

Efficacy and safety of semaglutide in non-alcoholic fatty liver disease

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Abstract

BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease. The prevalence and disease burden of NAFLD are projected to exponentially increase resulting in significant healthcare expenditures and lower health-related quality of life. To date, there are no approved pharmacotherapies for NAFLD or non-alcoholic steatohepatitis (NASH). Semaglutide has glycemic and weight loss benefits that may be advantageous for patients with NAFLD.

AIM

To investigate the efficacy and safety of semaglutide in patients with NAFLD.

METHODS

MEDLINE, CENTRAL, and EMBASE were searched from inception to May 1, 2023, to identify eligible randomized controlled trials (RCTs). Meta-analysis was performed using random effects model expressing continuous outcomes as mean differences (MD) or standardized MDs (SMD), and dichotomous outcomes as odds ratios (OR) with 95% confidence intervals (CI). Statistical heterogeneity was assessed using the Cochran's Q test and I² statistic.

RESULTS

Three RCTs involving 458 patients were included. Semaglutide increased the likelihood of NASH resolution (OR: 3.18, 95% CI: 1.70, 5.95; *P* < 0.001), impro-

vement in steatosis (OR: 2.83, 95%CI: 1.19, 6.71; $P = 0.03$), lobular inflammation (OR: 1.81, 95%CI: 1.11, 2.96; $P = 0.02$), and hepatocellular ballooning (OR: 2.92, 95%CI: 1.83, 4.65; $P < 0.001$), but not fibrosis stage (OR: 0.71, 95%CI: 0.15, 3.41; $P = 0.67$). Radiologically, semaglutide reduced liver stiffness (SMD: -0.48, 95%CI: -0.86, -0.11; $P = 0.01$) and steatosis (MD: -4.96%, 95%CI: -9.92, 0.01; $P = 0.05$). It also reduced alanine aminotransferase (MD: -14.06 U/L, 95%CI: -22.06, -6.07; $P < 0.001$) and aspartate aminotransferase (MD: -11.44 U/L, 95%CI: -17.23, -5.65; $P < 0.001$). Semaglutide led to improved cardiometabolic outcomes, including decreased HgA1c (MD: -0.77%, 95%CI: -1.18, -0.37; $P < 0.001$) and weight loss (MD: -6.53 kg, 95%CI: -11.21, -1.85; $P = 0.006$), but increased the occurrence of GI-related side effects (OR: 3.72, 95%CI: 1.68, 8.23; $P = 0.001$). Overall risk of serious adverse events was similar compared to placebo (OR: 1.40, 95%CI: 0.75, 2.62; $P < 0.29$).

CONCLUSION

Semaglutide is effective in the treatment of NAFLD while maintaining a well-tolerated safety profile. Future studies are required to evaluate its effects on fibrosis regression and different phases of NAFLD.

Key Words: Non-alcoholic fatty liver disease; Fatty liver; Metabolic-associated fatty liver; Semaglutide

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Core Tip: Semaglutide demonstrates significant histologic improvements, with a higher likelihood of non-alcoholic steatohepatitis resolution and improved steatosis, lobular inflammation, and hepatocellular ballooning, but it does not significantly improve fibrosis stage compared to placebo. Furthermore, semaglutide results in radiologic improvements in liver stiffness and steatosis, liver enzymes, as well as cardiometabolic effects on body weight and HgA1c, while maintaining a well-tolerated safety profile.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease, with an estimated worldwide prevalence of 32.4% [1,2]. The prevalence and disease burden of NAFLD are projected to exponentially increase, with mathematical models forecasting a 168% increase in the incidence of decompensated cirrhosis and a 178% increase in NAFLD-related deaths between 2015 and 2030. These projections highlight the significant healthcare expenditures and lower health-related quality of life associated with the disease [3-5].

NAFLD is a spectrum of liver disease characterized by hepatic steatosis in the absence of excessive alcohol consumption [6]. The majority of patients with NAFLD have NAFL, of which approximately 20% will develop non-alcoholic steatohepatitis (NASH) and have a risk of further progression to cirrhosis, hepatocellular carcinoma, and end-stage liver disease [3]. Although lean NAFLD is increasingly recognized, the majority of patients with NAFLD have one or more components of metabolic syndrome, which is also independently strongly associated with fibrosis progression [7,8].

GLP-1 receptor agonists (RAs) offer promising therapeutic options in NAFLD due to their beneficial glycemic and weight loss effects. GLP-1 receptors have been detected on human hepatocytes, and it is hypothesized that their activation by GLP-1 RAs can have positive effects on hepatic steatosis, lipotoxicity, fatty acid oxidation, and cytokines involved in hepatic inflammation and fibrosis [9,10]. Moreover, GLP-1 RAs may have indirect hepatoprotective benefits through increased insulin secretion in response to hyperglycemia, decreased glucagon secretion, delayed gastric emptying, and significant weight loss [11,12].

Among the GLP-1 RAs, semaglutide has demonstrated the greatest glycemic and weight loss benefits [13]. In a recent phase three trial of patients with overweight or obesity, semaglutide showed a significant decrease in body weight by 14.9% compared to 2.4% with placebo [14]. Additionally, semaglutide has shown reduced rates of major adverse cardiovascular events and a lower risk of adverse renal outcomes in patients with type 2 diabetes (T2DM) [15]. It has since been approved for the treatment of T2DM and chronic weight management.

Several randomized clinical trials have also demonstrated the beneficial effects of semaglutide in patients with NAFLD. A previous systematic review with meta-analysis was conducted to assess the impact of semaglutide on biochemical and radiologic measures of NAFLD [16]. However, more than 85% of the study's patients had diabetes or obesity rather than confirmed NAFLD. Additionally, no histological outcomes were reported, which are considered the gold standard for diagnosing and managing NAFLD. Since its publication, a recent randomized controlled trial (RCT) by Loomba *et al* [17] has been performed, focusing on semaglutide in patients with NASH and compensated cirrhosis. The purpose of this systematic review and meta-analysis is to provide an updated review on the efficacy and safety of semaglutide, focusing on patients with NAFLD, in order to more specifically reflect the NAFLD population and expand the current

understanding of semaglutide in NAFLD.

