The effect of pharmacological treatment and lifestyle modification in patients with non-alcoholic fatty liver disease: an umbrella review of meta-analyses of randomized controlled trials

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a liver disease that affects approximately 25 percent of the world's population, and various treatments have been applied for NAFLD patients. We compared the effectiveness of each intervention conducted to treat NAFLD by evaluating meta-analyses of pharmacological interventions and lifestyle modification including diet and exercise.

We searched Pubmed/Medline, Embase and Cochrane Library, and included meta-analyses of randomized controlled trials investigating the effects of pharmacological intervention and lifestyle modification on NAFLD. The quality of included meta-analyses was evaluated by AMSTAR-2. If the effect size was expressed as mean difference, it was converted to standardized mean difference based on the random-effects model.

A total of 1694 meta-analyses were identified, and 27 meta-analyses were eventually included in the review. Regarding pharmacological interventions, there was a high strength of evidence for the ALT reduction effect of silymarin on inactive controls (SMD=0.88, $p<0.01$, 7 trials, 518 participants). Meanwhile, it was confirmed that appropriate diet and exercise were important in reducing liver fat (SMD=1.51, $p<0.01$, 12 trials, 765 participants).

This umbrella review assessed the effects of pharmacological interventions and lifestyle modifications in the treatment of NAFLD. The results of this review can be utilized for clinical decisions when treating NAFLD patients.

ABBREVIATIONS

2hPG, 2-hour plasma glucose; A2, AMSTAR 2; A2-CD, AMSTAR 2 critical domain; ACB, acarbose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CB, choline bitartrate; CI, confidential interval; CRP, c-reactive protein; DBP, diastolic blood pressure; EP, ethyl polyenoate; GCZ, gliclazide; GGT, gamma-glutamyl transferase ; GLM, glimepride; GLP-1RA, glucagon-lie peptide 1 receptor agonist; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein cholesterol; HG TRT, hypoglycemic treatment; HOMA-IR, homeostatic model assessment for insulin resistance; HXHY therapy, HuoXueHuaYu therapy; I2, I-square; I2, I-square; IIT, intensive insulin therapy; IL-6, interleukin 6; LDL, low-density lipoprotein cholesterol, ; LM, lifestyle modification; MET, methionine; MI, minimal intervention; MTF, metformin; NASH, nonalcoholic steatohepatitis; NI, no intervention; NS, normal saline; PBO, placebo; PGT, pioglitazone; PPC, polyene phosphatidylcholine; SBP, systolic blood pressure; SG, sitagliptin; SILY, silymarin; SIM, simvastatin; SLB, silibinin; SMD, standardized mean difference; SPs, sulfated polysaccharides; TC, total cholesterol; TG, total glyceride; TNF-alpha, tumor necrosis factor alpha; TZD, thiazolidinedione; UC, usual care; UDCA, ursodeoxycholic acid; Vit, vitamin; WC, waist circumference; XZ, Xuezhikang;

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a liver disease caused by steatosis in hepatocytes without use of medication or significant alcohol consumption (20 g/day for men and 10g/d for women) [1,2,3]. NAFLD can be divided into nonalcoholic fatty liver (NAFL), which rarely leads to cirrhosis, and nonalcoholic steatohepatitis (NASH), which can develop into liver cirrhosis and liver-related deaths [4]. It is reported that approximately 25% of the population in the United States suffers from NAFLD, with similar prevalence rates in Europe and Asia [5].

Accordingly, many researchers are making efforts to develop NAFLD treatments in the field. [6] However, there are currently no officially approved NAFLD and NASH treatments. This does not mean that studies on the treatment of NAFLD have not been conducted. Lifestyle intervention has been used to treat NAFLD and have been found to be effective in reducing liver fat [7], but it is difficult to achieve and maintain[8]. Moreover, because insulin resistance and type-2 diabetes are related with NAFLD, treatments for type-2 diabetes are also used for NAFLD [9,10]. In recent years, elafibranor has received attention as new treatments, but it failed to be approved [11]. NAFLD is often accompanied by other diseases, so it is unclear whether it is a primary or secondary disease. In addition, it is difficult to understand the inner mechanism of NAFLD, so researchers have had trouble in developing treatments.

Although various interventions have been studied for NAFLD, and sufficient meta-analytic data exist, there is lack of a comprehensive summary of randomized controlled trials (RCT) of pharmacological interventions and lifestyle modifications. Moreover, it is difficult to apply the results of meta-analysis directly to patients because each study has different data organization

methods. Therefore, it is essential to organize in an accurate and standardized way which intervention methods can help improve health outcomes related to NAFLD.

