Systematic Review and Meta-Analysis

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Efficacy of dapagliflozin to treat nonalcoholic fatty liver disease in patients with type 2 diabetes

A meta-analysis

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Abstract

Introduction: Dapagliflozin shows some potential in treating nonalcoholic fatty liver disease complicated with type 2 diabetes, and this meta-analysis aims to explore the efficacy of dapagliflozin vs placebo to treat nonalcoholic fatty liver disease complicated with type 2 diabetes.

Methods: PubMed, EMbase, Web of science, EBSCO and Cochrane library databases have been searched through July 2024, and we included randomized controlled trials (RCTs) assessing the efficacy of dapagliflozin for nonalcoholic fatty liver disease complicated with type 2 diabetes.

Results: Five RCTs and 353 patients were included in the meta-analysis. Overall, compared with control intervention in patients with nonalcoholic fatty liver disease and type 2 diabetes, dapagliflozin treatment was able to significantly decrease ALT (standard mean difference [SMD] = −1.10; 95% confidence interval [CI] = −1.37 to −0.84; $P < .00001$), AST (MD = −1.32; 95% CI = −1.76 to −0.88; $P < .00001$) and HbA1c (SMD = −0.60; 95% CI = −1.02 to −0.17; $P = .006$), but demonstrated no influence on fasting glucose (SMD = −0.55; 95% CI = −1.10 to 0; $P = .05$), LDL-C (SMD = −0.19; 95% CI = −0.56 to 0.17; $P = .30$) or triglyceride (SMD = −0.30; 95% CI = −1.47 to 0.88; $P = .62$).

Conclusions: Dapagliflozin may benefit to treat patients with nonalcoholic fatty liver disease and type 2 diabetes.

Abbreviations: CI = confidence interval, RCTs = randomized controlled trials, SMD = standard mean difference.

Keywords: dapagliflozin, nonalcoholic fatty liver disease, randomized controlled trials, type 2 diabetes.

1. Introduction

nonalcoholic fatty liver disease (NAFLD) has emerged as the most prevalent chronic liver disease, affecting 25% of the general population.[1–3] The condition is particularly common among patients with type 2 diabetes, with approximately 75% of diabetic patients having NAFLD.[4–9] This comorbidity significantly increases the risk of progression to nonalcoholic steatohepatitis, fibrosis, cirrhosis, and ultimately hepatocellular carcinoma.[4,5]

Early diagnosis, assessment, and intervention are essential to prevent NAFLD progression. Current guidelines emphasize lifestyle modification as the primary treatment strategy, focusing on dietary changes and exercise for weight loss.[10,11] While no FDA-approved medications exist specifically for NAFLD treatment, research shows that only 3% to 6% of individuals achieve sustained, long-term weight loss through lifestyle changes alone.[12–14]

Sodium-glucose cotransporter 2 (SGLT2) inhibitors represent a novel class of oral antidiabetic medications that lower blood glucose by inhibiting glucose reabsorption in the proximal renal tubules and promoting urinary glucose excretion.[15] Dapagliflozin, a highly selective SGLT2 inhibitor, shows promising potential in reducing liver and visceral fat in patients with concurrent NAFLD and type 2 diabetes.[16] However, its therapeutic benefits remain incompletely understood. While recent studies have investigated dapagliflozin's efficacy in treating NAFLD with comorbid type 2 diabetes, the results have been inconclusive.[17–20] This meta-analysis aims to evaluate the efficacy of dapagliflozin compared to placebo in patients with both NAFLD and type 2 diabetes.

2. Materials and methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[21,22] As this study is a systematic review and meta-analysis of previously published research, neither ethical approval nor patient consent was required.

The authors have no funding and conflicts of interest to disclose.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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2.1. Search strategy and study selection

A comprehensive literature search was conducted across multiple databases including PubMed, EMbase, Web of Science, EBSCO, and the Cochrane Library. The search covered all publications from database inception through July 2024, using the following search terms: "nonalcoholic fatty liver disease" OR "steatohepatitis" AND "diabetes" AND "dapagliflozin." Reference lists of all screened full-text studies were manually reviewed to identify additional eligible trials. Studies were included if they met the following criteria: patients had a confirmed diagnosis of both nonalcoholic fatty liver disease and type 2 diabetes; the intervention compared dapagliflozin treatment against placebo; the study design was a randomized controlled trial (RCT). Studies involving patients with nonalcoholic fatty liver disease alone, without concurrent type 2 diabetes, were excluded from the analysis.

