E-ISSN 2250-0944

ISSN 2250-1150

doi: 10.48047/ijprt/15.02.219

GLP-1 Receptor Agonists for Hepatic Steatosis and Fibrosis in Type 2 Diabetes with NAFLD.

Mishal Rizwan[1], Alveena Fareed[2], Sarah Khan[3], Ali Hassan[4], FNU Nikeeta[5], Haleema Hammad[6]

Affiliations:

[1] Student (4th Year MBBS), Central Park Medical College, Lahore.

[2] Senior Registrar, Department of Gastroenterology, Sharif Medical City, Lahore.

[3] Senior Registrar, Department of Gastroenterology, University of Lahore Teaching Hospital.

[4] Assistant Professor, Department of Medicine, University College of Medicine and Dentistry (UCMD), Lahore.

[5] Medical Officer, Ghulam Muhammad Mahar Medical College, Sukkur / Shaheed Mohtarma Benazir Bhutto Medical University.

[6] Senior Registrar, Department of Medicine.

Corresponding author: mishalrizwan987@gmail.com

Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) may attenuate hepatic steatosis and modify fibrosis risk in type 2 diabetes mellitus (T2D) with nonalcoholic fatty liver disease. This prospective, parallel-group study evaluated once-weekly semaglutide added to standard diabetes care versus standard care alone over 48 weeks in adults with T2D and NAFLD confirmed by MRI-proton density fat fraction and vibration-controlled transient elastography. The primary endpoint was absolute change in liver fat (MRI-PDFF). Secondary endpoints included proportions achieving ≥30% relative PDFF reduction, ALT/AST changes, noninvasive fibrosis metrics (liver stiffness, FIB-4), and safety. Among 186 randomized participants (semaglutide n=93; control n=93), semaglutide produced greater absolute PDFF reduction (−8.7±6.1% vs −3.2±5.7%; $p<0.001$) and higher odds of achieving ≥30% relative PDFF reduction (58.1% vs 27.1%; adjusted OR 3.74, 95% CI 2.02–6.93; $p<0.001$). ALT fell more with semaglutide (−23.4±28.7 U/L vs −9.6±24.1 U/L; $p<0.001$), accompanied by modest but significant reductions in liver stiffness (−1.2±2.8 kPa vs −0.3±2.6 kPa; $p=0.01$) and improved FIB-4 (−0.19±0.42 vs −0.06±0.39; $p=0.01$). Safety was consistent with known class effects. These results demonstrate clinically meaningful improvements in hepatic steatosis and favorable shifts in noninvasive fibrosis markers over 48 weeks, supporting GLP-1RA use as a metabolic-liver strategy in T2D with NAFLD and aligning with emerging phase 3 histologic data for semaglutide in steatohepatitis.

Keywords: GLP-1 receptor agonist; MRI-PDFF; liver stiffness

Introduction

Metabolic dysfunction–associated steatotic liver disease represents the hepatic expression of metabolic syndrome and frequently coexists with T2D, conferring an elevated risk of progressive fibrosis, cirrhosis, and hepatocellular carcinoma. Within diabetes care, NAFLD prevalence exceeds 60%, and fibrosis progression is accelerated, rendering the liver a critical cardiovascular and renal risk amplifier. Recent nomenclature and guidance updates emphasize systematic risk stratification of patients with T2D using noninvasive tests to identify advanced fibrosis and guide referral, while prioritizing therapies that deliver weight loss, insulin sensitization, and cardiometabolic benefit. These developments have catalyzed investigation of incretin-based therapies that couple robust metabolic effects with potential hepatic benefits. 1-4

GLP-1RAs reduce body weight, improve glycemic control, and confer cardiovascular protection in T2D, positioning the class as a cornerstone for comprehensive risk modification. Mechanistically, GLP-1 signaling reduces caloric intake and body weight, improves peripheral insulin sensitivity, and may modulate hepatic de novo lipogenesis and adipose-liver crosstalk. The hepatic phenotype in NAFLD is tightly linked to positive energy balance and adiposopathy; accordingly, therapies producing sustained weight loss of 7–10% frequently achieve meaningful reductions in liver fat and biochemical inflammation. GLP-1RAs reliably deliver this magnitude of weight loss, providing a plausible biological basis for improvements in hepatic steatosis and downstream fibrosis risk.5-8

Randomized trials have substantiated these expectations. In biopsy-proven steatohepatitis, subcutaneous semaglutide achieved significantly higher rates of NASH resolution without worsening of fibrosis over 72 weeks compared with placebo, although fibrosis improvement did not meet statistical significance in that trial, likely reflecting the time course of collagen remodeling and the need for longer exposure or combination strategies.9-10 Importantly, more recent phase 3 data in metabolic dysfunction-associated steatohepatitis with moderate or advanced fibrosis indicate that once-weekly semaglutide 2.4 mg can improve histologic outcomes—

including higher proportions with fibrosis improvement—alongside large weight-loss effects, marking a step change in the evidence base and informing regulatory decisions in 2025.

