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ORIGINAL ARTICLE

Sodium-glucose cotransporter protein-2 inhibitors and glucagon-like peptide-1 receptor agonists versus thiazolidinediones for non-alcoholic fatty liver disease: A network meta-analysis

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Abstract

Aims Non-alcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disorders worldwide. Some hypoglycemic drugs can improve NAFLD. However, it is unclear which of these types of hypoglycemic drugs are more effective for NAFLD. Therefore, we conducted a network meta-analysis to determine the effect of thiazolidinediones (TZDs), sodium-glucose cotransporter 2 (SGLT2) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists on NAFLD patients.

Methods A literature search of PubMed, EMBASE, the Cochrane Library, and Medline was conducted, and the literature from database inception up to April 30, 2021 was obtained. Liver function tests, lipid profiles, body mass index (BMI) and glycemic parameters were obtained from randomized controlled trials. Weighted mean differences (WMDs), relative risks and 95% confidence intervals (CIs) were calculated for continuous outcomes, and the I^2 statistic was used to evaluate the heterogeneity of the studies.

Results In total, 22 trials, including 1361 patients, were selected. In direct meta-analysis, GLP-1 receptor agonists were superior to TZDs in decreasing alanine aminotransferase (WMD, −0.40, 95% CI: −0.60 to −0.20), γ-glutamyl transferase (WMD, −5.00, 95% CI: −6.47 to −3.53), BMI (WMD, −4.10, 95%CI: −6.55 to −1.65) and triglycerides (WMD, − 0.50, 95% CI: −0.68 to −0.32). Based on Bayesian network meta-analysis, the effect of SGLT-2 inhibitors on weight loss was superior to that of TZDs (WMD, −1.80, 95%CI: −3.30 to −0.41).

Conclusions GLP-1 receptor agonists and SGLT-2 inhibitors improved liver enzymes, BMI, blood lipid, blood glucose and insulin resistance in NAFLD patients.

Keywords Thiazolidinediones · Glucagon-like peptide-1 receptor agonist · Sodium-glucose cotransporter 2 inhibitors · Non-alcoholic fatty liver disease

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a pathological state of excess hepatic fat accumulation in the absence of significant alcohol consumption or other known factors

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that induce chronic liver damage [1]. NAFLD comprises a broad spectrum of diseases, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), liver cirrhosis and hepatocellular carcinoma [2]. NAFLD is a leading cause of chronic liver disorders, affecting approximately 25% of the global population [3, 4]. The prevalence of NAFLD is increasing.

The management of NAFLD mainly focuses on interventions pertaining to diet and lifestyle, including changes in energy intake, focus on weight loss, increased aerobic exercise and restriction of alcohol consumption [5]. Several drugs exhibited a definite histological effect on NAFLD in clinical trials and animal experiments. Insulin sensitizers, such as thiazolidinediones (TZDs), can improve the histological indications such as steatosis, inflammation, hepatocellular ballooning, and fibrosis in patients with NASH [6]. However, there are side effects such as weight gain and an increase in subcutaneous adipose tissue; these greatly reduce the efficacy of TZD treatment [7].

Novel oral hypoglycemic agents, such as sodium-glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, have gained attention for NAFLD treatment. SGLT-2 inhibitors increase urinary glucose excretion by inhibiting glucose reabsorption in the renal proximal tubule, thereby lowering blood glucose levels [8]. In addition, they significantly reduce the weight of mice while improving liver steatosis, inflammation, and fibrosis [9]. A prospective study showed that SGLT-2 inhibitors reduce liver fat and lower serum alanine aminotransferase (ALT) levels in patients with NAFLD and type 2 diabetes mellitus (T2DM) [10]. In addition, they improve liver function irrespective of the changes in the body weight in T2DM patients [11].

GLP-1, an incretin hormone, is secreted by the L cells in the distal ileum and proximal colon [12]. The role of GLP-1 receptor agonists in the treatment of T2DM is widely recognized in terms of promoting insulin secretion by pancreatic β cells and inhibiting glucagon secretion [13, 14]. A meta-analysis showed that GLP-1 receptor agonists reduce body weight in overweight or obese patients with or without T2DM [15]. GLP-1 receptor agonists and structured lifestyle interventions have similar effects pertaining to reducing body weight, liver fat fractions, and serum transaminase levels in obese adults with NAFLD [16]. A retrospective study showed that the use of GLP-1 agonists after 12 weeks of treatment decreases the amount of total body fat mass and liver stiffness in patients with NAFLD and T2DM [17].

Accumulating data indicate the potential therapeutic effects of the three antidiabetics on NAFLD; however, few studies have directly compared the efficacy of these agents for NAFLD. Several direct pairwise meta-analyses provide a comparison of each drug pair against a placebo or other agents [6, 18, 19]. We performed a systematic review and network meta-analysis (NMA) to compare the effectiveness of the three antidiabetic agents (TZDs, SGLT-2 inhibitors and GLP-1 receptor agonists) on BMI, liver enzymes, blood lipids and glycemic parameters in NAFLD patients.

Methods

This NMA was conducted following The Preferred Reporting Items for Systematic Reviews and Metaanalyses (PRISMA) extension statement for the reporting of systematic reviews incorporating NMAs of Health Care Interventions [20]. The protocol for this systematic review with NMA is registered on PROSPERO (CRD42020202514).

Selection criteria

Studies included in this NMA were randomized controlled trials (RCTs) that met the following inclusion criteria: (1) patients: adults with NAFLD (including NASH) proven through biopsy or imaging examination; (2) intervention: TZDs, GLP-1 receptor agonists or SGLT-2 inhibitors; (3) comparator: placebo or other agents that can be compared to the three interventions; (4) outcomes: primary outcomes were improvements in ALT, aspartate aminotransferase (AST) and γ-glutamyl transferase (GGT) levels; secondary outcomes included body mass index (BMI), blood lipids [total cholesterol, high density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol and triglycerides (TG)], glycemic parameters [glycosylated hemoglobin (HbA1c), glucose and homeostasis model assessment (HOMA-IR)]. We excluded (1) observational and non-randomized controlled trial studies, (2) interventions other than pharmacological therapy, including diet and lifestyle changes, and (3) patients with comorbidities that could affect the outcomes.

Search strategy

We searched PubMed, EMBASE, the Cochrane library and Medline databases from database inception until April 2021. Databases were searched using a combination of MeSH terms and entry terms. We limited the language included in this study to English.

Data abstraction and quality assessment

Characteristics of the included literature were extracted onto a standardized form in Microsoft Excel 2016 and EndNote X9 as follows: (1) study characteristics, primary author, year of publication, study design, geographical location and study duration; (2) treatment characteristics, sample sizes of each group and schedule of intervention; (3) outcome assessment,

change in liver aminotransferases (ALT, AST and GGT) levels, plasma levels of TG, total cholesterol (TC), LDL-C (low density lipoprotein cholesterol), HDL-C (high density lipoprotein cholesterol), FBG (fasting blood glucose), HOMA-IR and Hb1Ac from baseline in each treatment group. The risk of bias in each study was assessed with the Cochrane Risk of Bias assessment tool. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria for NMA to appraise the quality of evidence [21].

