptidyl-peptidase-4 inhibitor [DPP-4i], 18.6% for

Table 2. *The difference in efficacy between sodium-glucose cotransporter 2 inhibitor (SGLT-2i) and control*

SGLT-2i vs. control	No. of studies	Participants	Effect size	Difference	95% CI	p	Heterogeneity (I²) (%)
FPG	5	258	SMD	−0.33	−0.93–0.26	0.27	80
Blood pressure							
SBP	4	177	WMD	1.86	−2.40–6.12	0.39	34
DBP	3	138	WMD	0.13	−2.57–2.84	0.92	0
Lipid							
HDL-C	4	177	SMD	0.03	−0.27–0.32	0.86	0
LDL-C	3	138	SMD	−0.07	−0.47–0.33	0.73	27
TC	4	177	SMD	−0.03	−0.36–0.30	0.87	18
TG	3	138	SMD	−0.07	−0.40–0.27	0.69	0
Aminotransferase							
ALT	3	178	WMD	1.86	−2.42–6.15	0.39	0
AST	3	178	WMD	1.84	−1.57–5.26	0.29	29
HOMA-IR	3	204	WMD	0.12	−0.31–0.54	0.58	57

CI — confidence interval; WMD — weighted mean difference; SMD — standardized mean difference; FPG — fasting plasma glucose; SBP — systolic blood pressure; DBP — diastolic blood pressure; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; TC — total cholesterol; TG — triglyceride; ALT — alanine aminotransferase; AST — aspartate aminotransferase; HOMA-IR — homeostasis model assessment-insulin resistance

Table 3. *The incidence of adverse events between sodium-glucose cotransporter 2 inhibitor (SGLT-2i) and control*

SGLT-2i vs. control	No. of studies	Participants	RR	95% CI	p	Heterogeneity (I²) (%)
Any adverse events	8	1671	1.09	0.99–1.21	0.08	30
Nausea	3	1117	1.41	0.63–3.14	0.40	38
Diarrhoea	4	1208	0.48	0.26–0.88	0.02	0
Constipation	3	1417	0.86	0.49–1.52	0.60	1
Dizziness	4	1261	2.01	0.98–4.13	0.06	0
Headache	4	1119	0.97	0.65–1.46	0.90	0
Urinary tract infection	6	1392	1.91	1.17–3.11	0.009	0
Reproductive system infection	4	1327	4.09	2.31–7.26	< 0.001	0
Arthralgia	2	743	0.93	0.33–2.58	0.89	0
Allergies	3	655	1.03	0.35–3.03	0.96	0

RR — risk ratio; CI — confidence interval

sulfonylurea), and weight change from baseline –3.47kg (–1.21 kg for DPP-4i, –0.04 kg for sulfonylurea) [22]. The 52-week DURATION-8 RCT showed weight loss ≥5% in the dapagliflozin group (21.3%), which is more favourable than that in the exenatide group (14.1%) in patients with T2DM poorly controlled with metformin treatment [23]. It is now believed that SGLT-2i can reduce the threshold of glucose excretion in renal urine by inhibiting the main glucose transporter in renal proximal tubules, resulting in glucose discharging in urine to reduce blood glucose [7, 24]. This process leads further to partial heat loss and weight loss to a certain extent. The early stage of weight reduction may be caused by fluid loss, which is induced by mild osmotic diuresis. This influence diminishes with time, so in the later stage, the loss in weight is mainly caused by loss in fat mass [25].

Noticeably, the results of this study illustrated that the beneficial weight loss may be limited to 5% to 10%. It is speculated that this range in weight loss may be due to the small sample size or the fact that the drugs themselves have limitations on weight loss in the overweight/obese, non-diabetic individuals. There are also studies suggesting that the actual weight loss is less than the expected weight loss predicted by the metabolic data, which may be due to the calorie loss caused by sugar via urine, resulting in compensatory overeating, but this has not been confirmed at present [26]. It is

thought that as for T2DM patients, a more stringent diet management in addition to giving SGLT-2i may achieve greater control in blood glucose level and weight [27]. On the other hand, because sodium-glucose cotransporter 2 (SGLT2) is inhibited, sodium-glucose cotransporter 1 (SGLT1) may up-regulate reabsorption and partially inhibit renal glucose excretion, thus limiting the weight loss effect of SGLT-2i to a certain extent [28]. Therefore, some researchers proposed SGLT1/2 inhibitors, such as licogliflozin or sotagliflozin, which may be able to inhibit both SGLT1 and SGLT2, would play a more drastic role in weight loss than SGLT-2i [28]. Thus it can be recognized that the causes of weight loss in SGLT-2i therapy are multifaceted and may be more complex than we have illustrated at present [7].

