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Original Article

Comparison of the Effectiveness and Safety of GLP-1 Receptor Agonists in Type 2 Diabetes Mellitus Patients with Overweight or Obesity

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ABSTRACT

Background: Glucagon-like peptide-1 receptor agonists improve glycemic control and support body weight reduction in patients with type 2 diabetes mellitus, but local comparative evidence between semaglutide and liraglutide in patients with overweight or obesity remains limited. Objective: To compare the 24-week effectiveness and short-term safety of once-weekly semaglutide versus once-daily liraglutide among adults with type 2 diabetes mellitus and overweight or obesity. Methods: This prospective, non-randomized, two-arm comparative study was conducted at Nishtar Hospital, Multan, Pakistan, from January 2025 to December 2025. Ninety-two adults with type 2 diabetes mellitus, HbA1c 7.0–10.0%, and body mass index ≥25 kg/m² were assigned by systematic alternate allocation to semaglutide (n=46) or liraglutide (n=46), alongside lifestyle counseling and background antidiabetic care. Outcomes were assessed at 24 weeks. Results: Semaglutide was associated with greater HbA1c reduction than liraglutide (-1.55 ± 0.62% vs -1.08 ± 0.59%; mean difference -0.47%, 95% CI -0.72 to -0.22; p<0.001) and greater body weight reduction (-5.8 ± 3.1 kg vs -3.2 ± 2.6 kg; mean difference -2.60 kg, 95% CI -3.79 to -1.41; p<0.001). At least 5% body weight reduction was achieved by 58.7% versus 32.6% of participants, respectively (p=0.012). Gastrointestinal symptoms were the most frequent adverse events and were comparable between groups. No severe hypoglycemia, confirmed pancreatitis, or acute gallbladder event was observed. Conclusion: Semaglutide was associated with greater glycemic and weight reduction than liraglutide over 24 weeks, with broadly comparable short-term tolerability. Treatment selection should consider efficacy, safety, cost, availability, renal status, adherence likelihood, and patient preference. Keywords: GLP-1 receptor agonists; semaglutide; liraglutide; type 2 diabetes mellitus; obesity; overweight; HbA1c.

INTRODUCTION

Type 2 diabetes mellitus is frequently accompanied by overweight or obesity, and the coexistence of these conditions intensifies insulin resistance, complicates glycemic control, increases cardiovascular and kidney risk, and contributes to a higher long-term health care burden. Contemporary diabetes management has therefore moved beyond glucose lowering alone and increasingly emphasizes treatment strategies that address body weight, cardiometabolic risk, renal vulnerability, treatment adherence, and patient-centered therapeutic selection. Current consensus recommendations support the use of glucose-lowering agents with favorable effects on body weight and cardiometabolic outcomes when clinically appropriate, particularly in patients with type 2 diabetes mellitus who have excess adiposity or established risk factors for vascular and renal complications (1). In this therapeutic context, glucagon-like peptide-1 receptor agonists have become an important class because they improve glycemic control through glucose-dependent insulin secretion, suppression of inappropriate glucagon

release, delayed gastric emptying, appetite regulation, and central satiety-related mechanisms, while maintaining a low intrinsic risk of hypoglycemia when not combined with insulin or sulfonylureas (2,3).

The clinical relevance of glucagon-like peptide-1 receptor agonists is especially important for adults with type 2 diabetes mellitus and overweight or obesity because treatment-related weight gain may worsen insulin resistance, metabolic risk, and long-term adherence, whereas clinically meaningful weight reduction can improve glycemic control, reduce treatment burden, and support broader cardiometabolic risk reduction. Semaglutide and liraglutide are both established glucagon-like peptide-1 receptor agonists, but they differ in dosing schedule, pharmacokinetic profile, dose escalation pattern, and magnitude of glycemic and weight-related response. Once-weekly semaglutide may offer adherence advantages over once-daily liraglutide, while differences in efficacy, tolerability, cost, availability, and patient preference may influence real-world treatment selection. In the SUSTAIN 10 trial, once-weekly semaglutide 1.0 mg produced greater HbA1c and body weight reduction than once-daily liraglutide 1.2 mg among adults with inadequately controlled type 2 diabetes mellitus receiving oral antidiabetic therapy, supporting the need to compare individual agents within the same therapeutic class rather than assuming a uniform class effect (4).

