European Journal of Clinical Pharmacology (2023) 79:859–871
https://doi.org/10.1007/s00228-023-03490-8

RESEARCH

Effects of sodium-glucose cotransporter 2 inhibitors on renal risk factors in patients with abnormal glucose metabolism: a meta-analysis of randomized controlled trials

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Received: 23 February 2023 / Accepted: 28 March 2023 / Published online: 25 April 2023

Abstract

Aims Several trials have assessed the antihyperglycemic effects of sodium-glucose cotransporter 2 inhibitors (SGLT2Is) in patients with type 2 diabetes mellitus (T2DM). We conducted a quantitative analysis to assess the effects of SGLT2Is on renal risk factors in patients with abnormal glucose metabolism.

Materials and methods Randomized controlled trials (RCTs) were identified by searching the PubMed, Embase, Scopus, and Web of Science databases published before September 30, 2022. The intervention group received SGLT2Is as monotherapy or add-on treatment, and the control group received placebos, standard care, or active control. Risk of bias assessment was performed using the Cochrane risk of bias assessment tool. Meta-analysis was performed on studies with abnormal glucose metabolism populations and studies using the weighted mean differences (WMDs) as the measure of the effect size. Clinical trials providing changes in serum uric acid (SUA) were included. The mean change of SUA, glycated hemoglobin (HbA1c), body mass index (BMI), and estimated glomerular filtration rate (eGFR) were calculated.

Results After a literature search and detailed evaluation, a total of 11 RCTs were included for quantitative analysis to analyze the differences between the SGLT2I group and the control group. The results showed that SGLT2I significantly reduced SUA (MD = −0.56, 95% CI = −0.66 ~ −0.46, I^2 = 0%, P < 0.00001), HbA1c (MD = −0.20, 95% CI = −0.26 ~ −0.13, I^2 = 0%, P < 0.00001), and BMI (MD = −1.19, 95% CI = −1.84 ~ −0.55, I^2 = 0%, P = 0.0003). There was no significant difference in the reduction of eGFR observed in the SGLT2I group (MD = −1.60, 95% CI = −3.82 ~ 0.63, I^2 = 13%, P = 0.16).

Conclusions These results showed that the SGLT2I group caused greater reductions in SUA, HbA1c, and BMI but had no effect on eGFR. These data suggested that SGLT2Is may have numerous potentially beneficial clinical effects in patients with abnormal glucose metabolism. However, these results need to be consolidated by further studies.

Keywords Meta-analysis · Sodium-glucose cotransporter 2 inhibitors (SGLT2Is) · Type 2 diabetes · Uric acid · Diabetic nephropathy

Introduction

The global prevalence of diabetes mellitus is increasing rapidly, affecting human health and life span. Diabetic nephropathy is one of the most common complications and the most common cause of end-stage renal disease. About 35%–40% of people with diabetes will develop diabetic nephropathy [1]. Therefore, we should consider whether hypoglycemic therapy can reduce the risk of diabetic nephropathy and improve its prognosis. Studies have shown that SGLT2Is can reduce blood glucose by inhibiting the reabsorption of sodium and glucose in the proximal renal tubule and increasing the excretion of urinary glucose [2]. In addition to the hypoglycemic effect, the renal protective effect of SGLT2Is runs through the whole process of diabetic nephropathy. The significant renal protective features of SGLT2Is have led to their widespread use as a monotherapy or add-on therapy to other hypoglycemic agents in clinical practice [3]. The change in renal hemodynamics is one of the most important mechanisms of renal protection by these drugs [4]. At the same time, some

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studies have shown that SGLT2Is can reduce the risk factors of diabetic nephropathy, such as HbA1c, eGFR, body weight, and SUA. These may be an intermediate role of SGLT2Is in renal protection. Therefore, in this study, we aim to explore this association through a systematic review of the existing literature. In addition, we provide insight into the mechanisms underlying this association.

Recently, a meta-analysis based on randomized, placebo-controlled trials showed that SGLT2Is could reduce SUA, fasting plasma glucose, and HbA1c in diabetic patients [5]. However, there is a lack of sufficient data to indicate the role of SGLT2Is on renal risk factors. We need to provide more data to prove it. In addition, some previous meta-analyses have also evaluated the effect and safety of SGLT2Is on SUA [6–9]. However, these manuscripts were all published before 2017. Several recently published RCTs of SGLT2Is on renal risk factors need to be evaluated in new meta-analyses. Therefore, we collected data from nearly 5 years of randomized controlled trials and performed this meta-analysis to evaluate the effects of SGLT2Is on renal risk factors, including SUA, eGFR, HbA1c, and BMI in patients with abnormal glucose metabolism.

Materials and methods

Data sources and searches

The electronic databases of PubMed, Embase, Web of Science, and Scopus were searched to identify eligible RCTs using relevant search terms described in Table S1. Our search in all databases was restricted to the use of these terms in the title, abstract, and keyword. We identified articles published up to September 30, 2022. Trials that were published between 2018 and 2022 were manually searched. An English language restriction was imposed. We did a further manual search of the reference lists of all selected papers, previous similar reviews, and pooled analysis studies to look for possible missing papers.

Study selection

Studies meeting the following criteria were included according to the PICOS scheme: (1) population, patients with abnormal glucose metabolism; (2) intervention, SGLT2Is as monotherapy or add-on treatment; (3) comparison, placebo, active control, or standard care; (4) primary outcomes, change in SUA from baseline; secondary outcomes, changes in HbA1c, BMI, and eGFR from baseline; (5) design, randomized controlled trials. However, single-arm trials, trials with self-control and historical controls, and crossover trials were excluded.

Data extraction

The two investigators (Mengnan Li and Yunfeng Liu) independently extracted the following data: first author, year of publication, patient characteristics, comparison (placebo, active control, or standard care), intervention (type of SGLT2Is and dose regimen), duration of SGLT2I treatment, duration of diabetes, baseline SUA, BMI, HbA1c, eGFR, and outcomes (changes in SUA, HbA1c, BMI, and eGFR from baseline).

Quality assessment

Two independent reviewers (Mengnan Li and Yunfeng Liu) evaluated the studies according to the inclusion and exclusion criteria and assessed the risk of bias according to the Cochrane risk of bias tool [10]. The following domains were considered: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Disagreements were resolved in discussions.

Publication bias and statistical analysis

Publication bias was examined using funnel plot asymmetry. The effect of SGLT2Is on renal function was evaluated according to the changes in HbA1c, BMI, SUA, and eGFR. All four outcomes were assessed as continuous variables. We calculated pooled outcomes for the weighted mean differences (WMDs) and 95% confidence intervals (CIs) using a random-effects model. Heterogeneity was assessed using the I^2 statistic. Values > 50% were viewed as indicative of moderate-to-high heterogeneity [11]. We also carried out subgroup and sensitivity analyses to explore the causes of heterogeneity. Random-effects meta-regression analyses were used to evaluate the association between changes in some outcome measures and baseline characteristics. We used Review Manager version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) and Stata/SE 16.0 (Stata Corp., College Station, TX, USA) for all statistical analyses. The statistical level of significance was set at a P-value < 0.05.

