Clinical Research

Empagliflozin for liver and lipid profile in metabolic dysfunction-associated fatty liver disease: a meta-analysis

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ABSTRACT

BACKGROUND Metabolic dysfunction-associated fatty liver disease (MAFLD) is a common chronic liver condition often associated with obesity and diabetes. Empagliflozin, a sodium-glucose cotransporter 2 inhibitor, is an antidiabetic medication that improves glycemic control, insulin resistance, and body weight. This study aimed to examine the efficacy of empagliflozin in adults with MAFLD.

METHODS A comprehensive literature search was performed using the PubMed, ScienceDirect, Cochrane Library, Scopus, and Wiley Online Library databases. Randomized controlled trials assessing liver function, lipid profile, metabolic profile, and body composition were included. Weighted mean differences (WMDs) and 95% confidence intervals (CIs) were calculated using random-effects models, and study quality was assessed using the Cochrane Risk of Bias Tool for Randomized Trials.

RESULTS 6 RCTs with a total of 636 participants were analyzed. Empagliflozin significantly reduced alanine aminotransferase levels (WMD: −6.65 IU/l, 95% CI: −13.02 to −0.28; p = 0.04) and gamma-glutamyl transferase levels (WMD: −10.60 IU/l, 95% CI: −29.05 to −7.68; p<0.00001). A non-significant reduction in aspartate aminotransferase was observed (WMD: −4.69 IU/l, 95% CI: −9.89 to 0.51; p = 0.08). Empagliflozin significantly improved low-density lipoprotein cholesterol (p = 0.02) and total cholesterol (p = 0.05) levels but did not significantly affect triglycerides, high-density lipoprotein cholesterol, metabolic profiles, or body composition.

CONCLUSIONS This meta-analysis highlights the beneficial effects of empagliflozin on liver function and indicates the need for further research on its metabolic effects and long-term outcomes in managing MAFLD.

KEYWORDS meta-analysis, non-alcoholic fatty liver disease, sodium-glucose transporter 2 inhibitors, systematic review

Metabolic dysfunction-associated fatty liver disease (MAFLD) is the leading cause of chronic liver disease worldwide. It encompasses a clinical spectrum ranging from simple hepatic fat accumulation (steatosis) to more severe forms such as metabolic dysfunction-associated steatohepatitis (MASH). Unlike the older definition, which required exclusion of other liver diseases and significant alcohol consumption, MAFLD is diagnosed based on the presence of hepatic steatosis in conjunction with evidence of metabolic dysfunction, such as type 2 diabetes mellitus (T2DM), obesity/overweight, or at least two metabolic abnormalities.[1] The global rise in MAFLD prevalence parallels the increasing rates of non-communicable diseases, primarily driven by obesity and diabetes. A recent meta-analysis estimated that 32% of adults globally have MAFLD, with an incidence rate of 46.9 cases per 1,000 person-years, up from 26% in 2016.[2] In Asia,

MAFLD prevalence varies considerably depending on ethnicity, socioeconomic status, and data availability, with an average prevalence of 30.5%.[3]

MAFLD is a metabolic disease with complex mechanisms that are not fully understood. If left unmanaged, MAFLD may progress to cirrhosis or hepatocellular carcinoma.[4] Most patients exhibit features of metabolic syndrome, including dyslipidemia, hypertension, visceral obesity, and T2DM.[5] Factors like overnutrition, hormonal imbalances, and hyperinsulinemia drive hepatic fat build-up via *de novo* lipogenesis, elevating intrahepatic lipid levels and promoting triglyceride (TG) secretion as very low-density lipoprotein (LDL). Excessive free fatty acids lead to lipotoxicity, disrupt insulin signaling, and trigger oxidative stress and inflammation, thereby accelerating MAFLD progression.[6]

Given the associated cardiometabolic risks, including chronic kidney disease and cardiovascular complications, early and effective MAFLD management is crucial.[7] Lifestyle modifications, such as dietary changes and increased physical activity, remain the foundation of MAFLD management.[1] However, addressing comorbidities like T2DM and obesity has also shown therapeutic potential in improving liver histology and reducing steatosis.

