

Systematic Review and Meta-Analysis of Randomized Controlled Trials on the Effect of SGLT2 Inhibitor on Blood Leptin and Adiponectin Level in Patients with Type 2 Diabetes

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ABSTRACT

Sodium glucose cotransporter 2 (SGLT2) inhibitors are a new kind of hypoglycemic drugs that improve glucose homeostasis by inhibiting renal glucose reabsorption. Recent studies have shown that SGLT2 inhibitors can also mediate body metabolism through regulation of adipokines level, but the effects of SGLT2 inhibitors on the concentration of adipokines (leptin and adiponectin) remains controversial. This meta-analysis was set out to evaluate the changes in circulating leptin and adiponectin levels in patients with type 2 diabetes mellitus (T2DM) receiving SGLT2 inhibitors therapy. Ten randomized controlled trials (RCTs), that evaluated the effects of SGLT2 inhibitors on blood leptin and adiponectin levels in patients with type 2 diabetes, were identified by performing a systematic search of Pubmed, Embase, Cochrane, and Web of science databases through July 2018. Data were calculated using a random-effects model and presented as standardized mean difference (SMD) and 95% confidence interval (CI). Compared with placebo, treatment with SGLT2 inhibitors contributed to a decreased circulating leptin levels (SMD -0.29, 95% CI -0.56, -0.03) and an increased circulating adiponectin levels (SMD 0.30, 95% CI 0.22, 0.38). SGLT2 inhibitor treatment was associated with decreased circulating leptin levels and increased circulating adiponectin levels, which might contribute to the beneficial effects of SGLT2 inhibitors on metabolic homeostasis.

Introduction

T2DM is one of the most prevalent metabolic disorders around the world [1]. The characters of T2DM, insulin resistance, relative insulin deficiency, and gradual pancreatic β cell dysfunction are partly attributed to dysregulation of adipokines derived from adipose tis-

sue [2]. Since the discovery of leptin, the first identified adipokine in the 1990s, the list of adipokines has been increasing constantly and now includes some biological molecules such as adiponectin, resistin, visfatin, and IL-6 that have essential roles in glucose and lipid metabolism [3–5]. Leptin, a 16 kDA classical adipokine, is known to suppress food intake and mediate energy homeostasis including glucose and lipid metabolism [4]. Several gene polymorphisms of leptin have been reported to be associated with T2DM

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[6, 7]. In addition, leptin treatment could not only improve insulin resistance in patients, but also suppress liver gluconeogenesis as well as fasting hyperglycemia in diabetic mice [8]. The serum level of leptin is elevated paradoxically in obesity, which is due to the increased fat mass as leptin is synthesized and secreted by adipocytes [9], and this high level of leptin itself may induce leptin resistance and thus result in decreasing the ability of glucose utilization and interfering glucose metabolism. The another adipocytokine, adiponectin, is also an adipose-derived secretory protein, and plays a pivotal role in insulin signal and energy metabolism as well [10]. Adiponectin is well known to reduce glucose production in liver and suppress TNF- α signal that contributed to insulin resistance [11]. Meanwhile, it is established that adiponectin is negatively correlated with body weight, percentage of body fat and basal plasma insulin [12]. All the above evidence demonstrates that leptin and adiponectin may be an important factor for T2DM development. Also, these two kinds of adipokines have been reported to have cardiovascular protection [13].

SGLT2 inhibitors, an emerging kind of antidiabetic drugs, decrease plasma glucose by promoting urinary glucose excretion [14]. SGLT2 inhibitors are also reported to improve glycemic control as well as reduce risk of cardiovascular diseases [15, 16]. To explore how SGLT2 inhibitors improve the metabolic disturbances in type 2 diabetes patients, certain researches have been performed to study the changes in adipokines after SGLT2 inhibitors administration in patients with type 2 diabetes. However, previous results have been inconsistent [17–20], and the association between adipokines and SGLT2 inhibitors remains unclear. We therefore performed this meta-analysis with currently available clinical data to further evaluate the association between the treatment of SGLT2 inhibitor and circulating leptin or adiponectin concentrations in patients with T2DM.

