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NEPHROLOGY - REVIEW

Effect of SGLT2 inhibitor on renal function in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Objective This study summarizes the evidence from randomized controlled trials (RCTs) to assess the effects of SGLT2 inhibitors on renal function and albuminuria in patients with type 2 diabetes.

Materials/methods We searched PubMed, Web of Science, Cochrane Library and EMBASE for reports published up to March 2018 and included RCTs reporting estimated glomerular filtration rate (eGFR) and/or urine albumin/creatinine ratio (UACR) changes. Data extraction and assessment of research quality based on Cochrane risk biasing tools. Data were calculated to represent the standardized mean difference (SMD) for each study, and the SMDs with 95% confidence intervals (CIs) were pooled using a random effects model.

Results Fifty-one studies were included that evaluated eGFR levels, and 17 studies were included that evaluated UACR levels. A meta-analysis showed that SGLT2 inhibitors had no significant effect on eGFR levels (SMD −0.02, 95% CI −0.06, 0.03, $p=0.45$), and eGFR reduction was observed in the subsets of the duration of the trial 12 < duration ≤ 26 weeks (SMD −0.08, 95% CI −0.13, −0.02, $p=0.005$) and mean baseline eGFR < 60 ml/min per 1.73 square meters (SMD −0.22, 95% CI −0.37, −0.07, $p=0.004$). We found that SGLT2 inhibitors reduced UACR levels in patients with type 2 diabetes (SMD −0.11, 95% CI −0.17, −0.05, $p=0.0001$). Compared with monotherapy, the combination with other hypoglycemic agents can reduce albuminuria levels (SMD −0.13, 95% CI −0.19, −0.06, $p<0.0001$).

Conclusions The effect of SGLT2 inhibitor on eGFR in patients with T2DM was not statistically significant, but it was effective in reducing albuminuria levels.

Keywords SGLT2 inhibitor · Renal function · Type 2 diabetes mellitus · Meta-analysis

Introduction

There are 425 million people with type 2 diabetes mellitus (T2DM) in the world, and one in two is undiagnosed [1]. About 30–50% of patients with T2DM will have renal impairment, and 40–50% of patients will develop high and very high albuminuria [2, 3]. In many countries, such as the USA, diabetes accounts for 45.4% of the major causes of end-stage renal disease (ESRD) [4]. Thus, it is especially important for the prevention and treatment of diabetic kidney disease (DKD).

At present, DKD's treatment strategy is mainly to optimize the management of blood glucose and blood pressure, including drug, diet and lifestyle treatment, thereby reducing albuminuria and delaying the progression of kidney disease [5]. Blood glucose control is the core of DKD treatment, and the new hypoglycemic drug sodium-glucose co-transporter 2 (SGLT2) inhibitors bring more choices for blood glucose control. SGLT2 inhibitors reduce the glucose reabsorption capacity of the kidney by inhibiting the glucose transporter on the surface of the proximal tubules of the kidney, thereby increasing the glucose excretion in the urine of diabetic patients and lowering blood glucose [6]. In addition, SGLT2 inhibitors have potential cardiovascular protection [7, 8] and renal protection. Animal experiments

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have found that SGLT2 inhibitors can reduce albuminuria in normotensive BTBR ob/ob mice and improve diabetes-related glomerular hypertrophy and mesangial expansion [9]. A clinical trial showed canagliflozin reduces urinary albumin levels and delays nephropathy progression [10]. In large clinical randomized controlled trials (RCTs) completed so far, the EMPA-REG OUTCOME trial demonstrated that the addition of empagliflozin significantly reduced the risk of clinically relevant renal adverse events compared with the placebo group [11]. In the CANVAS-R Program, canagliflozin reduced the risk of albuminuria, renal replacement therapy, and death from renal causes [12]. Although the results of the RCTs are encouraging, Liu XY's meta-analytical results suggest that SGLT2 inhibitors does not have a significant effect on eGFR when comparing with placebos [13]. Therefore, this study summarizes the available evidence for RCTs to determine the effect of SGLT2 inhibitors on glomerular filtration rate (eGFR) and urinary albumin levels in T2DM patients.

Methods

Search strategy

The design, implementation, analysis and reporting of this study followed the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [14]. We searched the relevant RCTs published up to March 2018 in the PubMed, EMBASE, Cochrane Library and Web Of Science databases using the following terms in titles, abstracts and keywords: (canagliflozin OR dapagliflozin OR empagliflozin OR ipragliflozin OR remogliflozin OR tofogliflozin OR sergliflozin OR SGLT2 inhibitors OR sodium-glucose co-transporter 2 inhibitors OR sodium glucose co-transporter-2 inhibitors OR sodium-glucose transporter inhibitors OR SGLT2 inhibitors OR forxiga) AND (Type 2 Diabetes Mellitus OR NIDDM OR Maturity-Onset Diabetes OR Adult-Onset Diabetes Mellitus OR Ketosis-Resistant Diabetes Mellitus OR Non-Insulin-Dependent Diabetes Mellitus OR Slow-Onset Diabetes Mellitus OR Stable Diabetes Mellitus OR Maturity-Onset Diabetes Mellitus OR "Maturity Onset Diabetes Mellitus" OR MODY OR Non-insulin-Dependent Diabetes Mellitus) AND (randomized OR placebo). Literature search was not subject to language restrictions and only was limited to studies in humans.