Among pharmacological approaches, sodium-glucose cotransporter 2 (SGLT2) inhibitors, originally antidiabetic agents, have been recognized for their cardioprotective benefits.[8] Although several SGLT2 inhibitors have been evaluated, this study focuses on empagliflozin because of its favorable safety profile, robust cardiovascular and renal protective data, as well as emerging evidence supporting its hepatic effect.[9,10] Compared to other agents, empagliflozin has consistently improved liver enzyme levels, hepatic steatosis, and fibrosis markers across clinical trials.[11] This study aimed to address this gap by focusing on randomized controlled trials evaluating the effects of empagliflozin on liver function, lipid profiles, metabolic parameters, and body composition in patients with MAFLD.

METHODS

Data sources and search strategy

This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses 2020 guidelines.[12,13] The study protocol was registered in PROSPERO (No. CRD42024521269). We conducted the search through PubMed, ScienceDirect, Cochrane Library, Scopus, and Wiley Online Library from their inception to November 4, 2023. To ensure relevance, results were limited to articles published from 2013 to 2023. Grey literature sources and trial registries (e.g., ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform) were excluded due to time constraints. Boolean operators (OR and AND) were employed to optimize the search strategy. Full search strategies, including the fields searched, filters applied, and the number of articles retrieved per database, are detailed in Supplementary Table 1.

Study selection

Three authors (KFS, JCS, and GT) independently selected eligible studies. After removing duplicates, titles and abstracts were screened, followed by full-text assessment of potentially eligible articles based on the inclusion criteria. Discrepancies were resolved through discussion with a senior reviewer (ATS and SAS). Only articles published in English were included in this review. Eligibility criteria were as follows: adults aged 18–65 years diagnosed with MAFLD, confirmed by hepatic steatosis on imaging (ultrasound or magnetic resonance imaging) or histology, without significant alcohol consumption (<20 g/day for women; <30 g/day for men), viral hepatitis, or other secondary liver diseases. Studies were excluded if participants had secondary liver disease, severe comorbidities, were pregnant, or breastfeeding.

The intervention included empagliflozin (10–25 mg daily) for a minimum of 6 months. Participants with intolerance, contraindications, or severe renal impairment (estimated glomerular filtration rate <30 ml/min) were excluded. Eligible studies compared empagliflozin either to a placebo or standard care. The primary outcome was change in liver function (assessed by alanine aminotransferase [ALT] and asparatate aminotransferase [AST] levels), and the secondary outcome was change in lipid profile (including cholesterol, LDL, high-density lipoprotein [HDL], and TG), both measured at baseline and after 6 months.

Data extraction

Five reviewers (KFS, JCS, IF, GT, and ARJ) independently extracted relevant data using

standardized forms, including the first author, country, year, study design, inclusion criteria, study population, follow-up period, empagliflozin dose, participant age, and treatment outcomes. Outcomes were divided into several categories, including liver function and lipid profiles as primary outcomes, and metabolic profile and body composition as secondary outcomes. Biological indicators of liver function included AST, ALT, gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP). Lipid profiles were as follows: TGs, LDL, HDL, and total cholesterol. Glycemic indices comprised glycated hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), homeostatic model assessment of insulin resistance (HOMA-IR), and insulin. Body composition assessment included body weight (BW), body mass index (BMI), truncal fat mass, visceral adipose tissue (VAT) area, skeletal muscle index (SMI), android-to-gynoid ratio (A/G ratio), and android fat ratio (AFR). Where available, means and standard deviations were extracted for treatment outcomes; otherwise, data were transformed based on established formulas.

Statistical analysis

Review Manager (RevMan) version 5.3 (The Cochrane Collaboration, UK) was used to perform statistical analyses. Mean differences [MD] with 95% confidence intervals (CI) were used to assess continuous variables, applying a random-effects model and the inverse variance method. The Z-test was used (p<0.05 considered statistically significant) to examine the significance of the pooled data. Heterogeneity was assessed using the chi-squared and I^2 indices, with I^2>50% indicating high heterogeneity. In such cases, subgroup analyses were planned to explore potential sources of variability, including differences in empagliflozin dose, treatment duration, and timing of outcome measurements. Sensitivity analysis was conducted using the leave-one-out test. For continuous outcomes, such as ALT, AST, GGT, and ALP, the minimal clinically important difference was considered. Based on previous literature, a reduction of ≥10 U/l in ALT or AST levels was deemed clinically meaningful in patients with MAFLD.[14]

Quality assessment

Two independent reviewers (GT and ARP) evaluated the assessed study quality using version 2 of the Cochrane Risk of Bias Tool for Randomized Trials.[15] This tool examined various methodological domains, including the randomization process, intervention adherence, data reporting, outcome measurement, and other potential biases. Each domain was categorized as having low, high, or unclear risk. Disagreements were resolved through discussion and consensus with a third senior reviewer (SAS or ATV). Publication bias was evaluated visually using funnel plots, with asymmetry suggesting potential reporting bias or small study effects. The certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach, which considers risk of bias, inconsistency, indirectness, imprecision, and publication bias to rate the quality of evidence for each outcome as high, moderate, low, or very low.

