GMR
The Original

COMPARISON OF GLP-1 AGONIST, LIFE STYLE AND DIET MODIFICATION VS GLP-1 AGONIST ALONE FOR TREATMENT OF DIABETIC PATIENTS WITH MASLD

Fabiha Faiz[1], Kashif Malik[2], Muhammad Maqsood[3], Muhammad Rizwan Subhani[4]

[1]Postgraduate Resident, Department of Gastroenterology, Shaikh Zayed Hospital, Lahore, Pakistan
[2]Professor of Gastroenterology, Head of Gastroenterology Department, Sheikh Zayed Hospital, Lahore, Pakistan
[3]Senior Registrar, Medicine Department, Gujranwala Medical College, Teaching Hospital Gujranwala, Pakistan
[4]Registrar, Gastroenterology and Hepatology Department, Shaikh Zayed Hospital, Lahore, Pakistan
Correspondence Author: Dr. Fabiha Faiz, Email: fabihafaiz6@gmail.com

ABSTRACT

Objective: To assess the effectiveness of GLP-1 RAs therapy for patients with MASLD/T2DM and whether adding lifestyle and diet modifications to GLP-1 RA therapy provides additional benefit.
Study Design: Randomized Controlled trial.
Study setting and duration: Shaikh Zayed Hospital Lahore Department of Gastroenterology (December 2025- April 2026).
Methodology: A total of 72 patients with MASLD and T2DM participated in the study; they were randomized into two equal groups. Patients in Group A received GLP-1 RAs therapy alone, while patients in Group B received GLP-1 RAs therapy and lifestyle modification. The following measurements were assessed at baseline and follow-up: anthropometric measurements, fasting blood glucose, HbA1c, liver enzymes, and liver fat %age. Comparison of medians across groups for each measurement was done using the Mann-Whitney U test, with $p \leq 0.05$ being statistically significant.
Results: Participants treated with combination therapy showed a significantly larger decrease in BMI (3.15 (1.00) kg/m² v. 1.00 (0.40) kg/m²), waist circumference (11.00 (2.90) cm v. 3.90 (2.30) cm), fasting blood glucose (42.70 (12.10) mg/dL v. 15.35 (8.70) mg/dL), HbA1c (1.70 (0.40)% v. 0.70 (0.40)%), ALT (22.10 (6.60) U/L v. 7.90 (5.80) U/L), AST (19.95 (4.70) U/L v. 6.70 (6.40) U/L), and percentage of liver fat (4.75 (3.90)% v. 1.45 (3.30)%) than Group A participants (all $p<0.001$).
Conclusion: GLP-1 RAs therapy combined with lifestyle alterations and dietary modifications is more efficacious than GLP-1RAs monotherapy for improving anthropometric, glycemic, and hepatic outcomes among individuals with T2DM and MASLD.

Keywords: Alanine transaminase; Aspartate aminotransferase; GLP-1 Receptor Agonists; HbA_{1c}; MASLD; T2DM.

INTRODUCTION

Metabolic dysfunction associated Steatotic liver disease (MASLD) and type 2 diabetes mellitus (T2DM) have significant co-morbidity; at present about 38% of the general population worldwide has MASLD (previously known as NAFLD)(1), and increasingly, since about 2001, the rate of MASLD in people with T2DM has been higher than in the general population, e.g., 65.33% of T2DM patients worldwide in 2021(2) and projected to 33.5% of the general population by 2030(3). In Pakistan, the prevalence of adult diabetes is estimated to be around 30.8-31.4% by 2025, making it one of the highest in the world, while about 29-58% of T2DM patients are expected to have MASLD, depending on geographical distribution (i.e., in Punjab, local studies are reporting the incidence of NAFLD in patients with T2DM at 61.7%)(4).

GLP-1 receptor agonists (GLP-1 RAs), such as liraglutide, reduce liver fat (hepatic steatosis), fibrotic liver changes (fibrosis), and liver markers (enzymes) in patients with metabolic-associated steatosis liver disease (MASLD) associated with type 2 diabetes (T2DM) primarily by means of weight reduction and improved blood glucose

control(5). In an RCT published in 2025, weight reduction associated with a GLP-1 RAs (liraglutide) yielded similar results for reductions in steatosis compared to lifestyle changes but had additional benefits in improvement of metabolic parameters (e.g., blood glucose and lipids)(6). Several meta-analyses have consistently demonstrated that GLP-1 RAs are superior to placebo for the resolution of NASH and reduction of fat(7).
This study will compare GLP-1 RA monotherapy with GLP-1 RA combined with lifestyle/dietary changes for established hepatic and metabolic synergy for patients with MASLD and T2DM via a randomized controlled trial. There is scientific evidence available to support the effectiveness of glucagon-like peptide-1 receptor agonists (GLP-1RA). However, lifestyle interventions are fundamentally important, but there is a challenge for patients to adhere to these interventions. There are no randomised controlled trials that specifically examine the combination of GLP-1RA and lifestyle interventions for patients with fatty liver disease and type 2 diabetes. Pakistan is experiencing increased rates of MASLD-T2DM, and therefore, an integrated approach using lifestyle interventions and GLP-1RA will provide the best outcomes and may provide the knowledge and evidence to develop local treatment protocols.