Materials and Methods

Search strategy

Databases such as Pubmed, Embase, Cochrane, and Web of science were systematically searched without limitations in languages between January 1980 and April 2019. Specific terms like “Diabetes Mellitus, Type 2” or “type 2 diabetes mellitus” or “type 2 diabetes” or “Diabetes” or “diabetic mellitus” and “sglt2” or “sglt-2” or “sodium-glucose cotransporter 2 inhibitors” or “dapagliflozin” or “canagliflozin” or “empagliflozin” or “ipragliflozin” or “tofogliflozin” or “luseogliflozin” and “adipocytokines” or “adipokines” or “leptin” or “obese protein” or “ob protein” or “obese gene product” or “adiponectin” or “Adipocyte Complement Related Protein 30 kDa” or “apM 1 Protein” or “ACRP30 Protein” were selected to be the key words to sift out studies, which might be potentially relevant. Each reference lists of related meta-analysis or systemic review were also searched manually for identifying other eligible studies.

Inclusive and exclusive criteria

All the subjects included in this study had to be qualified with the following criteria: (1) RCTs of SGLT2 inhibitor treatment compared to placebo in type 2 diabetes patients as a monotherapy or add-on treatment and (2) The change of serum leptin and adiponectin level

from baseline of each subject in comparative groups should be available. Studies were excluded if they were nonrandomized trials, if they included patients with type 1 diabetes, or if they provide inadequate data about quantitative outcomes.

Data extraction

Two investigators (PLW and JTL) independently scrutinized each article without knowing the findings of each other, and reached a consensus including time of study, author names, sample sizes, circulating leptin and adiponectin concentrations, and background therapy. Overlapping data sets or study groups were excluded.

Quality assessment

Quality assessment of the identified randomized controlled trials was using Cochrane risk of bias tool based on the following items: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Two investigators (PLW and JTL) independently analyzed and judged each specific domain as low risk, unclear risk and high risk.

Data analysis

The statistical analysis was conducted using STATA 12.0. To assess the association between SGLT2 inhibitors use and the change of serum leptin and adiponectin level from baseline, standard mean difference and 95% confidence intervals for change of serum leptin and adiponectin concentrations in type 2 diabetes subjects were calculated, and combined by performing fix or random-effect model. Higgins I^2 test were conducted to estimate heterogeneity among studies. A I^2 -value $> 50\%$ was taken as a high level of heterogeneity, and the random effects model was performed to pool the size effect. If I^2 -value ≤ 50 was defined as a low level of heterogeneity, and the fix effects model were used for the analysis. To evaluate the sources of heterogeneity, we implemented subgroup analysis stratified by age, BMI and treatment duration. Sensitive analysis was performed to assess the influence of each single study on the change of circulating leptin and adiponectin levels. Publication bias were evaluated by Begg's test, where a p-value less than 0.1 was taken as evidence of small study effects.