MATERIALS AND METHODS

Search strategy and study selection

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines and was registered prospectively on the PROSPERO database (ID: CRD42023422487). Two independent reviewers (K.Z. and R.K.) evaluated the titles and abstracts of all identified studies based on predetermined inclusion and exclusion criteria (Supplementary Table 1). Any discrepancies were resolved through discussion with a third reviewer (T.H.).

Multiple databases, including MEDLINE, CENTRAL, EMBASE, and grey literature sources such as Clinicaltrials.gov and the World Health Organization International Clinical Trials Registries, were searched from inception to May 1, 2023 using a predefined search strategy (Supplementary Table 2). Additionally, a forward and backward citation search was performed on eligible studies using CitationChaser.

Data extraction and outcome measures

Two reviewers (K.Z. and R.K.) independently extracted the data using predetermined data collection forms. Any discrepancies were resolved through consultation with a third reviewer (T.H.).

The primary outcomes of interest for this study were histological improvement in NAFLD activity score, resolution of NASH with no worsening of liver fibrosis, and improvement in liver fibrosis without worsening of NASH, as defined by the NASH Clinical Research Network Criteria (CRN).

The secondary outcomes of interest included radiologic improvement in liver stiffness and steatosis, measured using either magnetic resonance elastography (MRE) or Fibroscan; changes in liver enzymes [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)]; cardiometabolic parameters such as body weight, HgA1c, total cholesterol, non-HDL cholesterol, and LDL cholesterol; as well as adverse events, including gastrointestinal-related side effects and serious adverse events.

Quality assessment

The risk of bias was independently conducted by two reviewers (K.Z. and R.K.) using the Cochrane risk-of-bias 2 tool for randomized trials. Due to the limited number of included studies, a funnel plot was not generated to assess publication bias. Finally, the quality of the evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.

Missing data

To address missing data, attempts were made to contact the study authors for the necessary information. In cases where the data could not be obtained, relevant values were extracted from figures, using the PlotDigitizer software, following Cochrane methodology. If the data was unavailable anywhere in the study, it was excluded from the analysis. Missing standard deviations (SD) for continuous outcomes were estimated using the available standard error, 95% confidence interval (CI), or *P* value. If these values were not available, SDs were imputed from other studies, as outlined by Furukawa *et al*[18].

Data synthesis and analysis

Continuous outcomes were presented as mean differences (MD) in change scores with corresponding 95%CI. The DerSimonian and Laird random-effects model was used given expected clinical and methodological diversity between the included studies. When outcomes were measured on different scales that could not be converted to a common scale, such as Fibroscan and MRE measurements, they were reported as standardized MDs (SMD) using Hedges' *G*. A correlation coefficient of $r = 0.4$, which is consistent with previous meta-analyses of liraglutide in NAFLD, was utilized [19].

Dichotomous outcomes were expressed as odds ratios (OR) with 95%CI. Statistical heterogeneity was assessed using Cochran's *Q* statistic and *I*² statistic, where $P < 0.10$ and $I^2 > 50\%$ were considered significant indicators of heterogeneity. The significance level for all other statistical tests was set at $P < 0.05$. RevMan version 5.4 (Copenhagen, Denmark) was used for all statistical analyses.

Sensitivity analysis was conducted using the leave-one-out method to evaluate the influence of each individual study on the overall estimate. Additional sensitivity analysis was performed comparing the outcomes using a fixed-effect model *vs* random-effect model. Subgroup analysis was performed by stratifying participants within the included studies based on their T2DM status. However, due to the limited number of included studies, additional sensitivity and subgroup analyses were not performed.

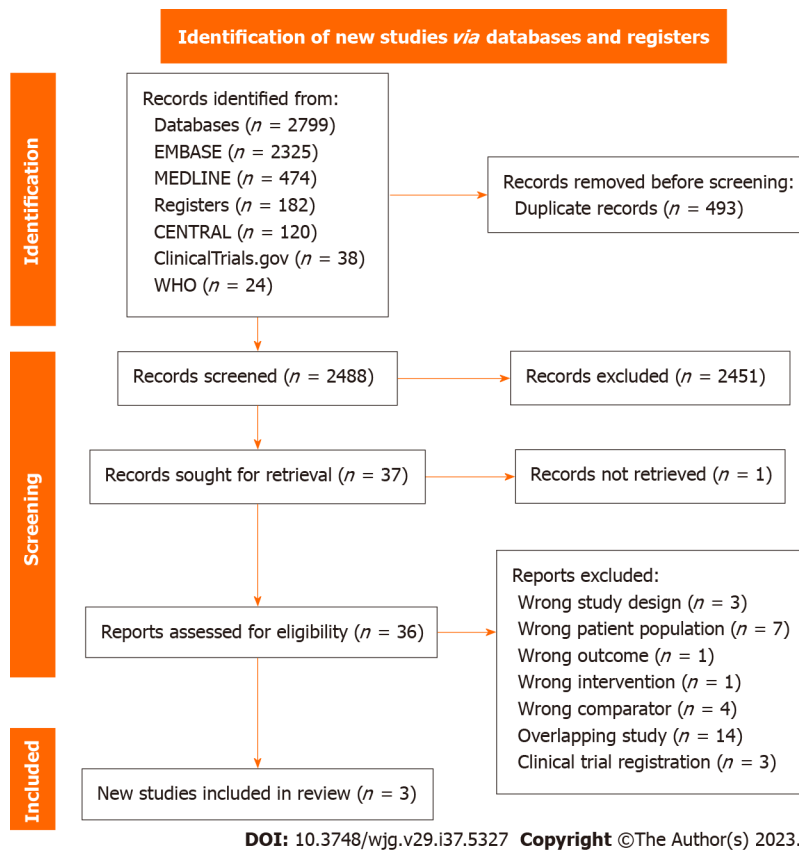


Figure 1 PRISMA flow diagram of study selection. WHO: World health organization.