2.2. Data extraction and outcome measures

The following information was extracted: author, number of patients, age, female, weight, body mass index and detail methods. Data were extracted independently by 2 investigators, and discrepancies were resolved by consensus. The primary outcomes were alanine aminotransferase (ALT) and aspartate-aminotransferase (AST). Secondary outcomes included HbA1c, fasting plasma glucose, LDL-C and triglyceride.

2.3. Quality assessment in individual studies

The methodological quality of included studies was evaluated using the modified Jadad scale, which assessed 3 key components: randomization (0–2 points); blinding (0–2 points); dropouts and withdrawals (0–1 point).[22,23] The total Jadad score ranges from 0 to 5 points. Study quality was categorized as follows: low quality: Jadad score ≤ 2; High quality: Jadad score ≥ 3.[24,25]

2.4. Statistical analysis

Standard mean difference (SMD) with 95% confidence intervals (CI) was calculated for all continuous outcomes. Heterogeneity was evaluated using the I^2 statistic, $I^2 > 50\%$ was considered indicative of significant heterogeneity.[26] Random-effects model was applied when significant heterogeneity was present. Fixed-effects model was used in the absence of significant heterogeneity. When significant heterogeneity was detected, 2 approaches were used to identify potential sources: sensitivity analysis through sequential omission of individual studies; subgroup analysis. All statistical analyses were performed using Review Manager Version 5.3.

3. Results

3.1. Literature search, study characteristics and quality assessment

Figure 1 demonstrated the detailed flowchart of the search and selection results. A sum of 205 publications were searched after the initial search of databases. A sum of 66 duplicates and 131 papers were excluded after checking the titles/abstracts. Three

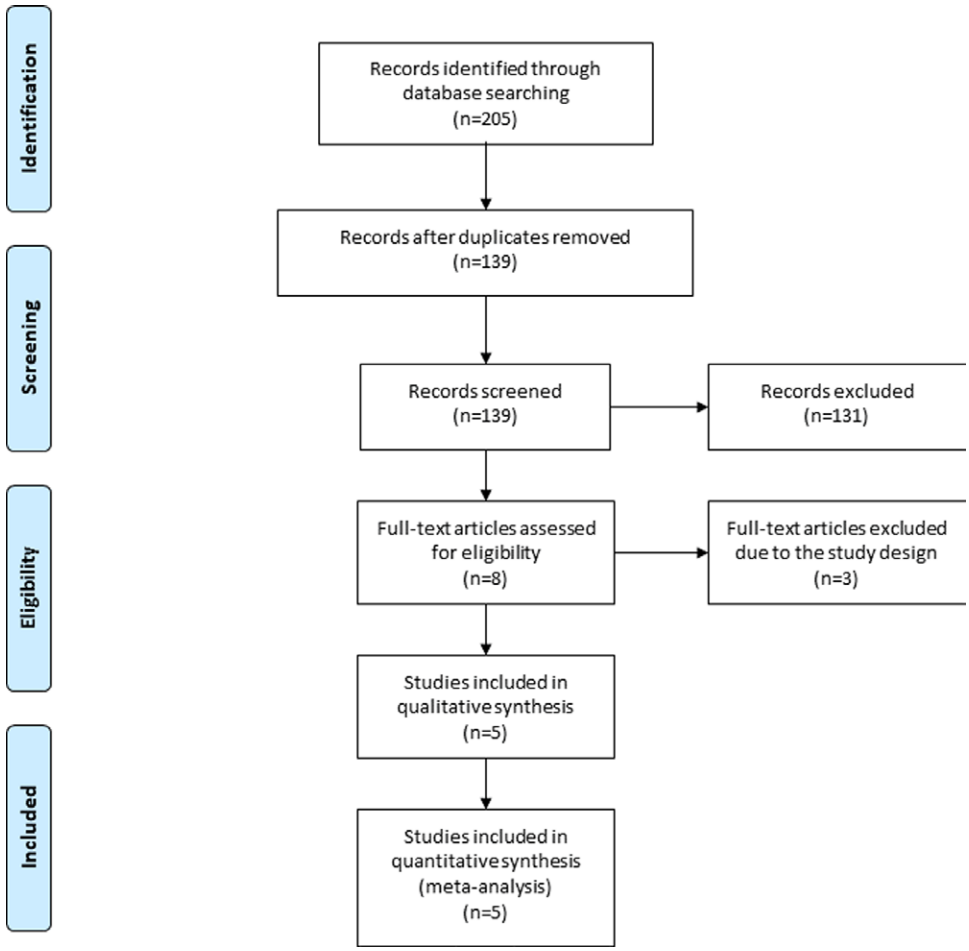

Figure 1. Flow diagram of study searching and selection process.