Results

Study selection and characteristics

A total of 4490 articles were collected by searching the various databases including PubMed ($n = 289$), Scopus ($n = 987$), Embase ($n = 1288$), and Web of Science ($n = 1926$) databases. Of these, 1637 were duplicates, leaving 2853

to be further evaluated. Most citations ($n = 1264$) were excluded due to unrelated trial design, article type, and non-English language. The remaining 1589 articles were carefully checked. A total of 1050 records were excluded by inspecting titles and abstracts. The remaining 539 articles were carefully assessed for data extraction in full text, and an additional 528 articles were excluded by reason of unrelated topic ($n = 400$), incomplete data ($n = 96$), patients selection ($n = 20$), and uninterested outcomes ($n = 12$). Finally, 11 studies met our criteria for systematic review, which was followed up with a meta-analysis (Fig. 1). No additional study was identified by manual search.

Characteristics of the included trials are summarized in Table 1. The included trials ($n = 11$) were RCTs from 2018 to 2022. A total of 489 patients were in the SGLT2I group, and 492 were in the placebo group. Most trials used a placebo ($n = 4$) and standardized hypoglycemic therapy ($n = 5$) as controls. We also included two trials with valsartan (80 mg bid) and liraglutide (0.9 mg qd) as controls respectively. Three types of SGLT2Is were mentioned in the studies, most of the trials were on dapagliflozin ($n = 5$) and empagliflozin ($n = 4$), which, respectively, used 5–10 mg of dapagliflozin and 10 mg of empagliflozin. We also included one study on ipragliflozin (5 mg qd) and one on dapagliflozin (5–10 mg qd) and empagliflozin (10 ~ 25 mg qd) in combination treatment. Participants were usually middle-aged. Two of these trials involved patients with diabetic nephropathy and prediabetic patients, respectively. The remaining experiments involved patients with type 2 diabetes. The duration of intervention in most trials was 12 or 24 weeks. The study by Hussain et al. had the shortest time of intervention (4 weeks). However, Hao et al. did not report the duration of the intervention. The changes in SUA, HbA1c, BMI, and eGFR of each study are reported in Table S2.

Quality assessment

For all of the included studies, a risk of bias assessment was carried out using The Cochrane Collaboration risk of bias tool (Fig. 2).

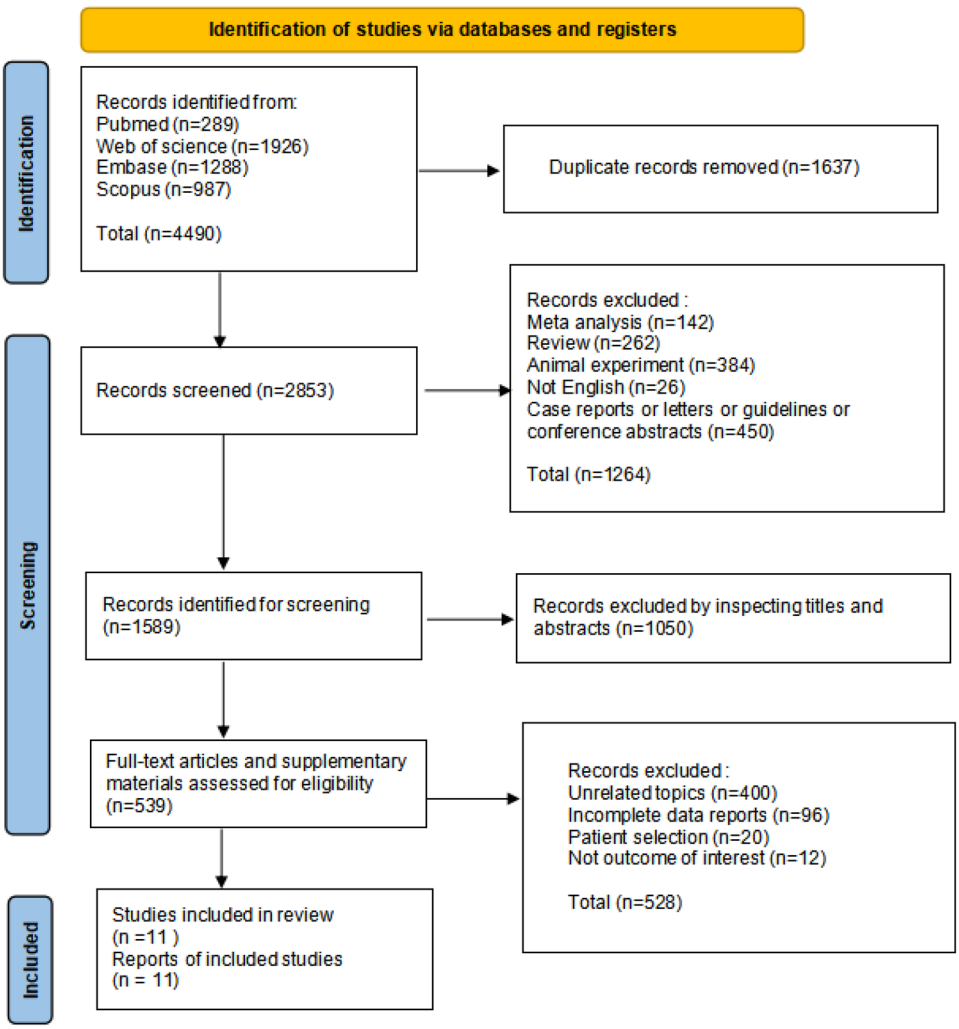


Fig. 1 Flow diagram demonstrating the study selection process in the meta-analysis