RESULTS

Study selection and characteristics

A total of 659 potentially eligible articles were initially identified from the online databases. After removing duplicates, 581 remained. Of these, 544 articles were excluded as unrelated. Further exclusions included studies that investigated other drugs (n = 6), assessed other outcomes (n = 5), employed inappropriate study designs (n = 12), or involved nonhuman subjects (n = 8).

Ultimately, six studies were included in the analysis. (Figure 1). These studies, conducted in Iran, India, Germany, France, and Egypt, included 636 patients with MAFLD who received either empagliflozin (10 or 25 mg) or placebo. Follow-up durations ranged from 12 to 24 weeks. Study characteristics are summarized in Table 1.

Heterogeneity and quality assessment

A random-effects model was applied for outcomes with significant heterogeneity (p<0.1); otherwise, a fixed-effects model was used (p>0.1).[16] All six included studies were random clinical trials.[17–22] Risk of bias evaluation was presented in Table 2 and study quality evaluated using a funnel plot (Figure 2).

Outcomes

The outcomes were divided into four categories: primary outcomes, including liver function and lipid profiles; and secondary outcomes, including metabolic profile and body composition assessment. The full GRADE assessment of the outcome is presented in Supplementary Table 2.

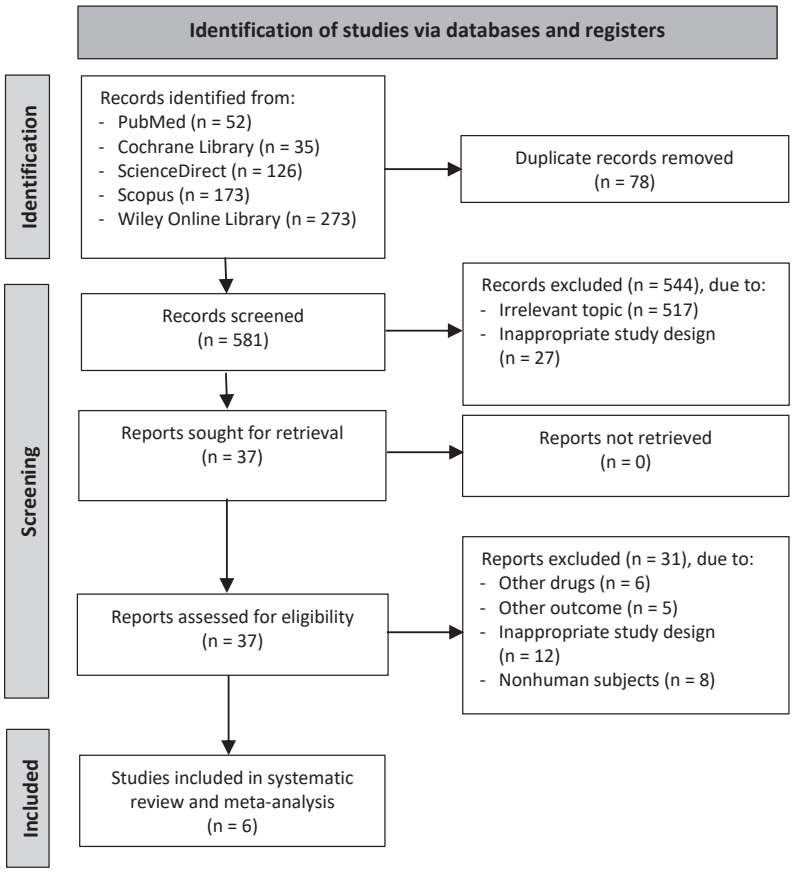

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart of the study selection process

Liver function

Liver function analysis included the assessment of ALT, AST, GGT, and ALP levels (Figure 3a–d). Empagliflozin significantly reduced ALT and GGT levels. Notably, the study by Kahl et al[19] contributed to the observed high heterogeneity in the ALT analysis. A significant reduction in ALP was also observed, though based on a single study. For AST, empagliflozin demonstrated a borderline effect in patients with MAFLD.