METHODOLOGY

Following the approval of the hospital's ethics committee, randomized controlled trial was undertaken in Department of Gastroenterology, Shaikh Zayed Hospital, for four months, from December 2025 to April 2026. The purpose of this study was to evaluate the effectiveness of adding GRP-1 agonist therapy combined with dietary and lifestyle modification to standard GRP-1 agonist treatment among patients diagnosed with metabolic dysfunction-associated steatotic liver disease (MASLD) and type 2 diabetes mellitus (T2DM).
The sample size was determined using the WHO sample size calculator as per the guidelines outlined in Flint et al.(8). The anticipated sample size for Group A was assumed to be at 70% and for Group B 30% comparative to the population of this study, for 95% confidence level with 90% power. Therefore, a sample size of 28 members was calculated for each group. This number was increased by 20% to account for possible dropouts and non-responses, resulting in a final sample size of 36 for each group, or 72 total.
Seventy-two patients were enrolled via non-probability convenience sampling through a lottery randomization method, with 36 assigned to each cohort (Group A: GRP-1 agonist therapy only; Group B: GRP-1 agonist and lifestyle modification/dietary change).

Inclusion criteria: The adult patients (18–70 years) of either gender, having diagnosed type 2 diabetes (T2DM), were eligible if their body mass index (BMI) was at least 27 kg/m2 and non-alcoholic fatty liver disease (NAFLD) confirmed by imaging to have hepatic steatosis, defined as on magnetic resonance imaging (MRI) using the proton density fat fraction (PDFF) method with the percentage of fat > 5% or Controlled Attenuation Parameter (CAP) with a score ≥ 248 dB/m.

Exclusion criteria: Exclusion criteria included significant alcohol use; chronic liver disease, other than MASLD; decompensated liver disease; being pregnant; having active malignancy; recent bariatric surgery; severe psychiatric illness; or intolerance to GLP-1 receptor agonists.
On recruitment into the study, patients were evaluated for their demographic characteristics, medical history, anthropometric measurements, four fasting glucose tests, HbA1c test, liver function test, lipid profile, and MRI fat content determination. In Group B, all participants received dietary counselling focused on caloric restriction and healthy eating patterns; physical activity was encouraged with at least 150 minutes of moderate-intensity exercise weekly. Assessing adherence to medications and lifestyle modifications, patients in Group B had their attendance documented, dietary recall documented, and followed at scheduled follow-up visits.
Reassessment of patients was carried out after 12 weeks of treatment. The primary outcome variable for this trial was percentage of participants who had achieved at least 30% reduction in liver fat content based on MRI-PDFF data. Secondary outcome variables included change in HbA1c, body weight, ALT (alanine aminotransferase), AST (aspartate aminotransferase), lipid profile, liver stiffness, and adherence to prescribed treatments. All data collected was analyzed with the Statistical Package for Social Sciences (SPSS) version 27. Numerical variables were expressed as mean ± standard deviation, while categorical variables were reported as frequencies and percentages. Independent samples t-tests were used to compare numerical variables between groups; chi-square tests was utilized to evaluate categorical variables. A p-value of ≤0.05 was considered significant.

RESULTS

At their final evaluation, both groups had similar anthropometric, glycemic, and hepatic values. Group "A" and Group "B"'s mean weights were 91.7±7.4 and 93.27±8.5, respectively; mean BMI was 32.79 kg/m2 in Group "A" and 33.84 kg/m2 in Group "B". Both groups had comparable baseline values of fasting blood glucose levels (Group A: 169.55

± 17.08 vs Group B: 168.90 ± 18.43) as well as other baseline measures, including HbA1c, ALT, AST, and liver fat percentage.

Overall, the intervention group that received combination GLP-1 therapy and lifestyle modification exhibited greater improvements following treatment. For example, at follow-up, Group B subjects had a mean weight of 83.29 ± kg compared to 87.55 ± 7.53 kg for subjects in Group A; Group B had a BMI of 30.71 ± 2.06 kg/m² compared to 31.89 ± 2.66 kg/m² for Group A; and Group B had a waist circumference of 99.47 ± 7.80 cm compared to 102.03 ± 5.80 cm for Group A.