RESULTS

Search results

A total of 2981 potentially eligible studies were identified, of which 493 duplicates were removed prior to screening. An additional 2451 studies were excluded based on titles and abstracts screening. Full text was obtained for 36 out of the 37 eligible studies. From these, we identified three studies that met our inclusion criteria and were included in the meta-analysis[17,20,21] (Figure 1).

Study characteristics

The study characteristics of the included summaries are outlined in Table 1. A total of 458 patients were included, with 321 receiving semaglutide and 137 receiving placebo. All studies were RCTs ranging from 48 wk to 72 wk in duration. Various doses of semaglutide were utilized. Newsome *et al*[20] compared daily doses of 0.1 mg, 0.2 mg, and 0.4 mg of semaglutide, whereas Flint *et al*[21] and Loomba *et al*[17] used daily doses of 0.4 mg and weekly doses of 2.4 mg, respectively. Furthermore, Flint *et al*[21] focused exclusively on patients with NAFL, while the other two studies only included patients with biopsy confirmed NASH. Both Newsome *et al*[20] and Loomba *et al*[17] conducted histological assessments. All studies included patients with and without T2DM.

Risk of bias assessment

The methodological qualities of the studies are summarized in the appendix, Supplementary Figure 1. The trial of Newsome *et al*[20] was classified as having a low risk of bias, while the other trials raised some concerns. Specifically, the study of Loomba *et al*[17] had concerns related to randomization, as a higher proportion of patients in the semaglutide group had an Ishak fibrosis score of 6, while more patients receiving placebo had a score of 4 or 5. Additionally, baseline measurements of MRE, hepatic collagen proportion, liver enzymes, and pro-C3 were slightly higher in the semaglutide group. Flint *et al*[21] raised concerns regarding missing data, as seven out of 34 patients in the semaglutide group discontinued treatment, and no sensitivity analysis was performed, or analysis conducted to address the resulting bias. The quality of the evidence was evaluated using the GRADE framework as illustrated in Table 2.

Outcome evaluation

Effect of semaglutide on histological parameters: Two studies, involving 391 patients, evaluated histological outcomes (Figure 2). Semaglutide was associated with a significantly higher likelihood of NASH resolution with no worsening of liver fibrosis (OR: 3.18, 95%CI: 1.70, 5.95; $P = 0\%$) (Figure 2A). However, there was no significant improvement in liver fibrosis stage without worsening of NASH (OR: 0.71, 95%CI: 0.15, 3.41; $P = 80\%$) (Figure 2B). Significant improvements

Table 1 Baseline characteristics of included studies

Ref.	Location sponsor	Study design	Sample size (n)	Demographics (%)	Intervention/comparator(s)	Outcomes assessed
Newsome <i>et al</i> [20], 2021	16 countries, 143 sites; Novo Nordisk	MC, DB, four-arm parallel-group RCT; duration: 72 wk; randomization: 3:3:3:1:1:1	320	Age (SD): 55.0 (10.6); male/female: 125(39)/195(61); T2DM: 199 (62)	Semaglutide: 0.1 mg SQ OD (n = 80); 0.2 mg SQ OD (n = 78); 0.4 mg SQ OD (n = 82); and placebo (n = 80)	Primary: Resolution of NASH; secondary: Liver fibrosis stage, total and component of NAS, ALT, AST, liver stiffness, liver steatosis, cardiometabolic parameters, adverse events
Flint <i>et al</i> [21], 2021	Germany, 2 sites; Novo Nordisk	Two-centre, DB, two-arm parallel-group RCT; duration: 72 wk; randomization: 1:1	67	Age (SD): 60.0 (9.3); male/female: 47(70)/20(30); T2DM: 49 (73)	Semaglutide: 0.4 mg SQ OD (n = 34); placebo (n = 33)	Primary: Liver stiffness MRE at week 48; secondary: Liver stiffness at week 24 and 72, liver steatosis, ALT, AST, cardiometabolic parameters, adverse events
Loomba <i>et al</i> [17], 2023	5 countries, 38 sites; Novo Nordisk	MC, DB, two-arm-parallel group RCT; duration: 48 wk; randomization: 2:1	71	Age (SD): 59.5 (8.0); male/female: 22(31)/49(61); T2DM: 53 (75)	Semaglutide: 2.4 mg SQ qw (n = 47); Placebo (n = 24)	Primary: Liver fibrosis stage; secondary: Liver stiffness, liver steatosis, NASH resolution, total and component of NAS, ALT, AST, cardiometabolic parameters, adverse events

MC: Multi-centre; DB: Double-blind; RCT: Randomized controlled trial; SD: Standard deviation; T2DM: Type 2 diabetes mellitus; SQ: Subcutaneous; OD: Once daily; qw: Weekly; NASH: Non-alcoholic steatohepatitis; NAS: NAFLD activity score; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; MRE: Magnetic resonance elastography.

were observed in all NAFLD Activity Score (NAS) components with OR 2.83 (95% CI: 1.19, 6.71; $I^2 = 57\%$) for steatosis, 1.81 (95% CI: 1.11, 2.96; $I^2 = 0\%$) for lobular inflammation, and 2.92 (95% CI: 1.83, 4.65; $I^2 = 0\%$) for hepatocellular ballooning (Figure 2C-E). Significant heterogeneity was noted for improvement in liver fibrosis stage.

Effect of semaglutide on radiologic parameters: All three studies reported radiologic parameters and semaglutide demonstrated a significant reduction in liver stiffness on MRE or Fibroscan, with a standardized MD of -0.48 (95% CI: -0.86, -0.11; $I^2 = 57\%$) (Figure 3A). Additionally, a significant reduction in liver steatosis on MRI proton density fat fraction (MRI-PDFF) was observed, with a MD of -4.96% (95% CI: -9.92, 0.01; $I^2 = 64\%$), although significant heterogeneity was noted (Figure 3B).

Effect of semaglutide on liver enzymes: All three studies evaluated ALT and AST, which showed a significant reduction of 14.06 U/L (95% CI: -22.06, -6.07; $I^2 = 0\%$) and 11.44 U/L (95% CI: -17.23, -5.65; $I^2 = 0\%$), respectively, compared to placebo. No significant heterogeneity was observed (Figure 4).