Lipid profiles

We evaluated triglyceride (TG), LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), and total cholesterol levels to assess the ability of empagliflozin to improve lipid profiles among patients with MAFLD. Empagliflozin significantly reduced LDL-C and total cholesterol levels. However, no statistically significant effects were observed for TG or HDL-C levels (Figure 3e–h).

Metabolic profiles

In this meta-analysis, we assessed the metabolic profiles of patients with MAFLD who received empagliflozin by evaluating their HbA1c, FPG, HOMA-IR, and insulin levels. The results showed no statistical significance for HbA1c, FPG, HOMA-IR, or insulin analysis. Figure 4a–d shows the effects of empagliflozin on metabolic profiles.

Body composition

There were no reduction in any of body composition assessment after empaglifozin administration in terms of BMI, VAT, SMI, BW, A/G ratio, and AFR (Figure 4e–j).

DISCUSSION

This systematic review and meta-analysis included 636 patients diagnosed with MAFLD who received empagliflozin therapy. We assessed the effect of the drug on liver function, lipid profiles, metabolic profile, and body composition, compared to placebo groups. Data were pooled from studies conducted in various countries, including Iran, India, Germany, France, and Egypt. Compared to a previous meta-analysis by Zhang et al,[23] this study incorporated a larger sample size and evaluated similar clinical outcomes. The findings suggest that empagliflozin may improve certain parameters in liver function and lipid profile outcomes.

Table 1. Characteristic of the included studies and patients

First author, year	Country	Study design	Study population	Sample size (n)	Empagliflozin dosage (mg)	Follow-up period (weeks)	Primary endpoint	Secondary endpoint
Elhini,[17] 2022	Egypt	Randomized and double-blinded clinical trial	- Age >18 years - T2DM, and using sulfonylurea for at least the previous 6 months - Any degree of liver steatosis on US.	256	25	24	LFC, NFS, and FIB-4 index	BMI, BW, waist-to-hip ratio, AST, ALT, ALP, GGT, FBG, 2-h PPG2, HbA1c, HOMA-IR, HOMA-B, insulin, total cholesterol, TGs, LDL, and HDL
Chehrehgosha,[18] 2021	Iran	Randomized, double-blind, placebo-controlled trial	- Aged 20–65 years - T2DM with HbA1c 7–10% - NAFLD with CAP ≥238 db/m	106	10	24	CAP and LSM	BMI, BW, truncal fat mass, VAT, SMI, A/G ratio, AFR, AST, ALT, ALP, FBG, HbA1c, HOMA-IR, HOMA2-IR, insulin, total cholesterol, TGs, LDL, and HDL
Gaborit,[19] 2021	France	Randomized, parallel-group, double-blind, phase 3 trial	- Age ≥18 years - HbA1c 7–10% - Renal eGFR >60 ml/min - On glucose-lowering therapy (metformin, sulfonylureas, glinides, DPP-4 inhibitors, and GLP-1 RA or basal insulin) at a stable dose for at least 3 months	51	10	12	Epicardial fat volume, PCr/ATP ratio, myocardial liver, and pancreatic fat content	BMI, BW, waist circumference, AST, ALT, GGP, FBG, HbA1c, total cholesterol, TGs, LDL, HDL, SBP, DBP, ejection fraction, LVM, E/A ratio, glycosuria, reticulocyte, and EPO
Taheri,[20] 2020	Iran	Prospective randomized, double-blind, placebo-controlled clinical trial	- Age 20–65 years - Had NAFLD, on the basis of evidence of hepatic steatosis in previous US imaging or liver function test	90	10	24	CAP, LSM, and NAFLD fibrosis score	BMI, BW, AST, ALT, fasting insulin, HbA1c, HOMA2, VAT, SMI, AFR, and truncal fat mass
Kuchay,[21] 2018	India	Randomized, open-label clinical trial	- Aged >20 years - Hepatic steatosis (MRI-PDFF >6%) - Uncontrolled T2DM (HbA1c >7.0%–<10.0%)	50	10	20	LFC	BMI, BW, AST, ALT, GGT, FPG, HbA1c, TGs, HDL, LDL, serum creatinine, and total bilirubin
Kahl,[22] 2020	Germany	Randomized, parallel-group, double-blind, phase 4 trial	- Age 18–75 years - BMI <45 kg/m² - Known history of diabetes duration ≤7 years - HbA1c of 6–8% - No previous antihyperglycemic treatment or a 1-month washout period	84	25	24	LFC, measures of whole-body/skeletal muscle, insulin sensitivity (M value), and hepatic insulin sensitivity	BMI, BW, FBG, uric acid, HMW adiponectin, ALT, AST, TGs, HDL, and LDL