There were also significant differences in fasting blood glucose and HbA1c levels between the two groups at follow-up, with Group B subjects having mean fasting blood glucose levels of 126.46 ± 19.00 mg/dL vs 154.45 ± 18.13 mg/dL for Group A, as well as a mean HbA1c level of 6.61 ± 0.97% compared to 7.94 ± 0.80% for Group A. The hepatic parameters evaluated showed improved results in Group B when compared to Group A, with lower follow-up ALT, AST, and liver fat percentage values as well.

Table I: Baseline and Follow-up Clinical, Anthropometric, Glycemic, and Hepatic Parameters among Study Groups (n=72)

Variable	Group A – GLP1 Alone (Mean ± SD) (n=36)	Group B – GLP1 + Lifestyle (Mean ± SD) (n=36)	Total (Mean ± SD)(n=72)
Baseline Weight (kg)	91.70 ± 7.44	93.27 ± 8.53	92.48 ± 7.99
Baseline BMI (kg/m²)	32.79 ± 2.56	33.82 ± 1.93	33.30 ± 2.31
Baseline Waist Circumference (cm)	105.84 ± 5.83	110.41 ± 7.11	108.13 ± 6.85
Baseline Fasting Glucose (mg/dL)	169.55 ± 17.08	168.90 ± 18.43	169.22 ± 17.65
Baseline HbA1c (%)	8.65 ± 0.76	8.36 ± 0.88	8.50 ± 0.83
Baseline ALT (U/L)	73.12 ± 9.88	72.07 ± 8.67	72.60 ± 9.24
Baseline AST (U/L)	61.55 ± 6.43	58.89 ± 9.18	60.22 ± 7.98
Baseline Liver Fat (%)	22.23 ± 3.75	23.60 ± 4.61	22.92 ± 4.23
Follow-up Weight (kg)	87.55 ± 7.53	83.29 ± 8.29	85.42 ± 8.15
Follow-up BMI (kg/m²)	31.89 ± 2.66	30.71 ± 2.06	31.30 ± 2.44
Follow-up Waist Circumference (cm)	102.03 ± 5.80	99.47 ± 7.80	100.75 ± 6.95
Follow-up Fasting Glucose (mg/dL)	154.45 ± 18.13	126.46 ± 19.00	140.46 ± 23.21
Follow-up HbA1c (%)	7.94 ± 0.80	6.61 ± 0.97	7.28 ± 1.11
Follow-up ALT (U/L)	65.63 ± 9.92	49.03 ± 10.63	57.33 ± 13.19
Follow-up AST (U/L)	54.96 ± 8.07	39.71 ± 9.56	47.33 ± 11.67
Follow-up Liver Fat (%)	20.73 ± 4.43	18.79 ± 4.51	19.76 ± 4.55

Values are presented as Mean ± Standard Deviation (SD). Group A = GLP-1 receptor agonist therapy alone; Group B = GLP-1 receptor agonist therapy combined with lifestyle modification. BMI = Body Mass Index; HbA1c = Glycated Hemoglobin; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase.

The median changes from baseline bodyweight to follow-up were 4.45 kg (IQR 2.60), 10.30 kg (IQR 2.70), and 7.40 kg (IQR 5.90) among the participants taking GLP-1 on its own, those taking GLP-1 with lifestyle changes, and all participants, respectively.

For average BMI, the median average changes from baseline to final follow-up were 1.00 kg/m² (IQR 0.40); 3.15 kg/m² (IQR 1.00); and 2.10 kg/m² (IQR 2.10) in groups A, B, and the total population, respectively.

A waist circumference reduction median of 3.90 cm (IQR 2.30) in Group A, compared to Group B at 11.00 cm (IQR 2.90), resulted in a total reduction median of 7.20 cm in the combined groups (IQR 7.10). Fasting blood glucose reductions occurred in the GLP-1 alone group at a median of 15.35 mg/dL (IQR 8.70) and in the combined group 42.70 mg/dL (IQR 12.10), representing an overall median reduction of 28.90 mg/dL (IQR 27.40).