Study selection

The retrieved literature was independently and parallelly screened by two authors (Minxiang Wu and Zhengyue Chen). In the first phase, the full text of the clinical randomized controlled trials related to the study was obtained by reading the title and abstract screening. In the second stage, after reading the full text, further screen the literature according to the standard, and contact the author as much as possible to obtain complete information of the literature with incomplete information. After the information is complete, decide whether to include it according to the inclusion criteria. If there is disagreement, negotiate or be assessed by a third party. Inclusion criteria for the original literature: (i) Being a randomized controlled trial with either parallel or cross-over design. (ii) Type 2 diabetes or meet the diagnostic criteria for type 2 diabetes. (iii) Reporting mean changes in eGFR or UACR before and after drug use. Exclusion criteria were: (i) Type 1 diabetes, non-diabetic or special type of diabetes. (ii) Research that does not meet the observed indicators. In addition, the included studies were divided into two groups, the experimental group: (i) SGLT2 inhibitor monotherapy. (ii) SGLT2 inhibitor + other hypoglycemic agents, control group: (i) placebo. (ii) Hypoglycemic agents other than SGLT2 inhibitors. (iii) Placebo + hypoglycemic agents other than SGLT2 inhibitors.

Data extraction

Two authors (Zhenyu Nie AND Xiongwei Yu) independently extracted the characteristic data of the study. (1) Basic information of the literature: author, year, published journal, study location and sponsor; (2) basic information of the tester: age, gender, sample size, ethnicity, loss of follow-up or withdrawal, baseline characteristics (HbA1C%, BMI, eGFR and diabetes duration); (3) basic information of the intervention method: the name of the intervention drug in the experimental group and the control group, the dosage, the combination, the treatment observation time; (4) mean changes (mean ± standard deviation) in eGFR and UACR in the experimental and control groups. The program GetData-Graph-Digitizer (http://www.getdata-graph-digitizer.com) was used to extract relevant data reported in figures but not in the text.

Quality assessment

The Cochrane criteria were used to assess the quality of the included studies. The evaluation of each study was as follows: randomized generation, allocation concealment, double blindness of the performers and participants, blinding of outcomes, incomplete outcome data, publication bias and other biases source.

Statistical analysis

Statistical analysis and meta-analysis were performed using RevMan V.5.3 software (Cochrane Collaboration, Oxford, UK) and STATA version 12.0 (Stata Corp,

College Station, TX). The heterogeneity between the original studies included in Cochran's Q test and I square estimation was used. I squared above 50% and $p < 0.05$ indicates significant heterogeneity. We compared the mean difference between baseline and endpoint for eGFR and UACR, expressed as mean ± standard deviation (SD). If the original document only reports the standard error (SE), we use the formula to convert, where SD = SEM × sqrt(n), where n is the sample size. If the original document only reports 95% confidence interval (CI), then SD = SQRT(n) × (upper-lower limit)/3.92, $n \geq 100$; SD = SQRT(n) × (upper-lower limit)/(TINV $(1 - 0.95, n - 1) \times 2$), $n \leq 60$, n represents the sample size, n is between 60 and 100, and both can be used. When multiple experimental groups appeared in the SGLT2 treatment group, data were included in the analysis according to the drug instruction. We used a random effects model for meta-analysis and a subgroup analysis to assess the source of heterogeneity, with effect sizes expressed as standardized mean differences (SMD) and 95% confidence intervals (CI). A subgroup analysis explored the effects of monotherapy or combination therapy, drug class, duration of trial, mean baseline eGFR, mean baseline age, mean baseline glycated hemoglobin (HAb1C%), duration of type 2 diabetes, and active or placebo control on eGFR and UACR.

Results

Search results

The initial literature search identified 1954 potential articles. After careful screening, a total of 52 articles met the inclusion criteria, and the process of step-by-step exclusion and selection is shown in Fig. 1. A total of 52 studies involving 17,797 subjects were included in the meta-analysis, of which 51 studies from 17,639 subjects reported an average change in eGFR, and 17 studies involving 4828 subjects reported UACR average change. Demographic and baseline biochemical parameters of the included studies are shown