2-h PPG=2-hour postprandial glucose; A/G ratio=android-to-gynoid fat ratio; AFR=android fat ratio; ALP=alkaline phosphatase; ALT=alananie aminotransferase; AST=aspartate aminotransferase; BMI=body mass index; BW=body weight; CAP=controlled attenuation parameter; DBP=diastolic blood pressure; DPP-4=dipeptidyl peptidase-4; E/A ratio=early-to-atrial filling ratio; eGFR=estimated glomerular filtration rate; EPO=erythropoietin; FIB-4=fibrosis-4; FBG=fasting blood glucose; FPG=fasting plasma glucose; GGT=gamma-glutamyl transferase; GLP-1 RA=glucagon-like peptide-1 receptor agonist; HbA1c=glycated hemoglobin A1c; HDL=high-density lipoprotein; HMW=high molecular weight; HOMA2=updated homeostasis model assessment; HOMA2-IR=updated homeostasis model assessment for insulin resistance; HOMA-B=homeostasis model assessment of β-cell function; HOMA-IR=homeostatic model assessment for insulin resistance; LDL=low-density lipoprotein; LFC=liver fat content; LSM=liver stiffness measurement; LVM=left ventricular mass; MRI-PDFF=magnetic resonance imaging-proton density fat fraction; NAFLD=non-alcoholic fatty liver disease; NFS=non-alcoholic fatty liver disease fibrosis score; PCr/ATP ratio=phosphocreatine-to-adenosine triphosphate ratio; SBP=systolic blood pressure; SMI=skeletal muscle index; T2DM=type 2 diabetes mellitus; TG=triglyceride; US=ultrasound; VAT=visceral adipose tissue

Table 2. Risk of bias assessment using the Cochrane Risk of Bias Tool for Randomized Trials

First author, year	D1	D2	D3	D4	D5	D6
Elhini,[17] 2022	+	+	+	+	+	+
Chehrehgosha,[18] 2021	+	+	+	+	+	+
Gaborit,[19] 2021	+	+	+	?	+	?
Taheri,[20] 2020	?	+	+	+	+	?
Kuchay,[21] 2018	?	?	+	+	+	+
Kahl,[22] 2020	+	+	+	+	+	+

+: low risk; ?: some concerns; domains: D1: bias arising from the randomization process; D2: bias due to deviation from intended interventions; D3: bias due to missing outcome data; D4: bias in measurement of the outcome; D5: bias in selection of the reported; D6: overall risk of bias

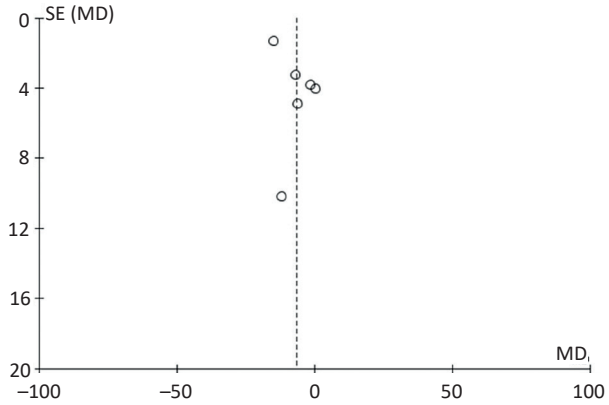

Figure 2. Funnel plot of studies included. MD=mean difference; SE=standard error

However, no significant differences were observed in the metabolic profile and body composition outcomes. It is important to assess these results carefully, as high heterogeneity across studies may have influenced the overall conclusion.

The analysis indicates that empagliflozin can better enhance liver function in patients with MAFLD better than in controls. Nevertheless, the presence of high heterogeneity and small sample size limits the robustness of these findings. Previous studies showed similar findings related to liver function.[23–25] A study in mice with diet-induced obesity showed that empagliflozin exerted metabolic and hepatic effects (mainly as an anti-inflammatory) by downregulating the concentration of intrahepatic glucosylceramides and increasing hepatic unsaturated TG.[26] Another study by Shinozaki et al[27] reported significant improvements in hepatic function after 1 year of empagliflozin treatment in 24 patients with MAFLD and T2DM. However, other studies have found no benefits of empagliflozin in MAFLD, with no significant improvement in the tested parameters.[10] This study discrepancy may be attributed to multiple factors, including sample size, study population, dosage variations, and follow-up duration.