HbA1c experienced a reduction of 0.70% (IQR 0.40) in Group A, 1.70% (IQR 0.40) in Group B, and an overall median change of 1.20% (IQR 1.00). There was also an improvement in the liver enzymes in the combined group, with ALT reduced by a median of 7.90 U/L (IQR 5.80) in Group A and 22.10 U/L (IQR 6.60) in Group B; AST decreased by

6.70 U/L (IQR 6.40) and 19.95 U/L (IQR 4.70) respectively, yielding overall median reductions of 15.00 U/L (IQR 14.20) and 13.10 U/L (IQR 13.30) respectively.
Liver fat percentage decreased by a median of 1.45% (IQR 3.30) in Group A compared to 4.75% (IQR 3.90) in Group B, yielding an overall median reduction of 3.10% (IQR 3.80). The median ages were 50.00 years old (IQR 18) for Group A, 47.50 years old (IQR 22) for Group B, and 49.00 years (IQR 20) for the total sample.

Table II: Comparison of Median Change in Anthropometric, Glycemic, and Hepatic Parameters Between Study Groups (n=72)

Variable	Group A – GLP1 Alone Median (IQR) (n=36)	Group B – GLP1 + Lifestyle Median (IQR) (n=36)	Total Median (IQR) (n=72)
Weight Change (kg)	4.45 (2.60)	10.30 (2.70)	7.40 (5.90)
BMI Change (kg/m²)	1.00 (0.40)	3.15 (1.00)	2.10 (2.10)
Waist Circumference Change (cm)	3.90 (2.30)	11.00 (2.90)	7.20 (7.10)
Fasting Blood Glucose Change (mg/dL)	15.35 (8.70)	42.70 (12.10)	28.90 (27.40)
HbA1c Change (%)	0.70 (0.40)	1.70 (0.40)	1.20 (1.00)
ALT Change (U/L)	7.90 (5.80)	22.10 (6.60)	15.00 (14.20)
AST Change (U/L)	6.70 (6.40)	19.95 (4.70)	13.10 (13.30)
Liver Fat Change (%)	1.45 (3.30)	4.75 (3.90)	3.10 (3.80)
Age (years)	50.00 (18.00)	47.50 (22.00)	49.00 (20.00)

Values are presented as Median (Interquartile Range, IQR). Change values represent absolute reduction from baseline to follow-up measurements. Group A = GLP-1 receptor agonist therapy alone; Group B = GLP-1 receptor agonist therapy combined with lifestyle modification. BMI = Body Mass Index; HbA1c = Glycated Hemoglobin; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase.

The sample of 72 subjects participating in the research consisted of equal numbers of males and females who received treatment either with a single GLP-1 medication (study group "A") or a combination of drugs and lifestyle modification (study group "B"). The average age of participants was 50 years old ("A") and 47.5 years old ("B"). Of these patients, 54.2% had better-than-expected adherence to their medications. 40.3% of participants who were taking GLP-1 therapy in addition to their regular lifestyle had some type of adverse effect but were able to manage it with the help of their doctor; this was more common in group "B" (47.7%) than in group "A" (33 %). Only participants in group "B" completed eight to 11 visits to the lifestyle counseling office (Table 3).

Table III: Distribution of Demographic Characteristics, Treatment Adherence, Lifestyle Session Attendance, and Side Effects Among Study Groups (n=72)

Variable	Group A – GLP1 Alone n (%) (n=36)	Group B – GLP1 + Lifestyle n (%) (n=36)	Total n (%) (n=72)
Gender			
Female	18 (50.0%)	16 (44.4%)	34 (47.2%)
Male	18 (50.0%)	20 (55.6%)	38 (52.8%)
GLP-1 Adherence			
Good	20 (55.6%)	19 (52.8%)	39 (54.2%)
Moderate	16 (44.4%)	17 (47.2%)	33 (45.8%)
Lifestyle Sessions Attended			
0 Sessions	36 (100.0%)	0 (0.0%)	36 (50.0%)
8 Sessions	0 (0.0%)	9 (25.0%)	9 (12.5%)
9 Sessions	0 (0.0%)	7 (19.4%)	7 (9.7%)
10 Sessions	0 (0.0%)	9 (25.0%)	9 (12.5%)
11 Sessions	0 (0.0%)	7 (19.4%)	7 (9.7%)
12 Sessions	0 (0.0%)	4 (11.1%)	4 (5.6%)
Side Effects			
No	24 (66.7%)	19 (52.8%)	43 (59.7%)

Yes	12 (33.3%)	17 (47.2%)	29 (40.3%)

Values are presented as frequency and percentage [n (%)]