Beyond histology, imaging and biochemical endpoints provide sensitive measures of therapeutic response. MRI-PDFF captures quantitative liver fat changes and correlates with biopsy-assessed steatosis, while transient elastography and composite scores such as FIB-4 track fibrosis risk. Meta-analytic syntheses and contemporary trials demonstrate that GLP-1RAs lower MRI-PDFF and aminotransferases and can favorably shift noninvasive fibrosis markers over 24–72 weeks, with effect sizes proportional to weight loss yet not fully explained by it, suggesting direct hepatic actions. These convergent data support GLP-1RAs as dual-purpose agents addressing systemic and hepatic pathobiology in T2D.

Clinical practice is rapidly evolving in response to these findings. Professional recommendations now prioritize assessment of steatotic liver disease in T2D and consider GLP-1RAs among therapies that may ameliorate liver fat and biochemical inflammation, while longer-term fibrosis modification is under active evaluation. The current study was designed to mirror real-world use by adding once-weekly semaglutide to standard diabetes therapy in adults with T2D and NAFLD confirmed by imaging, testing whether improvements observed in trials translate to clinically meaningful gains in liver fat, aminotransferases, and noninvasive fibrosis measures over 48 weeks.

Methodology

A prospective, randomized, open-label, assessor-blinded, controlled study was conducted at Central Park Medical College Lahore in adults aged 18–75 years with T2D (HbA1c 6.5–10.0%), BMI 27–45 kg/m², and NAFLD defined by MRI-PDFF ≥8% and elevated or historical ALT ≥30 U/L (males) or ≥19 U/L (females) or CAP ≥280 dB/m on transient elastography within 12 weeks. Exclusions comprised significant alcohol intake (>20 g/day females, >30 g/day males), other chronic liver diseases, decompensated cirrhosis, prior bariatric surgery, thyroid or Cushing disorders, GLP-1RA use within 6 months, and use of investigational agents for NASH. After verbal informed consent, participants were randomized 1:1 to semaglutide (titrated to 1.0 mg weekly target as tolerated) plus standard diabetes care versus standard care alone, each with structured lifestyle counseling. Epi Info (CDC) was used to calculate sample size assuming a

between-group difference in absolute MRI-PDFF change of 4.5% (SD 8.0), α=0.05, power 0.90, two-sided, requiring 168 participants; anticipating 10% attrition, 186 were planned. The primary endpoint was absolute change in MRI-PDFF from baseline to week 48. Secondary endpoints included proportion with ≥30% relative reduction in PDFF, change in ALT and AST, change in liver stiffness (kPa) by vibration-controlled transient elastography, change in FIB-4, body weight, HbA1c, and safety. Imaging personnel and laboratory adjudicators were blinded to allocation. Analyses used intention-to-treat with multiple imputation for missing week-48 outcomes. Continuous outcomes were compared with ANCOVA adjusted for baseline value, age, sex, and baseline BMI; categorical outcomes used logistic regression with the same covariates. Prespecified subgroup analyses examined baseline liver stiffness (<8 vs ≥8 kPa) and baseline HbA1c (<8 vs ≥8%). Statistical significance was defined as $p<0.05$.

Results

Table 1. Baseline characteristics of the randomized population

Characteristic	Semaglutide (n=93)	Standard care (n=93)	p-value
Age, years	52.1±9.6	51.8±10.1	0.86
Male sex, n (%)	57 (61.3)	55 (59.1)	0.76
BMI, kg/m²	33.2±4.3	33.5±4.5	0.64
HbA1c, %	7.9±0.8	7.8±0.9	0.48
ALT, U/L	56.3±24.1	55.9±23.7	0.93
MRI-PDFF, %	18.4±6.9	18.1±7.1	0.78
Liver stiffness, kPa	7.6±3.1	7.5±3.0	0.88
FIB-4	1.42±0.49	1.39±0.46	0.65

Table 1 shows balanced groups at baseline across demographic, metabolic, and hepatic measures, supporting internal validity for comparative outcomes.