Table 1 Characteristics of included studies

Author	SGLT2Is (doses)	Age (years)	Disease	Duration of diabetes	Duration of intervention	Control group	UA (mg/dl)	eGFR (ml/min/1.73 m^2)	HbA1c (%)	BMI (kg/m^2)
Hao et al. [41]	Dapagliflozin: 10 mg qd OAD	57.77 (12.29) 58.97 (10.50)	T2DM	3 mo	NR	SC	5.85 (1.72) 5.48 (1.74)	NR	9.89 (1.24) 10.14 (1.73)	27.34 (3.88) 25.90 (3.51)
Huang et al. [42]	Dapagliflozin: 10 mg qd Valsartan: 80 mg bid	56.21 (11.18) 55.67 (11.46)	DN	10.04 (2.31) y 9.65 (2.55) y	12 WK	AC	6.24 (1.17) 6.15 (1.15)	111.17 (29.22) 110.08 (27.64)	9.31 (1.72) 9.36 (1.44)	26.13 (2.35) 25.94 (2.51)
Hussain et al. [43]	Dapagliflozin: 5 ~ 10 mg qd + empagliflozin: 10 ~ 25 mg qd OAD	46 (11.5) 43 (13.2)	T2DM	8.2 (4.8) y 9.2 (6.2) y	4 WK	SC	7.5 (2.5) 7.1 (1.8)	NR	6.5 (3.2) 7.0 (2.8)	25.7 (3.2) 27.5 (4.2)
Tanaka et al. [44]	Ipragliflozin: 5 mg qd OAD	59.1 (11.2) 62.5 (13.5)	T2DM	NR	12 WK	SC	5.71 (1.43) 5.58 (1.23)	67.3 (18.2) 67.9 (16.9)	7.0 (0.5) 7.1 (0.6)	30.5 (7.0) 31.4 (5.1)
Okada et al. [45]	Empagliflozin: 10 mg qd PLA	NR	T2DM	NR	12 WK	PLA	5.44 (0.33) 5.35 (0.43)	69.17 (2.68) 69.56 (2.8)	6.64 (0.21) 6.64 (0.23)	NR
Satirapoj et al. [46]	Dapagliflozin: 10 mg qd OAD	55.9 (7.41) 59.9 (8.62)	T2DM	8.5 (4.76) y 9.0 (5.39) y	12 WK	SC	5.2 (1.06) 4.9 (1.62)	88.7 (16.40) 87.3 (15.62)	8.7 (1.06) 8.6 (1.08)	28.4 (4.23) 27.9 (4.85)
Ramírez-Rodríguez et al. [47]	Dapagliflozin: 10 mg qd PLA	51.5 (6.3) 46.7 (9.8)	Prediabetes	NR	12 WK	PLA	5.61 (1.18) 5.24 (1.70)	NR	5.8 (0.3) 5.8 (0.5)	30.3 (3.5) 33.0 (2.2)
Shimizu et al. [48]	Empagliflozin: 10 mg qd PLA	63.9 (10.4) 64.6 (11.6)	T2DM	38.3 (43.4) mo 32.4 (43.3) mo	24 WK	PLA	5.8 (1.4) 5.7 (1.5)	64.6 (15) 66.1 (15.7)	6.82 (1.00) 6.89 (0.92)	25.2 (3.7) 25.2 (4.1)
Hiruma et al. [49]	Empagliflozin: NR OAD	52.8 (9.7) 47.8 (11.5)	T2DM	3.9 (3.7) y 3.0 (2.7) y	12 WK	SC	5.8 (1.2) 6.3 (1.2)	86.5 (19.0) 87.1 (14.4)	7.1 (0.8) 7.0 (0.9)	28.6 (4.8) 30.0 (5.0)
Pollock et al. [50]	Dapagliflozin: 10 mg qd PLA;	64.7 (8.6) 64.7 (8.5)	T2DM	NR	24 WK	PLA	6.71 (1.66) 6.97 (1.56)	50.2 (13.0) 47.7 (13.5)	8.44 (1.0) 8.57 (1.2)	30.19 (5.3) 30.34 (5.6)
Nakaguchi et al. [12]	Empagliflozin: 10 mg qd Liraglutide: 0.9 mg qd	66.3 (9.5) 67.2 (9.0)	T2DM	19.0 (10.1) y 18.8 (9.9) y	24 WK	Liraglutide	5.7 (1.2) 5.3 (1.3)	67.1 (22.4) 63.3 (18.9)	8.08 (0.76) 8.04 (0.75)	25.8 (4.1) 26.4 (4.6)

SUA serum uric acid, *HbA1c* glycated hemoglobin, *eGFR* estimated glomerular filtration rate, *BMI* body mass index, PLA placebo, *AC* active control, *OAD* oral antidiabetic drug, *NR* none report, *SC* standard care, *T2DM* type 2 diabetes mellitus, *DN* diabetic nephropathy, *mo* month, *y* years, *WK* weeks, *SGLT2Is* sodium-glucose cotransporter 2 inhibitors