The Mann-Whitney U test to compare median reductions revealed statistically significant improvements in all measured clinical and laboratory parameters for those participants in the combined therapy group (Group B). Participants in Group B showed significantly larger median weight reductions compared to those in Group A [10.30 (IQR: 2.70) kg vs. 4.45 (IQR: 2.60) kg, $p < 0.001$]. Additionally, there were significantly larger median reductions in both BMI [3.15 (IQR: 1.00) vs. 1.00 (IQR: 0.40), $p < 0.001$] and waist circumference [11.00 (IQR: 2.90) cm vs. 3.90 (IQR: 2.30) cm, $p < 0.001$] between Groups B and A. The levels of fasting blood glucose were also significantly ($p < 0.001$) reduced in Group B compared with Group A [42.70 (IQR: 12.10) mg/dL vs. 15.35 (IQR: 8.70) mg/dL] as well as the levels HbA1c [1.70 (IQR: 0.40)% vs. 0.70 (IQR: 0.40)%, $p < 0.001$]; ALT [22.10 (IQR: 6.60) U/L vs. 7.90 (IQR: 5.80) U/L, $p < 0.001$]; AST [19.95 (IQR: 4.70) U/L vs. 6.70 (IQR: 6.40) U/L, $p < 0.001$]; and liver fat percentage [4.75 (IQR: 3.90)% vs. 1.45 (IQR: 3.30)%, $p < 0.001$]) were all significantly reduced in Group B when compared to Group A (Table 4).

Table IV: Comparison of Median Changes in Clinical and Biochemical Parameters between Study Groups with Associated p-values (n=72)

Variable	Group A – GLP1 Alone Median (IQR) (n=36)	Group B – GLP1 + Lifestyle Median (IQR) (n=36)	p-value
Weight Change (kg)	4.45 (2.60)	10.30 (2.70)	<0.001
BMI Change (kg/m²)	1.00 (0.40)	3.15 (1.00)	<0.001
Waist Circumference Change (cm)	3.90 (2.30)	11.00 (2.90)	<0.001
Fasting Blood Glucose Change (mg/dL)	15.35 (8.70)	42.70 (12.10)	<0.001
HbA1c Change (%)	0.70 (0.40)	1.70 (0.40)	<0.001
ALT Change (U/L)	7.90 (5.80)	22.10 (6.60)	<0.001
AST Change (U/L)	6.70 (6.40)	19.95 (4.70)	<0.001
Liver Fat Change (%)	1.45 (3.30)	4.75 (3.90)	<0.001
Age (years)	50.00 (18.00)	47.50 (22.00)	<0.001

Values are presented as Median (Interquartile Range, IQR). P-values were calculated using the Mann–Whitney U test. A p-value <0.05 was considered statistically significant. Group A = GLP-1 receptor agonist therapy alone; Group B = GLP-1 receptor agonist therapy combined with lifestyle modification. BMI = Body Mass Index; HbA1c = Glycated Hemoglobin; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase.

DISCUSSION

The present randomized controlled trial shows that the combined use of GLP-1 agonist therapy with lifestyle and dietary modifications (Group B, n=36) produces significantly better results than GLP-1 agonist therapy alone (Group A, n=36) for patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and type 2 diabetes mellitus (T2DM). In Group B, the average weight loss was significantly greater than Group A (10.30 kg [IQR: 2.70] vs. 4.45 kg [IQR: 2.60], $p < 0.001$), and there were also significantly greater mean reductions in BMI (Group B: 3.15 kg/m² [IQR: 1.00] vs. Group A: 1.00 kg/m² [IQR: 0.40]; $p < 0.001$) and waist circumference (Group B: 11.00 cm [IQR: 2.90] vs Group A: 3.90 cm [IQR: 2.30]; $p < 0.001$), as determined by the Mann-Whitney U Test. The differences also extended to improvements in glycemic control (median fasting blood glucose: Group B: 42.70 mg/dL [IQR: 12.10] vs Group A: 15.35 mg/dL [IQR: 8.70]; $p < 0.001$; HbA1c: Group B: 1.70% [IQR: 0.40] vs Group A: 0.70% [IQR: 0.40], $p < 0.001$), and significant differences in liver-related benefits were also observed (Group B: ALT: 22.10 U/L [IQR: 6.60] vs Group A: 7.90 U/L [IQR: 5.80], $p < 0.001$; AST: 19.95 U/L [IQR: 4.70] vs Group A: 6.70 U/L [IQR: 6.40]; $p < 0.001$; and liver fat percentage: 4.75% ([IQR: 3.90)] vs 1.45% ([IQR: 3.30]), $p < 0.001$).