Umbrella reviews aggregate all existing meta-analyses and present the high level overview on a topic [12]. We carried out an umbrella-review of meta-analyses to evaluate the effectiveness of pharmacological interventions and lifestyle modifications to treat NAFLD patients. This umbrella-review seeks to assist in evidence-based clinical decision making in NAFLD patient care. We reviewed all available data from the meta-analyses of RCTs of pharmacological interventions and lifestyle modifications for NAFLD treatment.

Materials and Methods

The review was conducted based on a preregistered protocol (PROSPERO: CRD42021235178), and according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [13].

Search strategy and selection

A literature search was conducted on Pubmed/Medline and Cochrane Library from inception to 6 February 2021 by the search terms in Supplement 2. We restricted the search to articles in English. Additional search was conducted on Embase on 2 September 2021. Two reviewers (KC, SP) independently performed this process and combined the results.

Two reviewers (KC and SP) screened the studies based on the title and abstract. Consequently, a full-text screening was conducted. Criteria for study selection was pre-determined based on the population, interventions, comparisons, outcomes, and study design. The meta-analysis of RCTs

in patients of any age and country with a diagnosis of NAFLD were selected. Patients were diagnosed based on ultrasonography or magnetic resonance imaging or histologic examination. All pharmacological interventions and lifestyle modifications were included, and the controls included both inactive-controlled and active-controlled groups. Specific inclusion and exclusion criteria are specified in Table 1.

If there were several meta-analyses on the same intervention, the meta-analyses were ranked by the process described in Supplement 5, and the highest ranked article was selected. If the lower ranked article contained health outcomes that was not included in the highest ranked article, the lower ranked article was used for those outcomes.

Data extraction

From the selected meta-analyses, two reviewers (KC and SP) extracted the first author's name, publication year, characteristics of participants, the number of primary studies and participants, intervention and related specific information (duration, dose, and route), control information, health outcomes, effect estimate, 95% confidence intervals, and p-value. After extracting the data, each reviewer checked each other's data.

The following health outcomes were included in this review: liver function indicator (e.g., ALT, AST, albumin, bilirubin), anthropometric parameter (e.g., BMI), lipid profile (e.g., TC, TG), glucose metabolism indicator (e.g., glucose, insulin level), and liver histological parameter (e.g., liver fat or steatosis, fibrosis).

Quality assessment

Two authors (KC and SP) evaluated the quality of included studies using A Measurement Tool to Assess Systematic Review 2 (AMSTAR 2) [14]. AMSTAR 2 contains sixteen domains in which

the meta-analysis can be assessed. Details on AMSTAR 2 are provided in Supplement 5. For each meta-analysis, the entire score of AMSTAR 2 and the score of the 'critical domains' of AMSTAR 2 are both presented.

Statistical Analyses

In the selected studies, standardized mean difference (SMD), and mean difference (MD) were used as the metric for effect size. Re-analysis was carried out for effect size expressed as MD by Comprehensive Meta-Analysis 3.0 (Biostat, NJ, USA). These data were converted to the same unit and converted to SMD with 95% confidence intervals. All the effect sizes obtained by a fixed-effect model were re-analysed by a random-effect model for correct comparison. As for health outcomes where a negative value represented favourable outcomes for NAFLD, the effect size was multiplied by minus. Therefore, for all the health outcomes, the larger the effect size, the better the treatment outcome of NAFLD. If calculated, I^2 and Egger's p were used to estimate heterogeneity and publication bias respectively.

Results

We conducted the search process described in Figure 1. The list of excluded articles and specific reasons for exclusion are provided in Supplement 4. A list of included articles is shown in Supplement 3.

There were 24 meta-analyses of RCTs regarding pharmacological interventions. For berberine, we included one meta-analysis and analyzed eight health outcomes [15]; for bicyclol, one meta-analysis and six outcomes [16]; for curcumin, one meta-analysis and 13 types of outems [17]; for