The lipid profile results in this study indicated that the empagliflozin group had lower LDL-C and total cholesterol levels than the control group. However, no significant differences were observed in TG and HDL-C levels. These findings are consistent with a previous study involving patients with MASH and T2DM, which revealed a significant reduction in total cholesterol levels (from 79.2 mg/dl to 68.4 mg/dl).[28] Another study also demonstrated a decrease in TG levels with empagliflozin, compared to control.[25] In an *in vivo* study using apolipoprotein E (ApoE) mice fed a high-fat diet, empagliflozin reduced total cholesterol, TG levels, liver steatosis, lobular inflammation, ballooning, and hepatocellular degeneration after 5 weeks of treatment.[29] The mechanisms involved result from the regulation of insulin resistance and glucose tolerance processes, as well as changes in the expression of enzymes that impact beta-oxidation and hepatic *de novo* lipogenesis.[18]

Analysis of the metabolic profile revealed no significant differences in HbA1c, fasting blood glucose (FBG), HOMA-IR, and insulin levels between patients with MAFLD treated with empagliflozin and those in the control group ($p>0.05$). This result may have been affected by the small sample size and heterogeneity of the study. Nevertheless, these results are consistent with those of some previous studies.[23,30,31] However, a different result was found by Mantovani et al,[30] where administering empagliflozin to patients with MAFLD and T2DM without a history of cardiovascular disease over 24 weeks significantly reduced FBG and HbA1c levels ($p<0.01$). Other studies have proposed that empagliflozin may play a preventive role in halting the progression from prediabetes to diabetes and in reducing HbA1c levels among patients with prediabetes.[32,33] Furthermore, an empagliflozin trial in ApoE$^{-/-}$ mice fed a Western diet demonstrated a decrease in both HOMA-IR and FBG levels.[29]

Body composition assessment of patients with MAFLD revealed no significant differences between the empagliflozin and control groups. This finding contrasts with several previous studies.[23,26] For example, Pokharel et al[26] found that patients with MAFLD and T2DM experienced an average weight loss of up to 2.78