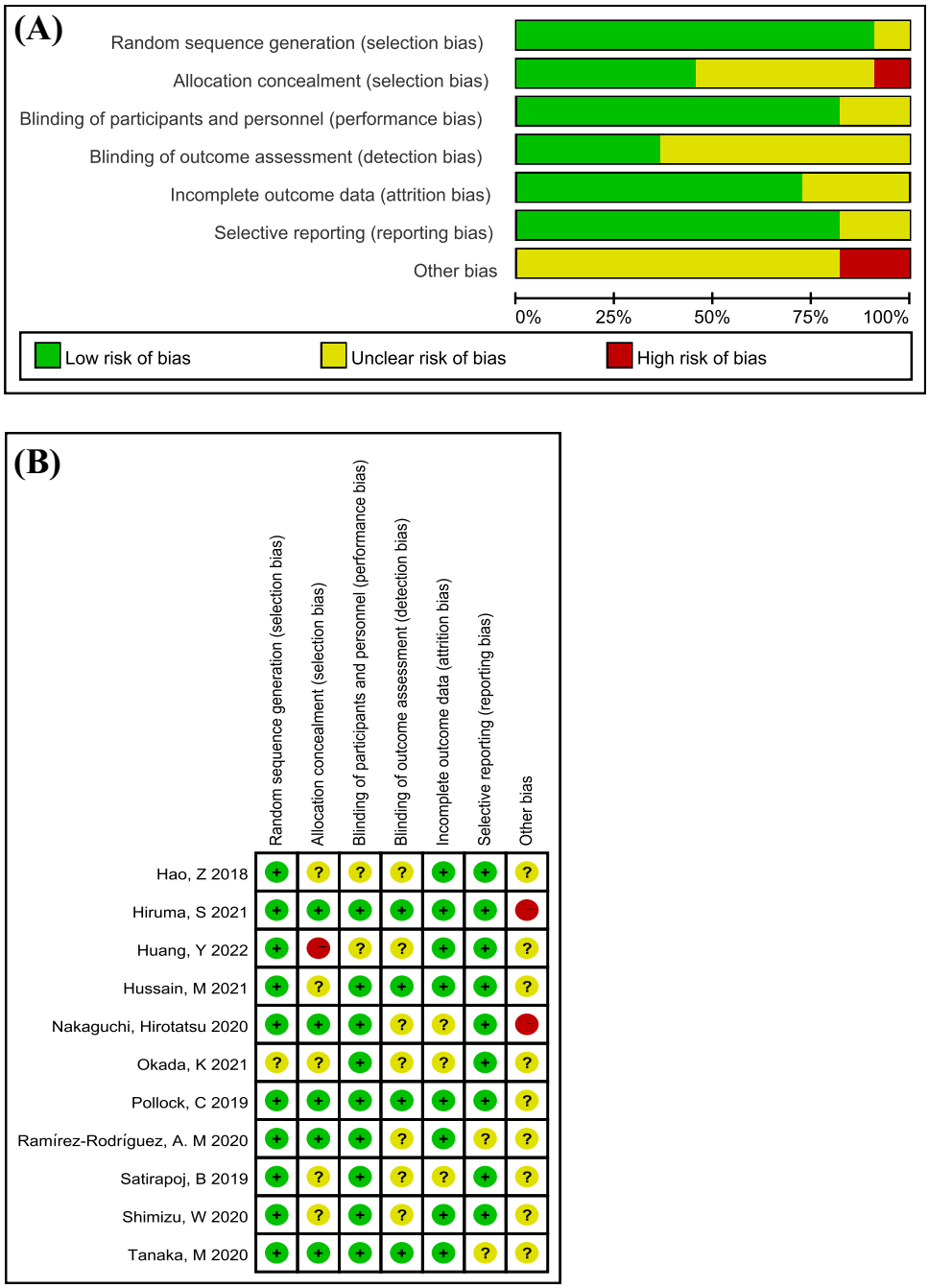


Fig. 2 **A** Methodological quality graph**. B** Methodological quality summary

Effect of SGLT2Is on SUA

In this meta-analysis, 11 studies were a two-group analysis between SGLT2Is and control groups to evaluate the association between SUA levels and SGLT2Is in a total of 981 patients. The results of the pooled analysis of 11 studies showed that patients in the SGLT2I group had a greater reduction in SUA than those in the control group (MD = −0.56, 95% CI = −0.66 ~ −0.46, $I^2 = 0\%$, $P < 0.00001$). There was little or no heterogeneity in the meta-analysis ($I^2 = 0\%$), suggesting a consistent drug effect (Fig. 3).

A subgroup analysis was performed according to the different control groups and baseline characteristics (Fig. 4). Compared with the placebo group ($n = 4$), the SGLT2I group reduced SUA concentration by 0.58 mg/dl more than the placebo group, and the difference was statistically significant (95% CI = −0.93 ~ −0.23, $I^2 = 51\%$, $P = 0.001$). Similarly, the SGLT2I group significantly reduced SUA concentration more than the active control group ($n = 7$, including metformin, insulin, and sulphonylureas) (MD = −0.59, 95% CI = −0.82 ~ −0.35, $I^2 = 0\%$, $P < 0.00001$) (Fig. 4A).

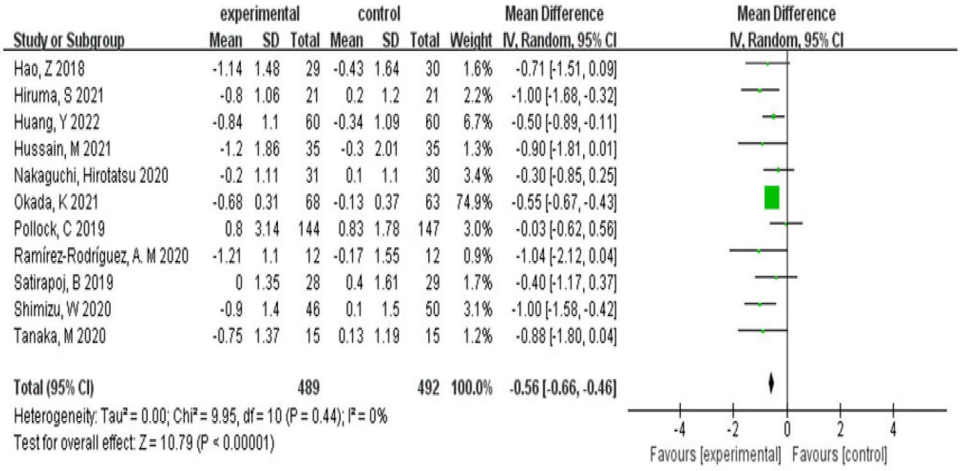


Fig. 3 Forest plot of comparison of uric acid reduction between SGLT2Is group and control group

There were ten studies that reported treatment time. We analyzed the indicator in the short-term ($n=7$; ≤ 12 weeks) and long-term ($n=3$; 24 weeks) subgroups, separately. The MD of reduction in SUA was greater in the short-term subgroup (MD = −0.57, 95% CI = −0.68 ~ −0.46, $I^2=0\%$, $P<0.00001$) than that in the long-term subgroup (MD = −0.44, 95% CI = −1.00 ~ 0.12, $I^2=65\%$, $P=0.12$), albeit not statistically significant in the long-term subgroup (Fig. 4B).

Ten studies have reported the effects of one type of SGLT2Is. We found that empagliflozin ($n=4$) reduced the SUA more than dapagliflozin ($n=5$) and ipragliflozin ($n=1$). There were significant differences in the decrease of SUA among different types (MD = −0.56, 95% CI = −0.68 ~ −0.43, $I^2=4\%$, $P<0.00001$) (Fig. 4C).

HbA1c was reported in 11 studies. According to HbA1c, we found that the MD of reduction in SUA was greater in the lower HbA1c subgroup ($n=5$; HbA1c < 8) (MD = −0.63, 95% CI = −0.78 ~ −0.48, $I^2=5\%$, $P<0.00001$) than that in the higher HbA1c subgroup ($n=6$; HbA1c > = 8) (MD = −0.38, 95% CI = −0.63 ~ −0.13, $I^2=0\%$, $P=0.003$) (Fig. 4D).

Seven studies reported the duration of diabetes. We found that the MD of reduction in SUA was greater in the short-term subgroup ($n=3$; ≤ 5 years) than that in the long-term subgroup ($n=4$; > 5 years or 10 years). There were significant differences in the decrease of SUA among different duration of diabetes (MD = −0.63, 95% CI = −0.86 ~ −0.40, $I^2=0\%$, $P<0.00001$) (Fig. 4E).

Random-effects meta-regression was performed to assess whether the reduction in SUA levels is dependent on the duration of diabetes, different types, the duration of SGLT2I treatment, and glycated hemoglobin levels. The results demonstrated that SUA change was not significantly correlated with the duration of diabetes, different types, duration of SGLT2I treatment, and glycated hemoglobin levels (Fig. S1) (Table 2).

No publication bias was found using the funnel plots (Fig. S2). There was little or no heterogeneity in the meta-analysis ($I^2=0\%$), suggesting a consistent drug effect.

Effect of SGLT2Is on BMI

Five studies reported the effect of SGLT2Is on BMI. Compared with the control group, SGLT2I significantly reduced BMI (MD = −1.19, 95% CI = −1.84 ~ −0.55, $I^2=0\%$, $P=0.0003$). Publication bias cannot be assessed due to the small number of included studies. There was little or no heterogeneity in the meta-analysis ($I^2=0\%$), suggesting a consistent drug effect (Fig. 5).