dipeptidyl peptidase 4 inhibitor (DDP4 inhibitor), one meta-analysis and two outcomes [18]; for glucagon-like peptide-1 receptor agonists (GLP-1 RA), two meta-analyses and 12 outcomes [19,20]; for HuoXueHuaYu (HXHY), one meta-analysis and five outcomes [21]; for omega-3 fatty acids, one meta-analysis and 13 outcomes [22]; for prebiotics, one meta-analysis and five outcomes [23]; for probiotics and synbiotics, three meta-analyses and 16 outcomes [24,25,26]; for resveratrol, two meta-analyses and 17 outcomes [27,28]; for silymarin, two meta-analyses and five outcomes [29,30]; for sodium-glucose co-transporter-2 inhibitor (SGLT2 inhibitor), three meta-analyses and 7 outcomes [18,31,32]; for thiazolidinedione (TZD), two meta-analyses and 11 outcomes [33,34]; and for ursodeoxycholic acid (UDCA), one meta-analysis and five outcomes [35]; for vitamin D, two meta-analyses and nine outcomes [36,37]; and for vitamin E, two meta-analyses and seven outcomes [38,39].

There were 3 meta-analyses regarding lifestyle modifications: For diet, one meta-analysis including 10 outcomes [40]; and for exercise, two meta-analyses including 11 outcomes [40,41].

Study characteristics of included meta-analyses are shown in Supplement 6.

Effect of pharmacological interventions and lifestyle modifications

Liver function

Alanine Aminotransferase

For ALT, there were 20 pharmacological interventions (139 trials, N≥9210). Compared to the inactive control group, the most effective intervention was synbiotics (n=6, N=321, SMD=1.64, 95% CI: 0.49 to 2.80, $p<0.01$, $I^2=95\%$) (Supplement 7-1, 8-1). HXHY therapy showed the largest

effect for ALT reduction versus the active control group. (n=6, N=418, SMD=1.71, 95% CI: 1.16 to 2.27, p<0.01, I^2=83%) (Figure 2, Supplement 7-2). Compared to the mixed control group, bicyclol showed the highest effect in terms of ALT reduction. Specifically, the effect was better when bicyclol was used alone (n=5, N=388, SMD=2.36, 95% CI: 1.46 to 3.27, p<0.01, I^2=91%), and the effect was slightly reduced when combination treatment was conducted. (n=12, N=1008, SMD=1.72, 95% CI: 1.15 to 2.29, p<0.01, I^2=93%) (Supplement 7-3, 8-2).

Two lifestyle modifications (22 trials, N≥2108) regarding ALT were included. Compared to usual care group, there was no intervention showing the significant result. (Figure 3, Supplement 7-4) Meanwhile, compared to the mixed control group, statistical significance was only obtained for 'Exercise (total)', which was the result of combined analysis of aerobic exercise and resistance exercise (n=11, N=1054, SMD=0.17, 95% CI: 0.05 to 0.30, p=NR, I^2=30%) (Figure 4, Supplement 7-5).

Aspartate Aminotransferase

There were 20 pharmacological interventions (123 trials, N≥7775) regarding AST. Synbiotics showed the highest effect size to inactive control as in ALT (n=6, N=321, SMD=1.66, 95% CI: 0.50 to 2.83, p=0.01, I^2=95%). (Supplement 7-1, 8-1) In comparison with the active control group, HXHY therapy had the highest effect size in AST reduction (n=5, N=354, SMD=2.28, 95% CI: 0.99 to 3.57, p<0.01, I^2=96%) (Figure 2, Supplement 7-2). Compared to the mixed control group, combination of berberine plus metformin showed the largest effect (n=3, N=226, SMD=0.77, 95% CI: 0.36 to 1.18, p<0.01, I^2=55%) (Supplement 7-3, 8-2).

There were 2 lifestyle modifications (20 trials, N≥2090) for AST. Aerobic exercise (n=6, N=618, SMD=0.26, 95% CI: 0.10 to 0.43, p=NR, I^2=60%) and resistance exercise (n=3, N=391, SMD=0.23, 95% CI: 0.03 to 0.43, p=NR, I^2=0%) showed a medium effect size in comparison with the mixed control group (Figure 4, Supplement 7-5).

Gamma-glutamyl Transferase

Four pharmacological interventions (33trials, N=2703) studied GGT. In comparison with the mixed control group, the most effective intervention was SGLT2 inhibitor (n=6, N=367, SMD=0.85, 95% CI: 0.08 to 1.62, p=0.03, I^2=92%) (Supplement 7-3, 8-2).

Two lifestyle modifications were carried out for GGT (12 trials, N≥1554). Compared to the usual care group, the most effective intervention was resistance exercise (n=2, N=371, SMD=0.24, 95% CI: 0.03 to 0.44, p=NR, I^2=0%) (Figure 3, Supplement 7-4).