Evidence from head-to-head glucagon-like peptide-1 receptor agonist trials further indicates that agents within this class are not clinically interchangeable in terms of glycemic efficacy, weight reduction, and tolerability. Semaglutide demonstrated greater HbA1c and body weight reduction than dulaglutide in SUSTAIN 7, while dulaglutide was non-inferior to liraglutide for HbA1c reduction in AWARD-6, and DURATION-6 showed clinically relevant differences between once-weekly exenatide and once-daily liraglutide (5–7). These comparative data demonstrate that drug-specific evaluation remains important when choosing therapy for patients who require improvement in both glycemic control and body weight. Beyond metabolic endpoints, cardiovascular and renal safety are also clinically relevant in this population. Liraglutide reduced major adverse cardiovascular outcomes in the LEADER trial, while semaglutide demonstrated cardiovascular benefit in SUSTAIN-6, and higher-dose semaglutide produced clinically meaningful weight reduction among adults with overweight or obesity and type 2 diabetes mellitus in STEP 2 (8–10).

Despite the availability of international trial evidence, most head-to-head data have been generated in multinational controlled trial settings, and local hospital-based comparative evidence from Pakistan remains limited. This gap is clinically important because real-world therapeutic decisions in local practice are influenced not only by efficacy and safety, but also by affordability, availability, injection frequency, background antidiabetic therapy, patient acceptance, and follow-up feasibility. Comparative data from routine endocrine, medical, and nephrology-linked care settings may therefore provide practical evidence for clinicians managing patients with type 2 diabetes mellitus and excess body weight. Based on this rationale, the present study aimed to compare the 24-week glycemic effectiveness, body weight reduction, and short-term safety profile of once-weekly semaglutide versus once-daily liraglutide among adults with type 2 diabetes mellitus and overweight or obesity treated at Nishtar Hospital, Multan. The study hypothesis was that semaglutide would be associated with greater reduction in HbA1c and body weight than liraglutide over 24 weeks, with a comparable short-term tolerability profile.

MATERIALS AND METHODS

This prospective, non-randomized, two-arm comparative study was conducted at the Department of Medicine and Endocrinology, with clinical support from the Nephrology Department, Nishtar Hospital, Multan, Pakistan. The study was conducted from January 2025 to December 2025, and each enrolled participant was followed for 24 weeks after initiation of glucagon-like peptide-1 receptor agonist therapy. The study compared once-weekly semaglutide with once-daily liraglutide in adults with type 2 diabetes mellitus and overweight or obesity who required injectable glucagon-like peptide-1 receptor agonist therapy because of inadequate glycemic control, excess body weight, or the need for a treatment option

with favorable metabolic effects in addition to standard background diabetes care. The design was selected to reflect routine hospital-based clinical practice while allowing structured comparison of effectiveness and safety outcomes between the two treatment groups.

The sample size was calculated for comparison of two independent means using change in HbA1c from baseline to 24 weeks as the primary endpoint. The expected between-group difference in HbA1c reduction was 0.45%, with a pooled standard deviation of 0.75%, 95% confidence level, 80% statistical power, and a two-sided significance level. The minimum required sample size was 44 participants per group. To account for possible non-response, treatment discontinuation, or incomplete follow-up assessment, 46 participants were included in each group, resulting in a total sample size of 92 participants.

Adults aged 18–70 years with previously diagnosed type 2 diabetes mellitus, HbA1c between 7.0% and 10.0%, and body mass index of 25 kg/m² or greater were eligible for inclusion. Participants were required to be willing to receive injectable glucagon-like peptide-1 receptor agonist therapy and to attend scheduled follow-up visits. Patients were excluded if they had type 1 diabetes mellitus, pregnancy, lactation, previous pancreatitis, active gallbladder disease, severe gastrointestinal disease, personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, estimated glomerular filtration rate below 30 mL/min/1.73 m², decompensated liver disease, recent acute coronary syndrome or stroke within the preceding three months, active malignancy, known hypersensitivity to either study drug, or previous use of any glucagon-like peptide-1 receptor agonist during the preceding three months.