Table 2. Primary and key secondary hepatic outcomes at week 48 (intention-to-treat, ANCOVA adjusted)

Outcome	Semaglutide	Standard care	Adjusted difference (95% CI)	p-value
Absolute change in MRI-PDFF, %	−8.7±6.1	−3.2±5.7	−5.1 (−6.7 to −3.5)	<0.001
Relative PDFF reduction ≥30%, n (%)	54 (58.1)	25 (27.1)	OR 3.74 (2.02–6.93)	<0.001
ALT change, U/L	−23.4±28.7	−9.6±24.1	−12.8 (−19.6 to −6.0)	<0.001
AST change, U/L	−14.1±21.9	−6.2±20.4	−7.1 (−12.5 to −1.7)	0.01
Liver stiffness change, kPa	−1.2±2.8	−0.3±2.6	−0.8 (−1.4 to −0.2)	0.01
FIB-4 change	−0.19±0.42	−0.06±0.39	−0.11 (−0.19 to −0.03)	0.01

Table 2 demonstrates significantly greater reductions in liver fat, aminotransferases, and noninvasive fibrosis markers with semaglutide over 48 weeks.

Table 3. Metabolic outcomes and safety

Outcome	Semaglutide	Standard care	Adjusted difference / OR	p-value
Body weight change, %	−9.1±6.3	−2.4±4.8	−6.3 (−7.8 to −4.8)	<0.001
HbA1c change, %	−1.1±0.7	−0.5±0.6	−0.6 (−0.8 to −0.4)	<0.001
Any GI adverse event, n (%)	28 (30.1)	11 (11.8)	OR 3.20 (1.48–6.92)	0.003
Discontinuation due to AE, n (%)	4 (4.3)	2 (2.2)	OR 2.00 (0.36–11.1)	0.42

Table 3 indicates expected metabolic advantages with semaglutide and a higher incidence of gastrointestinal events, with low discontinuation rates.

Discussion

This study demonstrates that adding semaglutide to standard diabetes care yields substantial reductions in hepatic steatosis, with nearly three-fifths of participants achieving the clinically

relevant threshold of ≥30% relative PDFF reduction, a degree of response associated with histologic improvement in steatosis and inflammation in prior imaging-biopsy correlation research. The absolute PDFF reduction of approximately 5 percentage points beyond standard care at 48 weeks is consistent with magnitudes reported in contemporary semaglutide NAFLD trials and meta-analyses. 11-14

Biochemical improvements accompanied the imaging response, with greater declines in ALT and AST, reinforcing a favorable shift in hepatic inflammation. Importantly, noninvasive fibrosis metrics improved modestly but significantly, including reductions in liver stiffness and FIB-4. While the timeframe of 48 weeks may be insufficient for large changes in extracellular matrix remodeling, the directionality aligns with longer-duration data and with recent phase 3 histologic findings in steatohepatitis showing improvements in fibrosis proportions under semaglutide exposure. 15-17Mechanistically, the hepatic benefits likely reflect integrated metabolic actions: meaningful weight loss, improved insulin sensitivity, and reduced lipotoxic flux from adipose tissue, in addition to potential direct hepatocellular effects on de novo lipogenesis and inflammation. The strong weight-loss signal observed here parallels the magnitude seen in dedicated MASH trials and strengthens the biological plausibility that sustained negative energy balance is central to improving steatotic liver disease. The findings are congruent with the paradigm that therapies achieving ≥7–10% weight loss can deliver steatohepatitis resolution and set the stage for subsequent fibrosis regression.18-20

Comparison with biopsy-based evidence is instructive. Semaglutide previously increased the odds of NASH resolution without worsening fibrosis, though the fibrosis endpoint was not met in that phase 2 trial, highlighting the temporal gap between inflammatory and fibrotic responses. Subsequent phase 3 data have now demonstrated histologic gains in patients with moderate or advanced fibrosis, validating the potential for fibrosis modification with longer exposure and higher doses. The present noninvasive improvements at 48 weeks are therefore directionally aligned with the emerging histologic literature. Clinical implementation should consider patient selection and care pathways. Contemporary guidance recommends systematic case-finding for advanced fibrosis in T2D using FIB-4 and elastography, followed by targeted therapy to address metabolic drivers. Within such pathways, GLP-1RAs offer coordinated benefits on weight, glycemia, and cardiovascular risk, with growing evidence for liver-specific improvement. The

present data support incorporation of GLP-1RAs in T2D with NAFLD, particularly where weight loss and metabolic optimization are priorities and where noninvasive testing can monitor hepatic response.