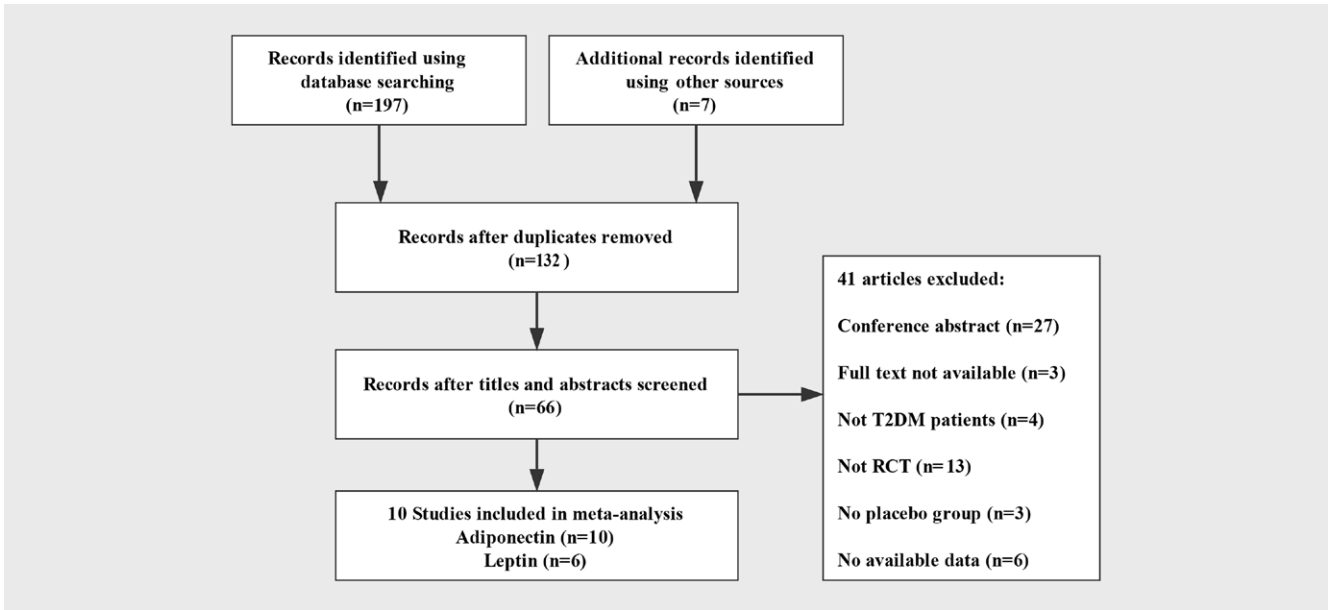
Compliance with ethics guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Results

Meta-analysis of the association of adipokines and T2DM

The search strategy first selected 132 articles. According to the inclusive and exclusive criteria, 1 988 subjects of 10 random placebo-controlled studies were acquired (► Fig. 1) [17, 20–28], and the characteristics of these studies are given in ► Table 1. The mean age of study cases was 57.8 years, the mean HbA1c was 64.92 mmol/mol, and the mean intervention duration was 20.2 weeks. Trial quality was determined using Cochrane risk of bias tool (► Fig. 2).



► **Fig. 1** Flowchart of the selection of eligible studies.

Association between SGLT2 inhibitor treatment and blood leptin levels

Six studies compared circulating leptin levels between the SGLT2 inhibitors and placebo groups, and a total numbers of 1 045 cases were identified for this evaluation. Compared with placebo group, use of SGLT2 inhibitors decreased leptin levels (SMD -0.29 , 95% CI -0.56 , -0.03 ; $p = 0.032$) (► **Fig. 3**). The I^2 -value was 77.7%, which implied a high level of heterogeneity among studies.

Subgroup analysis

Subgroup analysis stratified by age, BMI, and treatment duration was implemented, and the results are displayed in ► **Table 2**. As for leptin levels, in subgroup of age < 60 years, BMI < 30 kg/m², and treatment duration ≥ 24 weeks, patients receiving SGLT2 inhibitors therapy showed lower serum leptin levels than that of placebo group. No significant difference was observed in subgroup of age ≥ 60 years, BMI ≥ 30 kg/m², and treatment duration < 24 weeks in this analysis.

Sensitivity analysis and publication bias

To determine the influence of each single study on the overall results, we evaluated the stability of results with the use of a kick-out strategy. This method determines whether pooled values had significant fluctuation with the exclusion of each individual study. Sensitivity analysis displayed that after excluding of any study did not change the pooled result of this analysis (data not shown). In addition, after removal of the study conducted by Avogaro, the I^2 -value was decreased to 0. The sample size of Avogaro study was less than 50, and this study might be the source of heterogeneity among studies [17]. Begg's test suggested no certain evidence of publication bias, with a p-value of 0.536 (► **Fig. 1S**).