Table 1

Characteristics of included studies.

		Dapagliflozin group					Control group					
Number	Author	Number	Age (yr)	Female (n)	Weight (kg)	Body mass index (kg/m²)	Methods	Number	Age (yr)	Female (n)	Weight (kg)	Body mass index (kg/m²)	Methods	Jadad scores
1	Shi 2023	40	49.0 ± 9.15	13	84.8 ± 18.4	31.1 ± 5.28	Dapagliflozin (10 mg/d) for 24 wk	38	49.0 ± 9.15	11	81.9 ± 16.5	30.4 ± 4.48	Placebo	4
2	Phrueksotsai 2021	18	57.0 ± 6.9	13	73.8 ± 12.7	29.6 ± 4.0	Dapagliflozin (10 mg/d) for 12 wk	20	61.2 ± 7.2	13	71.0 ± 11.3	28.8 ± 4.1	Placebo	4
3	Hussain 2021	67	29 ± 16	20	90 ± 13.5	29.5 ± 2.5	Dapagliflozin (5–10 mg/d) for 12 wk	71	31 ± 14	19	85 ± 17.8	31.5 ± 3.0	Placebo	5
4	Aso 2019	33	56.2 ± 11.5	14	73.6 (61.9, 80.8)	27.6 ± 4.7	Dapagliflozin (5 mg/d) for 24 wk	24	57.1 ±13.8	9	74.9 (65.6, 81.6)	28.7 ± 3.5	Placebo	3
5	Eriksson 2018	21	65.0 ± 6.5	5	90.2 ± 8.7	30.5 ± 2.8	Dapagliflozin (10 mg/d) for 12 wk	21	65.6 ± 6.1	4	93.0 ± 12.2	30.3 ± 3.1	Placebo	4

Data are mean ± SD or median (inter-quartile ranges).

studies were removed because of the study design and 5 RCTs were finally included in the meta-analysis.[17–20,27]

The baseline characteristics of 5 eligible RCTs were summarized in Table 1. The 5 studies were published between 2018 and 2023, and total sample size was 353. The doses of dapagliflozin ranged from 5 to 10 mg daily, while the treatment durations were 12 weeks or 24 weeks. Among the 5 studies included here, 3 studies reported ALT and AST,[17,18,20] four studies reported HbA1c,[17,18,20,27] 3 studies reported fasting glucose,[17,18,20] while 2 studies reported LDL-C and triglyceride.[17,20] Jadad scores of the 5 included studies varied from 3 to 5, and all 5 studies had high quality.

3.2. Primary outcomes: ALT and AST

Compared to control group for patients with nonalcoholic fatty liver disease and with type 2 diabetes, dapagliflozin treatment was able to significantly decrease ALT (SMD = −1.10; 95% CI = −1.37 to −0.84; $P < .00001$) with low heterogeneity among the studies ($I^2 = 40\%$, heterogeneity $P = .19$, Fig. 2), and AST (MD = −1.32; 95% CI = −1.76 to −0.88; $P < .00001$) with significant heterogeneity among the studies ($I^2 = 57\%$, heterogeneity $P = .10$, Fig. 3).

3.3. Sensitivity analysis

Significant heterogeneity remained for AST. As shown in Figure 3, the study conducted by Hussain et al[18] showed results that were almost out of range of the others and probably contributed to the heterogeneity. After excluding this study, the results suggested that dapagliflozin treatment was still associated with higher procedure success (SMD = −1.09; 95% CI = −1.49 to −0.70; $P < .00001$), and no heterogeneity remained ($I^2 = 0$, $P = .59$).

3.4. Secondary outcomes

In comparison with control group for nonalcoholic fatty liver disease complicated with type 2 diabetes, dapagliflozin treatment substantially decreased HbA1c (SMD = −0.60; 95% CI = −1.02 to −0.17; $P = .006$; Fig. 4), but showed no effect on fasting glucose (SMD = −0.55; 95% CI = −1.10 to 0; $P = .05$; Fig. 5), LDL-C (SMD = −0.19; 95% CI = −0.56 to 0.17; $P = .30$; Fig. 6) or triglyceride (SMD = −0.30; 95% CI = −1.47 to 0.88; $P = .62$; Fig. 7).

4. Discussion

Our meta-analysis included 5 RCTs and 353 patients with nonalcoholic fatty liver disease complicated with type 2 diabetes. The results revealed that dapagliflozin treatment was capable to decrease ALT, AST and HbA1c, but showed no effect on fasting glucose, LDL-C or triglyceride. These suggested that dapagliflozin treatment could improve hepatic function and glycemic control for these patients.