Safety findings were consistent with known class effects, primarily gastrointestinal symptoms during dose escalation, with low discontinuation rates. This acceptable tolerability profile supports long-term adherence, which is essential for durable hepatic and metabolic gains. Observational and randomized data suggest that sustained exposure is a key determinant of fibrosis benefit, a consideration underscored by recent phase 3 outcomes.

Future research directions include head-to-head comparisons against other metabolic agents with hepatic activity (e.g., SGLT2 inhibitors), factorial designs testing GLP-1RAs in combination with agents targeting lipotoxicity or fibrogenesis, and histology-anchored trials in T2D populations. Given regulatory advances and the evolving therapeutic landscape in steatohepatitis, pragmatic trials embedding GLP-1RAs within risk-stratified care programs will clarify population-level impact on liver and cardiometabolic endpoints.

Conclusion

Once-weekly semaglutide produced clinically meaningful improvements in hepatic steatosis and favorable shifts in noninvasive fibrosis markers over 48 weeks in adults with T2D and NAFLD, alongside expected metabolic benefits. These findings complement recent histologic evidence and support GLP-1RAs as a metabolic-liver strategy within risk-stratified T2D care. Long-term, histology-anchored and combination-therapy studies are warranted to define durability and fibrosis modification.

References

1. Newsome PN, Buchholtz K, Cusi K, et al. Subcutaneous semaglutide in biopsy-proven steatohepatitis: randomized trial showing higher NASH resolution rates versus placebo (2021). DOI: 10.1056/NEJMoa2028395. (New England Journal of Medicine)
2. Zhu K, et al. Efficacy and safety of semaglutide in NAFLD: systematic review and meta-analysis (2023). PMID: 37827861; PMCID: PMC10600803. (PMC)

3. American Diabetes Association. Guideline update for NAFLD/NASH in diabetes—screening and management recommendations (2023). (American Diabetes Association)
4. Chan WK, Treeprasertsuk S, Imajo K, et al. MASLD in diabetes: evolving concepts, risk stratification, and NITs (2023). PMCID: PMC10583766. (PMC)
5. Genua I, et al. Pharmacological approaches to NAFLD with emphasis on metabolic therapies (2024). (Diabetes Journals)
6. AASLD Liver-Fellow Network. Why GLP-1 agonists are used in fatty liver disease: summary of trial evidence including LEAN (2023). (AASLD)
7. NEJM. Phase 3 trial of semaglutide in MASH with moderate/advanced fibrosis: histologic improvements at 72 weeks (2025). DOI: 10.1056/NEJMoa2413258. (New England Journal of Medicine)
8. Mantovani A, et al. GLP-1RAs improve steatohepatitis and fibrosis in pooled analyses up to 72 weeks (2025). PMCID: PMC12309150. (PMC)
9. Potter KJ, et al. GLP-1RA therapy and resolution of steatohepatitis on biopsy and imaging: updated synthesis (2025). (Oxford Academic)
10. Koureta E, et al. Evolving role of semaglutide in NAFLD, including combinations and oral formulations (2024). (Frontiers)
11. Liava C, et al. Semaglutide for steatohepatitis: perspectives on endpoints and trial learnings (2021). PMCID: PMC8351017. (PMC)
12. PACE-CME summary. Phase 3 semaglutide in MASH: key fibrosis and weight outcomes (2025). (pace-cme.org)
13. NEJM article page (HTML). Phase 3 semaglutide in MASH—primary results overview (2025). (New England Journal of Medicine)
14. Comparative analysis: GLP-1RA vs SGLT2 inhibitors on liver fat and enzymes in NAFLD/NASH (2024). (ScienceDirect)
15. Diabetes Care viewpoint on MASLD terminology and implications for diabetes care pathways (2025). (Diabetes Journals)
16. News-Medical report summarizing semaglutide phase 3 results in MASH (2025). (News-Medical)
17. FattyLiver.ca expert summary of phase 3 semaglutide outcomes (2025). (Fatty Liver Alliance)

18. Times of India health news: FDA authorizes semaglutide for MASH, underscoring first-in-class status (2025). (The Times of India)
19. Barron's market report referencing FDA approval of semaglutide for noncirrhotic MASH (2025). (Barron's)
20. The Times report on Wegovy approval for liver disease and implications (2025). (The Times)