Effect of SGLT2Is on eGFR

Six studies reported the effect of SGLT2Is on eGFR. There was no significant difference in the reduction of eGFR observed in the SGLT2I group compared with that in the control group (MD = −1.60, 95% CI = −3.82 ~ 0.63, $I^2=13\%$, $P=0.16$) (Fig. 6). Considering the impact of the variation in the follow-up period, we analyzed the indicator in the short-term ($n=4$; ≤ 12 weeks) and long-term ($n=2$; ≥ 24 weeks) subgroups, separately. In the short-term subgroup, SGLT2Is could significantly reduce eGFR (MD = −2.79, 95% CI = −3.74 ~ −1.84, $I^2=0\%$, $P<0.00001$). In the long-term subgroup, SGLT2Is could increase eGFR (MD = 1.86, 95% CI = −3.55 ~ 7.28, $I^2=0\%$, $P=0.50$), but the results were not significant (Fig. 7). Publication bias cannot be assessed due to the small number of included studies. There was little or no heterogeneity in the meta-analysis ($I^2=13\%$), suggesting a consistent drug effect.

Effect of SGLT2Is on HbA1c

Eight studies reported the effect of SGLT2Is on HbA1c. There was a significant difference in the reduction of HbA1c observed in the SGLT2I group compared with that in the control group in seven studies (MD = −0.20, 95% CI = −0.26 ~ −0.13, $I^2=0\%$,

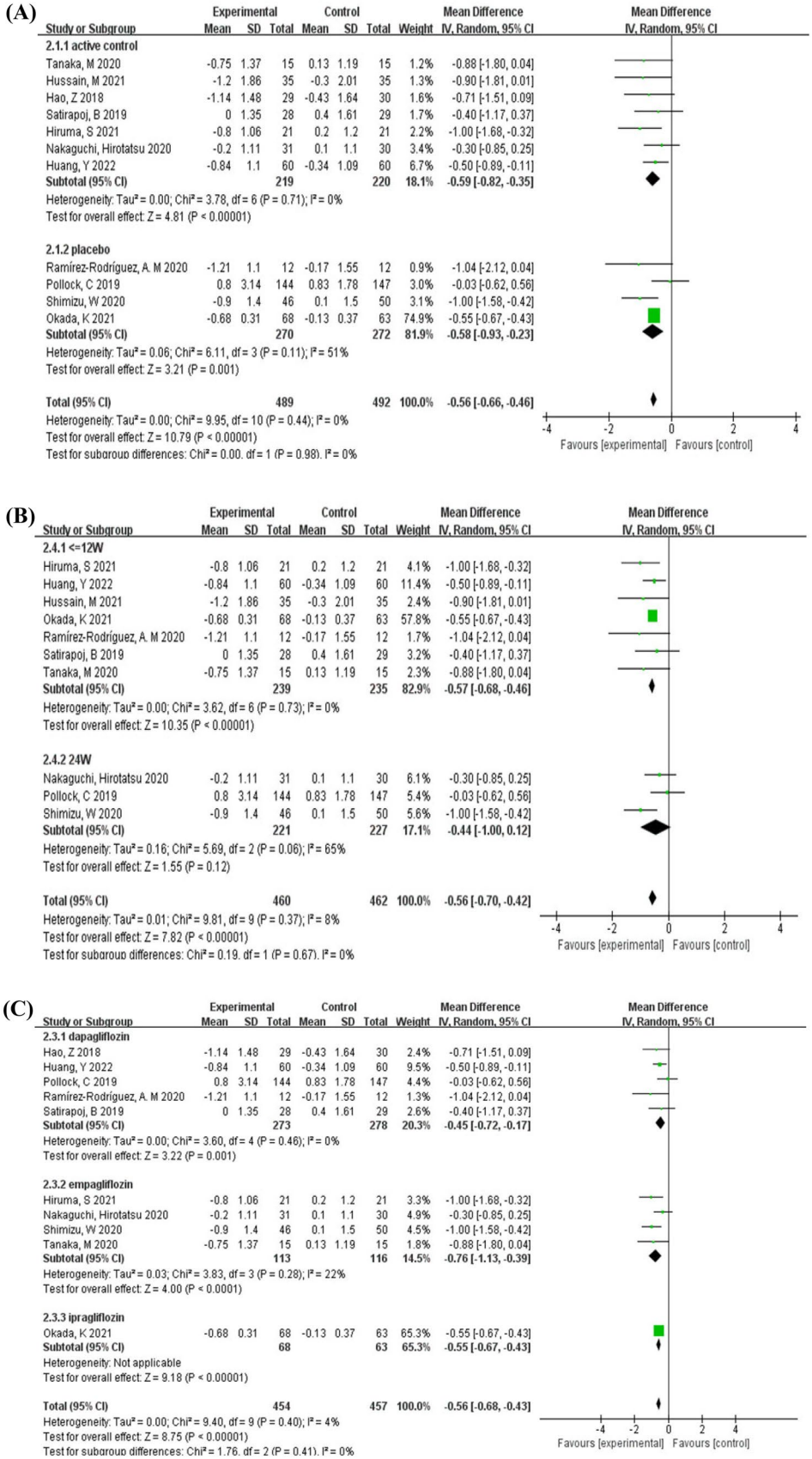
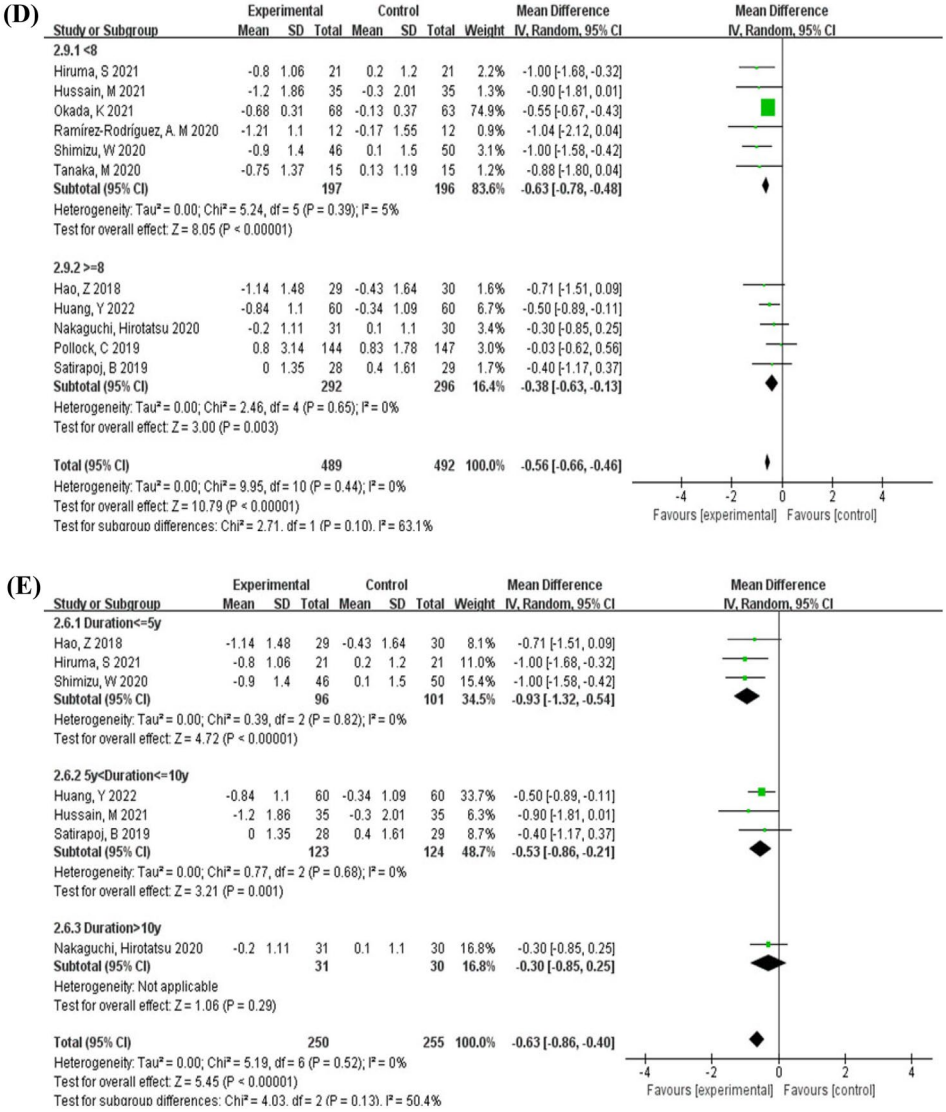