Statistical methods

When the data were reported as measures before and after intervention, we calculated the mean change and standard deviations for change. When only the median, range and size of a sample were provided, we estimated them using the method proposed by Stela Pudar Hozo [22]. When the mean and standard deviation of the calculated change in value were provided, we directly used these data.

Direct meta-analysis was performed using a random-effects model to estimate the weighted mean difference (WMD) and 95% confidence intervals (CIs). We used STATA software (Stata Statistical Software Release 16; Stata Corp, USA) to perform direct comparisons and draw the forest plots. Statistical heterogeneity was assessed using the I^2 statistic, with values > 50% indicating significant heterogeneity.

Owing to the limited number of trials based on direct comparison, we used indirect comparisons to explore the difference in efficacy between the two treatments. To perform indirect comparisons, we performed a random-effects Bayesian network meta-analysis using R version 4.0.2 (R Core Team, Vienna, Austria) with the GeMTC package for statistical analyses. We modeled the comparative efficacy of any two interventions as a function of each intervention relative to the reference intervention (i.e., placebo and metformin in this study). The consistency of the network was evaluated by comparing direct estimates to indirect estimates. The node splitting method was used to estimate the effect of the indirect comparison. We assessed the probability that each intervention as the most efficacious in improving outcomes, the second best, the third best, and so on, to rank the intervention hierarchically in the NMA.

Results

A schematic diagram of the study selection process is shown in Fig. 1. In total, 5301 unique studies were identified using our search strategy. By reading the full text, 22 RCT studies were reserved for this NMA [7, 16, 23–42] (Fig. 2).

Characteristics and quality of included studies

Table 1 summarizes the characteristics of the RCTs included in the NMA. Overall, these 22 trials included 1351 participants with NAFLD. A summary of the risk of bias of the included RCTs is shown in Supplementary Fig. 1. All interventions were implemented as intended and completed outcome reporting; overall, the studies were at a low-to-moderate risk of bias.

Improvement in ALT

Direct Meta-analysis: Compared to TZDs, GLP-1 receptor agonists (WMD, −0.40, 95%CI: −0.60 to −0.20) were associated with an improvement in ALT levels in patients with NAFLD (Fig. 3). SGLT-2 inhibitors (WMD, −6.00, 95%CI: −9.13 to −2.86) were superior to the placebo in lowering ALT levels. Compared to metformin, SGLT-2 inhibitors (WMD, −3.60, 95%CI: −6.71 to −0.49) improved ALT levels in patients with NAFLD. However, metformin and placebo were associated with increased ALT levels. There was no difference between TZDs and SGLT-2 inhibitors in improving ALT levels in patients with NAFLD.

Network Meta-analysis: Compared to placebo, SGLT-2 inhibitors and GLP-1 receptor agonists were associated with significant improvements in ALT (Supplementary Fig. 4A). TZDs and GLP-1 receptor agonists had the highest probability of being ranked first and second for improving ALT, respectively, whereas SGLT-2 inhibitors had the highest probability of being ranked third (Supplementary Fig. 5A).

Improvement in AST levels

Direct Meta-analysis: TZDs were associated with a decrease in AST levels (WMD, −11.25, 95%CI: −17.16 to −5.35) when compared to that with a placebo (Fig. 4). In the only head-to-head trial, metformin was superior to GLP-1 receptor agonists in improving AST levels (WMD, 4.30, 95%CI: 3.03–5.57). No significant differences were found among the other interventions.

Network Meta-analysis. Consistent with the results of direct comparisons, TZDs were superior to placebo in decreasing AST levels (Supplementary Fig. 4B). Overall, TZDs were ranked the highest for improvements in AST, whereas GLP-1 receptor agonists and SGLT-2 inhibitors had the highest probabilities of being ranked third and fourth, respectively (Supplementary Fig. 5B).