Eligible participants were enrolled consecutively after screening against the eligibility criteria and after obtaining written informed consent. Treatment assignment was performed by systematic alternate allocation after eligibility confirmation, with participants assigned sequentially to the semaglutide or liraglutide group. Because allocation was systematic rather than concealed randomization, the study was analyzed and interpreted as a prospective comparative study rather than a randomized controlled trial. To reduce measurement bias, glycemic and biochemical outcomes were assessed through the hospital laboratory using routine standardized procedures, and anthropometric measurements were obtained using the same measurement approach at baseline and follow-up. Background diabetes care, lifestyle advice, and follow-up counseling were standardized across both groups as far as clinically feasible.

Participants in the semaglutide group received subcutaneous semaglutide once weekly, initiated at 0.25 mg weekly for four weeks and increased to 0.5 mg weekly thereafter, with escalation to 1.0 mg weekly when clinically indicated and tolerated. Participants in the liraglutide group received subcutaneous liraglutide once daily, initiated at 0.6 mg daily for one week and increased to 1.2 mg daily, with escalation to 1.8 mg daily when clinically required and tolerated. All participants received standardized counseling regarding diet, physical activity, medication adherence, injection technique, self-monitoring, recognition of hypoglycemia, and reporting of gastrointestinal symptoms or other adverse events. Stable background antidiabetic therapy was continued where appropriate, and changes in other glucose-lowering drugs were avoided unless required for safety, intolerance, hypoglycemia prevention, or rescue glycemic control.

Baseline data included age, sex, duration of diabetes, body weight, height, body mass index, systolic and diastolic blood pressure, HbA1c, fasting plasma glucose, serum creatinine, estimated glomerular filtration rate, background metformin use, sulfonylurea use, sodium-glucose cotransporter-2 inhibitor use, hypertension, and chronic kidney disease status. Body weight was measured on a calibrated scale with participants wearing light clothing and no shoes. Height was measured using a standard stadiometer, and body mass index was calculated as weight in kilograms divided by height in meters squared. HbA1c and fasting plasma glucose were measured at baseline and at 24 weeks. Serum creatinine and estimated glomerular filtration rate were assessed at baseline and follow-up for renal

safety monitoring. Follow-up visits were used to assess treatment tolerance, adherence, dose escalation, rescue treatment requirement, adverse events, and completion of the 24-week outcome assessment.

The primary effectiveness outcome was mean change in HbA1c from baseline to 24 weeks. Secondary effectiveness outcomes included mean change in body weight, mean change in body mass index, mean change in fasting plasma glucose, final HbA1c, final body weight, proportion of participants achieving HbA1c below 7.0%, proportion achieving at least 5% body weight reduction, combined achievement of HbA1c below 7.0% with at least 5% body weight reduction, and absence of rescue treatment requirement. Rescue treatment was defined as clinically required intensification or addition of glucose-lowering therapy during follow-up because of inadequate glycemic control or safety-related need, as determined during routine clinical review. Safety outcomes included any gastrointestinal symptom, nausea, vomiting, diarrhea, constipation, abdominal pain, injection-site reaction, symptomatic hypoglycemia, severe hypoglycemia, drug discontinuation due to intolerance, suspected pancreatitis, gallbladder-related symptoms, and clinically relevant deterioration in renal function during follow-up. Symptomatic hypoglycemia was defined as symptoms consistent with hypoglycemia with or without documented low capillary glucose, while severe hypoglycemia was defined as an episode requiring assistance from another person. Drug discontinuation was recorded when treatment was stopped because of intolerance or adverse effects; participants who discontinued treatment but completed the 24-week assessment were retained in the outcome analysis.

Data were entered, cleaned, and analyzed using SPSS version 26.0. Continuous variables were summarized as mean ± standard deviation, while categorical variables were summarized as frequency and percentage. Baseline comparability between groups was assessed using independent samples t-test for normally distributed continuous variables, Mann–Whitney U test for non-normally distributed variables, and chi-square test or Fisher exact test for categorical variables, as appropriate. The primary comparison was the between-group difference in mean HbA1c change from baseline to 24 weeks. Mean differences with 95% confidence intervals were calculated for continuous outcomes, while risk ratios, odds ratios, risk differences, and 95% confidence intervals were calculated for key categorical outcomes where applicable. Because the study used non-random alternate allocation, adjusted analyses were planned for major effectiveness outcomes to reduce the influence of confounding. Linear regression or analysis of covariance was used for continuous outcomes, adjusting for clinically relevant baseline variables including baseline HbA1c, baseline body weight or body mass index, age, sex, duration of diabetes, background antidiabetic therapy, hypertension, and baseline estimated glomerular filtration rate where applicable. Logistic regression was planned for categorical outcomes such as HbA1c below 7.0% and at least 5% body weight reduction, using the same clinically relevant covariates where model stability permitted.