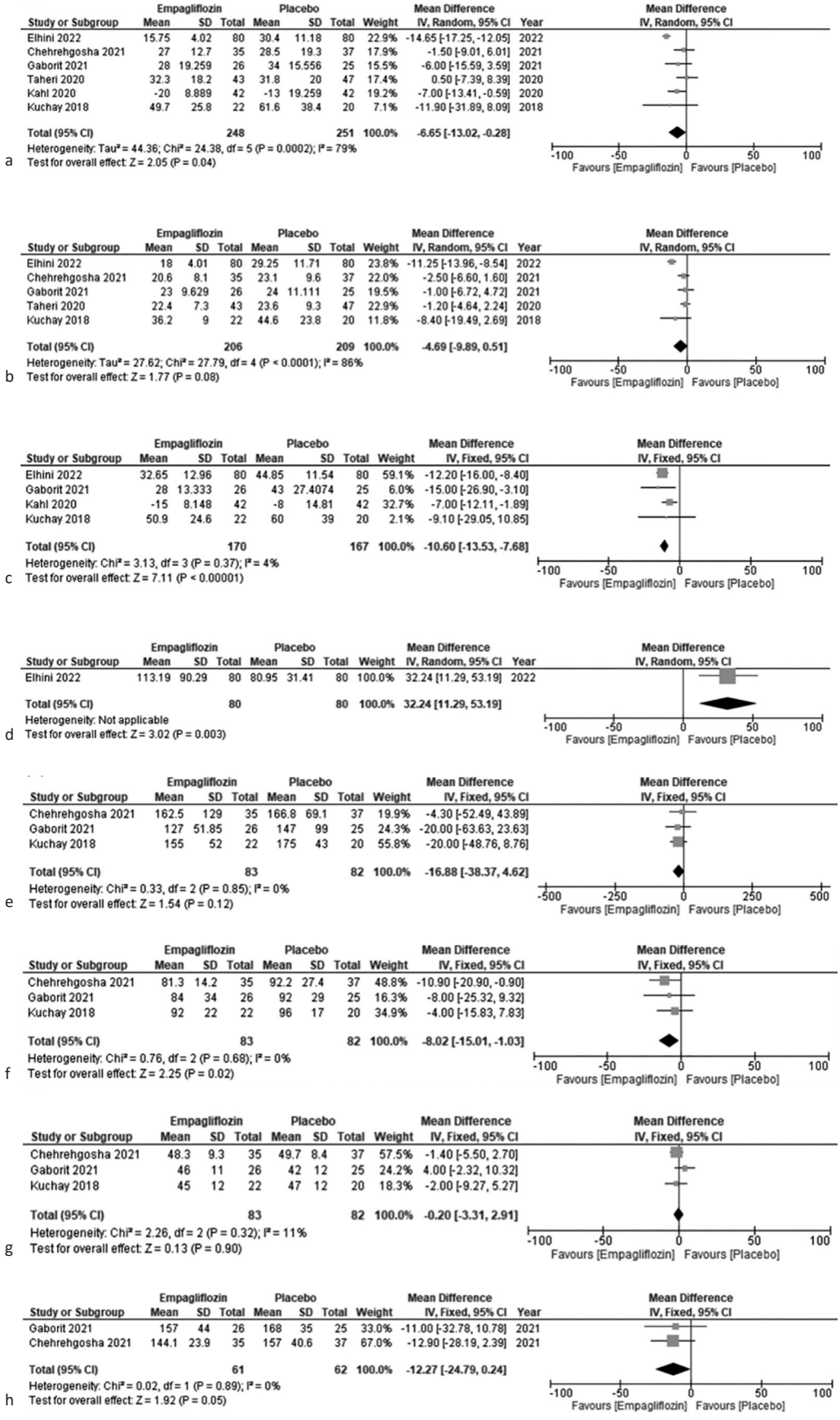

Figure 3. Forest plot of empagliflozin effects on ALT (a), AST (b), GGT (c), ALP (d), TGs (e), LDL-C (f), HDL-C (g), and total cholesterol (h). ALT=alanine aminotransferase; ALP=alkaline phosphatase; AST=aspartate aminotransferase; CI=confidence interval; GGT=gamma-glutamy-ltransferase; HDL=high-density lipoprotein; LDL=low-density lipoprotein; SD=standard deviation