In terms of the sensitivity analysis, significant heterogeneity was found for AST. We found no heterogeneity after excluding the study conducted by Hussain et al.[18] Hussain study reported the doses of 5 to 10 mg/day dapagliflozin, while the other 2 studies documented the dose of 10 mg/day dapagliflozin. These suggested that the doses of dapagliflozin were critical for the efficacy assessment in patients with patients with nonalcoholic fatty liver disease complicated with type 2 diabetes, and the doses of 5 to 10 mg/day dapagliflozin may have better efficacy based on the results of Figure 3.

Our meta-analysis demonstrates that dapagliflozin effectively improves both hepatic function and glycemic control in patients with concurrent nonalcoholic fatty liver disease and type 2 diabetes. The mechanisms underlying nonalcoholic fatty liver

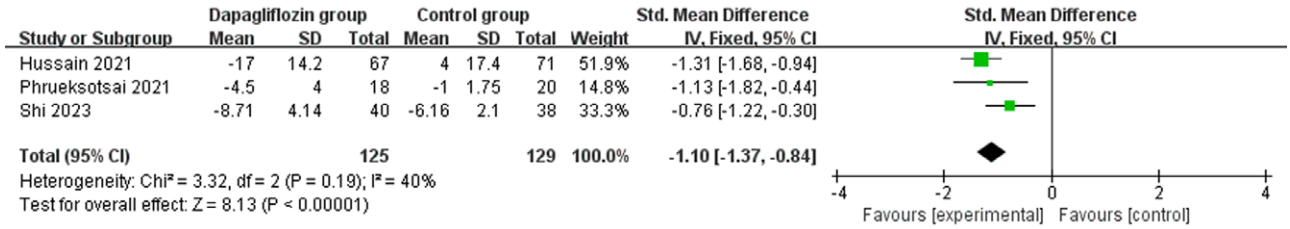

Figure 2. Forest plot for the meta-analysis of ALT. ALT = alanine aminotransferase.

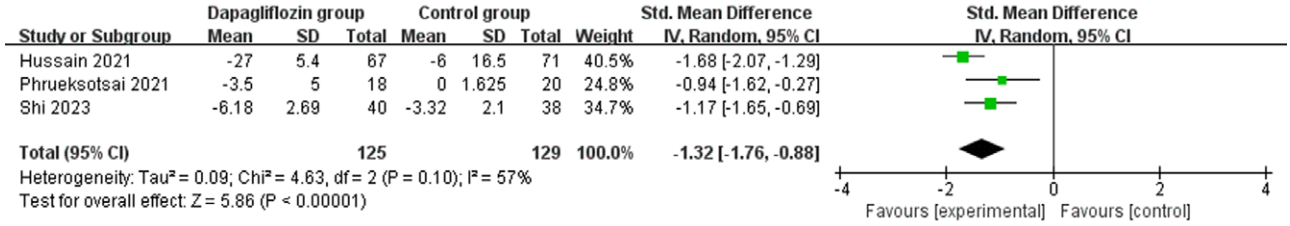

Figure 3. Forest plot for the meta-analysis of AST. AST = aspartate-aminotransferase.

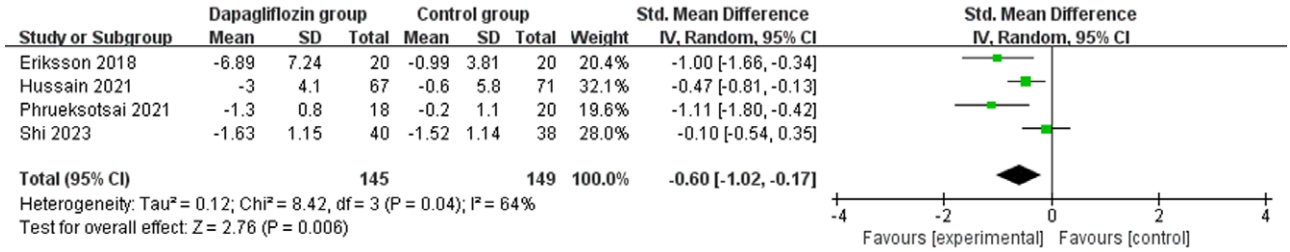

Figure 4. Forest plot for the meta-analysis of HbA1c.