Association between SGLT2 inhibitor treatment and blood adiponectin levels

Ten randomized controlled studies including 1988 patients were suitable for analysis of the association between SGLT2 inhibitor therapy and circulating adiponectin levels. The result revealed that treatment of SGLT2 inhibitor was significantly elevated the blood adiponectin levels compared to placebo (SMD 0.30, 95% CI 0.22, 0.38; $p < 0.001$) (► **Fig. 4**). The I^2 -value was 66.4%, suggesting a high level of heterogeneity among studies.

Subgroup analysis

As for adiponectin levels, a statistically significant increase was also found in subgroup of age < 60 years and BMI < 30 kg/m², but the study remained with high heterogeneity (► **Table 2**). No significant difference was observed in subgroup of age ≥ 60 years and BMI ≥ 30 kg/m² in this analysis. Additionally, despite the higher heterogeneity, patients in subgroup of treatment duration ≥ 24 weeks or not showed increased serum adiponectin levels.

Sensitivity analysis and publication bias

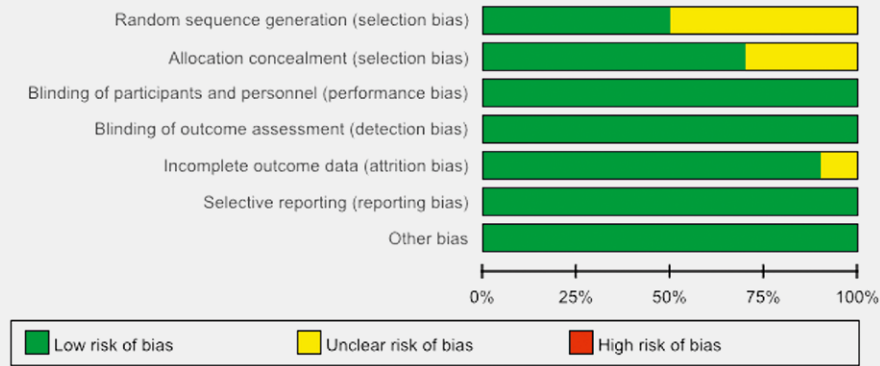
In the meta-analysis of the association of SGLT2 inhibitor therapy and leptin concentration, the result did not change significantly after removal of any study from the pooled research, which indicated a stable model of our analysis. Also, after removal of the study conducted by Avogaro, the I^2 -value was decreased from 66.4% to 58.3%. Begg's test indicated no statistically significant publication bias, with a p-value of 0.216 (► **Fig. 2S**).

Discussion

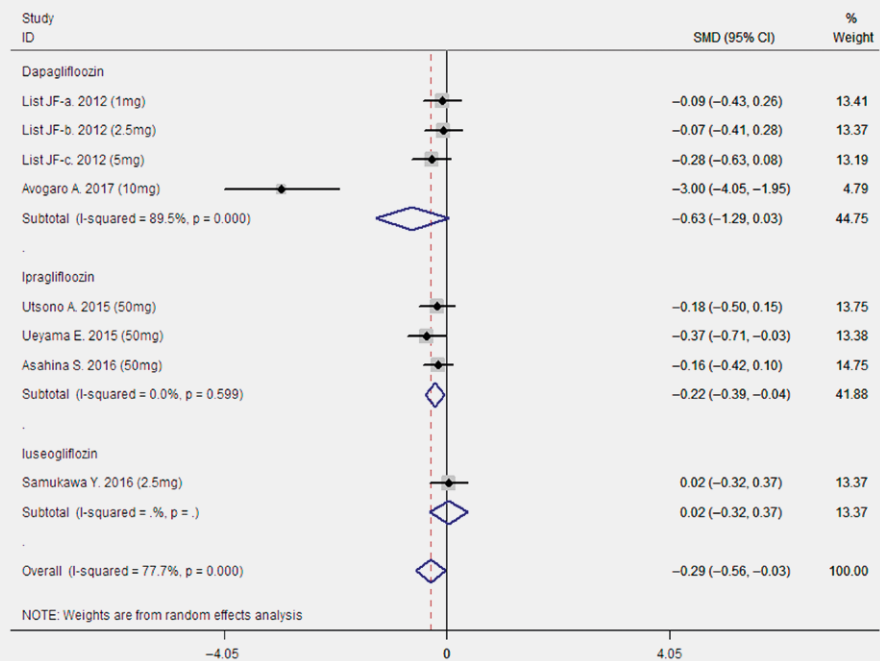
Recent studies have shown that use of SGLT2 inhibitor can improve the insulin resistance [29, 30], which could be explained by the decrease of glucose toxicity in response to induced urinary glucose