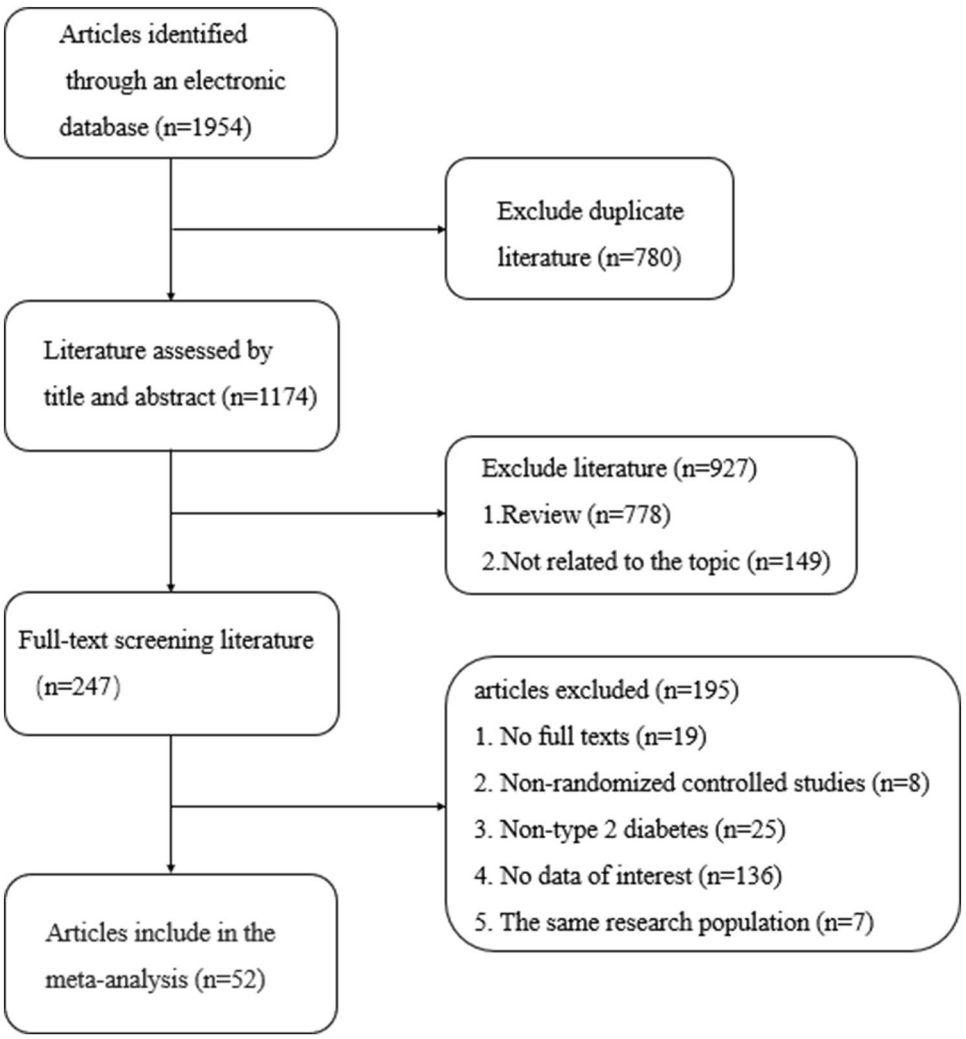

Fig. 1 Flowchart of the multi-phase for study selection

Table 1 Characteristics of included studies

Study	Mean age (year)	Sample size		Trial duration (week)	T2DM duration (year)	Mean eGFR	Mean BMI	Mean HAblC%	Control	Dose	Drug combination	Indicator reported
		Case	Control									
Dapagliflozin												
Ji et al. [15]	51.4	128	132	24	1.22	92.9	25.6	8.25	Placebo	5 mg	–	eGFR
Bailey et al. [16]	51.5	64	75	24	1.59	84.8	N/R	N/R	Placebo + metformin	5 mg	–	eGFR UACR
Kohan et al. [17]	66.5	83	84	104	16.3	44.9	N/R	8.42	Placebo	5 mg	–	eGFR UACR
Wilding et al. [18]	57.0	24	23	12	12.8	86.7	35.2	8.4	Placebo + insulin	10 mg	Insulin	eGFR
Strojek et al. [19]	60.3	142	145	48	7.4	81.8	29.7	8.14	Placebo + glimepiride	5 mg	Glimepiride	eGFR
Yang et al. [20]	57.5	139	133	24	12.5	88.3	26.5	8.55	Placebo + insulin	10 mg	Insulin/OAD (s)	eGFR
Bolinder [21]	60.7	89	90	24	5.75	84.3	31.9	7.2	Placebo + metformin	10 mg	Metformin	eGFR UACR
Araki et al. [22]	58.1	122	60	16	14.9	78.1	26.6	8.37	Placebo	5 mg	Insulin	eGFR UACR
Draeger et al. [23]	56.9	99	101	16	5.33	85.4	32.4	7.86	Placebo + metformin	5 mg bid	Metformin	eGFR
Nauck et al. [24]	58.5	400	401	52	6.5	90.0	31.4	7.7	Glipizide	5 mg	Metformin	eGFR UACR
Wilding et al. [25]	59.1	211	193	104	13.3	78.0	33.04	8.55	Placebo + Insulin	5 mg	Insulin	eGFR UACR
Heerspink et al. [26]	55.9	24	25	12	6.5	N/R	N/R	7.6	Placebo	10 mg	Metformin +/− sulfonylurea	eGFR
Canagliflozin												
Rosenstock et al. [27]	54.6	237	237	26	3.4	88.5	32.7	8.8	Metformin	100 mg	–	eGFR
Inagaki et al. [28]	58.3	90	93	24	5.2	83.1	25.7	8.01	Placebo	100 mg	–	UACR
Stenlöf et al. [29]	55.2	195	192	52	4.35	87.3	31.5	8.05	Placebo/SITA[a]	100 mg	–	eGFR
Bode et al. [30]	63.9	237	237	104	11.9	76.9	31.6	7.8	Placebo	100 mg	metformin +/− sulfonylurea	eGFR
Schernthaner et al. [31]	56.7	377	378	52	9.6	88.9	31.6	8.1	Sitagliptin	300 mg	Metformin + sulfonylurea	eGFR
Sha et al. [32]	62.8	18	18	12	8.5	97.3	30.3	7.65	Placebo	300 mg	Metformin	eGFR
Qiu et al. [33]	57.8	93	93	18	6.9	85.9	32.7	7.65	Placebo	50 mg bid	Metformin	eGFR

Table 1 (continued)