Anthropometric parameter

Body Mass Index

There were 14 pharmacological interventions on BMI (63 trials, N≥3203). Compared to inactive control group, prebiotics showed statistically significant effect size (n=2, N=NR, SMD=0.49, 95% CI: 0.13 to 0.86, p=0.01, I^2=41%) (Supplement 7-1, 8-1). GLP-1 RA outperform mixed control in terms of decreasing BMI (n=6, N=NR, SMD=0.89, 95% CI: 0.19 to 1.59, p<0.01, I^2=90%) (Supplement 7-3, 8-2).

Body weight

Five interventions studied body weight (22trials, N≥1196). The most effective intervention against the mixed control group was SGLT2 inhibitor administration (n=5, N=265, SMD=1.29, 95% CI: 0.30 to 2.23, p=0.01, I^2=92%). TZD showed a negative effect on body weight loss (n=4, N=329, SMD=-0.30, 95% CI: -0.51 to -0.08, p=0.01, I^2=0%) (Supplement 7-3, 8-2).

Other outcomes

For waist circumference reduction, there were four pharmacological interventions (11 trials, N≥ 416). Compared to the inactive control group, curcumin was effective in decreasing WC (n=3, N=219, SMD=1.01, 95% CI: 0.71 to 1.30, p<0.01, I^2=96%) (Supplement 7-1, 8-1).

Meanwhile, TZD was used for body fat reduction, but it did not make statistically significant results (n=3, N=241, SMD=-0.24, 95% CI: -0.49 to 0.02, p=0.07, I^2=0%) (Supplement 7-3, 8-2)

Lipid profile

Total Cholesterol

For TC, there were 16 pharmacological interventions (84trials, N≥4363). Curcumin was found to be effective in reducing total cholesterol when compared to inactive control (n=6, N=375, SMD=0.65, 95% CI: 0.24 to 1.05, p<0.01, I^2=74%) (Supplement 7-1, 8-1). In comparison with the active control group, HXHY therapy showed the only significant effect size (n=4, N=278,

SMD=0.47, 95% CI: 0.14 to 0.81, p=0.01, I^2=44%) (Figure 2, Supplement 7-2). Both bicyclol (n=11, N=958, SMD=0.64, 95% CI: 0.42 to 0.87, p<0.01, I^2=65%) and berberine (n=7, N=231, SMD=0.58, 95% CI: 0.25 to 0.91, p<0.01, I^2=69%) showed high effect size compared to the mixed control group (Supplement 7-3, 8-2).

For TC, there were 2 lifestyle modifications (18 trials, N≥2048). Resistance exercise was revealed to be effective in decreasing TC in comparison with usual care (n=2, N=371, SMD=0.31, 95% CI: 0.10 to 0.51, p=NR, I^2=38%) (Figure 3, Supplement 7-4). Meanwhile, exercise outperformed the mixed control regarding TC reduction (n=9, N=1034, SMD=0.22, 95% CI: 0.09 to 0.34, p=NR, I^2=0%) (Figure 4, Supplement 7-5).

Low-density Lipoproteins

There were nine pharmacological interventions investigating LDL (45 trials, N≥2346). Curcumin outperform inactive control group regarding LDL reduction (n=6, N=375, SMD=1.03, 95% CI: 0.11 to 1.94, p=0.03, I^2=94%) (Supplement 7-1, 8-1). Compared to the mixed control group, the most effective intervention was berberine (n=6, N=449, SMD=0.79, 95% CI: 0.26 to 1.31, p<0.01, I^2=85%) (Supplement 7-3, 8-2).

There were two lifestyle modifications on LDL (16 trials, N≥1452). Resistance exercise showed a significant effect in decreasing LDL compared to the usual care group (n=2, N=371, SMD=0.35, 95% CI: 0.15 to 0.56, p=NR, I^2=0%) (Figure 3, Supplement 7-4). The results for aerobic and resistance exercise showed significant effect size compared to the mixed control group (n=8, N=996, SMD=0.26, 95% CI: 0.13 to 0.39, p=NR, I^2=0%) (Figure 4, Supplement 7-5).

High-density Lipoproteins

There were seven pharmacological interventions on HDL (25 trials, N≥350). In comparison with the mixed control group, liraglutide, a type of GLP-1 RA, showed no significant effect on HDL (n=2, N=NR, SMD=0.17, 95% CI: -0.12 to 0.46, p=0.25, I^2=43%) (Supplement 7-3, 8-2).