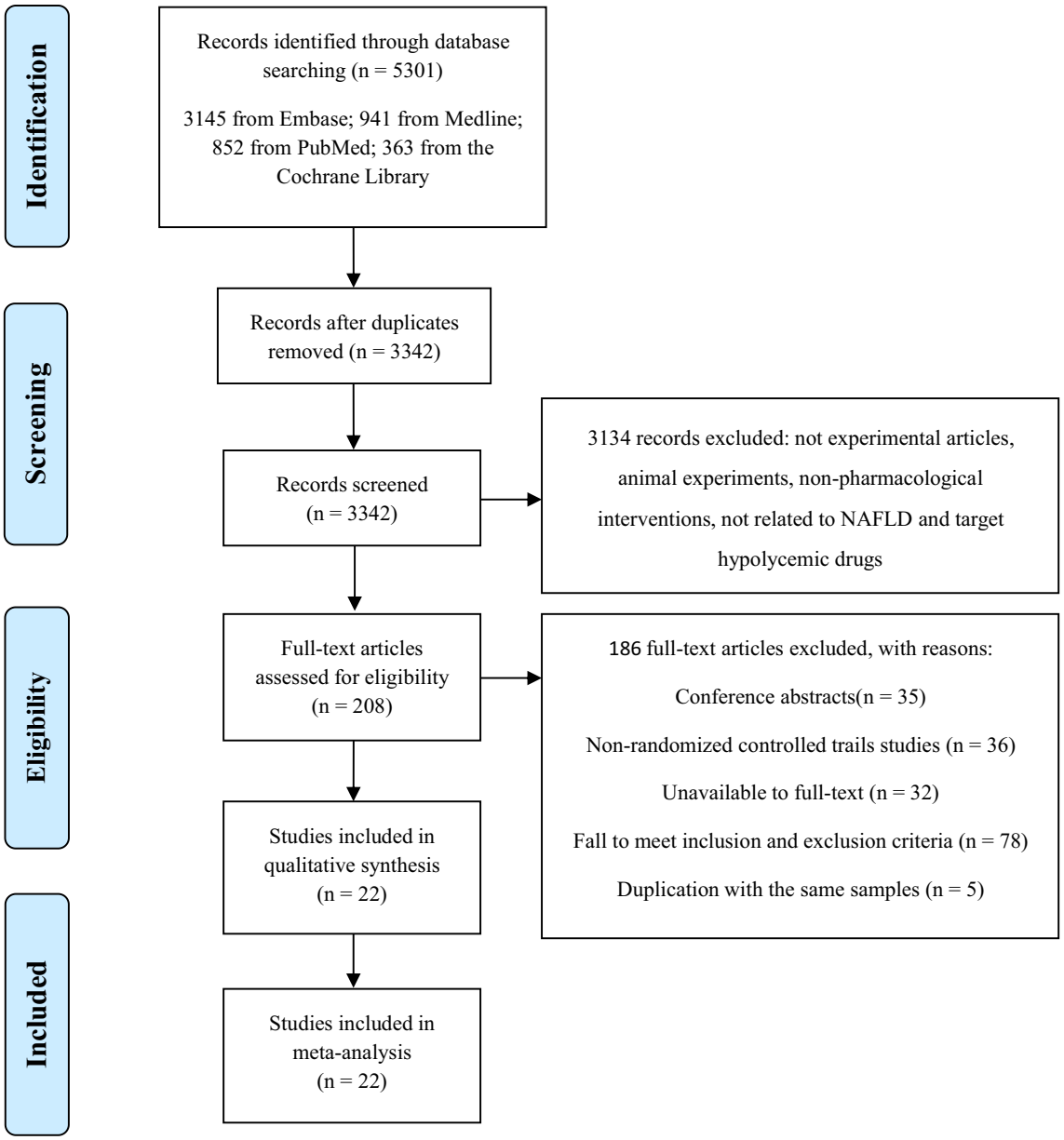

Fig. 1 Flow diagram of the study selection

Improvement in GGT

Direct Meta-analysis: GLP-1 receptor agonists were superior to TZDs in decreasing GGT (WMD, −5.00, 95%CI: −6.47 to −3.53) (Fig. 5). However, there was no significant difference between TZDs and SGLT-2 inhibitors.

Network Meta-analysis: Owing to the wide range of confidence intervals, no intervention was clearly superior to others in the comparative effectiveness NMA of active interventions (Supplementary Fig. 4C). However, the ranking of efficacy showed that GLP-1 receptor agonists and TZDs had the highest probability of being ranked first and second for improving GGT, respectively, whereas SGLT-2 inhibitors had the highest probability of being ranked third (Supplementary Fig. 5C).

Effect on Weight Loss.

Direct Meta-analysis: GLP-1 receptor agonists were significantly superior to TZDs (WMD, −4.10, 95%CI: −6.55 to −1.65), placebo (WMD,−1.50, 95%CI: −2.49 to −0.51), and metformin (WMD, − 0.60, 95%CI: −0.94 to − 0.26) for weight loss (Fig. 6). In addition, compared to that with the placebo and metformin, SGLT-2 inhibitors significantly reduced the weight of NAFLD patients.

Network Meta-analysis: Compared to TZDs, GLP-1 receptor agonists (WMD, −2.20, 95%CI: −3.80 to −0.85) and SGLT-2 inhibitors (WMD, −1.80, 95%CI: −3.30

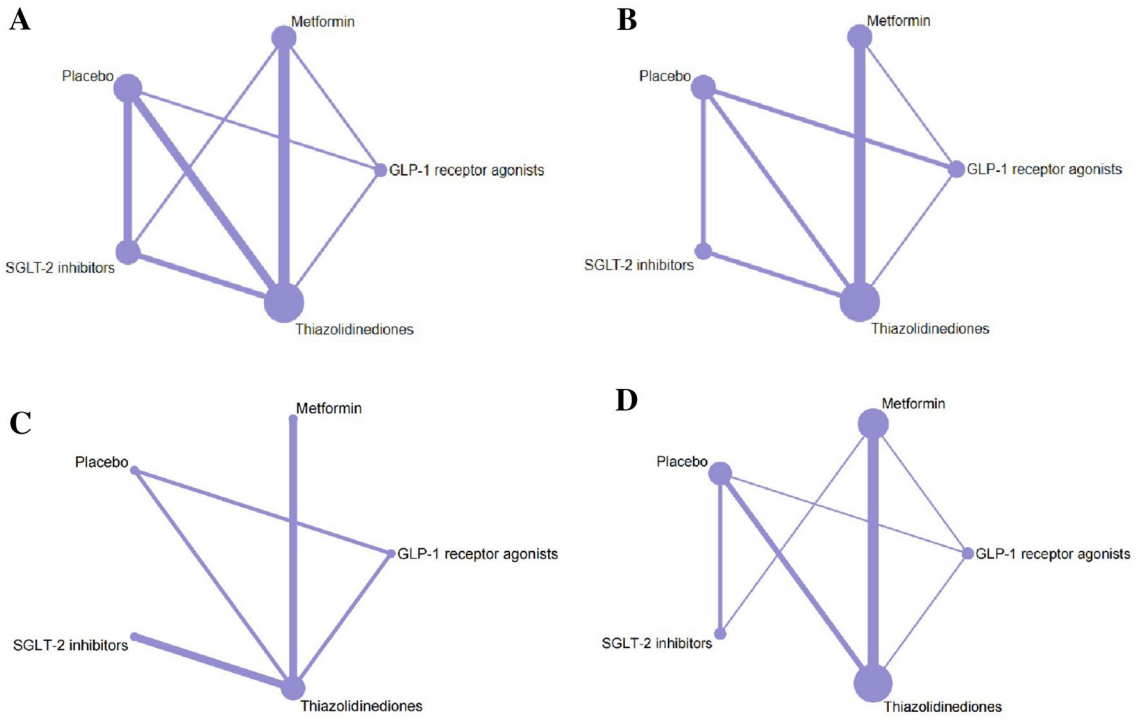

Fig. 2 Network plots of included studies with the available direct comparisons of **(a)** alanine aminotransferase (ALT), **(B)** aspartate aminotransferase (AST), **(C)** γ-glutamyl transferase(GGT)and (D) body mass index (BMI)

to −0.41) were associated with weight loss (Supplementary Fig. 4D). GLP-1 receptor agonists and SGLT-2 inhibitors had the highest probability of being ranked as first- and second-best interventions for weight loss, respectively, whereas TZDs had the highest probability of being ranked last (Supplementary Fig. 5D).

Improvement in blood lipid profiles

Direct Meta-analysis: Compared to TZDs, GLP-1 receptor agonists (WMD, −0.50, 95%CI: −0.68 to −0.32) were associated with decreased TG (Supplementary Fig. 6). Compared to metformin, GLP-1 agonists could be more beneficial in reducing TG. Moreover, SGLT-2 inhibitors were superior to TZDs in improving TC (WMD, −0.10, 95%CI: −0.15 to −0.05). Compared to that with placebo, SGLT-2 inhibitors, GLP-1 receptor agonists, and TZDs slightly increased HDL cholesterol levels in NAFLD patients. In the only head-to-head trial, GLP-1 receptor agonists reduced TC, when compared to that with metformin.