Effect of semaglutide on cardiometabolic parameters: All three studies evaluated total body weight, which revealed a significant reduction of 6.53 kg (95% CI: -11.21, -1.85; $I^2 = 0\%$) compared to placebo, with no significant heterogeneity observed (Figure 5A).

Overall, semaglutide also significantly decreased HgA1c by 0.77% (95% CI: -1.18, -0.37; $I^2 = 75\%$) compared to placebo (Figure 5B). Subgroup analysis of participants within the studies, stratified by T2DM status, showed a significant reduction in HgA1c among patients with T2DM (MD: -1.10%, 95% CI: -1.48, -0.72; $I^2 = 29\%$), but not among those without (MD: -0.37%, 95% CI: -0.79, 0.06; $I^2 = 61\%$). Heterogeneity was no longer significant with the subgroup analysis.

Regarding lipid panel results, semaglutide was not associated with a significant difference in triglycerides (MD: -24.03 mg/dL, 95% CI: -60.94, 12.88; $I^2 = 42\%$), total cholesterol (MD: -7.31 mg/dL, 95% CI: -51.66, 37.03; $I^2 = 87\%$), non-HDL cholesterol (MD: -7.52 mg/dL, 95% CI: -49.32, 34.27; $I^2 = 84\%$), and LDL cholesterol (MD: -4.72 mg/dL, 95% CI: -56.23, 46.79; $I^2 = 92\%$), although significant heterogeneity was observed (Supplementary Figure 2).

Adverse events with semaglutide: Semaglutide was associated with a significantly higher occurrence of gastrointestinal-related side effects compared to placebo (OR: 3.72, 95% CI: 1.68, 8.23; $I^2 = 49\%$) (Figure 6A). However, the overall risk of serious adverse events was comparable between the two groups (OR: 1.40, 95% CI: 0.75, 2.62; $I^2 = 0\%$) (Figure 6B).

Sensitivity and subgroup analysis

Each article was individually excluded to examine the influence of each study on the overall effect-size estimate (Supplementary Table 3). Most of the outcomes remained unchanged; however, when Newsome *et al*[20] was removed, the effect size for resolution of NASH, steatosis, lobular inflammation, and hepatocellular ballooning became non-significant. The effect estimates for liver stiffness when restricted to MRE and excluding Fibroscan as used in the study by Newsome *et al*[20], also became non-significant. However, there was no longer any heterogeneity observed.

Regarding cardiometabolic outcomes, the significant effect of semaglutide on body weight was no longer sustained when the trial by Flint *et al*[21] was excluded. Furthermore, when Newsome *et al*[20] was removed, there was a significant

Table 2 Grading of recommendations assessment, development, and evaluation summary of findings table

Outcomes	Anticipated absolute effects ¹ (95%CI)		Relative effect (95%CI)	Number of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with semaglutide			
Resolution of NASH with no worsening of liver fibrosis assessed with: Liver biopsy	183 per 1000	416 per 1000 (276 to 571)	OR 3.18 (1.70 to 5.95)	301 (2 RCTs)	+++O: Moderate ²
Improvement in liver fibrosis stage without worsening of NASH assessed with: Liver biopsy	317 per 1000	248 per 1000 (65 to 613)	OR 0.71 (0.15 to 3.41)	301 (2 RCTs)	++OO: Low ^{2,3,4}
Liver stiffness assessed with: MRI-PDFF or Fibroscan	-	SMD 0.48 lower (0.86 lower to 0.11 lower)	-	350 (3 RCTs)	++++: High
Liver steatosis assessed with: MRE	The mean liver steatosis ranged from -0.57% to -2.57%	MD 4.96 % lower (9.92 lower to 0.01 higher)	-	138 (2 RCTs)	+++O: Moderate ³
ALT	The mean ALT ranged from 1.90 U/L to -11.22 U/L	MD 14.06 U/L lower (22.06 lower to 6.07 lower)	-	458 (3 RCTs)	++++: High
AST	The mean AST ranged from 1.50 U/K to -5.76 U/K	MD 11.44 U/K lower (17.23 lower to 5.65 lower)	-	458 (3 RCTs)	++++: High
Serious adverse events	109 per 1000	147 per 1000 (84 to 244)	OR 1.40 (0.75 to 2.62)	456 (3 RCTs)	+++O: Moderate ^{2,4}

¹The risk in the intervention group [and its 95% confidence interval (95%CI)] is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI).

²Few events.

³Possibly substantial heterogeneity.

⁴Wide confidence interval including no effect and does not exclude appreciable benefit or harm.

GRADE Working Group grades of evidence. High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. CI: Confidence interval; MD: Mean difference; OR: Odds ratio; SMD: Standardised mean difference; MRI-PDFF: MRI proton density fat fraction; MRE: Magnetic resonance elastography.