There were two lifestyle modifications investigating HDL (18 trials, N≥2028). Compared to the usual care group, aerobic and resistance exercise showed no effect in increasing HDL (n=1, N=27, SMD=0.07, 95% CI: -0.69 to 0.83, p=NR, I^2=not applicable) (Figure 3, Supplement 7-4).

Triglyceride

For TG, 21 pharmacological interventions were carried out (113 trials, N≥8119).In comparison with inactive control, probiotics showed statistically significant effect (n=5, N=266, SMD=0.28, 95% CI: 0.03 to 0.52, p=0.03 I^2=0%) (Supplement 7-1, 8-1). Compared to the active control group, bicyclol showed the only significant effect (n=7, N=620, SMD=0.05, 95% CI: -0.25 to 0.35, p=0.74, I^2=0%) (Figure 2, Supplement 7-2). The treatment which used bicyclol alone was the most effective intervention for TG reduction in comparison with the mixed control group (n=5, N=388, SMD=2.39, 95% CI: 1.00 to 3.79, p<0.01, I^2=96%) (Supplement 7-3, 8-2).

For TG, 2 lifestyle modifications were conducted (16trials, N≥1992). Resistance exercises outperformed usual care in terms of decreasing TG (n=2, N=371, SMD=0.32, 95% CI: 0.11 to 0.52, p=NR, I^2=0%) (Figure 3, Supplement 7-4).

Glucose Metabolism

Fasting blood glucose

There were ten pharmacological interventions regarding fasting blood glucose (44 trials, N≥2590). Compared to inactive control, curcumin and vitamin D3 showed statistically significant effect (Supplement 7-1, 8-1). In comparison with the mixed control group, the combination therapy of berberine and metformin showed the largest effect size (n=4, N=270, SMD=0.84, 95% CI: 0.23 to 1.46, p=0.01, I^2=82%) (Supplement 7-3, 8-1). Meanwhile, there was one intervention investigating 2-hour plasma glucose (2hPG) (4 trials, N=329). For 2hPG reduction, berberine was superior to mixed control (n=4, N=329, SMD=0.34, 95% CI: 0.12 to 0.57, p<0.01, I^2=0%) (Supplement 7-3, 8-2).

For fasting blood glucose, two lifestyle modifications were conducted (21 trials, N≥1992). No intervention showed statistically significant effect size.

Insulin

There were various types of insulin measured, such as fasting insulin and serum insulin. When the type of insulin was not specified, it was simply named 'insulin'.

Eight pharmacological interventions reported insulin values (35 trials, N≥1062). Compared to inactive control, prebiotics were effective to improve fasting insulin (n=6, N=NR, SMD=0.71, 95% CI: 0.30 to 1.12, p<0.01, I^2=0%) (Supplement 7-1, 8-1). TZD plus lifestyle modification showed the largest effect for fasting insulin improvement versus the mixed control group (n=2, N=97, SMD=0.66, 95% CI: 0.22 to 1.10, p<0.01, I^2=14%) (Supplement 7-3, 8-2).

Two lifestyle modifications examined insulin values (8 trials, N≥324). In terms of improving fasting insulin, the combination of aerobic and resistance exercise outperformed the usual care group (n=1, N=27, SMD=0.80, 95% CI: 0.01 to 0.16, p=0.91, I^2=21%) (Figure 3, Supplement 7-4).

Homeostatic Model Assessment for Insulin Resistance

There were ten pharmacological interventions on HOMA-IR (45 trials, N=2541). Vitamin D3 / and calcitriol outperformed inactive control in terms of improving HOMA-IR (n=6, N=395, SMD=1.32, 95% CI: 0.34 to 2.30, I^2=95%) (Supplement 7-1, 8-1).

There were two lifestyle modifications regarding HOMA-IR (10 trials, N≥1500). Aerobic exercise outperformed usual care (n=3, N=379, SMD=0.42, 95% CI: 0.22 to 0.63, p=NR, I^2=0%) (Figure 4, Supplement 7-5).

HbA1c

There were three pharmacological interventions on HbA1c (14 trials, N=923). Berberine showed a medium effect size in comparison with the mixed control group (n=5, N=373, SMD=0.45, 95% CI: 0.19 to 0.70, p<0.01, I^2=29%) (Supplement 7-3, 8-2).

There were one intervention reporting HbA1c values (5 trials, N=200).Diet and exercise didn't show significant effect size compared to mixed control group (n=5, N=200, SMD=0.35, 95% CI: -0.12 to 0.82, p=0.15, I^2=61%) (Figure 4, Supplement 7-4).