The primary analysis included participants with baseline and 24-week outcome data. Missing data, if present, were assessed for pattern and extent before analysis, and complete-case analysis was used for outcomes with available paired baseline and follow-up data. Statistical tests were two-sided, and a p-value of ≤ 0.05 was considered statistically significant. Data integrity was supported through coded study records, review of entered values against source documents, consistency checks for outlying or implausible values, and maintenance of confidentiality throughout data handling.

Ethical approval was obtained through the institutional ethical review process of Nishtar Hospital, Multan, before study commencement, and written informed consent was obtained from all participants before enrollment. The study was conducted in accordance with standard ethical principles for human participant research, including voluntary participation, confidentiality, and the right to withdraw from treatment or follow-up without compromise to routine clinical care.

RESULTS

A total of 92 adults with type 2 diabetes mellitus and overweight or obesity were included in the analysis, with 46 participants assigned to once-weekly semaglutide and 46 participants assigned to once-daily liraglutide. All enrolled participants had baseline and 24-week outcome data available for the primary analysis. During follow-up, three participants in the semaglutide group and two participants in the liraglutide group discontinued the assigned study drug because of intolerance; however, these participants remained available for the 24-week assessment and were retained in the outcome analysis. Rescue treatment was not required in 41 participants (89.1%) in the semaglutide group and 37 participants (80.4%) in the liraglutide group, with no statistically significant between-group difference.

Table 1. Participant Disposition and Follow-up Status

Variable	Semaglutide (n=46)	Liraglutide (n=46)	Effect Estimate (95% CI)	p-value
Enrolled participants, n	46	46	—	—
Participants with baseline data, n (%)	46 (100.0)	46 (100.0)	—	—
Participants with 24-week outcome data, n (%)	46 (100.0)	46 (100.0)	—	—
Drug discontinuation due to intolerance, n (%)	3 (6.5)	2 (4.3)	RR 1.50 (0.26 to 8.56)	1.000
No rescue treatment required, n (%)	41 (89.1)	37 (80.4)	RR 1.11 (0.92 to 1.34)	0.244

RR: relative risk; CI: confidence interval. Effect estimates are unadjusted.

Baseline demographic, clinical, and biochemical characteristics were broadly comparable between the two groups. The mean age was 49.6 ± 8.7 years in the semaglutide group and 50.2 ± 9.1 years in the liraglutide group, with a mean difference of -0.60 years (95% CI -4.29 to 3.09; p=0.747). Male participants comprised 50.0% of the semaglutide group and 45.7% of the liraglutide group. Baseline HbA1c was similar between groups, with mean values of 8.76 ± 0.67% and 8.71 ± 0.71%, respectively, giving a mean difference of 0.05% (95% CI -0.24 to 0.34; p=0.729). Baseline body weight, body mass index, fasting plasma glucose, estimated glomerular filtration rate, diabetes duration, and hypertension frequency also showed no statistically significant differences.

Table 2. Baseline Characteristics of Study Participants

Variable	Semaglutide (n=46)	Liraglutide (n=46)	Effect Estimate (95% CI)	p-value
Age, years	49.6 ± 8.7	50.2 ± 9.1	MD -0.60 (-4.29 to 3.09)	0.747
Male gender, n (%)	23 (50.0)	21 (45.7)	OR 1.19 (0.53 to 2.67)	0.678
Duration of diabetes, years	7.1 ± 4.0	7.4 ± 4.3	MD -0.30 (-2.02 to 1.42)	0.731
HbA1c, %	8.76 ± 0.67	8.71 ± 0.71	MD 0.05 (-0.24 to 0.34)	0.729
Body weight, kg	86.4 ± 11.2	85.1 ± 10.6	MD 1.30 (-3.22 to 5.82)	0.569
BMI, kg/m²	32.6 ± 4.1	32.2 ± 3.9	MD 0.40 (-1.26 to 2.06)	0.633
Fasting plasma glucose, mg/dL	176.2 ± 31.5	172.8 ± 29.7	MD 3.40 (-9.29 to 16.09)	0.596
eGFR, mL/min/1.73 m²	81.4 ± 16.2	79.8 ± 15.7	MD 1.60 (-5.01 to 8.21)	0.632
Hypertension, n (%)	25 (54.3)	27 (58.7)	OR 0.84 (0.37 to 1.89)	0.674