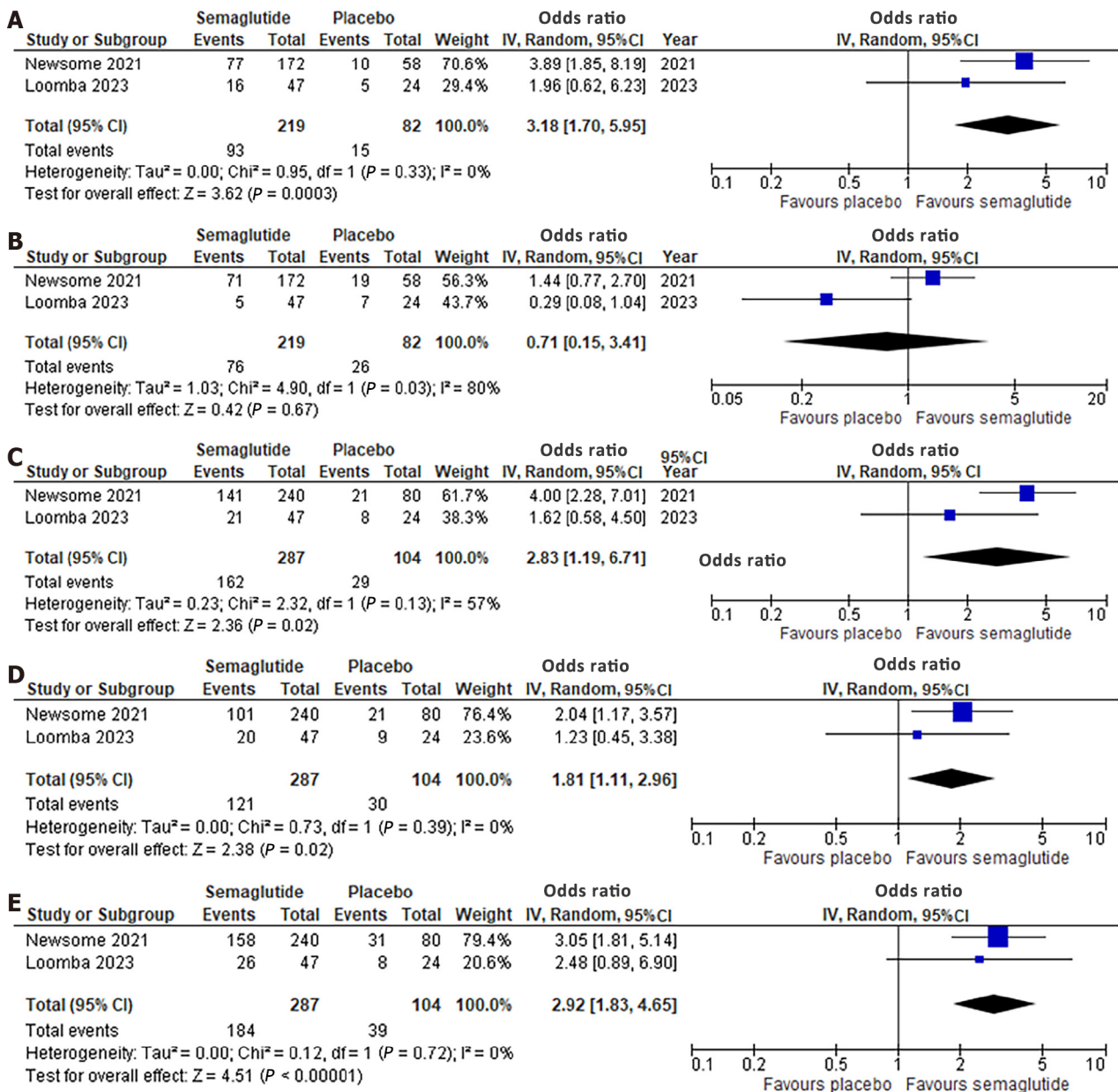
decrease in triglycerides, total cholesterol, and non-HDL cholesterol. Additionally, the exclusion of Newsome *et al*[20] led to a significant reduction in LDL-cholesterol, whereas the exclusion of Loomba *et al*[17] resulted in significant increases. No significant differences were observed in the sensitivity analysis when comparing the fixed-effect model to the random-effect model (Supplementary Table 4).

DISCUSSION

In this systematic review and meta-analysis, semaglutide demonstrated significant histologic improvements, with a higher likelihood of NASH resolution and improved NAS components, but it did not significantly improve fibrosis stage compared to placebo. Furthermore, semaglutide resulted in radiologic improvements in liver stiffness and steatosis, liver enzymes, as well as cardiometabolic effects on body weight and HgA1c, while maintaining a well-tolerated safety profile.

In the systematic review with meta-analysis on the impact of semaglutide on biochemical and radiologic measures of NAFLD conducted by Dutta *et al*[16], the majority of included patients did not have confirmed NAFLD. Out of the four RCTs included, only two involved patients with NAFLD. The other two trials focused on the cardiovascular outcomes of semaglutide in patients with type 2 diabetes and the efficacy of semaglutide in weight loss for patients with obesity. Since these two trials did not separately report outcomes for the NAFLD subgroup, they were not included in our systematic review and meta-analysis. Furthermore, the meta-analysis did not include any histological outcomes, which are considered the gold standard for NAFLD diagnosis and management. In contrast, our paper exclusively focuses on the NAFLD population, reports histological outcomes, and provides an updated review that includes the recent RCT conducted by Loomba *et al*[17].

Previous studies have demonstrated an association between histological resolution of NASH and decrease in NAS components with improvement in fibrosis stage[22,23]. However, despite improvements in other histologic outcomes, our meta-analysis did not observe an improvement in liver fibrosis. Of note, Loomba *et al*[17] had an imbalance in baseline characteristics, with a higher proportion of patients in the semaglutide group exhibiting higher grade fibrosis and non-invasive markers of inflammation compared to the placebo group. This imbalance may have reduced the treatment effect



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Figure 2 Effect of semaglutide on histologic parameters. A: Resolution of non-alcoholic steatohepatitis (NASH) with no worsening of liver fibrosis; B: Improvement in liver fibrosis stage without worsening of NASH; C: Improvement in steatosis; D: Improvement in lobular inflammation; E: Improvement in hepatocellular ballooning. 95%CI: 95% confidence intervals.

estimate and resulted in the observed heterogeneity. Furthermore, the proportion of patients with improved fibrosis in the placebo group in the trial of Newsome *et al*[20] (33%) was higher than that reported in the LEAN trial (14%) or the pooled placebo outcomes of 23 RCTs involving patients with NAFLD (21%), possibly contributing to the non-significant treatment effect estimate[24,25]. Despite no difference in the improvement of fibrosis, Newsome’s trial observed that a smaller proportion of patients in the semaglutide group (5%) experienced worsening of fibrosis compared to the placebo group (19%), suggesting a potential benefit[20]. It is possible that a longer follow-up time may be required to achieve improvements in fibrosis, particularly since most of the patients had advanced fibrosis, and the timeline for improvement in fibrosis remains unclear.