Histological parameter

Liver fat

There were four pharmacological interventions on liver fat (22 trials, N=1363). Compared to the mixed control group, GLP-1 RA was the most effective intervention to reduce liver fat (n=7, N=371, SMD=1.16, 95% CI: 0.92 to 1.40, p<0.01, I^2=94%) (Supplement 7-3, 8-2).

There were three lifestyle modifications that examined liver fat (22 trials, N=2159). Diet and exercise were the most effective interventions to reduce liver fat compared to mixed control (n=12, N=765, SMD=1.51, 95% CI: 0.72 to 2.31, p<0.01, I^2=95%) (Figure 4, Supplement 7-5).

Fibrosis

Two pharmacological interventions were conducted on fibrosis (8 trials, N=668). Vitamin E showed a medium effect size compared to inactive control (n=3, N=241, SMD=0.30, 95% CI: 0.05 to 0.56, p=0.02, I^2=0%) (Supplement 7-1, 8-1).

Discussion

Incorporating evidence from 27 meta-analyses of RCTs of pharmacological interventions and lifestyle modifications in NAFLD treatment, including approximately 30 health outcomes of five categories, this umbrella review presents an evidence-based meta-analytic view for NAFLD treatment. The current review can help patients with NAFLD and clinicians make medical decisions. It can provide information on what pharmacological interventions are needed and what lifestyle modifications are available.

In order to improve liver function, HXHY therapy was the most effective pharmacological intervention compared to placebo controls. However, in the case of HXHY therapy, since there is only one meta-analysis reported so far, further research is likely to be needed for actual clinical utilization. Bicyclol, silymarin, and SGLT2 inhibitors were also shown to be effective interventions. Also, synbiotics intake and exercising steadily under consultation with a doctor are likely to help improve liver function.

Managing anthropometric parameters, which are important in obesity and diabetes treatment, is also important for NAFLD [42]. The use of GLP-1 RA and SGLT2 inhibitors has been demonstrated to effectively improve these figures. Meanwhile, TZD proved to have a negative effect on anthropometric parameters. Given that treatments using TZD are currently underway in NAFLD patients [43], further studies seem to be needed on the negative effects of TZD on the anthropometric parameter. On the other hand, prebiotics and omega-3 fatty acids were also shown to have a positive effect on BMI reduction. Although not shown in this review, continuous exercise has been reported to improve NAFLD as well as lead to weight loss [42].

In terms of improving the lipid profile, bicyclol, and berberine plus metformin combination treatment were shown to be effective. Both treatments showed large effect size and were statistically significant. Meanwhile, curcumin and synbiotics outperformed the control group in lipid profile improvement. Omega-3 fatty acid significantly decreased TC and TG, but increased LDL.

Resveratrol was shown to be effective in reducing HOMA-IR levels and improving insulin resistance, but not in lowering blood glucose and increasing insulin levels. When berberine and

metformin are used together, blood glucose and HbA1c could be reduced, but it is not known how they affect insulin levels. In addition, treatment with TZD had a positive effect on improving insulin levels, but showed insignificant results in improving HOMA-IR. Thus, improving glucose metabolism does not seem to require the use of a particular drug, but rather the appropriate use of the necessary medication in accordance with the patient's situation.

Looking at histological parameters, GLP-1 RA and SGLT 2 inhibitors were shown to be effective in reducing liver fat. In addition, vitamin E was shown to reduce liver fat, fibrosis, and inflammation. These results are consistent with the guidelines of the American Association for the Study of Liver Disease, which today recommends vitamin E as a short-term treatment for NAFLD. [4]

The findings of this study should be considered with some limitations. First, this review did not include the recent attention-grabbing pharmacological interventions, such as obeticholic acid and elafibranor. This is because meta-analyses have not yet been carried out due to insufficient clinical trials. Further accumulation of data would make it possible to proceed with meta-analyses on these drugs.[8] In addition, there were treatments that proved to help treat NAFLD through several studies, such as bariatric surgery [44,45,46], but have not been addressed in this study because there was no meta-analysis consisting of only RCT.Second, we only included meta-analyses of RCTs, but many of the results of meta-analyses reported statistically insignificant effect size and significant heterogeneity. Since each study had different populations, diagnostic criteria, and control groups, caution is needed when comparing effect sizes directly. Also, even with the same treatment, there are cases where they have progressed over different periods, the treatment period

for each study presented in Supplement 6 should be considered.

Third, we did not include information on side effects. Therefore, when making clinical decisions based on the results of this review, sufficient consideration should be given to the safety of the medication for the patient's situation. Fourth, only quantitatively evaluated figures were collected from the meta-analysis.