▶ **Table 1** Characteristics of the 10 studies included in the meta-analysis.

Studies [Ref.]	Region	Patients (n)	Treatment	Treatment duration	Background therapy	Patients characteristics			
						Age (years)	BMI (kg/m ²)	HbA1c (mmol/mol)	
Samukawa Y, 2014 [20]	Japanese	79/79 (Placebo)	Luseogliflozin (2.5 mg)	24 weeks	None	58.9 ± 10.1	25.98 ± 4.88	65.46 ± 9.95	65.79 ± 8.74
Kadowaki T, 2015 [21]	Japanese	328/66 (Placebo)	Tofogliflozin (2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg)	12 weeks	Diet/exercise ± metformin	55.27 ± 10.29	30.55 ± 4.91	30.37 ± 5.47	63.61 ± 8.09
List JF, 2012 [22]	USA, Canada, Mexico et al.	214/68 (Placebo)	Dapagliflozin (1 mg, 2.5 mg, 5 mg)	24 weeks	Non	52.87 ± 10.42	31.55 ± 5.63	32.47 ± 4.91	63.17 ± 11.26
Utsono A, 2015 [23]	Japanese	112/56 (Placebo)	Ipragliflozin (50 mg)	24 weeks	Metformin	56.2 ± 10.67	25.96 ± 4.41	25.47 ± 3.09	66.67 ± 7.87
Samukawa Y, 2016 [24]	Japanese	95/50 (Placebo)	Luseogliflozin (2.5 mg)	24 weeks	diet/exercise ± OHAs	67.9 ± 8.9	25.45 ± 4.18	25.81 ± 3.95	60.87 ± 7.43
Ueyama E, 2015 [25]	Japanese	118/46 (Placebo)	Ipragliflozin (50 mg)	24 weeks	diet/exercise ± OHAs	63.9 ± 6.59	25.84 ± 3.45	24.96 ± 3.36	58.80 ± 5.90
Asahina S, 2016 [26]	Japanese	168/87 (Placebo)	Ipragliflozin (50 mg)	16 weeks	Insulin ± OHAs	58.7 ± 11.1	25.61 ± 3.53	26.42 ± 3.81	71.28 ± 8.42
Araki E, 2014 [27]	Japanese	173/56 (Placebo)	Tofogliflozin (10 mg, 20 mg, 40 mg)	24 weeks	None	57.39 ± 9.69	25.28 ± 4.08	26.00 ± 4.11	68.09 ± 8.42
Gao L, 2016 [28]	China	117/45 (Placebo)	Dapagliflozin (10 mg)	18 weeks	None	55 ± 7	25.5 ± 4.4	25.5 ± 3.1	64.37 ± 5.46
Avogaro A, 2017 [17]	Italy	15/16 (Placebo)	Dapagliflozin (10 mg)	12 weeks	Insulin ± OHAs	66.3 ± 1.8	28.4 ± 1.4	32.8 ± 1.4	66.12 ± 2.19



► **Fig. 2** Study quality as estimated by Cochrane scores.