Study	Mean age (year)	Sample size		Trial duration (week)	T2DM duration (year)	Mean eGFR	Mean BMI	Mean HAblC%	Control	Dose	Drug combination	Indicator reported
		Case	Control									
Ji et al. [34]	56.1	223	226	18	6.6	94.0	25.5	7.9	Placebo	100 mg	Metformin +/− sulfonylurea	eGFR
Lavalle et al. [35]	55.5	368	366	52	6.75	89.4	32.2	7.9	Sitagliptin + metformin	100 mg	Metformin	eGFR
Wilding et al. [36]	57.1	157	156	52	9.6	89.2	33.0	8.1	Placebo	100 mg	metformin +/− sulfonylurea	eGFR
Cefalu et al. [37]	56.4	483	482	52	6.5	N/R	31.0	7.8	Glimepiride	100 mg	Metformin +/− sulfonylurea	eGFR UACR
Forst et al. [38]	57.5	113	115	52	10.3	85.9	32.4	8.0	Placebo/SITA[a]	100 mg	Metformin +/− sulfonylurea	eGFR
Yale et al. [39]	68.85	90	90	26	16	39.9	32.8	7.95	Placebo	100 mg	Metformin +/− sulfonylurea	eGFR UACR
Rodbard et al. [40]	57.4	107	106	26	9.95	90.85	32.0	8.45	Placebo	100 mg	Metformin + sitagliptin	eGFR
Empagliflozin												
Kadowaki et al. [41]	58.3	109	109	12	N/R	85.2	25.45	7.94	Placebo	10 mg	–	eGFR
Lewin et al. [42]	69.5	132	133	52	N/R	89.0	31.7	8.05	Linagliptin	10 mg	–	eGFR UACR
Roden et al. [43]	55.6	224	228	76	N/R	87.2	28.5	7.89	Placebo	10 mg	–	eGFR
Hadjadj et al. [44]	53.2	169	168	24	N/R	92.45	30.3	8.65	Metformin	10 mg	–	eGFR
Nishimura et al. [45]	62.7	20	21	4	N/R	79.6	24.5	8.0	Placebo	10 mg	–	eGFR
DeFronzo et al. [46]	56.1	137	128	52	N/R	90.6	30.75	8.0	Linagliptin	10 mg	metformin	eGFR UACR
Ross et al. [47]	58.3	214	107	16	N/R	89.5	31.9	7.79	Placebo	10 mg	Insulin	eGFR
Søfteland et al. [48]	55.1	109	108	24	N/R	91.7	30.4	7.97	Placebo	10 mg	Linagliptin + metformin	eGFR UACR
Haring et al. [49]	55.7	217	207	24	N/R	89.6	28.9	7.92	Placebo	10 mg	Metformin	eGFR
Rosenstock et al. [50]	58.3	169	170	78	N/R	84.5	31.9	8.25	Placebo	10 mg	Insulin/metformin/sulfonylurea	eGFR
Rosenstock et al. [51]	56.0	186	188	52	N/R	83.7	34.7	8.36	Placebo	10 mg	Insulin +/− metformin	eGFR
Kovacs et al. [52]	54.65	168	165	76	N/R	84.9	29.2	8.11	Placebo	10 mg	Metformin	eGFR

Table 1 (continued)

Study	Mean age (year)	Sample size		Trial duration (week)	T2DM duration (year)	Mean eGFR	Mean BMI	Mean HAblC%	Control	Dose	Drug combination	Indicator reported
		Case	Control									
Merker et al. [53]	55.7	217	207	76	N/R	89.6	28.9	7.9	Placebo	10 mg	Metformin	eGFR
Haering et al. [54]	56.95	225	225	76	N/R	86.7	28.1	8.15	Placebo	10 mg	metformin	eGFR
Tikkanen et al. [7]	60.45	276	271	12	N/R	84.2	32.4	7.88	Placebo	10 mg	Pioglitazone +/− insulin	eGFR
Zinman et al. [8]	63.1	2345	2333	162	N/R	74.05	30.6	8.07	Placebo	10 mg	Insulin/metformin/sulfonylurea	eGFR
Barnett et al. CKD2 [55]	62.9	98	95	52	N/R	71.3	31.6	8.05	placebo	10 mg	Insulin + OAD (s)	eGFR UACR
Barnett et al. CKD3 [55]	64.9	187	187	52	N/R	44.9	30.2	7.96	Placebo	25 mg	Insulin + OAD (s)	eGFR UACR
Barnett et al. CKD4 [55]	64.1	37	37	52	N/R	23.2	30.4	8.11	Placebo	25 mg	Insulin + OAD (s)	eGFR UACR
Ipragliflozin												
Fonseca et al. [56]	53.0	67	53	12	4.6	N/R	31.5	7.94	Placebo	50 mg	–	eGFR
Kashiwagi et al. (The BRIGHTEN study) [57]	59.4	62	67	16	N/R	N/R	25.5	8.32	Placebo	50 mg	–	eGFR
Wilding et al. [58]	58.0	68	66	12	5.85	N/R	31.5	7.72	Placebo	50 mg	Metformin	eGFR
Lu et al. [59]	53.7	87	83	24	6.16	148.9	26.8	7.74	placebo	50 mg	metformin	eGFR UACR
Kashiwagi et al. (The EMIT study) [60]	59.7	165	75	24	10.45	84.7	25.3	8.37	Placebo	50 mg	Sulfonylurea	eGFR UACR
Kashiwagi et al. (The SPOTLIGHT study) [61]	56.2	97	54	24	6.8	91.0	27.1	8.3	Placebo	50 mg	Pioglitazone	eGFR UACR
Kashiwagi et al. CKD2 [62]	63.1	60	23	24	8.1	70.2	25.5	7.1	Placebo	50 mg	Sulfonylurea/pioglitazone	eGFR UACR
Kashiwagi et al. CKD3 [62]	65.6	58	23	24	10.9	51.3	25.7	7.16	Placebo	50 mg	Sulfonylurea/pioglitazone	eGFR UACR

Table 1 (continued)

Study	Mean age (year)	Sample size		Trial duration (week)	T2DM duration (year)	Mean eGFR	Mean BMI	Mean HAblC%	Control	Dose	Drug combination	Indicator reported
		Case	Control									
Tofogliflozin												
Kaku et al. [63]	56.7	58	56	24	6.2	85.3	25.5	8.4	Placebo	20 mg	–	eGFR
Ertugliflozin												
Terra et al. [64]	56.45	156	153	26	4.87	87.4	33.2	8.1	Placebo	5 mg	–	eGFR