Although liver biopsy remains the gold standard for diagnosing and staging NAFLD, MRE and MRI-PDFF are effective non-invasive assessments of liver stiffness and steatosis, respectively. MRI-PDFF is significantly associated with histological NASH CRN steatosis grade, independent of age, sex, and other NASH parameters[26]. This correlation has been demonstrated in several other studies[27,28]. Both MRE and MRI-PDFF are considered more accurate than ultrasound-based transient elastography in detecting fibrosis and steatosis, respectively, and remain effective in patients with obesity, which is a common comorbidity in patients with NAFLD[29].

However, the accuracy of MRI-PDFF is limited by the extent of hepatic fibrosis. Permutt *et al*[30] demonstrated that the association between MRI and histology-determined steatosis remained relatively stable at fibrosis stages 0-3 but significantly dropped at stage 4. Similarly, Idilman *et al*[27] showed that the correlation between liver biopsy and MRI-

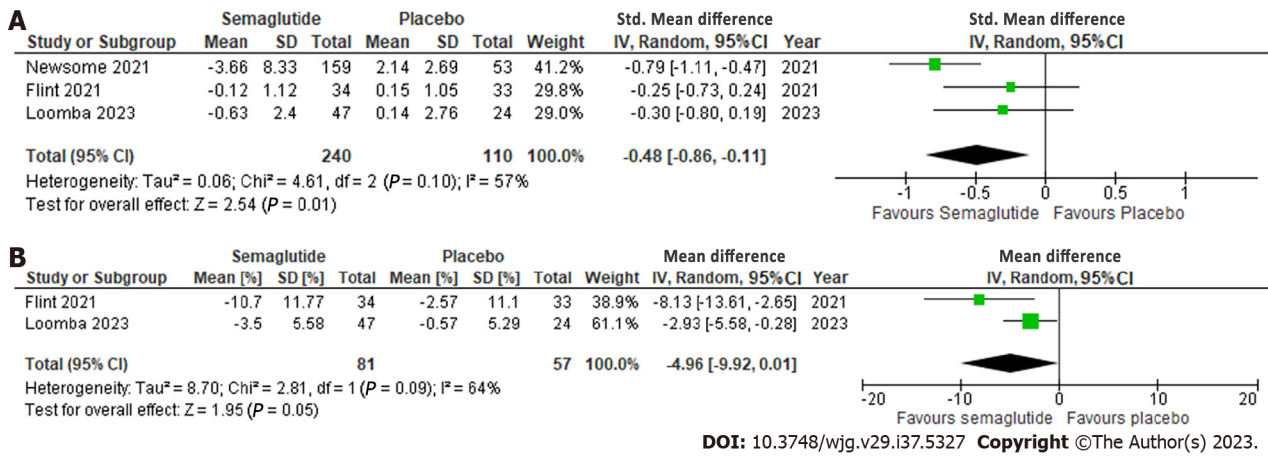


Figure 3 Effect of semaglutide on radiologic parameters. A: Liver stiffness assessed by magnetic resonance enterography or Fibroscan; B: Liver steatosis assessed by MRI proton density fat fraction. 95%CI: 95% confidence intervals.

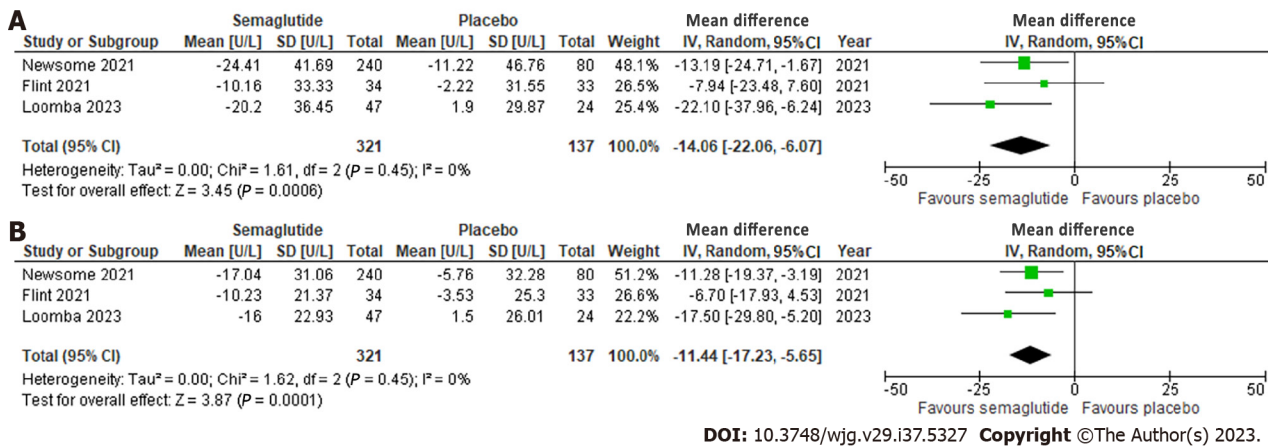


Figure 4 Effect of semaglutide on liver enzymes. A: Alanine aminotransferase; B: Aspartate aminotransferase. 95%CI: 95% confidence intervals.

determined steatosis was less pronounced when fibrosis was present ($r = 0.60$) than when fibrosis was absent ($r = 0.86$). In contrast, liver stiffness measured using MRE is less influenced by fibrosis and provides a more accurate prediction of liver fibrosis in patients with more advanced fibrosis[31]. The decreased reproducibility and accuracy of MRI PDFF in higher fibrosis stages may explain the substantial heterogeneity observed in liver steatosis in our study, especially considering that the population of the included studies had advanced fibrosis. Heterogeneity in liver stiffness, although not statistically significant, became negligible when Fibroscan was removed and only MRE was utilized to measure liver stiffness.