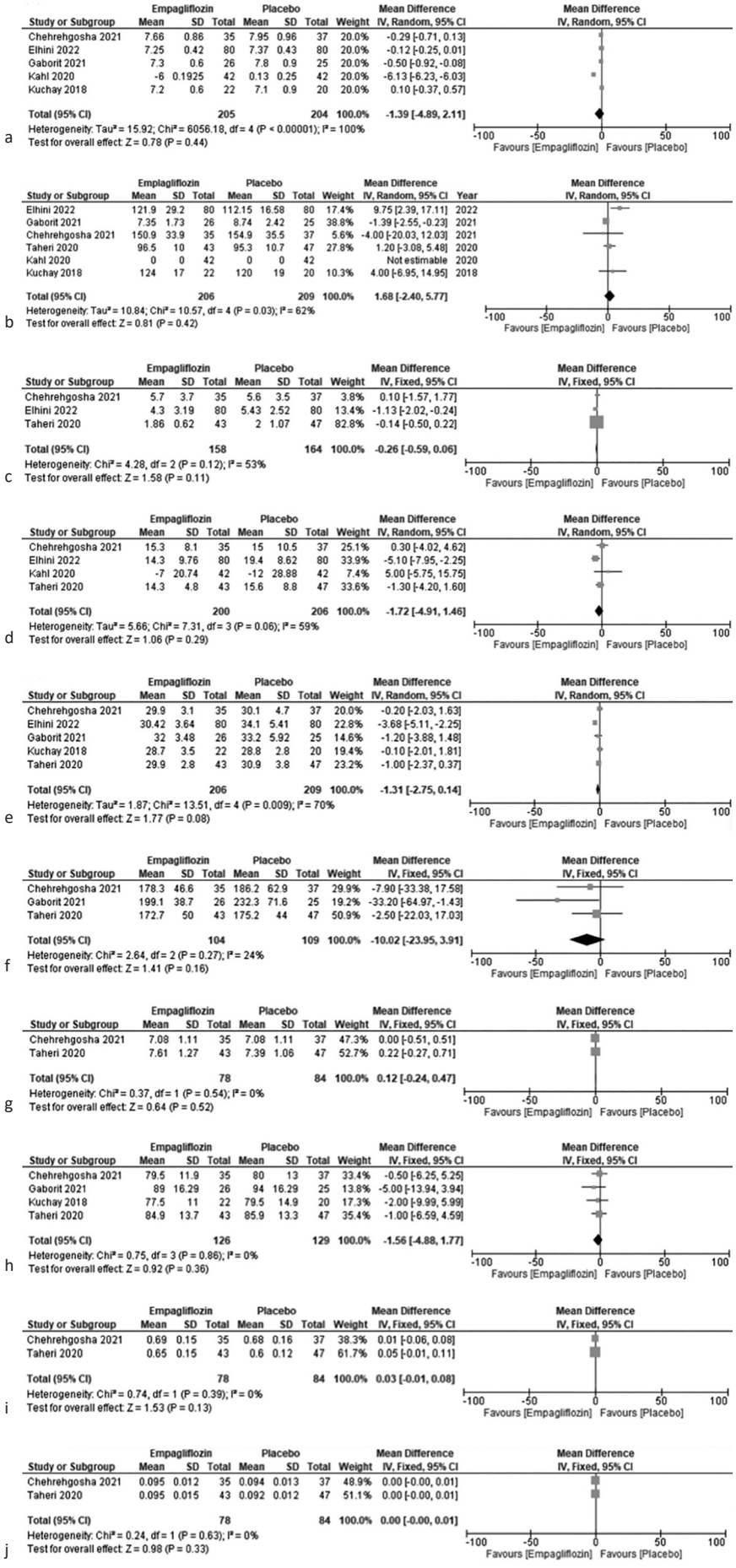

Figure 4. Forest plot of empagliflozin effects on HbA1c (a), FPG (b), HOMA-IR (c), insulin (d), BMI (e), VAT (f), SMI (g), BW (h), A/G ratio (i), and AFR (j). A/G ratio=android-to-gynoid ratio; AFR=android fat ratio; BMI=body mass index; BW=body weight; FPG=fasting plasma glucose; HbA1c=glycated hemoglobin A1c; HOMA-IR=homeostatic model assessment of insulin resistance; SD=standard deviation; SMI=skeletal muscle index; VAT=visceral adipose tissue

kg after 6 months of empagliflozin therapy (p = 0.002). Other studies that have reported promising results were conducted *in vivo*.[34] The possible mechanism of BW loss involves a metabolic shift toward increased fat utilization. Additionally, empagliflozin increases thermogenesis, as evidenced by elevated levels of uncoupling protein 1 (UCP 1) levels in both brown and white adipose tissues. This mechanism allows the body to utilize more energy without storing it. Empagliflozin also increases adipocyte browning, which has a higher thermogenic potential. Brown adipose tissue contains mitochondria that produce heat instead of energy in the respiratory chain, making it an effective strategy for reducing BW.[35]

Based on the GRADE assessment (Supplementary Table 2), the certainty of evidence ranged from high to low. The evidence supporting the effects of empagliflozin on ALT and TG levels was of moderate certainty, downgraded due to risk of bias and imprecision. Certainty was low for AST, total cholesterol, and HDL-C, mainly because of inconsistencies and wide CI. Evidence concerning adverse events was of high certainty, with consistent reporting across studies. Overall, while these findings suggest beneficial effects, further high-quality studies are needed to strengthen the evidence.

Although this study provided valuable insights into the use of empagliflozin in individuals with MAFLD, there were some limitations. First, it included relatively few trials with short follow-up durations, potentially affecting the efficacy of empagliflozin in this population. Second, some outcomes could not be analyzed across all studies because of differences in the reported endpoints. Third, high heterogeneity was observed in several outcomes, likely attributable to variations in empagliflozin dosage and treatment durations. Consequently, the findings should be interpreted with caution because underlying biases or confounders may exist.

In conclusion, this meta-analysis provides evidence supporting the beneficial effects of empagliflozin therapy on liver function and lipid profiles in patients with MAFLD. This study suggests that empagliflozin can reduce lipid levels, including LDL-C and total cholesterol, and show possible MAFLD improvements in liver function markers such as ALT, GGP, and ALP. Additionally, metabolic parameters such as HbA1c and FBG were inconsistent across studies, indicating the need for further investigation. These results could be beneficial in clinical practice to ensure caution is exercised when prescribing empagliflozin solely for metabolic optimization in this patient population. While some studies have shown potential benefits of empagliflozin in BW reduction, this study did not identify significant differences in body composition between the empagliflozin and control groups. These findings highlight that holistic and comprehensive management, including lifestyle interventions and other medications, remain essential. Further research, including a network meta-analysis with larger sample sizes, longer follow-up periods, and dose variations, is needed to better understand the role of empagliflozin in the management of MAFLD.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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