Network Meta-analysis: Compared to metformin and placebo, GLP-1 receptor agonists significantly reduced TG levels in NAFLD patients. GLP-1 receptor agonists were superior to metformin in decreasing LDL cholesterol. The effects of TZDs on HDL and LDL cholesterol levels, compared to that with the placebo, were consistent with the results of the direct comparison (Supplementary Fig. 7). Overall, GLP-1 receptor agonists were ranked highest in improving blood lipid levels, except TC levels. SGLT-2 inhibitors had the highest probability of being ranked first to improve TC levels (Supplementary Fig. 8).

Other outcomes

We compared the effects of several drugs on FBG, HOMA-IR and HbA1c (Supplementary Fig. 9 and 10). The effects of these hypoglycemic drugs on fasting blood sugar levels are well established. Our results corroborated this through direct comparisons or indirect comparisons. The effect of GLP-1 receptor agonists on FBG was better than that of metformin, a classic hypoglycemic drug. Compared to metformin, SGLT-2 inhibitors were more effective in reducing Hb1Ac. The ranking of efficacy showed that GLP-1 receptor agonists had the highest probability of being ranked first for improving FBG, HOMA-IR, and HbA1c (Supplementary Fig. 11).

Sensitivity analysis and network coherence

We performed a sensitivity analysis to identify sources of heterogeneity in this NMA (Supplementary Tables 1–4). The results of the sensitivity analysis were similar to that of the primary results. Our analysis revealed that the studies by Rana [31] were the main sources of heterogeneity

Table 1 Characteristics of the Included Studies

Study, year	Study design	Location	Time period	Intervention *N* = ITT	Control *N* = ITT	Main results
Ito [23]	SB	Japan	24 W	Pioglitazone *N* = 34	Ipragliflozin *N* = 32	Ipragliflozin was superior to pioglitazone in decreasing VFA, SFA and serum adiponectin
Kinoshita [24]	DB	Japan	28 W	Pioglitazone *N* = 33	Dapagliflozin *N* = 32	Dapagliflozin was superior to pioglitazone in decreasing bodyweight, VFA, serum ferritin and adiponectin
Zhang [25]	DB	China	24 W	Pioglitazone *N* = 30	Liraglutide *N* = 30	Liraglutide was superior to pioglitazone in decreasing bodyweight, BMI, waist circumference, 1H-MRS, Fetuin-A, FBG and 2 h-glucose
Cusi [26]	DB,PC, SC	USA	72 W	Pioglitazone *N* = 50	Placebo *N* = 51	Pioglitazone was superior to placebo in improving adipose tissue, hepatic, and muscle insulin sensitivity, also was associated with improvement in individual histologic scores, including the fibrosis score
Belfort [7]	PC	USA	24 W	Pioglitazone *N* = 26	Placebo *N* = 21	Pioglitazone was superior to placebo in decreasing ALT, AST, hepatic fat content. and improving hepatic insulin sensitivity. Compared with placebo, pioglitazone improved hepatic insulin sensitivity and histologic findings
Aithal [27]	DB, PC	US	48 W	Pioglitazone *N* = 37	Placebo *N* = 37	Compared with placebo, pioglitazone therapy was associated with an increase in weight and a reduction in glucose, HbA1c, insulin C peptide level, alanine aminotransferase level, and ferritin
Ratziu [28]	DB, PC	France	48 W	Rosiglitazone *N* = 32	Placebo *N* = 31	Compared with placebo, rosiglitazone improves steatosis and transaminase levels despite weight gain
Armstrong [29]	DB,PC,MC	UK	48 W	Liraglutide *N* = 23	Placebo *N* = 22	Compared with placebo, Liraglutide improves steatosis, hepatocyte ballooning, BMI
Eriksson [30]	DB,MS	Sweden	12 W	Dapagliflozin *N* = 21	Placebo *N* = 21	Compared with placebo, dapagliflozin improves ALT, AST, GGT, body weight and abdominal fat volumes
Akyüz [42]	NB	Turkey	48 W	Rosiglitazone *N* = 11	Metformin *N* = 12	No statistically significant differences were seen between the two treatment groups
Rana [31]	NB	India	24 W	Pioglitazone *N* = 33	Metformin *N* = 31	No comparison of the difference in changes between the two interventions

Table 1 (continued)

Study, year	Study design	Location	Time period	Intervention *N* = ITT	Control *N* = ITT	Main results
Hajiaghamohammadi [32]	NB	Iran	8 W	Pioglitazone *N* = 22	Metformin *N* = 22	Pioglitazone was superior to metformin in decreasing FBS,TG, serum insulin level, and HOMA index
Razavizade [33]	DB	Iran	16 W	Pioglitazone *N* = 40	Metformin *N* = 40	No statistically significant differences were seen between the two treatment groups with regard to the changes of laboratory parameters and LFC from baseline to four months post-treatment
Shahebrahimi [69]	SB	Iran	12 W	Pioglitazone *N* = 31	Metformin *N* = 31	Rosiglitazone was superior to metformin in reducing the severity of NAFLD, serum insulin levels, and HOMA-IR
Omer [34]	SC	Turkey	48 W	Rosiglitazone *N* = 20	Metformin *N* = 22	Rosiglitazone was superior to metformin in decreasing ALT, AST, ALP, and HOMA-IR
Fan [35]	SB	China	48 W	Exenatide *N* = 49	Metformin *N* = 68	BMI, waist-to-hip ratio, 2-h PPG, ALT, AST, γ-GT, and hs-CRP were markedly lower, and AST/ALT ratio and adiponectin in the exenatide group were dramatically higher than in the metformin group
Feng [36]	SB	China	96 W	Liraglutide *N* = 29	Metformin *N* = 29	Liraglutide was superior to metformin in decreasing blood glucose
Tian [37]	SB	China	12 W	Liraglutide *N* = 52	Metformin *N* = 75	Liraglutide was superior to metformin in improving AST, ALT, weight, BMI, C-reactive protein and adiponectin
Shibuya [38]	SC	Japan	24 W	Luseogliflozin *N* = 16	Metformin *N* = 16	Luseogliflozin was superior to metformin in improving L/S, VFA, Hb1Ac and BMI
Yoneda [39]	SC,PC	Japan	24 W	Pioglitazone *N* = 19	Tofogliflozin *N* = 21	Pioglitazone was superior to tofogliflozin in decreasing AST、ALT and TG
Guo [40]	SC,PC	China	26 W	Liraglutide *N* = 31	Placebo *N* = 30	In the liraglutide group, AST, ALT, HOMA-IR and intrahepatic content of lipid decreased significantly from baseline
Phrueksotsai [41]	SC,DB	Thailand	12 W	Dapagliflozin *N* = 18	Placebo *N* = 20	Dapagliflozin treatment for 12 weeks is associated with improvement in hepatic fat content, a decrease in visceral fat and bodyweight, enhanced glycemic control, and improved liver biochemistry among patients with NAFLD

PC, placebo controlled; SB, single blinded; NB, non-blinded; DB, double-blinded; SC, single center; MC, multi center