Semaglutide showed a significant association with moderate decreases in ALT and AST, which have previously been correlated with histologic response, fibrosis regression, and reduced progression in NAFLD[22,32]. However, both the LEAN trial and a meta-analysis of liraglutide in NAFLD did not observe significant reductions in liver enzymes[24,33]. Despite being in the same drug class with similar mechanisms of action, there may be intrinsic differences between effect of semaglutide and liraglutide. Furthermore, our study demonstrated a significant improvement in HgA1c and a reduction of 6.53 kg in body weight in the semaglutide compared to placebo group. The superior metabolic outcomes associated with semaglutide, compared to liraglutide, may lead to a more effective reduction in hepatocellular stress and injury, resulting in a significant decrease in liver enzymes. Vilar-Gomez *et al*[34] previously demonstrated that patients with weight losses $\geq 10\%$ had the highest rates of NAS reduction, NASH resolution and fibrosis regression. Therefore, semaglutide appears to be particularly beneficial for patients with both NAFLD and features of metabolic syndrome.

The safety profile of semaglutide was comparable to that reported in the recent phase 3 trial with once-weekly dosing in patients with obesity and trials from the SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) programs[14,35]. Gastrointestinal-related side effects, including nausea, constipation, vomiting, and abdominal pain, were significantly more prevalent in patients receiving semaglutide compared to placebo. These side effects are well-documented among the GLP-1 RA class. In all RCTs included in our review, adverse events mostly occurred during treatment initiation or the dose-escalation period. These symptoms become less pronounced with gradual up-titration and are often self-limiting, subsiding after a few weeks. Furthermore, the risks of serious adverse events were not different between semaglutide and placebo.

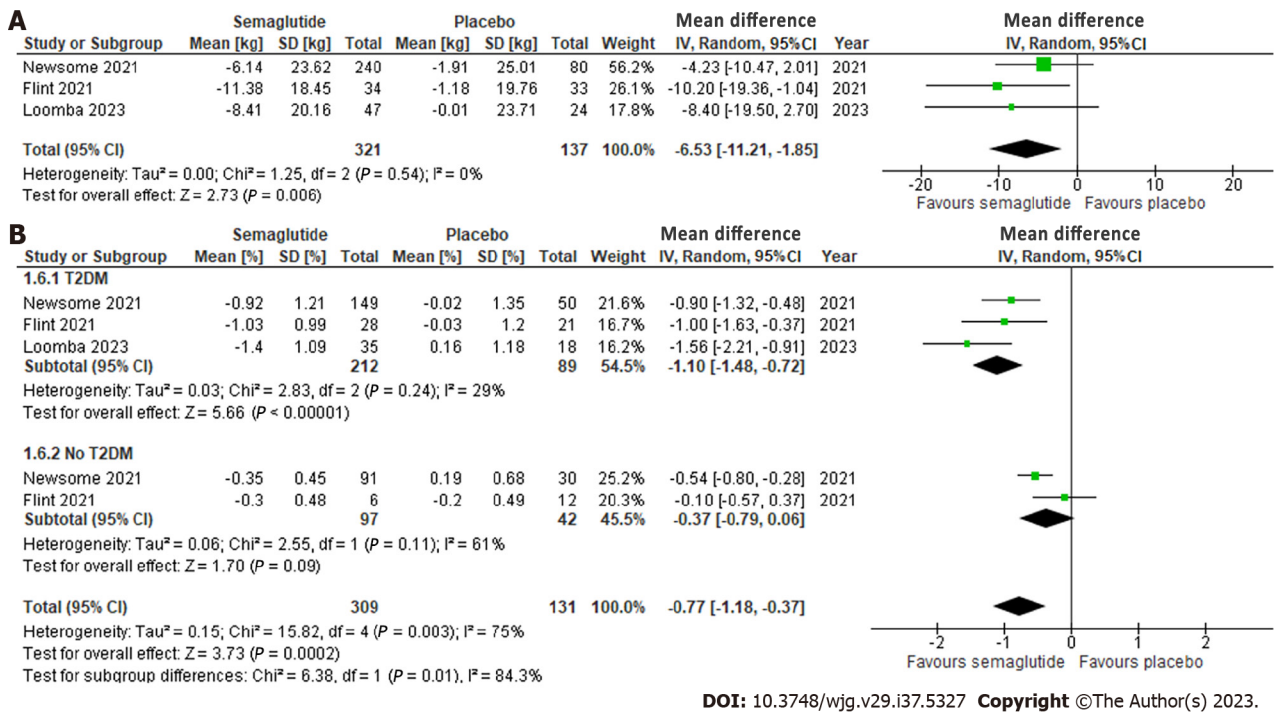


Figure 5 Effect of semaglutide on cardiometabolic parameters. A: Body weight; B: HgA1c in patients with type 2 diabetes (T2DM) vs without T2DM. 95%CI: 95% confidence intervals.

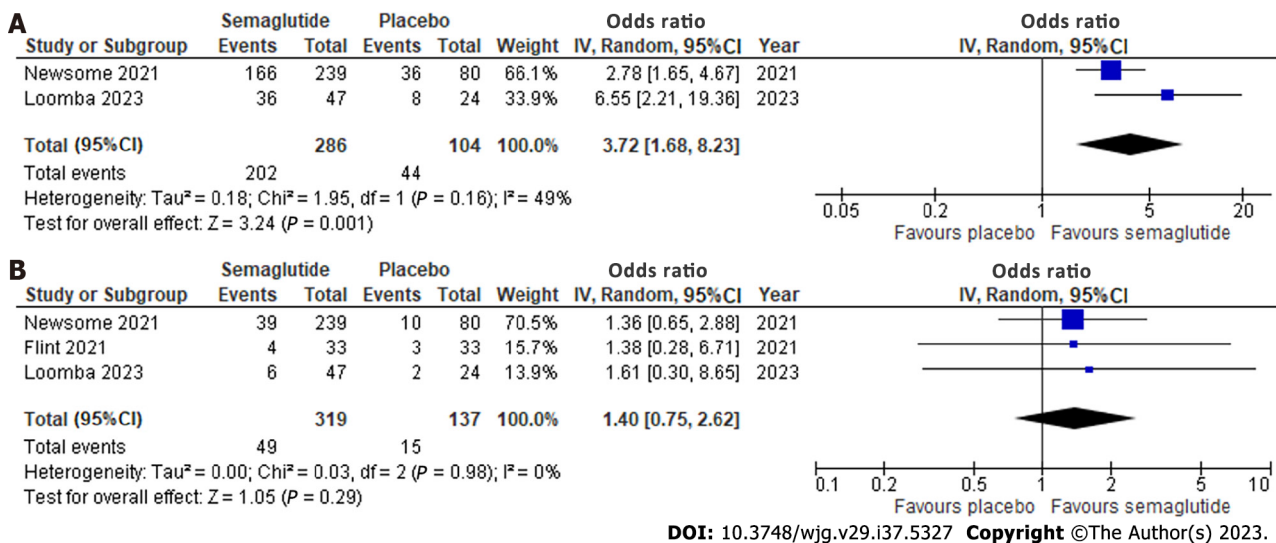


Figure 6 Adverse events with semaglutide. A: Gastrointestinal related side effects; B: Serious adverse events. 95%CI: 95% confidence intervals.