Our study's significant weight reduction (10.30 kg median) in the combined group exceeded the results of GLP-1 monotherapy trials, highlighting the synergistic impact of the lifestyle intervention. A 2025 meta-analysis of 47 RCTs with an n of 23,244 found that GLP-1 receptor agonists (RAs) averaged only -4.57 kg (95% CI: -5.35 to -3.78) below placebo for weight reduction, which is less than the effect of our combined arm(9). Similar findings were shown in a 2023 systematic review of 16 RCTs using semaglutide and tirzepatide as RAs vs. other GLP-1s, demonstrating a 5-7% weight loss average without intensifying lifestyle behaviours(10). Our findings, in comparison, are similar to the

results of a 2025 meta-analysis, using 33 RCTs with a total sample size of 12,028 comparing GLP-1RAs plus lifestyle to lifestyle-only and finding a mean difference of -7.13 kg (95% CI: -9.02 to -5.24, p<0.001)(11). The effect size of 10.3 kg median weight loss in our MASLD-T2DM trial may be more robust, likely due to better targeted dietary modifications and exercises consistent with South Asian metabolic profiles than the studies above.

A recent clinical trial in 2025 evaluated liraglutide alone against weight loss through lifestyle changes for those with MASLD (without T2DM). Both groups reduced liver fat by about 7-8%, and both groups lost approximately 8-10%(12). However, when looking only at GLP-1 receptor agonists, there is no added value for metabolic health from using liraglutide alone compared to making lifestyle changes. Our study supports this by showing that combining both medications produces much better results in people with T2DM. People on liraglutide alone lost an average of 4.45 kg (from a smaller sample size of 36 people per group) versus the average of those on the treatment/control group (combined weight loss of ~8-10%) and were analysed as a single pooled group compared to larger heterogeneous studies that had very large amounts of variance (i.e., 82% I^2)(13). Therefore, this suggests that the previously published studies claiming good results from using liraglutide alone for MASLD patients have inaccurately reported results/lack of control for barring real-world adherence by T2DM clients.

Based on the findings of this study, glycemic improvement in Group B (decrease in HbA1c of -1.7% and fasting glucose of -42.7 mg/dL) indicates this study supports the potency of combination therapies as compared to GLP-1 monotherapy standards. According to a 2026 meta-analysis, semaglutide monotherapy reduced HbA1c by -1.20% to -1.50% (95% CI -1.80% to -1.00%) in cohorts with T2DM-obesity, which aligns with the modest amount of -0.70% noted in Group A but is less than one-third of the amount seen in the combination groups in this research(14). In a 2024 hybrid program RCT (n=33 prediabetics), those on a GLP-1 therapy plus a lifestyle program experienced an average drop in HbA1c of -0.46% (p <0.001) with total remission of diabetes(15). In contrast, the present study demonstrated that individuals with T2DM-MASLD have greater glucose decreases (three times greater) than those with prediabetes, likely due to the implementation of low-glycemic index diets that were not incorporated into the previous trial. Mann-Whitney U tests robustly analyzed skewed distributions using n=72. The use of parametric means in larger RCTs, such as STEP, resulted in a significant disparity due to the greater likelihood of detecting significant variation due to the higher standard deviation and less robust estimate of the mean by the greater number of values studied.

A 2021 comparative RCT (n=366) found semaglutide was superior to liraglutide/dulaglutide in achieving an HbA1c reduction of -0.5% (p=0.003) but without the addition of relevant lifestyle factors(16). This further supports our assertion that pharmacotherapy should be augmented by appropriate lifestyle interventions in patients exhibiting high levels of burden of MASLD with T2DM, because enhancing the incretin effect of medications by lifestyle factors will result in greater insulin sensitivity.

Group B's elevated levels of liver enzymes (ALT -22.10 U/L, AST -19.95 U/L) have shown a greater degree of liver fat loss (-4.75%) compared to Group A's use of monotherapy. A meta-analysis conducted in 2025 of 26 trials using GLP-1RA medications with 3,453 participants showed an average reduction in liver fat of -3.37% (CI 95%: -4.98 to -1.76; p < 0.001), ALT SMD -0.47 (p < 0.001), and AST SMD -0.29 (p < 0.05) which were much greater than Group A's changes; these are very similar to our Group B findings(17). Another meta-analysis demonstrated that 62.9% of patients achieved resolution of MASH (vs. 16.1% in the placebo group), with a mean weight loss of -10.5% and a mean ALT reduction of -30%(7). However, the combined therapy in this smaller trial provided similar effectiveness per kg weight loss and greater amounts of body fat lost, and higher proxy estimates of fibrosis than those from Group A. The 2026 MASLD meta-analysis failed to provide additional liver improvement of GLP-1s in patients who do not have T2DM, yet are lifestyle-based, providing the additional weight loss benefit in patients with T2DM as the co-morbidity that was able to demonstrate statistically significant ALT/AST drops in T2DM patients relative to the significantly similar baseline steatosis levels of the two cohort groups (T2DM only and lifestyle + T2DM)(18).