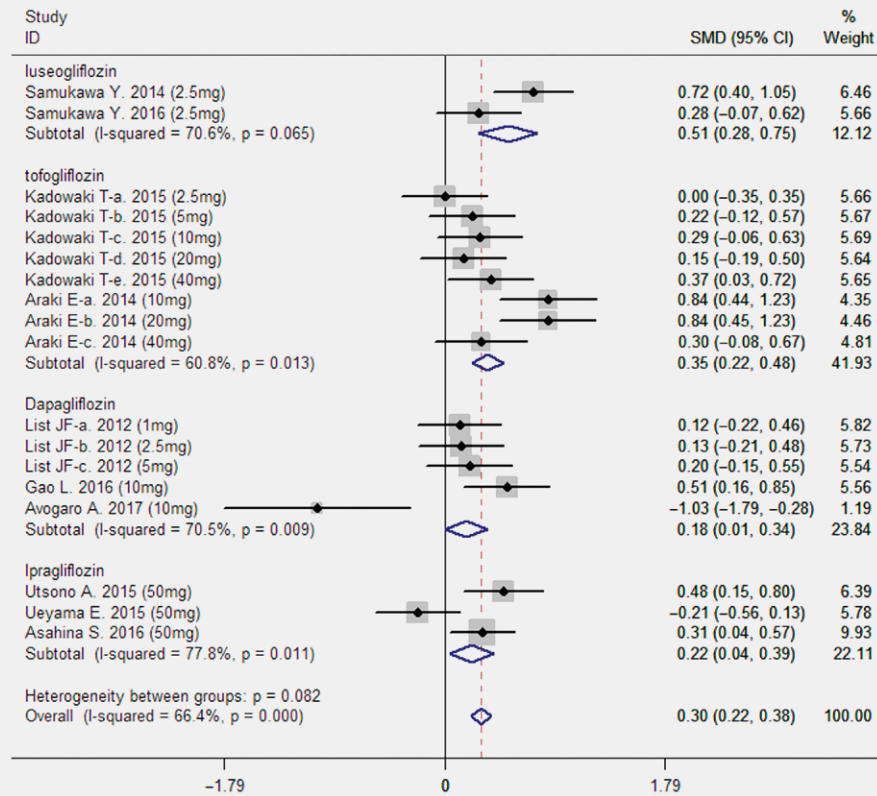


► **Fig. 3** Meta-analysis of the effect of SGLT2i treatment versus placebo on serum leptin levels.

excretion and weight loss. Additionally, insulin resistance is related to increased circulating leptin and decreased serum adiponectin concentrations [31]. Our study indicated that use of SGLT2 inhibitor decreased circulating leptin while elevated circulating adiponectin, suggesting that SGLT2 inhibitor may improve insulin resistance through regulation of the circulating adipokines. It is worth noting that whether SGLT2 mediating concentrations of adipokines plays the primary role in improving systemic insulin sensitivity. Friedman et al. have reported that congenital leptin deficiency is related to hyperphagia, hyperlipidemia as well as insulin resistance [3]. Also, leptin replacement therapy can reverse liver and muscle insulin resistance in patients with severe lipodystrophy [8]. Regarding adiponectin, it improves insulin sensitivity by binding to Adi-

poR1 and AdipoR2 resulting in AMPK pathway activation [32]. Then AMPK accelerates cellular metabolism and stimulates glucose uptake and fatty acid oxidation, thereby bringing about an improvement of insulin sensitivity [33]. The study of Lodish et al. showed that treatment of adiponectin improved muscle insulin sensitivity in mice, consistent with decreased body weight [34]. SGLT2 inhibitor is likely to be involved in regulation of other types of adipokines. Whether the pooled effect of SGLT2 inhibitor on adipokines contributing to improved insulin resistance, or overall metabolic homeostasis, remains to be explored.

T2DM is positively associated with the incidence and mortality of cardiovascular disease, which is the leading cause of death in T2DM patients [35]. Some studies have shown that single and in-



► Fig. 4 Meta-analysis of the effect of SGLT2i treatment versus placebo on serum adiponectin levels.