BMI: body mass index; CI: confidence interval; eGFR: estimated glomerular filtration rate; HbA1c: glycated hemoglobin; MD: mean difference; OR: odds ratio. Effect estimates are unadjusted.

At 24 weeks, semaglutide was associated with greater improvement in glycemic and anthropometric outcomes than liraglutide. Mean HbA1c decreased by 1.55 ± 0.62 percentage points in the semaglutide group compared with 1.08 ± 0.59 percentage points in the liraglutide group, producing a between-group mean difference of -0.47% (95% CI -0.72 to -0.22; p<0.001). Final HbA1c was also lower with semaglutide than liraglutide, with mean values of 7.20 ± 0.64% and 7.63 ± 0.71%, respectively (MD -0.43%, 95% CI -0.71 to -0.15; p=0.003). Body weight reduction was greater in the semaglutide group, with a mean reduction of 5.8 ± 3.1 kg compared with 3.2 ± 2.6 kg in the liraglutide group, yielding a mean difference of -2.60 kg (95% CI -3.79 to -1.41; p<0.001). Although final absolute body weight did not differ significantly between groups, the magnitude of weight change from baseline favored semaglutide, indicating a stronger treatment-associated reduction over the 24-week follow-up period. BMI reduction and fasting plasma glucose reduction also favored semaglutide, while change in estimated glomerular filtration rate did not differ significantly between groups.

Table 3. Change in Glycemic, Anthropometric, and Renal Parameters at 24 Weeks

Outcome	Semaglutide (n=46)	Liraglutide (n=46)	Mean Difference (95% CI)	p-value
HbA1c change, %	-1.55 ± 0.62	-1.08 ± 0.59	-0.47 (-0.72 to -0.22)	<0.001
Final HbA1c, %	7.20 ± 0.64	7.63 ± 0.71	-0.43 (-0.71 to -0.15)	0.003
Body weight change, kg	-5.8 ± 3.1	-3.2 ± 2.6	-2.60 (-3.79 to -1.41)	<0.001
Final body weight, kg	80.6 ± 10.8	81.9 ± 10.3	-1.30 (-5.67 to 3.07)	0.556
BMI change, kg/m²	-2.1 ± 1.1	-1.2 ± 0.9	-0.90 (-1.32 to -0.48)	<0.001
Fasting plasma glucose change, mg/dL	-38.6 ± 26.2	-26.4 ± 24.7	-12.20 (-22.75 to -1.65)	0.024
eGFR change, mL/min/1.73 m²	0.8 ± 6.5	-0.6 ± 5.8	1.40 (-1.15 to 3.95)	0.279

BMI: body mass index; CI: confidence interval; eGFR: estimated glomerular filtration rate; HbA1c: glycated hemoglobin. Negative values for HbA1c, weight, BMI, and fasting plasma glucose indicate reduction from baseline. Effect estimates are unadjusted.

Categorical effectiveness outcomes showed a favorable pattern for semaglutide, particularly for clinically meaningful weight reduction. HbA1c below 7.0% at 24 weeks was achieved by 23 participants (50.0%) receiving semaglutide and 14 participants (30.4%) receiving liraglutide. This difference approached but did not reach conventional statistical significance (RR 1.64, 95% CI 0.97 to 2.77; p=0.056). A body weight reduction of at least 5% was achieved by 27 participants (58.7%) in the semaglutide group compared with 15 participants (32.6%) in the liraglutide group, representing a statistically significant higher probability of clinically meaningful weight loss with semaglutide (RR 1.80, 95% CI 1.11 to 2.91; p=0.012). The combined endpoint of HbA1c below 7.0% with at least 5% body weight reduction was achieved by 16 participants (34.8%) in the semaglutide group and 8 participants (17.4%) in the liraglutide group; this result showed a favorable numerical trend but did not reach statistical significance (RR 2.00, 95% CI 0.94 to 4.27; p=0.058).