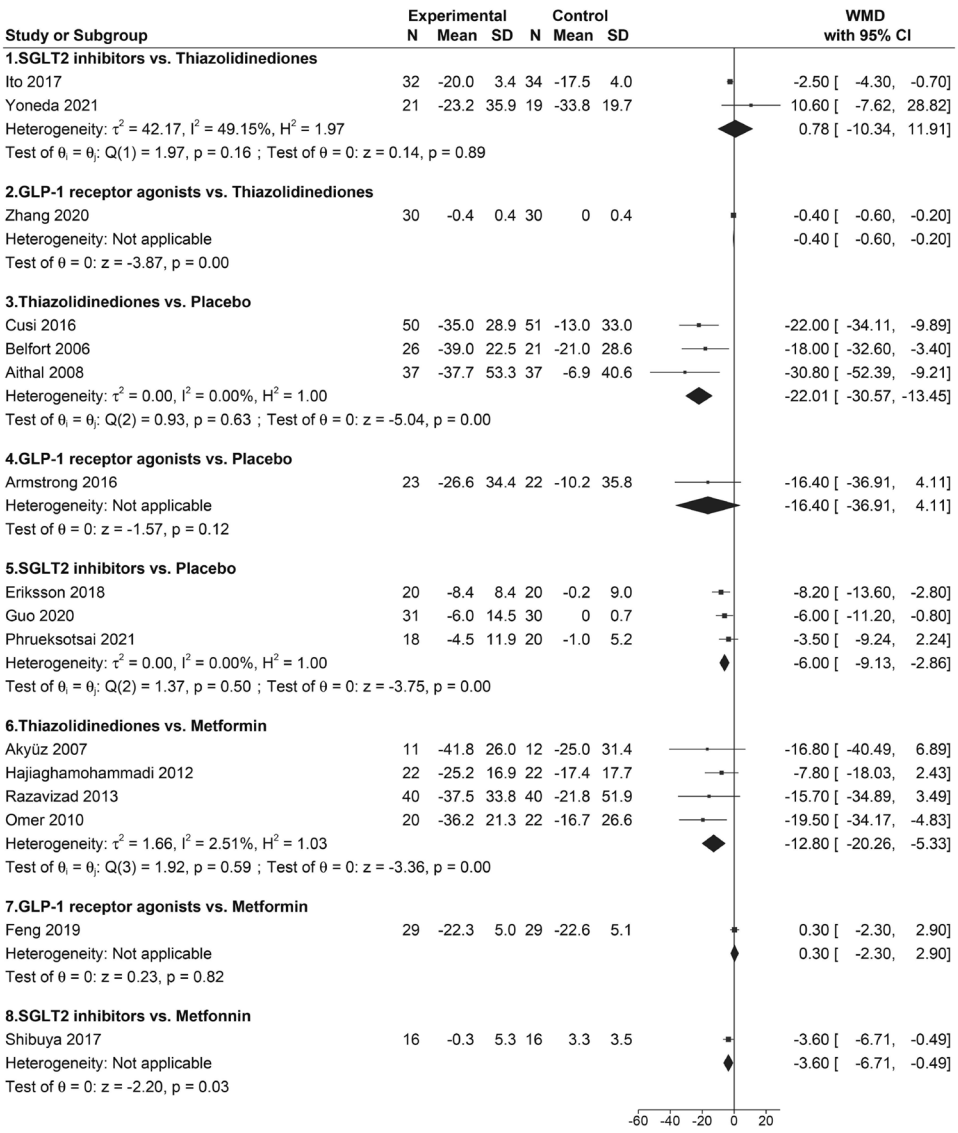

Fig. 3 Direct meta-analysis of different pharmacological interventions for improving alanine aminotransferase (ALT) in patients with NAFLD

in terms of the results pertaining to BMI; excluding these results effectively removed the variations. The NMA between TZDs and metformin showed no significant differences, but the difference between these two groups was not the main concern of our study. The network evaluating ALT showed some inconsistency in one (SGLT-2 inhibitors versus placebo, $P = 0.049$) comparison. There was one inconsistency in the comparison of the efficacy of HOMA-IR between the TZDs and placebo groups ($P = 0.045$). Overall, there were no significant differences between the direct and indirect estimates (Supplementary Table 5–15). Therefore, we believe that our results are robust.

Quality of evidence

The quality of the indirect evidence was generally low owing to the imprecision. For the ALT, AST and GGT outcomes, the effects of GLP-1 receptor agonists, TZDs and SGLT-2 inhibitors were supported by low-quality evidence, as compared to outcomes with the placebo (reduced owing to imprecision and inconsistency). For the same outcomes, the effect of GLP-1 receptor agonists, TZDs and SGLT-2 inhibitors, compared to that with metformin, was supported by low-quality evidence (reduced owing to imprecision caused by a low number of events). Table 2 and Supplementary Table 16 and 17 provide details of the GRADE quality of evidence for this NMA.

