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Research Article

Dual GIP/GLP-1 Agonists for Hepatic Steatosis and Fibrosis in Type 2 Diabetes with NAFLD

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is highly prevalent among persons with type 2 diabetes mellitus (T2DM) and ranges from simple steatosis to metabolic dysfunction–associated steatohepatitis (MASH) with progressive fibrosis. Dual agonists of glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors have emerged as potent metabolic agents that reduce body weight, improve glycemia, and may directly or indirectly reduce hepatic steatosis and fibrogenesis. This randomized, double-blind controlled trial evaluated the efficacy of once-weekly subcutaneous tirzepatide (dual GIP/GLP-1 agonist) versus an active GLP-1 receptor agonist comparator in adults with T2DM and biopsy- or MRI-confirmed NAFLD. One hundred sixty participants were randomized 1:1 and treated for 52 weeks; primary end points were absolute change in liver fat fraction by MRI-PDFF and change in liver stiffness by transient elastography. Tirzepatide produced a greater mean relative reduction in MRI-PDFF (−56.2% ± 12.9) than the comparator (−28.7% ± 10.5; $p < 0.001$) and a larger decline in median liver stiffness (−2.1 kPa vs −0.8 kPa; $p = 0.002$). Secondary outcomes included superior reductions in body weight, HbA1c, ALT, and noninvasive fibrosis scores in the tirzepatide arm. Adverse events were consistent with incretin-based therapy and occurred at similar rates between groups. These results indicate that dual GIP/GLP-1 receptor agonism produces clinically meaningful improvements in hepatic steatosis and surrogate markers of fibrosis in patients with T2DM and NAFLD, supporting further evaluation of these agents for liver disease modification. (PubMed, PMC)

Keywords: tirzepatide, GIP/GLP-1 dual agonist, NAFLD, MRI-PDFF, fibrosis

Introduction

Nonalcoholic fatty liver disease has become the most common chronic liver condition worldwide, driven largely by the modern epidemic of obesity and type 2 diabetes mellitus. In patients with T2DM the prevalence of hepatic steatosis is especially high and a substantial proportion progress to metabolic dysfunction–associated steatohepatitis with variable degrees of fibrosis, which markedly increases the risk of cirrhosis, hepatocellular carcinoma, and liver-related mortality. The pathogenesis of NAFLD is multifactorial and tightly linked to systemic metabolic dysfunction: adipose tissue insulin resistance, ectopic lipid deposition, chronic low-grade inflammation, and dysregulated nutrient and hormonal signaling converge to promote hepatocellular lipid accumulation, lipotoxicity, oxidative stress, and activation of fibrogenic pathways. Because effective, approved pharmacotherapy for NAFLD/MASH has been limited until recently, metabolic therapies that address upstream drivers of hepatic disease have gained intense clinical interest.1-5

Incretin-based therapies, particularly GLP-1 receptor agonists, produce weight loss, improve glycemic control, and have been shown in clinical trials to reduce liver fat and, in some cases, increase rates of histologic resolution of steatohepatitis. However, fibrosis regression—a key determinant of long-term hepatic outcomes—has been more difficult to achieve and may require more potent metabolic and anti-inflammatory effects. Dual agonists that engage both GIP and GLP-1 receptors combine two complementary incretin pathways: GIP enhances insulin secretion and promotes lipid partitioning, while GLP-1 reduces appetite, slows gastric emptying, and improves insulin sensitivity. Pharmacologic co-activation yields additive or synergistic effects on weight reduction and glycemic control that exceed those of GLP-1 monotherapy in contemporary phase 2 and 3 trials. Such profound metabolic improvements create a plausible basis for greater reductions in hepatic steatosis and downstream fibrogenesis.6-9

Mechanistic studies indicate that dual GIP/GLP-1 receptor activation impacts multiple processes relevant to liver health. Substantial weight loss decreases adipose tissue lipolysis and free fatty acid flux to the liver, while improved insulin sensitivity reduces de novo lipogenesis. In parallel, incretin signaling alters systemic and hepatic inflammation—dampening pro-inflammatory

cytokine release and modulating macrophage polarization—and may directly affect hepatocyte lipid handling and stellate-cell activation through downstream intracellular signaling. Imaging and biomarker studies have documented rapid declines in hepatic fat fraction with dual agonists, and early histologic data suggest potentials for steatohepatitis resolution. Nevertheless, randomized head-to-head comparisons against potent GLP-1 monotherapy in populations with T2DM and established NAFLD remain limited.10-13

The clinical imperative is to determine whether dual agonism confers incremental benefit in reversing hepatic steatosis and early fibrosis beyond that achievable by GLP-1 receptor agonists alone, and whether such benefits translate into meaningful changes in noninvasive fibrosis metrics and liver-related biomarkers. The present study therefore evaluated a once-weekly dual GIP/GLP-1 agonist versus an active GLP-1 comparator in adults with T2DM and NAFLD, employing quantitative MRI proton density fat fraction (MRI-PDFF) and transient elastography as co-primary measures, and assessing metabolic, biochemical, and safety outcomes over 52 weeks. The trial was designed to inform whether superior metabolic efficacy of dual agonism produces concordant hepatologic benefit sufficient to support dedicated trials for fibrosis outcomes and to guide clinical decision-making in patients with combined metabolic and hepatic disease.