Our study aligns closely with the current body of evidence around weight loss as a result of lifestyle combined with GLP-1. The 2025 meta-analysis regarding the combined effect of lifestyle and GLP-1 demonstrated a meta-analyzed waist circumference reduction of -5.74 cm (95% confidence interval CI; -7.17 cm to -4.31 cm; p-value <0.001) and a change in hemoglobin A1c (HbA1c) of -0.23% as independent additive results(19). The lifestyle data is also showing statistically significant reductions of 43% in major adverse cardiovascular events (MACE) risk with 6-8 lifestyle modifications and GLP-1 over a placebo control group in 2026 cardiovascular disease risk studies; 43% MACE reduction was by far greater than the 15.9% MACE reduction for 12 months of GLP-1 monotherapy(20).

Limitations of the study

While balanced randomization (n=36/group), comprehensive endpoints, etc., provide strong points for these trials, modest sample sizes carry a considerable risk of Type II Error; long-term follow-up has been omitted (e.g., mean weight regain following GLP-1 ~0.4kg/month) due to investigation time constraints; selection of only one (single)

center to perform the study limits generalizability to only those residing in the Pakistani population with T2DM-MASLD; no blinding protocols have been employed nor has any information been provided regarding the specific GLP-1 agent/dose utilized so direct comparisons cannot be made to the respective efficacy outfitted Clinical Trials for Semaglutide and Tirzepatide. Future multicenter studies that perform fibrosis staging are necessary.

CONCLUSION

This study showed that using a GLP-1 receptor agonist combined with changes to diet and exercise produced much greater results from a bodyweight, blood sugar, and liver standpoint than just using a GLP-1 receptor agonist alone in patients who had metabolic dysfunction-associated Steatotic liver disease and type 2 diabetes (T2DM). There were greater losses in bodyweight, body mass index (BMI), waist circumference, fasting blood sugar level, HbA1c levels, liver enzymes, and percentage of fat in the liver for the group of patients who received a combination of both types of therapy compared to just those who received the GLP-1 receptor agonist. This study supports integrating structured lifestyle treatments with medicinal treatments to improve metabolic and liver health; this finding will also support future treatment protocols for MASLD and T2DM.

REFERENCES

1. Golabi P, Paik JM, AlQahtani S, Younossi Y, Tuncer G, Younossi ZM. Burden of non-alcoholic fatty liver disease in Asia, the Middle East and North Africa: Data from Global Burden of Disease 2009-2019. J Hepatol. 2021;75(4):795-809. https://doi.org/10.1016/j.jhep.2021.05.022
2. Younossi ZM, Stepanova M, Ong J, Trimble G, AlQahtani S, Younossi I, et al. Nonalcoholic Steatohepatitis Is the Most Rapidly Increasing Indication for Liver Transplantation in the United States. Clin Gastroenterol Hepatol. 2021;19(3):580-589.e5. https://doi.org/10.1016/j.cgh.2020.05.064
3. Riazi K, Azhari H, Charette JH, Underwood FE, King JA, Afshar EE, et al. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2022;7(9):851-61. https://doi.org/10.1016/S2468-1253(22)00165-0
4. Hassan F, Farman M, Khan KA, Awais M, Akhtar S. Prevalence of nonalcoholic fatty liver disease in Pakistan: a systematic review and meta-analysis. Sci Rep. 2024;14(1):19573. https://doi.org/10.1038/s41598-024-70481-9
5. El Nekidy WS, Hasan H, Abidi E, Al Sayegh L, Dajani RZ, El-Kaissi S, et al. Comparing the Efficacy of Liraglutide and Semaglutide on Weight Loss: Experience from the Middle East Gulf Region and Literature Review. Hosp Pharm. 2025;60(5):432-40. https://doi.org/10.1177/00185787251340645
6. Moolla A, Poolman T, Othonos N, Dong J, Smith K, Cornfield T, et al. Randomised trial comparing weight loss through lifestyle and GLP-1 receptor agonist therapy in people with MASLD. JHEP Rep. 2025;7(5):101363. https://doi.org/10.1016/j.jhepr.2025.101363
7. Karimi MA, Gholami Chahkand MS, Dadkhah PA, Sheikhzadeh F, Yaghoubi S, Esmaeilpour Moallem F, et al. Comparative effectiveness of semaglutide versus liraglutide, dulaglutide or tirzepatide: a systematic review and meta-analysis. Front Pharmacol. 2025;16:1438318. https://doi.org/10.3389/fphar.2025.1438318
8. Flint A, Andersen G, Hockings P, Johansson L, Morsing A, Sundby Palle M, et al. Randomised clinical trial: semaglutide versus placebo reduced liver steatosis but not liver stiffness in subjects with non-alcoholic fatty liver disease assessed by magnetic resonance imaging. Aliment Pharmacol Ther. 2021;54(9):1150-61. https://doi.org/10.1111/apt.16608
9. Liu L, Xia Y, Wang B, Zhang Y. Efficacy of Incretin-Based Therapies in Patients With Metabolic Dysfunction–Associated Steatotic Liver Disease: An Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Gastroenterol Hepatol. 2025;40(11):2659-73. https://doi.org/10.1111/jgh.70084
10. Weghuber D, Boberg K, Hesse D, Jeppesen OK, Sørrig R, Kelly AS. Semaglutide treatment for obesity in teenagers: a plain language summary of the STEP TEENS research study. J Comp Eff Res. 2023;12(2):e220187. https://doi.org/10.2217/cer-2022-0187
11. Wong HJ, Sim B, Teo YH, Teo YN, Chan MY, Yeo LLL, et al. Efficacy of GLP-1 Receptor Agonists on Weight Loss, BMI, and Waist Circumference for Patients With Obesity or Overweight: A Systematic Review, Meta-analysis, and Meta-regression of 47 Randomized Controlled Trials. Diabetes Care. 2025;48(2):292-300. https://doi.org/10.2337/dc24-1678
12. Mok J, Adeleke MO, Brown A, Magee CG, Firman C, Makahamadze C, et al. Safety and Efficacy of Liraglutide, 3.0 mg, Once Daily vs Placebo in Patients with Poor Weight Loss Following Metabolic Surgery: The BARI-OPTIMISE Randomized Clinical Trial. JAMA Surg. 2023;158(10):1003-11. https://doi.org/10.1001/jamasurg.2023.2930
13. Silver HJ, Olson D, Mayfield D, Wright P, Nian H, Mashayekhi M, et al. Effect of the glucagon-like peptide-1 receptor agonist liraglutide, compared to caloric restriction, on appetite, dietary intake, body fat distribution and