Fig. 4 **A** Subgroup analysis based on different controls. **B** Subgroup analysis based on duration of SGLT2Is treatment. **C** Subgroup analysis based on different types of SGLT2Is. **D** Subgroup analyses based on glycated hemoglobin levels. **E** Subgroup analysis based on duration of diabetes

Fig. 4 (continued)



$P < 0.00001$) (Fig. 8). When we excluded one study at a time to assess the stability of the results, there was a significant change in the pooled MD or 95% CI when Nakaguchi et al.'s study was excluded (Fig. S3). The MD of HbA1c changed from −0.03 (95% CI = −0.34 ~ 0.28, $I^2 = 89\%$, $P = 0.85$) to −0.20 (95% CI = −0.26 ~ −0.13, $I^2 = 0\%$, $P < 0.00001$). Nakaguchi et al.'s study showed that the liraglutide group reduced SUA concentration by 0.89 mg/dl more than the empagliflozin group [12]. The result of the original study resulted in a lack of robustness. Therefore, we removed this paper from the meta-analysis.

Finally, to assess the publication bias of the results in the present meta-analysis, we constructed funnel plots using Review Manager. The symmetry of the HbA1c funnel plot shows that there was a low risk of publication bias (Fig. S4).

Table 2 The results of meta-regression analysis on the effects of SGLT2Is on SUA reduction based on treatment duration, duration of diabetes, different types of SGLT2Is, and glycated hemoglobin levels

	Duration of treatment		Duration of diabetes		Different types of SGLT2Is		Glycated hemoglobin levels	
	Coefficient	*P*-value	Coefficient	*P*-value	Coefficient	*P*-value	Coefficient	*P*-value
SGLT2Is	0.129 [−0.282,0.540]	0.496	0.330 [−0.991,0.760]	0.105	−0.051 [−0.315,0.213]	0.667	0.345 [−0.088,0.778]	0.105

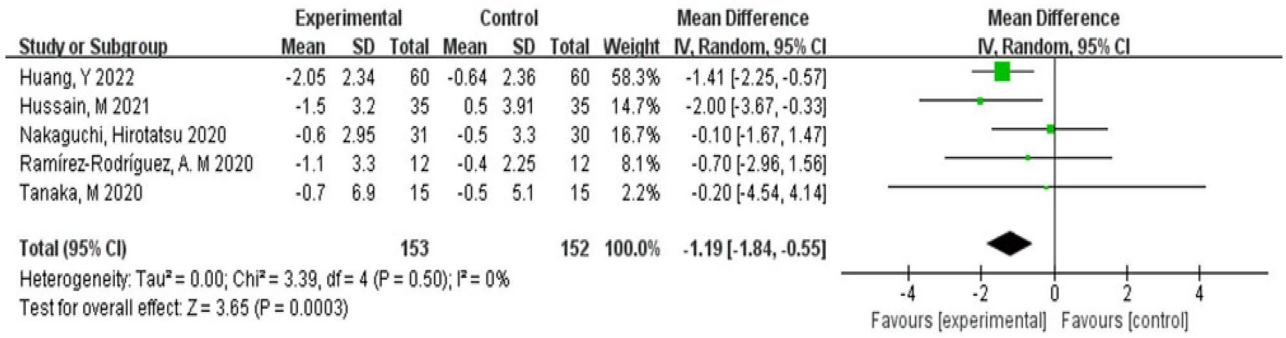


Fig. 5 Forest plot of comparison of BMI reduction between SGLT2Is group and control group

Discussion

In this meta-analysis, we provide evidence that SGLT2I significantly reduces SUA, HbA1c, and BMI. While there were no significant changes in eGFR after the use of SGLT2Is, these results suggested the beneficial effects of SGLT2Is on diabetic nephropathy risk factors. It is therefore vital to study SGLT2I protective effects against diabetic nephropathy in patients with abnormal glucose metabolism.

SUA level is closely related to early renal disease in T2DM patients, which can lead to the progression and deterioration of renal disease in T2DM patients [13–15]. Many studies have shown that SUA can affect renal function through a variety of mechanisms, including the induction of inflammatory pathways [16], ischemia [17], or lower eGFR [18]. The subsequent appearance of high blood uric acid and low urinary uric acid excretion (UUAE) levels further increases the risk of diabetic nephropathy [19]. There is controversy in the current study as to whether the effect of SUA on renal function decline depends on the baseline blood uric acid level or the ΔUA [20, 21]. Allopurinol or febuxostat is known to significantly reduce SUA, but further studies have shown that these drugs did not result in a clinically meaningful improvement in kidney outcome [22, 23]. If the glucose-lowering drugs themselves could lower SUA, then we could avoid the use of additional drugs. SGLT2Is have been found to significantly reduce SUA. This meta-analysis reached a similar conclusion. The results of the present study show that SUA levels decreased by 0.56 mg/dl more in the SGLT2I group than in the control group. The underlying mechanism involves the renal SLC2A9 (GLUT9) transporter, which transports uric acid and d-glucose. SGLT2Is lead to increased urinary glucose excretion, accompanied by increased uric acid exchange at the apical membrane of renal tubular cells. This subsequently causes increased excretion of uric acid and hypouricemia [24].