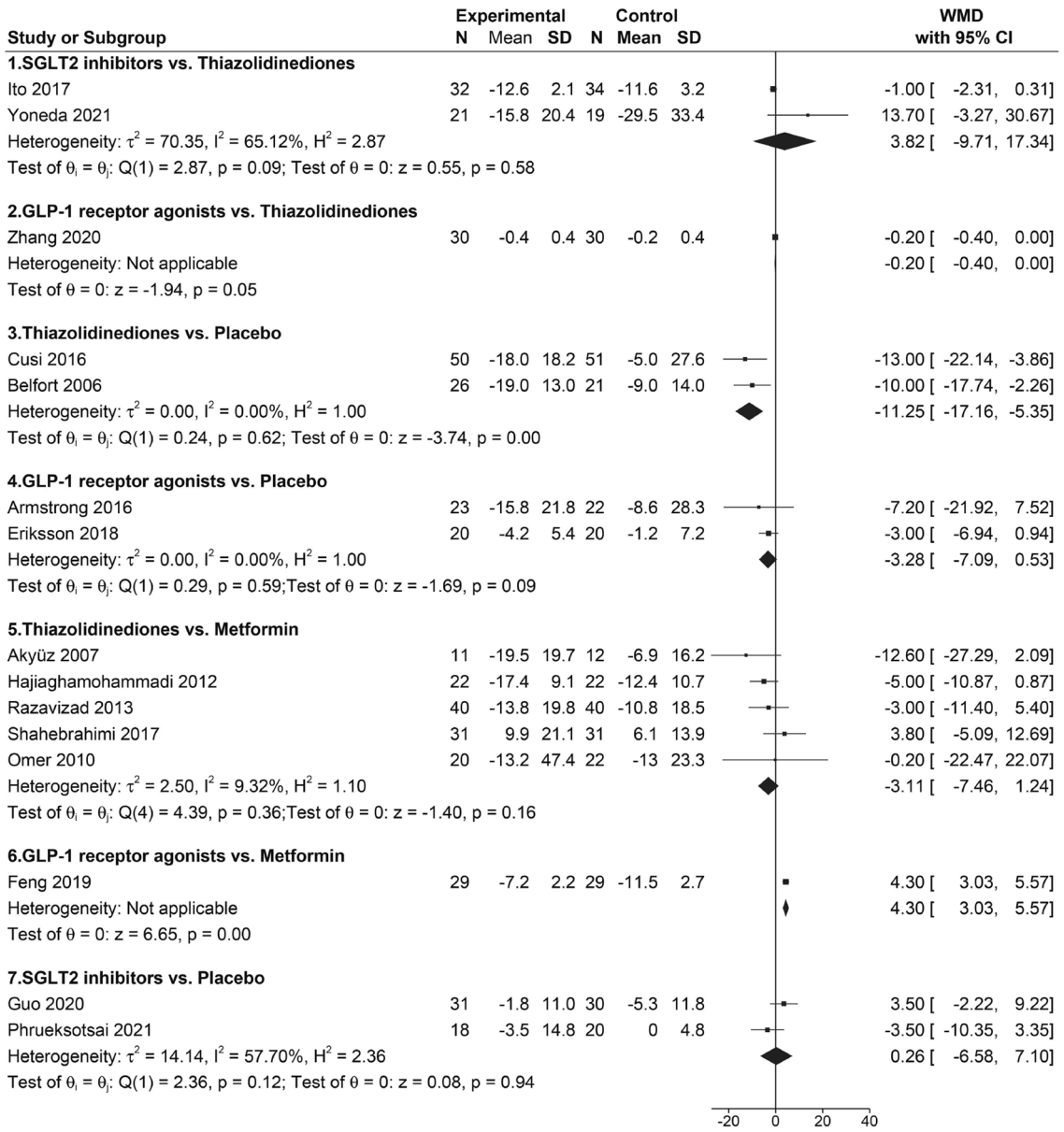

Fig. 4 Direct meta-analysis of different pharmacological interventions for improving aspartate aminotransferase (AST) in patients with NAFLD

Discussion

There is increasing interest in the potential value of hypoglycemic drugs for the treatment of NAFLD [43–45]. The classic hypoglycemic drugs, TZDs are proven to improve the histology of patients with NAFLD. Recently, two novel hypoglycemic drugs, SGLT-2 inhibitors and GLP-1 receptor agonists, were shown to ameliorate NAFLD [18, 46]. The main aim of this NMA was to evaluate the effect of these medications on NAFLD, specifically on liver enzymes and other metabolism-related indicators. To the best of our knowledge, this is the first meta-analysis to compare the efficacies of TZDs, GLP-1 receptor agonists and SGLT-2 inhibitors in patients with NAFLD.

The natural course of NAFLD is dynamic, and liver enzyme levels are closely related to NAFLD activity. ALT, a marker of hepatic inflammation, is regarded as an important indicator of disease improvement [47]. A recent study confirmed that the serum ALT level is a good indicator of histological changes and can be used as an effective indicator of treatment [48]. For patients with lower baseline AST levels, NASH is more likely to resolve spontaneously. Meanwhile, higher AST levels are associated with a greater risk of progression to advanced fibrosis [49]. Serum GGT levels are

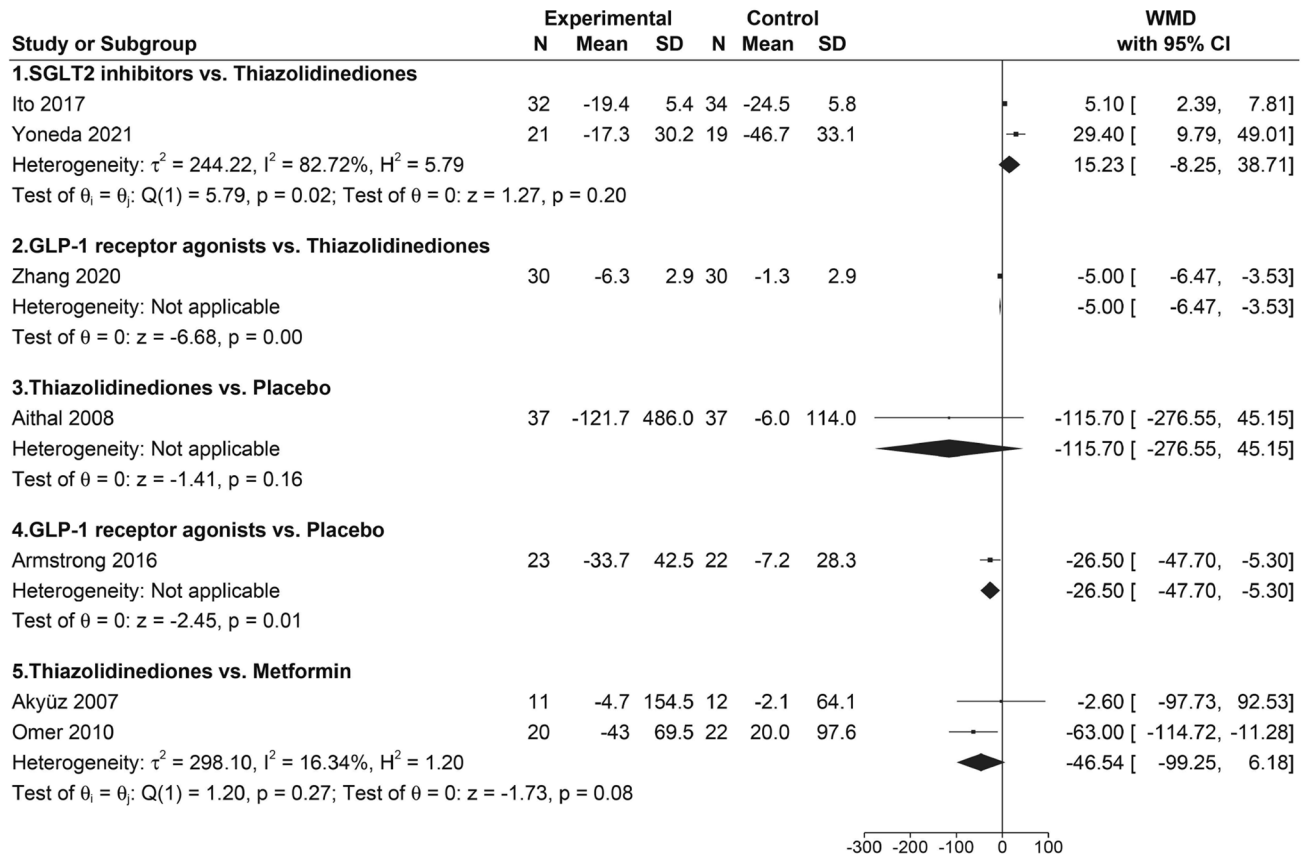

Fig. 5 Direct meta-analysis of different pharmacological interventions for improving γ-glutamyl transferase (GGT) in patients with NAFLD

strongly associated with increased mortality in patients with hepatic steatosis [50]. In the direct comparison, compared to TZDs, GLP-1 receptor agonists significantly decreased serum concentrations of ALT, AST and GGT in NAFLD patients. In the subsequent network analysis, GLP-1 receptor agonists ranked first in the possibility of improving the effects of ALT and GGT. Therefore, GLP-1 receptor agonists have beneficial effects on liver injury in NAFLD. A previous meta-analysis showed that compared to TZDs, SGLT-2 inhibitors reduced ALT levels more significantly [19]. However, in this study, there was no statistically significant difference in the improvements in response to the two medications, with respect to ALT levels. This could be attributed to the differences in the background glucose-lowering therapies in some studies included in the previous meta-analysis.