N/R not reported, *UACR* urine albumin/creatinine ratio, *eGFR* estimated glomerular filtration rate, *OAD(s)* oral anti-diabetes drugs, *SITA* Sitagliptin, *BMI* body mass index, *HAbIC%* glycosylated hemoglobin

[a]The first 26 weeks of treatment were treated with placebo as the control group, and the last 26 weeks of treatment with sitagliptin as the control group

in Table 1. The SGLT2 inhibitors used in the experimental group include: dapagliflozin, canagliflozin, empagliflozin, ipragliflozin, tofogliflozin and ertugliflozin. In the control group, 35 were placebo controls and 17 were other antidiabetic drug controls, including metformin, glimepiride, glipizide, linagliptin, sitagliptin and insulin. The included studies were published between 2009 and 2018 and the duration of the trial ranged from 4 weeks to 162 weeks.

The quality assessments are shown in Supplement Figs. 3 and 4, of which 38 studies describe the generation of random sequences, 15 studies have inadequate blinding, 42 studies have low bias in loss of follow-up, and 49 studies show lower reporting bias.

Effect of SGLT2 inhibitor on eGFR

A meta-analysis from 51 RCT data showed that SGLT2 inhibitors had no significant effect on eGFR levels (SMD −0.02, 95% CI −0.06, 0.03, $p=0.45$) (Fig. 2). Sensitivity analysis was conducted and the results remained consistent with the pooled effect. In the subgroup analysis, eGFR reduction was observed in the subsets of the duration of the trial 12 < duration ≤ 26 weeks (SMD −0.08, 95% CI −0.13, −0.02, $p=0.005$) and mean baseline eGFR < 60 ml / min per 1.73 square meters (SMD −0.22, 95% CI −0.37, −0.07, $p=0.004$). The results of the complete subgroup analysis are shown in Table 2.

Effect of SGLT2 inhibitor on UACR

A meta-analysis from 17 RCT data showed that SGLT2 inhibitors reduced UACR levels in patients with type 2 diabetes (SMD −0.11, 95% CI −0.17, −0.05, $p=0.0001$) (Fig. 3). The sensitivity analysis results are consistent with the pool analysis results. In the subgroup analysis (Table 2), we observed a significant decrease in UACR levels associated with empagliflozin (SMD −0.22, 95% CI −0.33, −0.11, $p=0.0001$), with trial duration of 26 < duration ≤ 52 weeks (SMD −0.15, 95% CI −0.23, −0.07, $p=0.0002$), with age ≤ 60 (SMD −0.10, 95% CI −0.16, −0.03, $p=0.007$) and > 60 (SMD −0.15, 95% CI −0.25, −0.04, $p=0.005$), with eGFR baseline ≤ 60 (SMD −0.18, 95% CI −0.33, −0.02, $p=0.03$) and > 60 (SMD −0.10, 95% CI −0.17, −0.03, $p=0.004$) with BMI > 30 (SMD −0.13, 95% CI −0.20, −0.07, $p<0.0001$), with HbAlC% ≤ 8 (SMD −0.11, 95% CI −0.20, −0.03, $p=0.009$) and > 8 (SMD −0.13, 95% CI −0.21, −0.05, $p=0.002$), with active as control group (SMD −0.08, 95% CI −0.16, −0.01, $p=0.03$) and placebo as control group (SMD −0.15, 95% CI −0.24, −0.06, $p=0.0009$) and with other antidiabetic combinations (SMD −0.13, 95% CI −0.19, −0.06, $p<0.0001$).