Subgroup analyses of baseline characteristics revealed that SUA reduction decreased with higher HbA1c and longer duration of disease or intervention. In a meta-analysis [5], it was found that empagliflozin had the highest rate of SUA reduction, which was consistent with our subgroup analysis results. The meta-regression of Zhao et al. [9] showed that the reduction of SUA was associated with the duration of SGLT2I treatment. However, another meta-analysis showed that the reduction of SUA was not related to the dose and duration of SGLT2I treatment but was related to the duration

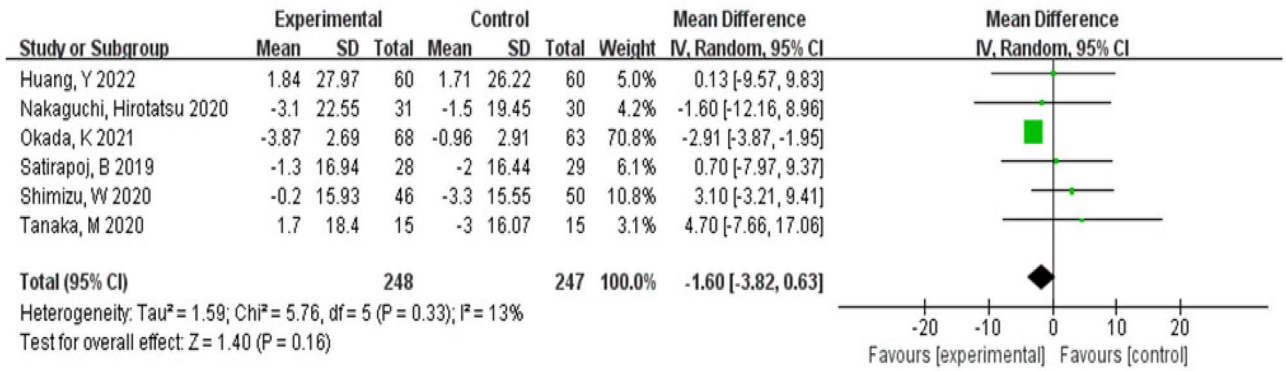


Fig. 6 Forest plot of comparison of eGFR changes between SGLT2Is group and control group

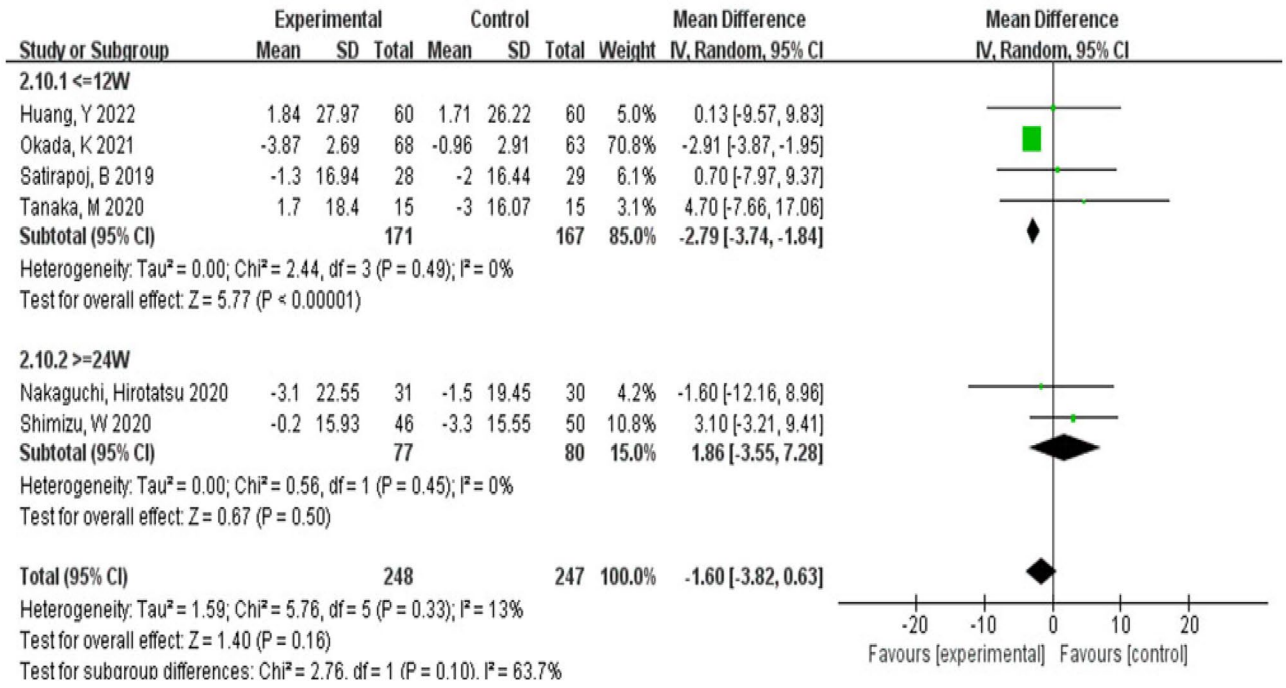


Fig. 7 Subgroup analysis based on follow-up period

of diabetes [5]. In contrast, the decrease in SUA was not associated with the duration of diabetes, duration of treatment, and type of SGLT2Is in our study. The differences may be due to the mean treatment period, the number of patients, and different analysis tools. Several similar meta-analyses have been published previously [6–8, 25]. Although they all reached similar conclusions on the outcome of SUA, this paper conducted subgroup analysis and regression analysis from different perspectives rather than repeating the existing meta-analysis. In addition, this article mainly included RCT studies in the past 5 years, which provided updated and more comprehensive data support for the effect of SGLT2Is on uric acid reduction.