To date, various studies have been conducted to treat patients with NAFLD, but the evidence for pharmacological interventions and lifestyle modifications for NAFLD treatment is limited. Therefore, further well-designed RCTs of high quality with large sample size, including diverse treatment methods and control groups are warranted.

This umbrella-review provides the most comprehensive explanation for the effectiveness of pharmacological interventions and lifestyle modifications to treat NAFLD. The results of this review and the meta-analyses included in the review can be utilized in clinical practice and medical research, and contribute to medical development, combined with future research.

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Tables

Table 1. Application of the PICOS (Participants, Interventions, Comparisons, Outcomes, Study design) systematic search strategy

	Inclusion	*Exclusion*
Participants	Patients of any age, any country with a diagnosis of all spectra ranging from mild to severe NAFLD (including NASH). Diagnosed based on ultrasonography or magnetic resonance imaging or histologic examination. Include both patients with and without metabolic diseases (e.g., obesity, type 2 diabetes melitus)	Animal. NAFLD patients who were diagnosed based on serum liver enzyme levels Patients with liver transplant
Interventions	All pharmacological treatments and lifestyle modifications for NAFLD Berberine, bicyclol, DDP4 inhibitor (saxagliptin, sitagliptin, vildagliptin), GLP-1 RA (exenatide, dulaglutide, liraglutide, semaglutide), HXHY drugs, resveratrol, silymarin, SGLT2 inhibitor (canagliflozin dapagliflozin, empagliflozin, ipragliflozin, luseogliflozin), TZD (pioglitazone, rosiglitazone), and UDCA	
Comparisons	Any relevant control groups, such as inactive controls, active controls, mixed controls, usual care, and lifestyle modification.	
Outcomes	Any outcome which is indicated by SMD and MD values, including liver function indicator (e.g., ALT, AST, GGT), anthropometric parameter (e.g., BMI, weight), lipid profile (e.g., TC, TG), plasma glucose (e.g., blood glucose and insulin level, HOMA-IR), and liver histology.	
Study design	Only the meta-analysis of randomized-controlled-trials	Meta-analysis of studies other than RCT

TABLE AND FIGURE LEGENDS

Table1. Application of the PICOS (Participants, Interventions, Comparisons, Outcomes, Study design) systematic search strategy

Fig 1. PRISMA flow chart

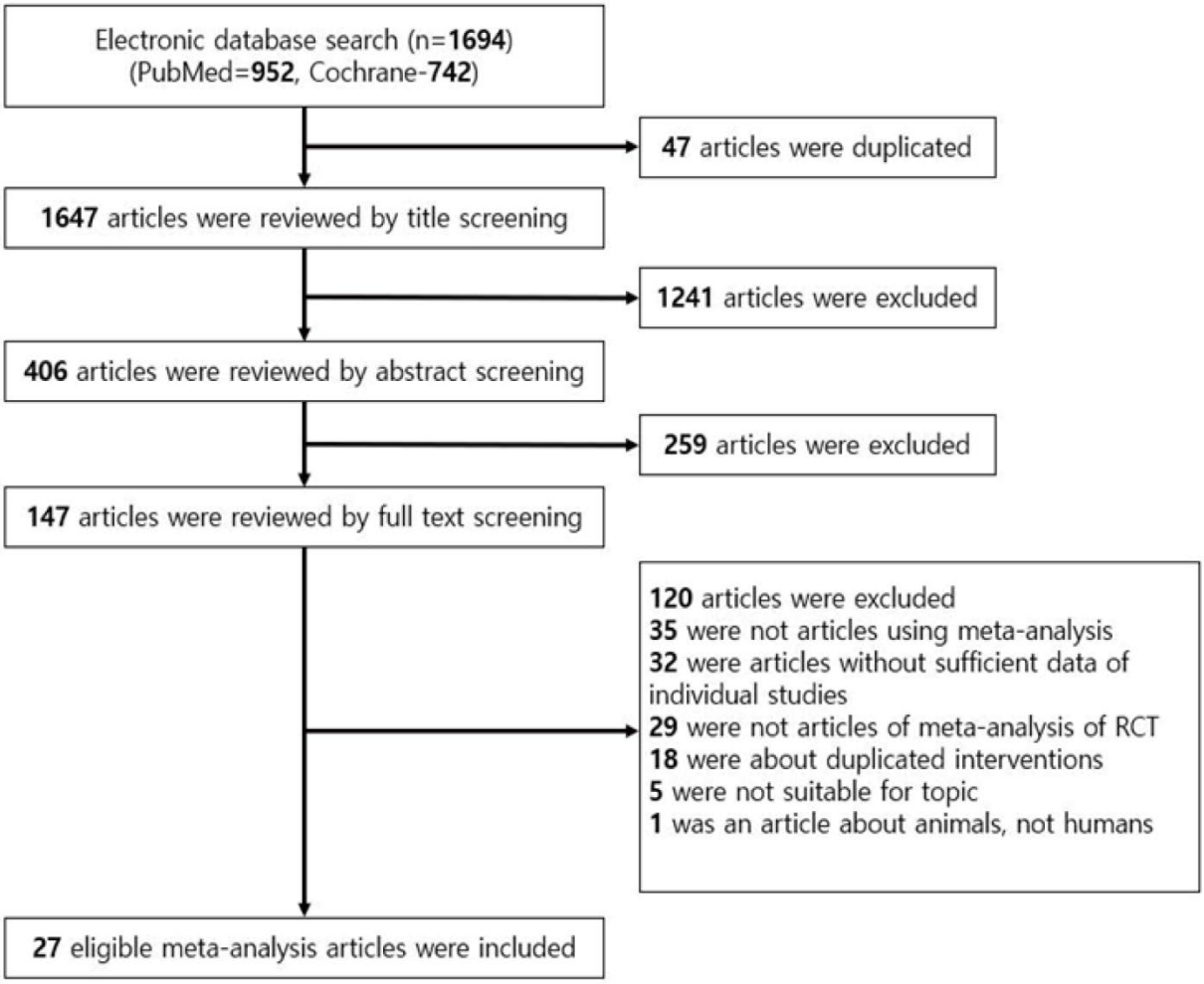
Fig. 2. Effects of pharmacological interventions for NAFLD treatment compared to active controls. Diamonds means significant difference from control. $p \leq 0.05$; Circles indicate non-significant effects.