BMI is positively related to the presence of NAFLD, and significant weight loss can improve NAFLD [51]. Several studies have confirmed that obesity is an independent risk factor for the occurrence and development of NAFLD [52, 53]. GLP-1 receptor agonists and SGLT-2 inhibitors significantly reduced the BMI, while TZDs induced weight gain. NMA indicated that GLP-1 receptor agonists had the best effect on improving BMI. Diet and exercise that results in sustained weight loss of 7–10% can improve liver fat content and fibrosis [54]. A previous meta-analysis reported that weight loss ≥ 7% can improve the disease activity of NAFLD [55]. Therefore, the reduction in BMI indicates that GLP-1 receptor agonists and SGLT-2 inhibitors are beneficial in reducing liver fat. This is of great significance for the application of these two drugs for treating NAFLD patients, who are overweight or obese. TZDs, in addition to weight gain, exhibit serious adverse effects such as bladder cancer, osteoporosis, female fractures, and even congestive heart failure [56]. This limits the application of TZDs in treating NAFLD. Based on the histological improvements in the NASH patients in response to TZDs, we believe that TZDs can be used for patients with NASH, especially those with T2DM, who have previously been treated with TZDs.

NAFLD is regarded as a liver manifestation of metabolic syndrome [57, 58]. Dyslipidemia and insulin resistance are the basis of NAFLD pathogenesis. Approximately 50% of patients with hyperlipidemia have fatty infiltration of the liver [59]. Therefore, we analyzed the related indicators of glucose and lipid metabolism. GLP-1 receptor agonists had the best effect on improving blood lipids, except TC;

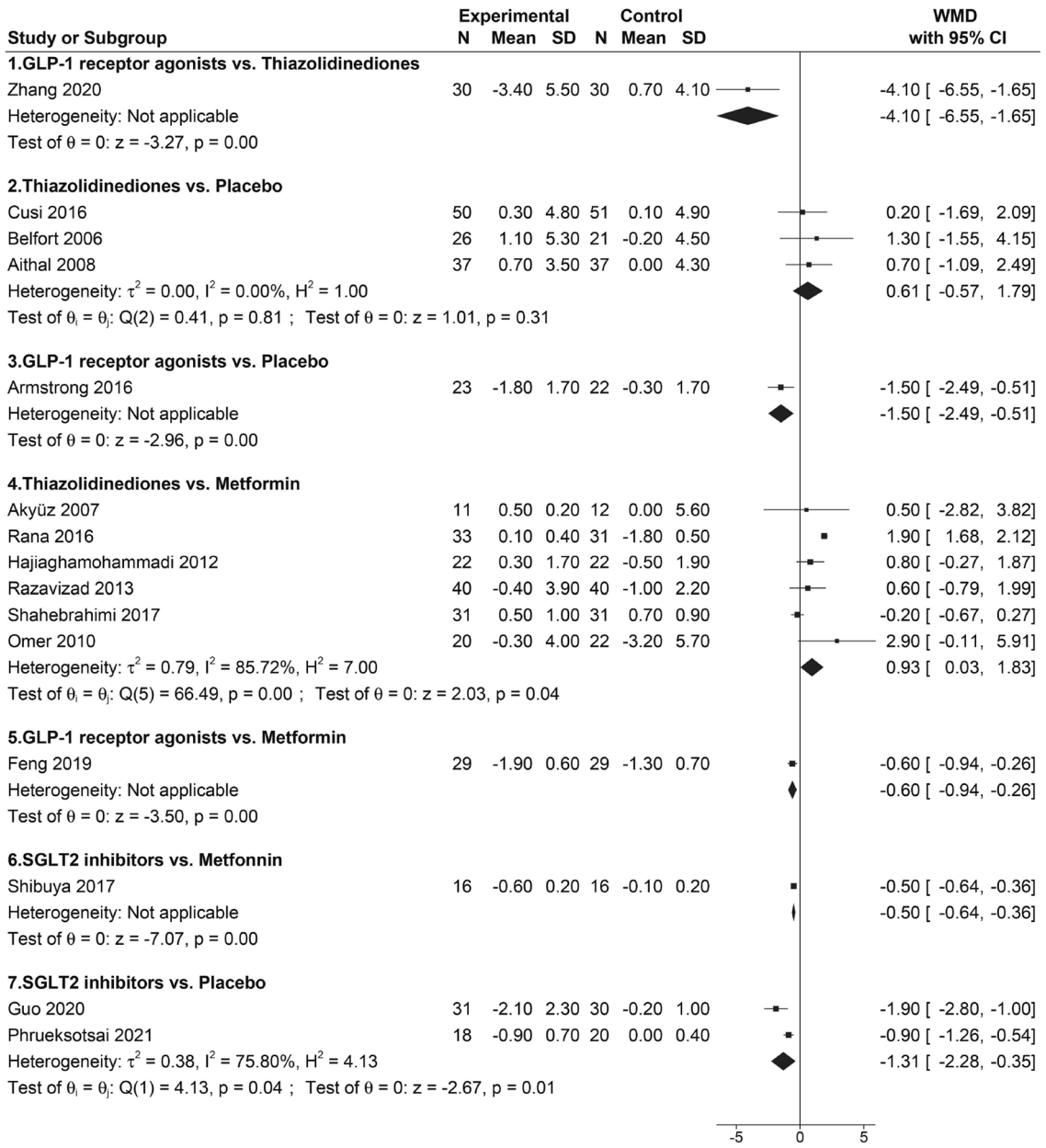

Fig. 6 Direct meta-analysis of different pharmacological interventions for improving body mass index (BMI) in patients with NAFLD

SGLT-2 inhibitors had the strongest effect on reducing TC levels. In addition, GLP-1 receptor agonists were better than TZDs in reducing FBG levels.