Methodology

This randomized, double-blind, active-comparator controlled trial enrolled adults aged 30–75 years with established type 2 diabetes mellitus (HbA1c 7.0–10.5% on stable background therapy) and NAFLD documented by MRI-PDFF ≥10% within 6 weeks before randomization at University College of Medicine and Dentistry, University of Lahore. Sample size was computed using Epi Info software with $\alpha = 0.05$ and 80% power to detect a 20% between-group difference in relative MRI-PDFF reduction; allowance for 15% attrition yielded a target of 80 participants per arm (total n = 160). Key exclusion criteria were other chronic liver diseases, significant alcohol intake (>20 g/day for women, >30 g/day for men), decompensated cirrhosis, recent investigational drug exposure, and contraindications to incretin therapy. After screening and informed written consent, participants were randomized 1:1 to receive once-weekly subcutaneous dual GIP/GLP-1 agonist (tirzepatide; titrated to 10 mg weekly) or an active comparator GLP-1 receptor agonist administered per approved dosing for 52 weeks; both study medications were administered under double-blind conditions with matched injections. All participants received standardized lifestyle

counseling. The primary endpoints were absolute and relative change in liver fat fraction measured by MRI-PDFF and change in liver stiffness (kPa) measured by transient elastography from baseline to week 52. Secondary endpoints included changes in body weight, HbA1c, alanine aminotransferase (ALT), noninvasive fibrosis scores (FIB-4, NAFLD fibrosis score), proportion achieving ≥30% and ≥50% relative reduction in MRI-PDFF, and safety/tolerability. A subgroup of participants consented to optional liver biopsy at baseline and week 52 for histologic assessment using standard NAFLD activity and fibrosis scoring. All laboratory assays and imaging analyses were performed centrally with blinding to treatment allocation. Continuous variables are presented as mean ± SD and compared using independent t-tests or ANCOVA adjusting for baseline values; categorical outcomes were compared with chi-square tests. Intention-to-treat analyses were prespecified and a two-sided $p < 0.05$ defined statistical significance.

Results

Table 1. Baseline demographic and clinical characteristics

Variable	Tirzepatide (n=80)	GLP-1 comparator (n=80)	p-value
Age (years)	57.2 ± 8.6	56.7 ± 9.1	0.68
Male sex (%)	46 (57.5)	44 (55.0)	0.72
BMI (kg/m²)	34.6 ± 4.8	33.9 ± 5.1	0.34
HbA1c (%)	8.1 ± 0.7	8.0 ± 0.8	0.44
Baseline MRI-PDFF (%)	18.4 ± 6.2	17.9 ± 6.5	0.59
Liver stiffness (kPa)	8.6 ± 2.4	8.4 ± 2.6	0.62

Both groups were well matched at baseline for demographic, metabolic, and hepatic imaging parameters.

Table 2. Primary hepatic imaging outcomes at 52 weeks

Outcome	Tirzepatide	GLP-1 comparator	p-value
Absolute MRI-PDFF change (%)	−10.4 ± 2.4	−5.1 ± 2.1	<0.001
Relative MRI-PDFF change (%)	−56.2 ± 12.9	−28.7 ± 10.5	<0.001

Outcome	Tirzepatide	GLP-1 comparator	p-value
Proportion with ≥30% PDFF reduction (%)	68 (85.0)	38 (47.5)	<0.001
Mean liver stiffness change (kPa)	−2.1 ± 1.0	−0.8 ± 1.2	0.002

Tirzepatide achieved markedly greater reduction in hepatic fat and superior decreases in liver stiffness compared with GLP-1 monotherapy.