► Table 2 Subgroup analysis of included studies.

Groups	Leptin					Adiponectin				
	n	SMD (95% CI)	p	I ² (%)	p (heterogeneity)	n	SMD (95% CI)	p	I ² (%)	p (heterogeneity)
Age										
≥60 years	3	-0.94 (-1.97, 0.08)	0.072	93.10	0	3	-0.24 (-0.83, 0.35)	0.43	81.60	0.004
<60 years	5	-0.15 (-0.29, -0.01)	0.035	0	0.926	15	0.36 (0.23, 0.48)	0	50.70	0.013
BMI										
≥30	4	-0.63 (-1.29, 0.03)	0.060	89.50	0	9	0.14 (-0.01, 0.29)	0.072	37.00	0.122
<30	4	-0.17 (-0.32, -0.01)	0.033	0	0.471	9	0.44 (0.23, 0.65)	0	70.90	0.001
Duration										
≥24 weeks	6	-0.16 (-0.30, -0.02)	0.026	0	0.635	8	0.20 (0.01, 0.39)	0.043	56.90	0.023
<24 weeks	2	-1.53 (-4.32, 1.25)	0.281	96.30	0	10	0.36 (0.15, 0.57)	0.001	72.10	0

tensive hypoglycemic therapy is not conducive to T2DM patients with cardiovascular risk [36, 37]. Therefore, cardiovascular benefits must be considered in the treatment of diabetes. Several studies have proven that SGLT2 therapy significantly reduced the risk of cardiovascular events [15, 16], but the underlying mechanisms are not yet clear. The effect of SGLT2 on adipokines may also be re-

lated to the mechanism of cardioprotection. The peripheral effects of leptin include activation of inflammatory responses, oxidative stress, thrombosis and atherosclerosis, thereby resulting in endothelial dysfunction and atherosclerotic plaque [38, 39]. And leptin treatment was reported to attenuate atherosclerotic lesions in leptin-deficient low-density lipoprotein receptor mice [40]. Apart

from leptin, adipokines including adiponectin, may be linked with the pathogenesis of cardiovascular disease. Low adiponectin levels are connected to increased risk of cardiovascular disease [41, 42]. Adiponectin protects against atherosclerosis through suppression of the expression of monocyte adhesion molecules and synthesis of inflammatory factors by inhibiting nuclear factor-kappa B [11, 43]. Adiponectin also is known to target extracellular signal-regulated kinase and thus suppress proliferation of vascular smooth muscle cells [44]. Although it is unable to elucidate whether the changes of adipokines were directly regulated by SGLT2 inhibitors, these changes of leptin and adiponectin did have clear cardiovascular benefits. Based on above consideration, our study may partly explain the protective effect of SGLT2 on cardiovascular disease by regulation of circulating adipokines.

Several limitations of this study deserve some serious consideration. First, some confounding variables including age, BMI and control of glucose are difficult to avoid, which might affect the overall estimation. Second, some of the included studies have a small sample size, resulting in a high level of heterogeneity in circulating leptin and adiponectin concentration, which weaken the strength of the evidence of our study. Third, the number of studies regarding specific types of SGLT2 inhibitors is relatively small, and thereby have difficulty to explore the effect of each type of SGLT2 inhibitors on adipokines. Finally, it is uncertain whether the changes of adipokines are the direct effect of SGLT2 inhibitors, or whether they are secondary to the reduced body fat or the regulation of adipose tissue function. Therefore, more experiments should be carried out in the future to clarify the relationship between SGLT2 inhibitors use and changes of adipokines, and thereby further verify our findings.

Conclusions

SGLT2 inhibitor therapy was associated with a decreased circulating leptin levels and an increased circulating adiponectin levels, which might contribute to the beneficial effects of SGLT2 inhibitors on metabolic homeostasis, such as improved insulin resistance and reduced cardiovascular risk.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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