Our study has several limitations. The included RCTs are clinically heterogeneous from each other, with patients across the spectrum of NAFLD. Flint *et al*[21] recruited patients with NAFL, whereas Newsome and Loomba’s trials involved patients with NASH and NASH-related cirrhosis, respectively. The heterogeneous patient population limits the applicability of the results, as treatment and response across the spectrum of NAFLD may differ. Additionally, a range of doses of semaglutide was used across the trials, including 0.1 mg, 0.2 mg, 0.4 mg once daily, and 2.4 mg weekly. However, this is less of a concern as once-weekly dosing has been shown to be comparably effective in the obesity population, and unpublished data suggests similar plasma concentrations to daily dosing[14,17]. Furthermore, histologic outcomes were only reported for patients with NASH or NASH-related cirrhosis, but not for patients with NAFL. Therefore, the effect of semaglutide on histologic outcomes in the NAFL population remains unclear. Lastly, the limited number of eligible studies restricted our ability to perform subgroup analysis comparing outcomes in NAFL, NASH, and NASH-related cirrhosis populations, or meta-regression to investigate heterogeneity and the effect of covariates on the effect sizes.

CONCLUSION

In conclusion, our meta-analysis of RCTs demonstrates that semaglutide has beneficial histologic, radiologic, liver enzyme, and cardiometabolic effects in patients with NAFLD, with a well-tolerated safety profile. Semaglutide is particularly beneficial for patients with NAFLD and features of metabolic syndrome, given its notable effects on lowering HbA1c and promoting weight loss. However, the results are limited by the small number of included studies and clinical heterogeneity, which restricts the generalizability these findings across the spectrum of NAFLD. Additional RCTs with larger sample sizes and longer durations are required to characterize the effects of semaglutide on fibrosis regression and its role in the different phases of NAFLD.

ARTICLE HIGHLIGHTS

Research background

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease. The prevalence and disease burden of NAFLD are projected to exponentially increase resulting in significant healthcare expenditures and lower health-related quality of life. To date, there are no approved pharmacotherapies for NAFLD or non-alcoholic steatohepatitis (NASH).

Research motivation

Several randomized clinical trials have demonstrated the beneficial effects of semaglutide in patients with NAFLD. Prior systematic review with meta-analysis assessing the impact of semaglutide did not report histological outcomes and were not focused on a NAFLD specific population.

Research objectives

This study aimed to review the efficacy and safety of semaglutide, focusing on patients with NAFLD, in order to more specifically reflect the NAFLD population and expand the current understanding of semaglutide in NAFLD.

Research methods

MEDLINE, CENTRAL, EMBASE, and grey literature sources were searched from inception to May 1, 2023, to identify eligible randomized controlled trials (RCTs) using a predefined search strategy. Predetermined outcomes were extracted, and quality assessment was performed using the Cochrane risk-of-bias 2 tool and GRADE framework. Meta-analysis was performed using random effects model expressing continuous outcomes as mean differences (MD) or standardized MDs (SMD), and dichotomous outcomes as odds ratios (OR) with 95% confidence intervals (CI). Statistical heterogeneity was assessed using the Cochran's Q test and I^2 statistic.

Research results

A total of three RCTs involving 458 patients were included. Semaglutide increased the likelihood of NASH resolution (OR: 3.18, 95%CI: 1.70, 5.95; $P < 0.001$), improvement in steatosis (OR: 2.83, 95%CI: 1.19, 6.71; $P = 0.03$), lobular inflammation (OR: 1.81, 95%CI: 1.11, 2.96; $P = 0.02$), and hepatocellular ballooning (OR: 2.92, 95%CI: 1.83, 4.65; $P < 0.001$), but not fibrosis stage (OR: 0.71, 95%CI: 0.15, 3.41; $P = 0.67$). Radiologically, semaglutide reduced liver stiffness (SMD: -0.48, 95%CI: -0.86, -0.11; $P = 0.01$) and steatosis (MD: -4.96%, 95%CI: -9.92, 0.01; $P = 0.05$). It also reduced ALT (MD: -14.06 U/L, 95%CI: -22.06, -6.07; $P < 0.001$) and AST (MD: -11.44 U/L, 95%CI: -17.23, -5.65; $P < 0.001$).

Semaglutide led to improved cardiometabolic outcomes, including decreased HgA1c (MD: -0.77%, 95%CI: -1.18, -0.37; $P < 0.001$) and weight loss (MD: -6.53 kg, 95%CI: -11.21, -1.85; $P = 0.006$), but increased the occurrence of GI-related side effects (OR: 3.72, 95%CI: 1.68, 8.23; $P = 0.001$). Overall risk of serious adverse events was similar compared to placebo (OR: 1.40, 95%CI: 0.75, 2.62; $P < 0.29$).

Research conclusions

Semaglutide demonstrated significant histologic improvements, with a higher likelihood of NASH resolution and improved NAS components, but it did not significantly improve fibrosis stage compared to placebo. Furthermore, semaglutide resulted in radiologic improvements in liver stiffness and steatosis, liver enzymes, as well as cardiometabolic effects on body weight and HgA1c, while maintaining a well-tolerated safety profile.

Research perspectives

Additional RCTs with larger sample sizes and longer durations are required to characterize the effects of semaglutide on fibrosis regression and its role in the different phases of NAFLD.

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FOOTNOTES

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