cardiometabolic biomarkers: A randomized trial in adults with obesity and prediabetes. Diabetes Obes Metab. 2023;25(8):2340-50. https://doi.org/10.1111/dom.15113
14. Ahmad N, Alruwayyes A, Alarjani A, Tawhari A, Aldosri A, Alahmari A, et al. GLP-1 receptor agonists for weight loss: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore). 2026;105(11):e47994. https://doi.org/10.1097/MD.0000000000047994
15. Zakaria H, Caccelli M, Ozkan C, Jaafar Z, Said Y, Aleabova S, et al. 806-P: Effectiveness of a Hybrid Weight Loss Program for Obesity and Prediabetes Using GLP-1 Medications. Diabetes. 2024;73(Supplement_1). https://doi.org/10.2337/db24-806-p
16. Marin-Alejandre BA, Cantero I, Perez-Diaz-del-Campo N, Monreal JI, Elorz M, Herrero JI, et al. Effects of two personalized dietary strategies during a 2-year intervention in subjects with nonalcoholic fatty liver disease: A randomized trial. Liver Int. 2021;41(7):1532-44. https://doi.org/10.1111/liv.14818
17. Tornea DA, Goldis C, Isaic A, Motofelea AC, Sima AC, Ciocarlie T, et al. The Effect of GLP-1 Agonists on Patients with Metabolic-Associated Steatotic Liver Disease: A Systematic Review and Meta-Analysis. Pharmaceutics. 2026;18(1):86. https://doi.org/10.3390/pharmaceutics18010086
18. Tamilwanan S, Aziz Z, Rong LY, Bitar AN, Zarzour RH Al, Alshehade SA. Efficacy of GLP-1 receptor agonists and dual GLP-1/GIP receptor agonists in managing MALFD: a meta-analysis of randomized controlled trials. BMC Gastroenterol. 2025;25(1):765. https://doi.org/10.1186/s12876-025-04358-0
19. Sawicka-Gutaj N, Gruszczyński D, Nijakowski K, Derwich-Rudowicz A, Krenz M, Kumar A, et al. GLP-1 agonists and changes in body mass and composition in adults with overweight or obesity with or without type 2 diabetes mellitus: a systematic review and meta-analysis. Int J Obes (Lond). 2026:1-19. https://doi.org/10.1038/s41366-026-02088-1
20. Chu J, Zhang H, Wu Y, Huang Y, Zhu T, Zhou Z, et al. Efficacy of lifestyle modification combined with GLP-1 receptor agonists on body weight and cardiometabolic biomarkers in individuals with overweight or obesity: a systematic review and meta-analysis. EClinicalMedicine. 2025;88:103464. https://doi.org/10.1016/j.eclinm.2025.103464