Weight loss is essential for patients with type 2 diabetes. In addition to the potential benefits of lowering blood glucose levels, there are also some renal benefits. There is evidence of the benefit of weight loss in reducing proteinuria in overweight and obese patients [26]. And another study

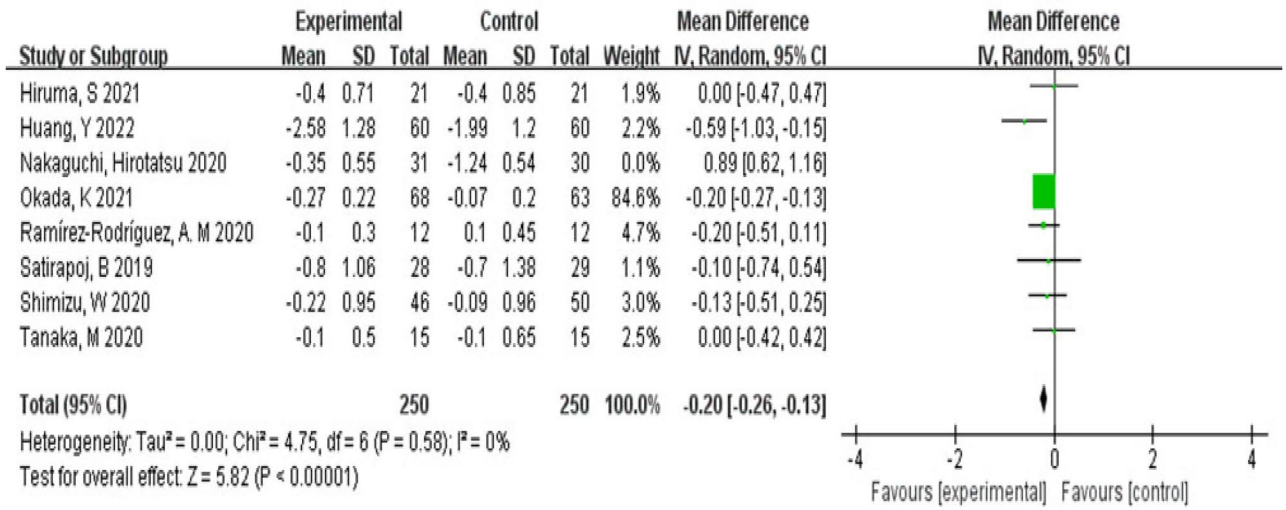


Fig. 8 Forest plot of comparison of HbA1c reduction between SGLT2Is group and control group

noted that weight loss can lead to a reduction in blood pressure [27]. Interestingly, weight loss also has the effect of reducing uric acid. These results will reduce the incidence of diabetic nephropathy complications. The results of this meta-analysis indicated that compared with the control group, SGLT2I significantly reduced BMI (MD = −1.19, 95% CI = −1.84 ~ −0.55, I^2 = 0%, P < 0.001), which is in line with previous findings. The mechanism of weight loss has been partially understood. First, the SGLT2I-mediated increase in urine glucose can reduce fat mass [28], thereby reducing chronic inflammation [29] and body weight. Second, brown fat is known to fight obesity, and SGLT2Is can induce the browning of white adipose tissue to reduce body weight [30]. Third, the insulin-sparing effect of SGLT2Is may also have contributed to weight loss in patients who used insulin [31]. In addition, some studies have further found that SGLT2Is have a better weight loss effect in patients with normal renal function than in patients with reduced renal function [32].

Studies have shown that hypoglycemic therapy significantly reduces renal deterioration and macroalbuminuria [33]. In this study, SGLT2I therapy was more effective than the control group in the treatment of type 2 diabetes and was more effective in improving glycated hemoglobin control, indicating that SGLT2Is can effectively control glucose and protect the kidney, which is consistent with the results of previous studies. Of note, SGLT2I therapy should be used with caution in patients with very high levels of HbA1c and is contraindicated in patients with a history of diabetic ketoacidosis [34]. In addition, it has been reported that in patients with stage 2 or 3 diabetic nephropathy, the addition of SGLT2I significantly reduced HbA1c. However, no reduction in HbA1c was observed in stage 4 patients with chronic kidney disease. Therefore, the use of SGLT2Is is contraindicated in patients with severe chronic kidney disease [35]. In addition, studies have shown that in patients 75 years and older treated with SGLT2Is, the reduction of HbA1c is diminished and may increase the risk of decreased blood volume, which may affect renal function. Therefore, SGLT2Is should be used with caution in the elderly [34].

Interestingly, existing studies suggest that the effect of SGLT2Is on eGFR may depend on the duration of treatment. Early treatment decreases eGFR, which remains stable or increases after long-term treatment [36, 37]. Consistent with these findings, we found that within 12 weeks of treatment, eGFR decreased more in SGLT2Is than in the control group. In contrast, after 24 weeks of treatment, there was an increase in eGFR in the SGLT2I group, although the result was not significant. These findings may suggest a renal protective effect of SGLT2Is in the long run. Furthermore, although an acute, modest decrease in eGFR occurs initially, it has been shown not to affect the progression of kidney disease [38, 39]. The mechanism of early reduction of eGFR by SGLT2Is has been partially investigated. There have been several studies showing that SGLT2Is activate tubule-glomerular feedback and increase renal tubular back pressure by increasing fluid and electrolyte delivery to the macula densa. This results in a decrease in intraglomerular pressure and eGFR [37, 40].

Limitation

Some limitations of this meta-analysis should be noted. (1) We did not exclude patients with diabetic nephropathy. Their uric acid levels may have been elevated as the disease progressed, which could have affected the results. (2) We included a small number of studies with inconsistent follow-up times and different background treatments. (3) All the included original data were not accessed, and most experiments did not emphasize the measurement methods of each indicator. These factors may have a potential impact on the results. (4) Because of the limited data in the included literature, we were limited to performing subgroup analyses on the basis of baseline. For example, we were unable to perform subgroup analyses of doses, and there were few types of SGLT2Is involved.

Conclusion

In conclusion, this meta-analysis provides evidence of the effect of SGLT2Is on SUA, BMI, HbA1c, and eGFR. These findings suggest a beneficial effect of SGLT2Is on renal risk factors in patients with abnormal glucose metabolism.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00228-023-03490-8.

Acknowledgements The coauthors thank the National Natural Science Foundation of China (81973378, 82073909), Research Project Supported by Shanxi Scholarship Council of China (2020-0172), and the Shanxi Provincial Central Leading Local Science and Technology Development Fund Project (YDZJSX2022A059) for their support.

Author contribution Mengnan Li and Jian Zhang searched and reviewed studies, extracted and analyzed the data, and drafted and proofed the manuscript. Mengnan Li contributed to data collection and statistical analyses and reviewed the manuscript. Mengnan Li reviewed and edited the manuscript. Yunfeng Liu, Yi Zhang, Minmin Han, Jiaxin Zhang, and Guimei Yang directed the project and contributed to the discussion as well as reviewed and edited the manuscript.

Funding This work was supported by the National Natural Science Foundation of China (No. 82073909 and 81973378), the Research Project Supported by Shanxi Scholarship Council of China (No. 2020–172), and the Shanxi Provincial Central Leading Local Science and Technology Development Fund Project (YDZJSX2022A059).

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding authors upon reasonable request.

Declarations

Competing interests The authors declare no competing interest.

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