Because SGLT-2i is a class of anti-hyperglycaemic agents that is used in diabetic treatments, the risk of hypoglycaemia should be taken into consideration when used in non-diabetic people. The results of this meta-analysis showed that SGLT-2i had no effect on the risk of hypoglycaemia in the overweight/obese, non-diabetic population, which is consistent with data recorded by the US Food and Drug Administration.

In terms of other metabolic indicators, SGLT-2i showed no significant effect on blood pressure, lipids, or aminotransferase in overweight/obese, non-diabetic individuals. An analysis of studies observed moderate reductions in SBP and DBP in treatments with SGLT-2i, which provides additional clinical benefit in the aspect of the cardiovascular system for the majority of T2DM patients [29]. Also, it has been reported that SGLT-2i may reduce plasma volume and blood pressure by promoting osmotic diuretic and sustained natriuretic effects in T2DM patients [30]. Improved ventricular load may be partly associated with cardiovascular protection [31]. Notably, Zannad et al. performed a DAPA-HF and EMPEROR-reduced meta-analysis showing that SGLT-2i (empagliflozin or dapagliflozin) reduces all-cause and cardiovascular death and hospitalisations for heart failure, and improves renal outcomes in patients with heart failure and a reduced ejection fraction with or without diabetes [32]. Li et al. found that SGLT-2i did not increase the risk of dyslipidaemia in T2DM patients overall, but the increase in BMI may elevate the risk [33]. A meta-analysis showed that SGLT-2i reduces alanine aminotransferase (ALT), and aspartate transaminase (AST) in patients with T2DM and protects the liver [34]. However, the trial of overweight patients with non-alcoholic fatty liver disease and without T2DM revealed that SGLT-2i does not change hepatic triacylglycerol content and does not give statistically significant improvement in hepatic steatosis after 12 weeks of administration [35].

There are some differences in results between our metabolic analysis and the above studies, which may be due to the small sample size included or the different internal environments in different populations. Most of the above studies focused on patients with T2DM, while this study was conducted in overweight/obese individuals without diabetic conditions. Current studies fail to focus on the obese population without diabetes. This meta-analysis paves a path to a promising future of applying SGLT-2i for anti-obesity treatment.

As for safety, SGLT-2i administration was generally well tolerated in the overweight/obese, non-diabetic individuals. It has been widely studied that SGLT-2i treatment is associated with increased risk of urinary tract and genital infections, which may be closely related to the mechanism of action of the drugs. Most of these infections are mild to moderate. SGLT-2i elevates glucose level in urine. The glucosuria environment can promote the growth and reproduction of bacteria, and the environment is also an inducer of increasing bacterial adhesion to the uroepithelium, resulting in increased risk of infections in the urinary tract and genitals [36]. In addition, participants in the SGLT-2i intervention groups had significantly fewer adverse events in terms of diarrhoea than those in the control groups. The increased diarrhoea appearance may be caused by the use of metformin in some participants in the control groups in this meta-analysis study. Studies have found that metformin is prone to cause adverse drug reactions in the gastrointestinal tract, most commonly diarrhoea and nausea [37]. In comparison, SGLT-2i appeared to reduce the risk of diarrhoea.

All data in this meta-analysis were from RCTs, and the quality of each study was assessed in the process of inclusion. However, the existence of limitations is undeniable. Firstly, due to the limited number of studies and inconsistent follow-up time, the extracted outcome indicators were not analysed separately according to the follow-up time, so it is difficult to judge whether the different duration of SGLT-2i use has any more specific and finer effects on treating overweight/obese, non-diabetic individuals. Moreover, this study did not address the longer-term efficacy and safety of SGLT-2i treatment (maximum follow-up time of 48 weeks in the included study). Finally, due to the variety in dosage, type, etc. of SGLT-2i and limited sample size of these RCTs, the relationships between dosage and weight loss and other outcomes were not included in this study. Although there are limitations, this study is the first meta-analysis that focus on the effects of SGLT-2i treatment in overweight/obese, non-diabetic individuals, which is a potentially new option for managing obesity. Future studies are essential in the aspects mentioned above.

Conclusion

SGLT-2i is associated with a limited loss in weight and waist circumference in overweight/obese, non-diabetic individuals. There was no statistically significant effect on other metabolic parameters, including FPG, blood pressure, lipids, aminotransferase, and HOMA-IR. In terms of safety, SGLT-2i significantly increases the risk of urogenital infections. As for future prospects, more studies with higher quality, longer-term trials as well as larger samples should be carried out to investigate the efficacy and safety of using SGLT-2i in the management of overweight/obese, non-diabetic individuals.

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