To facilitate comparison, we included metformin as an intermediate comparator to perform a NMA of a group other than the placebo group. Metformin, a first line hypoglycemic drug, has a positive therapeutic effect on NAFLD [60–63]. A clinical trial comparing the effects of metformin and vitamin E in NAFLD patients showed that the intrahepatic triacylglycerol content was significantly reduced in patients treated with metformin [60]. When metformin was combined with diet management, the degree of lipid content reduction in the liver was greater than that in patients undergoing diet management alone; the weight loss was similar between the two groups [61]. In addition, 25–30% of patients exhibited improved histological characteristics of steatosis following the treatment with metformin [62]. In this study, the two novel hypoglycemic drugs were better than metformin in improving ALT, BMI, FBG and HbA1c levels. At the same time, SGLT-2 inhibitors were more effective in improving insulin resistance. Considering the relationship between these indicators and NAFLD and comparing the results between the two drugs and metformin, we believe that GLP-1 receptor agonists

Table 2 Pooled WMD of improvement in liver function test, lipid profile, BMI and glycemic parameters Derived From Direct and Network Meta-analysis With Different Pharmacological Interventions in NAFLD Patients

Outcomes	GLP-1A vs TZDs		SGLT-2I vs TZDs		GLP-1A vs SGLT-2I	
	Direct	Mixed	Direct	Mixed	Direct	Mixed
BMI	−4.10 (−6.55, −1.65) moderate	−2.20 (−3.80, −0.85) moderate	NA	−1.80 (−3.30, −0.41) moderate	NA	−0.39 (−2.20, 1.30) low
ALT	−0.40 (−0.60, −0.20) moderate	4.00 (−5.40, 14.00) moderate	0.78 (−10.34, 11.91) moderate	6.40 (−0.99, 16.00) moderate	NA	−2.20 (−15.00, 8.50) low
AST	−0.20 (−0.40, 0) moderate	2.90 (−3.50, 10.00) moderate	3.82 (−9.71, 17.34) moderate	4.50 (−2.00, 13.00) moderate	NA	−1.60 (−11.00, 6.80) low
GGT	−5.00 (−6.47, −3.53) moderate	0.80(−76.00, 110.00) moderate	15.23 (−8.25, 38.71) moderate	14.00(−56.00, 90.00) moderate	NA	−13.00(−120.00, 120.00) low
TG	−0.50 (−0.68, −0.32) moderate	−0.49 (−0.84, −0.05) low	0.25 (−0.33, 0.83) moderate	0.15 (−0.16, 0.52) low	NA	−0.64 (−1.10, −0.14) low
HDL	−0.20 (−0.01, 0.41) moderate	0 (−0.08, −0.13) low	−0.06 (−0.24, 0.12) moderate	−0.02 (−0.12, 0.05) low	NA	0.03 (−0.07, 0.19) low
LDL	0(−0.56, 0.56) moderate	−0.39 (−0.67, 0.01) low	−0.16 (−0.36, 0.05) high	−0.16 (−0.37, 0.13) low	NA	−0.23 (−0.60, 0.19) low
TC	0.20 (−0.52, 0.92) moderate	0.17 (−0.32, 0.65) low	−0.10 (−0.15, −0.05) high	−0.17 (−0.58, 0.22) low	NA	0.34 (−0.25, 0.94) low
FBG	−1.30 (−2.86, 0.26) moderate	−0.89 (−1.40, −0.42) low	0.23 (−0.06, −0.51) high	0.27 (−0.02, 0.59) low	NA	−1.20 (−1.70, −0.66) low
HOMA-IR	−1.00 (−2.70, 0.70) moderate	−1.10 (−3.40, 1.10) low	1.00 (0.60, 1.40) high	0.34 (−1.40, 1.80) low	NA	−1.40 (−3.90, 1.20) low
Hb1Ac	−0.50 (−1.39, 0.39) moderate	−0.56 (−3.30, 1.60) low	0.72 (−1.83, 3.26) low	−0.15 (−1.90, 1.40) low	NA	−0.41 (−3.30, 2.00) low

*Sodium-glucose cotransporter protein-2 inhibitors:SGLT-2I; glucagon-like peptide-1 receptor agonists:GLP-1A; thiazolidinediones:TZDs; NA: not available

and SGLT-2 inhibitors might have additional benefits for NAFLD patients with type 2 diabetes or obesity.

Currently, there are only a few studies on the combined use of these three drugs for NAFLD. Considering the serious adverse effects of TZDs, a drug with similar therapeutic effects but relatively lesser side effects is a more appropriate therapeutic choice. This was the goal of this NMA. GLP-1 receptor agonists and SGLT-2 inhibitors exhibit complementary effects (on gluconeogenesis, thermogenesis and energy expenditure) [64, 65]; therefore, the combination of these two drugs could have a favorable effect on weight and blood glucose control in NAFLD patients. A recent meta-analysis confirmed that the combination of GLP-1 receptor agonists and SGLT-2 inhibitors reduces body weight, HbA1c levels and systolic blood pressure in diabetic patients, when compared to that in patients treated with GLP-1 receptor agonists or SGLT-2 inhibitor alone [66]. In addition, unlike TZDs, the side effects of these two types of drugs are minor and rarely require the discontinuation of therapy [67, 68]. Therefore, the combination of GLP-1 receptor agonists with SGLT-2 inhibitors has broad application prospects for the treatment of NAFLD; however, this hypothesis needs to be verified through well-designed RCTs in the future.

We limited this analysis to well-designed RCTs and performed quality assessment to reduce possible bias; however, this meta-analysis still had several limitations. The low acceptance of invasive biopsy and the limited results of abdominal ultrasound in the clinical studies resulted in insufficient data on the histological changes and quantification of liver steatosis. Considering the relationship among NAFLD, obesity and metabolic syndrome, this study mainly evaluated whether these medicines could improve NAFLD from the perspective of biochemical indicators, and further research is needed to evaluate the effect of these drugs on liver histology. In addition, the number of studies included was relatively small, which might have caused inhomogeneity and inconsistency between the direct and indirect comparisons. Therefore, larger RCTs are needed to further validate these results.

Conclusion

This study suggests that GLP-1 receptor agonists and SGLT-2 inhibitors can improve liver enzymes, the BMI, blood lipid, blood glucose, and insulin resistance in NAFLD patients. Therefore, these two drugs could be effective for

treating NAFLD. This article summarizes existing literature on NAFLD and provides promising insights into potential therapeutics for its treatment. Nevertheless, the investigation of these agents for the treatment of NAFLD is new and the number and quantity of published studies are limited. To further verify the specific effects of these drugs on NAFLD and the underlying mechanisms, larger RCTs with imaging and tissue data are necessary in the future.

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Author contributions C.D. reviewed the literature and designed the review, C.D. and Y.T. conducted the search for the systematic review and interpreted the data, W.Z. and P.H. conducted the statistical analysis, J.R. and P.L. prepared the figures and tables, X.H. revised the manuscript, and all authors reviewed the manuscript.

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Declarations

Conflict of interest The authors declare no competing interests.

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