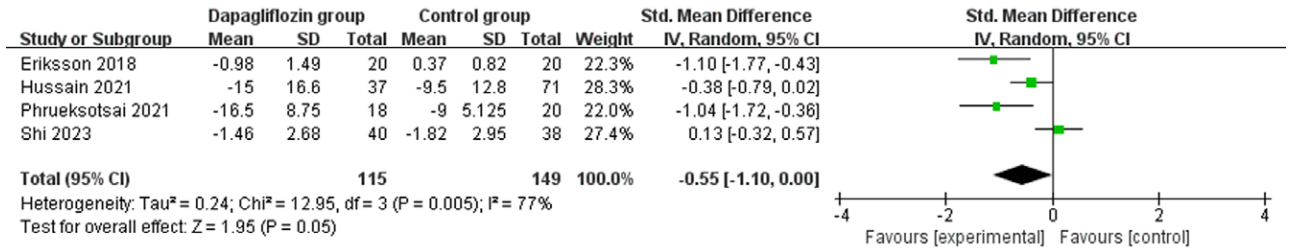

Figure 5. Forest plot for the meta-analysis of fasting glucose.

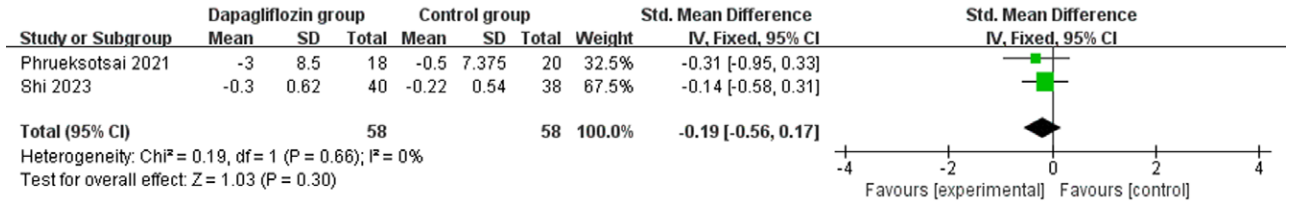

Figure 6. Forest plot for the meta-analysis of LDL-C.

disease (NAFLD) are highly intricate, involving multiple factors such as insulin resistance, oxidative stress, lipotoxicity, and mitochondrial dysfunction. Each of these pathways contributes to disease progression, highlighting the complexity of NAFLD pathology.[28] Inhibition of inflammatory and oxidative stress factors is critical to reduce the rate of progression and the risk of cardiovascular disorders.[29–31] Preclinical studies have demonstrated that SGLT2 inhibitors can significantly modify energy metabolism by enhancing fat oxidation. This metabolic shift produces several beneficial effects: reduction in hepatic ectopic

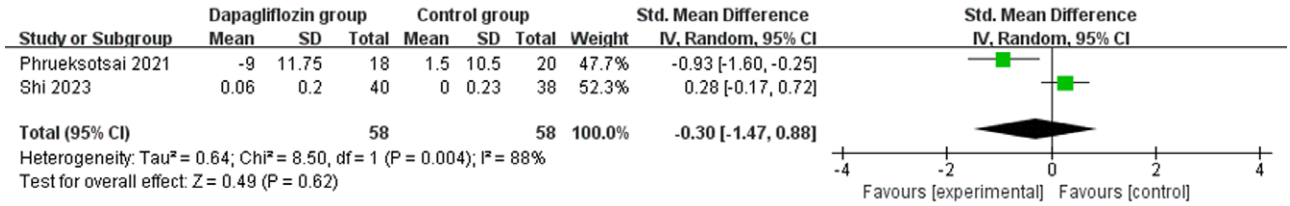

Figure 7. Forest plot for the meta-analysis of triglyceride.

fat storage, decrease in overall body weight and fat content, prevention of proinflammatory cytokine release from adipose cells. These mechanisms, particularly the reduction in inflammatory responses, are significant because inflammation is a key driver in the progression of nonalcoholic steatohepatitis. The anti-inflammatory effects of SGLT2 inhibitors may therefore help prevent disease progression.[32,33]

We also should consider some limitations. Firstly, our analysis is based on 5 RCTs, and 4 of them have a relatively small sample size (n < 100). Future studies with large patient sample are needed to confirm our findings. Secondly, there is significant heterogeneity for some outcomes, which may be caused by different doses and combination methods of dapagliflozin. Thirdly, different severity levels of nonalcoholic fatty liver disease in patient with type 2 diabetes may affect the pooling results.

5. Conclusions

Dapagliflozin may have favorable effect on the treatment of nonalcoholic fatty liver disease for patient with type 2 diabetes.

Author contributions

Conceptualization: Hua Duan.
Project administration: Fangyuan Chen.
Resources: Fangyuan Chen.
Software: Hua Duan.
Visualization: Fangyuan Chen.
Writing – original draft: Hua Duan.
Writing – review & editing: Hua Duan.

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