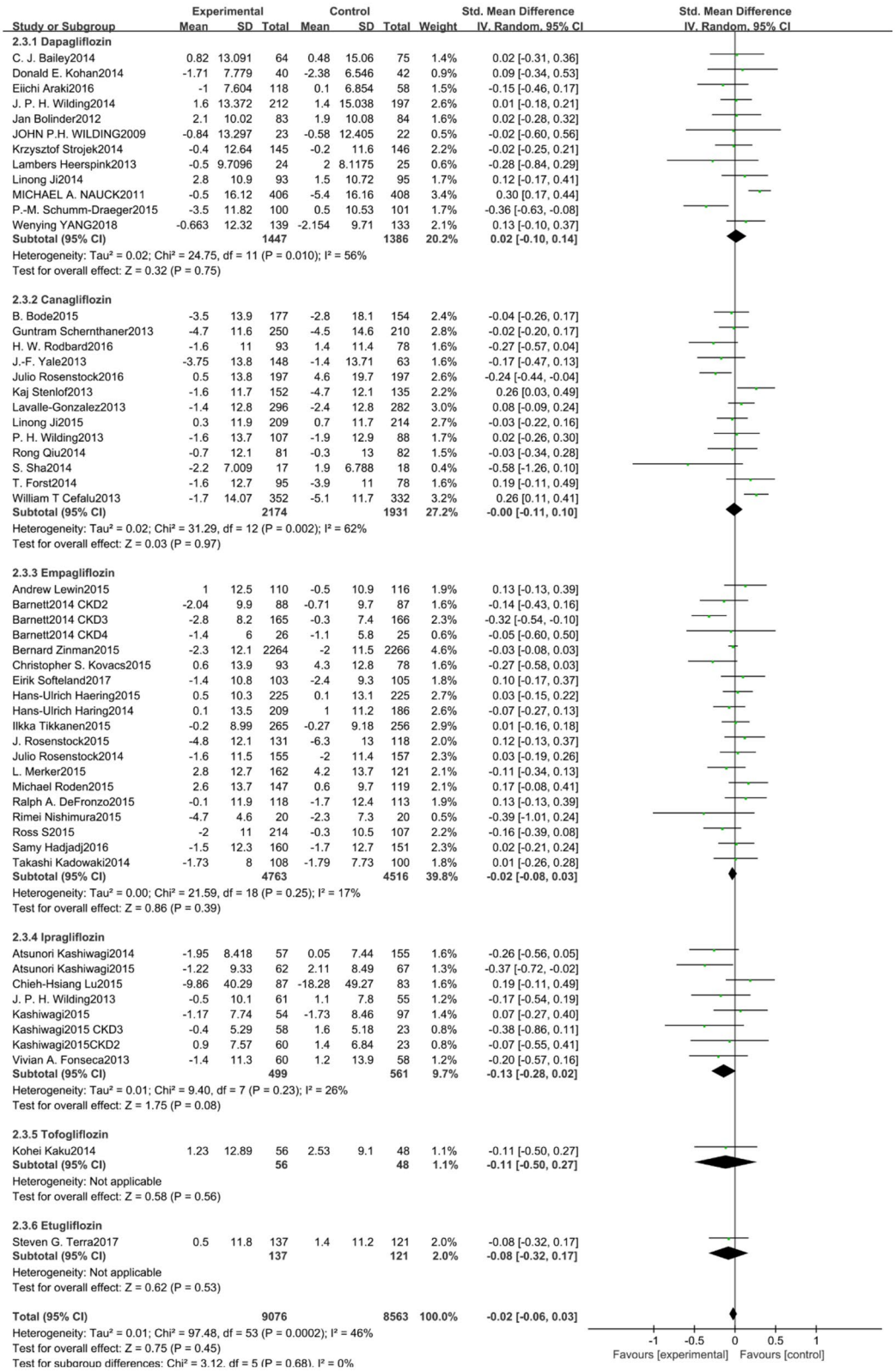

Fig. 2 Forest plot of meta-analysis of the effect of SGLT2 inhibitor on eGFR. Data are pooled SMDs with 95% CIs

Table 2 The effects of SGLT2 inhibitor on renal function based on subgroup analysis

Parameter	Number of SMD included	Subgroup	95% CI	*I*-squared (%)	*p* for subgroup (random effect)	*p* for test subgroup differences
eGFR						
Drug	12	Dapagliflozin	−0.10, 0.14	56%	0.75	0.68
	19	Empagliflozin	−0.08, 0.03	17%	0.39	
	8	Ipragliflozin	−0.28, 0.02	26%	0.08	
	13	Canagliflozin	−0.11, 0.10	62%	0.97	
	1	Ertugliflozin	−0.06, 0.03	N/R	0.53	
	1	Tofogliflozin	−0.5, 0.27	N/R	0.56	
Trial duration (w)	30	12 < duration ≤ 26	−0.13, −0.02	7%	0.005*	0.02*
	14	26 < duration ≤ 52	−0.02, 0.17	63%	0.13	
	9	52 < duration	−0.06, 0.03	0%	0.53	
Mean baseline age (years)	38	Age ≤ 60	−0.06, 0.06	51%	0.96	0.19
	15	60 < age	−0.12, 0.01	10%	0.07	
eGFR baseline (ml/min per 1.73 square meters)	5	eGFR ≤ 60	−0.37, −0.07	0%	0.004*	0.005*
	44	60 < eGFR	−0.04, 0.04	35%	0.99	
BMI (kg/m^2)	19	BMI ≤ 30	−0.11, 0.03	15%	0.29	0.53
	32	30 < BMI	−0.07, 0.05	58%	0.80	
Mean baseline HAblC%	26	HAblC% ≤ 8	−0.11, 0.05	61%	0.48	0.73
	27	8 < HAblC%	−0.07, 0.04	32%	0.68	
Mean duration of diabetes (years)	6	Duration ≤ 5	−0.19, 0.15	60%	0.83	0.91
	18	5 < duration ≤ 10	−0.1, 0.1	60%	0.98	
	10	10 < duration	−0.13, 0.07	10%	0.53	
Control	15	Active	−0.06, 0.13	65%	0.45	0.13
	39	Placebo	−0.09, 0.00	19%	0.05	
Monotherapy	15	Yes	−0.11, 0.08	36%	0.74	0.95
	39	No	−0.07, 0.03	50%	0.49	
UACR						
Drug	6	Dapagliflozin	−0.15, 0.04	1%	0.25	0.15
	6	Empagliflozin	−0.33, −0.11	0%	0.0001*	
	5	Ipragliflozin	−0.26, 0.06	0%	0.21	
	3	Canagliflozin	−0.21, 0.04	0%	0.18	
Trial duration (w)	11	12 < duration ≤ 26	−0.19, 0.00	0%	0.06	0.20
	7	26 < duration ≤ 52	−0.23, −0.07	0%	0.0002*	
	2	52 < duration	−0.15, 0.18	0%	0.88	
Mean baseline age (years)	11	Age ≤ 60	−0.16, −0.03	0%	0.007*	0.41
	9	60 < age	−0.25, −0.04	0%	0.005*	
eGFR baseline (ml/min per 1.73 square meters)	5	eGFR ≤ 60	−0.33, −0.02	13%	0.03*	0.40
	14	60 < eGFR	−0.17, −0.03	0%	0.004*	
BMI (kg/m^2)	7	BMI ≤ 30	−0.24, 0.02	0%	0.1	0.74
	11	30 < BMI	−0.20, −0.07	0%	< 0.0001*	
Mean baseline HAblC%	7	HAblC% ≤ 8	−0.20, −0.03	0%	0.009*	0.80
	12	8 < HAblC%	−0.21, −0.05	0%	0.002*	
Mean duration of diabetes (years)	1	Duration ≤ 5	−0.14,0.53	N/R	0.24	0.27
	7	5 < duration ≤ 10	−0.17, 0.00	0%	0.05	
	6	10 < duration	−0.2, 0.04	0%	0.18	
Control	7	Active	−0.16, −0.01	0%	0.03*	0.56
	13	Placebo	−0.24, −0.06	0%	0.0009*	
Monotherapy	4	Yes	−0.18, 0.16	23%	0.89	0.22
	16	No	−0.19, −0.06	0%	< 0.0001*	