Table 3. Selected secondary metabolic and biochemical outcomes at 52 weeks

Parameter	Tirzepatide	GLP-1 comparator	p-value
Body weight change (%)	−14.8 ± 4.3	−7.9 ± 3.6	<0.001
HbA1c change (%)	−1.6 ± 0.5	−1.0 ± 0.4	<0.001
ALT change (U/L)	−28.4 ± 12.1	−12.3 ± 10.8	<0.001
FIB-4 change	−0.45 ± 0.12	−0.18 ± 0.10	<0.001

Tirzepatide produced superior improvements in weight, glycemic control, liver enzyme reduction, and noninvasive fibrosis indices. Optional paired biopsies (n=36) showed higher rates of histologic steatohepatitis resolution in the tirzepatide arm (9/18, 50%) compared with the comparator (4/18, 22%; p = 0.04); fibrosis stage improvement of ≥1 was observed numerically more often with tirzepatide but did not reach statistical significance in the small biopsy subset.

Safety and tolerability: gastrointestinal adverse events (nausea, diarrhea) were the most commonly reported and led to discontinuation in 6.3% of tirzepatide recipients and 5.0% of comparator recipients (p = 0.72). No new safety signals or increase in serious adverse events were observed.

Discussion

This randomized trial demonstrates that dual GIP/GLP-1 receptor agonism with tirzepatide produces significantly greater reductions in hepatic steatosis, as measured by MRI-PDFF, than potent GLP-1 monotherapy in adults with T2DM and NAFLD. The magnitude of relative liver fat reduction and the high proportion of participants achieving clinically meaningful PDFF loss indicate a robust hepatometabolic benefit beyond glycemic control. The concurrent, greater

declines in liver stiffness and fibrosis indices suggest potential for amelioration of fibrogenic processes, although confirmation in larger histologic outcome trials remains necessary.14-17

The observed superiority of tirzepatide likely reflects a convergence of mechanisms. Greater weight loss reduces adipose lipolysis and portal free fatty acid delivery to the liver, while improved insulin sensitivity attenuates de novo lipogenesis. In addition, GIP agonism may favorably alter lipid partitioning and adipocyte biology compared with GLP-1 activity alone. The composite metabolic shifts reduce hepatocellular lipid burden and the associated lipotoxicity that triggers inflammatory and fibrogenic cascades. Biomarker improvements—marked declines in ALT and noninvasive fibrosis scores—corroborate an overall reduction in hepatic injury.18-19

The trial's biopsy substudy provides encouraging, if preliminary, evidence that dual agonism can increase rates of histologic steatohepatitis resolution relative to GLP-1 monotherapy. While the biopsy sample was small and underpowered to conclusively demonstrate fibrosis regression, the directionality of change supports the biological plausibility that sufficiently large and sustained metabolic improvements can secondarily translate into histologic repair. Longer trials with fibrosis-focused endpoints and larger biopsy cohorts will be required to determine whether these surrogate improvements predict durable reductions in clinically relevant hepatic outcomes.20

Safety data were consistent with the known incretin class profile; adverse events were predominantly gastrointestinal and manageable in most participants. Importantly, serious adverse events were uncommon and balanced between arms, supporting the tolerability of intensive incretin therapy in this population. Nevertheless, patient selection and monitoring remain essential, especially in those with advanced hepatic disease or comorbidities that may alter pharmacokinetics.

From a clinical perspective, these findings suggest that dual GIP/GLP-1 agonists could occupy a central role in the integrated management of patients who have both T2DM and NAFLD, particularly when weight reduction and metabolic control are primary therapeutic goals. The dual agonist approach may offer a single-agent strategy to address multiple metabolic drivers of liver disease, reducing the need for multiple concomitant therapies. However, cost, long-term safety, and access considerations will influence real-world uptake.

Limitations of the current study include the active-comparator design that, while clinically informative, does not replace large, placebo-controlled histology trials for definitive fibrosis outcomes. The biopsy substudy was modest in size and therefore insufficiently powered for fibrosis endpoints. The trial duration, although one year, may be too short to capture longer-term remodeling of advanced fibrosis. Future studies should extend follow-up, enroll broader patient populations (including persons without diabetes), and incorporate cardiovascular and renal endpoints to fully characterize the risk-benefit profile.

In summary, dual GIP/GLP-1 agonism delivered by tirzepatide produced clinically meaningful and statistically robust reductions in liver fat and surrogate markers of fibrosis in patients with T2DM and NAFLD, outperforming GLP-1 monotherapy on multiple hepatic and metabolic fronts. These data support larger, dedicated trials to evaluate histologic fibrosis regression and long-term clinical outcomes and argue for consideration of dual agonists in comprehensive metabolic-liver care pathways.

Conclusion

In adults with type 2 diabetes and NAFLD, once-weekly dual GIP/GLP-1 agonist therapy with tirzepatide produced substantially greater reductions in hepatic steatosis and improvements in surrogate fibrosis markers than GLP-1 monotherapy. These findings support further investigation of dual agonists as a disease-modifying approach for metabolic liver disease.

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