Fig. 3. Effects of lifestyle modifications for NAFLD treatment compared to usual intervention and lifestyle modification. Diamonds means significant difference from control. $p \leq 0.05$; Circles indicate non-significant effects. (Total) means that the result is a combination of studies using one drug alone and studies using the drug and other drugs together.

Fig. 4. Effects of lifestyle modifications for NAFLD treatment compared to mixed controls. Diamonds means significant difference from control. $p \leq 0.05$; Circles indicate non-significant effects. (Total) means that the result is a combination of studies using one drug alone and studies using the drug and other drugs together.

Figures

Figure 1



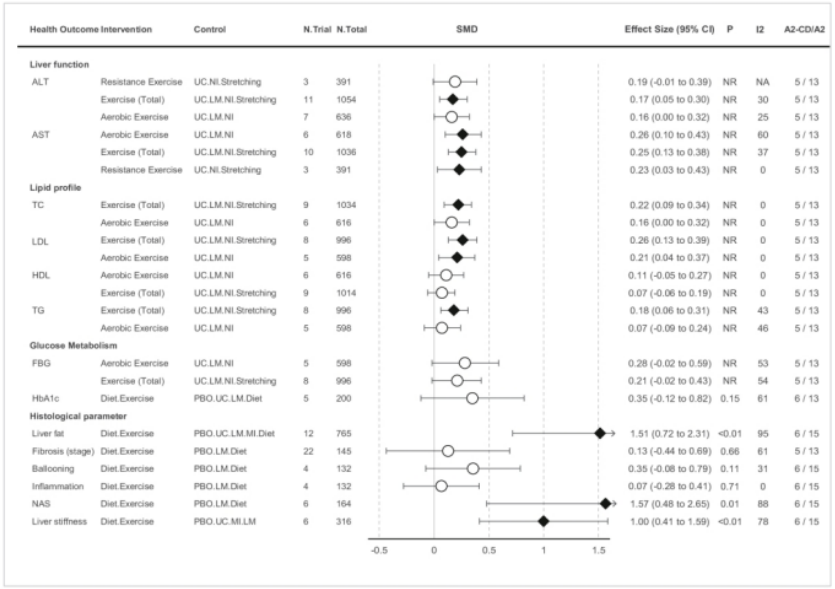


Fig. 4. Effects of lifestyle modifications for NAFLD treatment compared to mixed controls. Diamonds means significant difference from control. p≤0.05; Circles indicate non-significant effects. (Total) means that the result is a combination of studies using one drug alone and studies using the drug and other drugs together.

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