N/R not reported

*$p < 0.05$

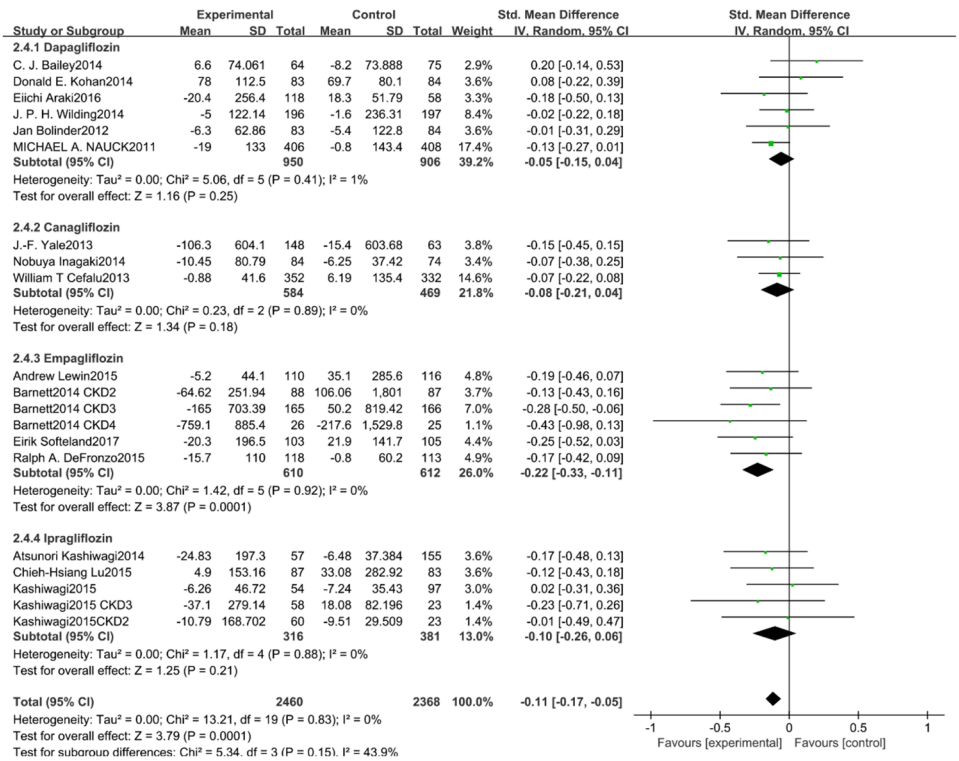

Fig. 3 Forest plot of meta-analysis of the effect of SGLT2 inhibitor on UACR. Data are pooled SMDs with 95% CIs

Publication bias

It was not found that there was a publication bias for eGFR and UACR level in the overall study included (Begg's test, $Pr > |z| = 0.018$, Egger's test, $p = 0.085$; Begg's test, $Pr > |z| = 0.581$, Egger's test, $p = 0.953$; respectively) (Supplement Fig. 1 and Table 1).

Discussion

We pooled the results of existing RCTs for meta-analysis and hope to find evidence that SGLT2 inhibitors are protective against kidneys in T2DM patients. The results of this meta-analysis suggested that SGLT2 inhibitors had no significant effect on eGFR in patients with T2DM, but reduced albuminuria, indicating the renal protective effect of SGLT2. Subgroup analysis suggested that SGLT2 had a time-varying effect on eGFR, and short-term application may reduce eGFR levels, but renal function did not worsen in the long-term. In addition, the effect of SGLT2 inhibitors on eGFR was also associated with basal eGFR. In the UACR subgroup analysis, the effect of SGLT2 inhibitors on albuminuria appeared to be related to the extent of BMI, and compared with monotherapy, the combination with other hypoglycemic agents can reduce albuminuria levels.

Our meta-analysis suggested that SGLT2 inhibitors had no significant effect on eGFR, similar to the results of previous meta-analyses [65], but from a subgroup analysis, the duration of application of SGLT2 may have an impact on eGFR, it affects renal hemodynamics during the early application phase of SGLT2. In the early stage of diabetic nephropathy, hyperglycemia can cause the glomerulus to be in ultrafiltration state, but the mechanism remains elusive. The elevated blood glucose may up-regulate the expression of SGLT1 and SGLT2 on the surface of the renal tubule [66, 67], and the ability to reabsorb sodium chloride and glucose is enhanced [68, 69], the sodium chloride content reaching the macula densa is reduced [70]. Based on the tube tubuloglomerular feedback (TGF) mechanism [71], it causes the glomerular afferent arteriolar vasodilation resulting in increased renal blood flow. Finally, a high filtration state occurs and the high filtration state continues to cause damage to the glomerulus [72]. The application of the SGLT2 inhibitor may can increase the concentration of sodium chloride reaching the distal tubule and reverse the glomerular afferent arteriolar vasodilation, thereby restoring the hemodynamics of the glomerulus. This phenomenon occurs in SGLT2 knockout diabetic mice [73]. It is for this reason that patients with SGLT2 inhibitors have experienced a decline in eGFR in a short period of time. However, in the long run, eGFR will stabilize to a certain extent [8], and even return to the baseline value after stopping the drug [55], indicating that this is the result of drug action rather than impaired kidney function. In the subgroup analysis, we also observed the effect of eGFR baseline on the efficacy of

the drug; however, there are few reports of SGLT2 inhibitors in patients with chronic kidney disease (CKD). This subgroup analysis suggested that the use of SGLT2 inhibitors in patients with impaired baseline renal function may have an impact on eGFR. Barnett et al. [55] found that CKD patients with SGLT2 inhibitors resulted in a decrease in eGFR at the initial stage and then remained stable. At 52 weeks, patients with CKD2 and CKD3 with SGLT2 inhibitors had slightly lower eGFR levels than placebo, and the level of eGFR in patients with CKD4 was slightly higher than that in the placebo group, but returned to baseline values after discontinuation of the drug. Similarly, a similar situation was seen in the study by Kohan [17] and Yale [74], which illustrates the renal protection of SGLT2. However, it has been reported in the literature that the use of SGLT2 inhibitors in CKD patients and mouse models failed to alter renal hemodynamics or urinary albumin excretion [75], and the hypoglycemic effect of SGLT2 is dependent on eGFR, urinary glucose excretion decreased with increasing renal impairment [76]. But on the other hand, the lack of sample size for SGLT2 inhibition in CKD patients may lead to false positive results. In general, the exact effects and disadvantages of applying SGLT2 inhibitors in patients with CKD are not clear; therefore, we should be cautious about the use of SGLT2 inhibitors in CKD patients.

The effect of SGLT2 on reducing albuminuria in patients with T2DM is significant, which may be related to its hemodynamic changes in the glomerulus, which reduces albumin excretion by reducing glomerular hypertension. The results of this meta-analysis are consistent with other studies. Vallon et al. used empagliflozin to slow kidney weight and UACR levels in diabetic mice [77]. In the analysis of five clinical trial data, SGLT2 inhibitors reduced urinary albumin levels in T2DM patients with albuminuria [78]. In addition, we found in Barnett et al. that the most significant period of decrease in albuminuria is after eGFR decline, which is the early and mid-term application of SGLT2 [55]. Overall, these studies consistently indicate that the SGLT2 inhibitor significantly reduces UACR; these data support the renal protection of SGLT2 inhibitors, given that increased UACR is a predictor of important manifestations and progression of DKD. Some researchers have found that empagliflozin does not alleviate albuminuria caused by diabetes in diabetic mice with elevated blood glucose, suggesting that kidney protection of SGLT2 inhibitors is dependent on glycemic control [79]. In a multicenter prospective observational study, SGLT2 inhibitors improved more HbAlC% at higher baseline HbAlC% [80]. However, Herspink et al. found that support for SGLT2 to reduce urinary albumin is primarily mediated through hemodynamic changes, rather than glucose dependence [10], which led to the question of whether SGLT2 inhibitors reduce the effect of albuminuria depend on blood glucose levels. Our subgroup analysis suggested that SGLT2 reduces albuminuria levels without relying on baseline HbAlC%. The combination of SGLT2 inhibitors with other hypoglycemic agents may be superior to SGLT2 inhibitors alone in reducing renal protection such as albuminuria. First, blood glucose is a major risk factor for the progression of DKD. Strict control of blood glucose can improve albuminuria levels and prognosis in patients with DKD [81]. Compared with SGLT2 monotherapy, the combination with other hypoglycemic drugs significantly reduces HAblC% [27]. Secondly, SGLT2 inhibitors have a weight-reducing effect at the same time as hypoglycemic [21]. It has been reported in the literature that obesity is associated with albuminuria levels in patients with T2DM [82], and combination therapy with SGLT2 inhibitors has a more significant weight loss effect [27]. Third, blood pressure is also an important factor affecting urinary albumin excretion [83], and the antihypertensive effect of SGLT2 inhibitors across the border provides another protective mechanism for the kidney [7]. In the study included in this meta-analysis, the drugs combined with SGLT2 inhibitors were hypoglycemic agents. Can SGLT2 inhibitors be used in combination with traditional RASS blockers? Some studies have shown that when RAAS blockers are combined with SGLT2 inhibitors, their renal protection is greater than the use of any of these drugs alone [84, 85]. However, patients who are not responding to RAAS blockers may also not respond to SGLT2 inhibitors [86].

In this subgroup analysis, we also observed some interesting results. Empagliflozin appears to show a stronger reduction in albuminuria than other SGLT2 inhibitors, but this phenomenon has not been reported in other studies, probably because empagliflozin is widely used and has a large sample size. In addition, reported in the literature that SGLT2 inhibitors are more beneficial for patients with higher BMI in terms of hypoglycemia and hypotension [87]. We conclude that this may be the reason why SGLT2 inhibitors have a better reduction in albuminuria in patients with higher BMI. Our research has some limitations. First, although we conducted a comprehensive search, there may be some studies in the electronic literature that are not included. Second, since the number of studies reporting renal endpoint events is currently insufficient, we can only use eGFR and UACR to assess renal function. Third, we included the study data according to the recommended dose of the drug description, but the doses used in a few studies were not performed according to the instructions, which may cause some results to be unexplained.

Conclusion

Overall, a meta-analysis found that SGLT2 inhibitors can reduce eGFR in the short term, but have renal protection in the long term. When applying SGLT2 inhibitors, attention should be paid to patients' baseline eGFR levels and should be used cautiously in CKD patients. SGLT2 inhibitors can effectively reduce albuminuria and, combined with other hypoglycemic agents, can protect kidney function through a variety of mechanisms.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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