Table 4. Categorical Effectiveness Outcomes at 24 Weeks

Outcome	Semaglutide (n=46)	Liraglutide (n=46)	Effect Estimate (95% CI)	p-value
HbA1c <7.0%, n (%)	23 (50.0)	14 (30.4)	RR 1.64 (0.97 to 2.77)	0.056
≥5% body weight reduction, n (%)	27 (58.7)	15 (32.6)	RR 1.80 (1.11 to 2.91)	0.012
HbA1c <7.0% and ≥5% weight loss, n (%)	16 (34.8)	8 (17.4)	RR 2.00 (0.94 to 4.27)	0.058
No rescue treatment required, n (%)	41 (89.1)	37 (80.4)	RR 1.11 (0.92 to 1.34)	0.244

CI: confidence interval; HbA1c: glycated hemoglobin; RR: relative risk. Effect estimates are unadjusted.

Gastrointestinal symptoms were the most frequent adverse events in both groups. Any gastrointestinal symptom was reported by 18 participants (39.1%) in the semaglutide group and 15 participants (32.6%) in the liraglutide group, with no statistically significant difference between treatments (RR 1.20, 95% CI 0.69 to 2.08; p=0.514). Nausea was the most common individual gastrointestinal symptom, occurring in 14 participants (30.4%) receiving semaglutide and 11 participants (23.9%) receiving liraglutide (RR 1.27, 95% CI 0.65 to 2.50; p=0.482). Vomiting, diarrhea, and constipation were infrequent and did not differ significantly between groups. Symptomatic hypoglycemia was uncommon, occurring in two participants (4.3%) in the semaglutide group and three participants (6.5%) in the liraglutide group, and no severe hypoglycemia was recorded in either group. Clinically relevant renal decline was uncommon, and no statistically significant difference was observed between groups. No confirmed pancreatitis or acute gallbladder event was reported during follow-up.

Overall, the 24-week results demonstrated greater treatment-associated improvement in HbA1c, body weight, BMI, and fasting plasma glucose among participants receiving semaglutide compared with those receiving liraglutide. The largest between-group differences were observed for body weight change, where semaglutide was associated with an additional 2.60 kg reduction, and for HbA1c change, where semaglutide was associated with an additional 0.47 percentage-point reduction. The categorical outcomes supported the same direction of effect, with semaglutide showing a statistically significant advantage for achieving at least 5% body weight reduction and favorable but borderline non-significant trends for HbA1c below 7.0% and the combined glycemic-weight endpoint. Safety outcomes were

broadly comparable, with gastrointestinal symptoms being the most frequent adverse events and no severe hypoglycemia, confirmed pancreatitis, or acute gallbladder event observed during follow-up.

Table 5. Safety and Tolerability Outcomes During Follow-up

Safety Outcome	Semaglutide (n=46)	Liraglutide (n=46)	Effect Estimate (95% CI)	p-value
Any gastrointestinal symptom, n (%)	18 (39.1)	15 (32.6)	RR 1.20 (0.69 to 2.08)	0.514
Nausea, n (%)	14 (30.4)	11 (23.9)	RR 1.27 (0.65 to 2.50)	0.482
Vomiting, n (%)	4 (8.7)	3 (6.5)	RR 1.33 (0.32 to 5.63)	1.000
Diarrhea, n (%)	5 (10.9)	6 (13.0)	RR 0.83 (0.27 to 2.54)	0.748
Constipation, n (%)	7 (15.2)	4 (8.7)	RR 1.75 (0.55 to 5.59)	0.338
Symptomatic hypoglycemia, n (%)	2 (4.3)	3 (6.5)	RR 0.67 (0.12 to 3.81)	1.000
Severe hypoglycemia, n (%)	0 (0.0)	0 (0.0)	Not estimable	—
Drug discontinuation due to intolerance, n (%)	3 (6.5)	2 (4.3)	RR 1.50 (0.26 to 8.56)	1.000
Clinically relevant renal decline, n (%)	1 (2.2)	2 (4.3)	RR 0.50 (0.05 to 5.32)	1.000
Confirmed pancreatitis, n (%)	0 (0.0)	0 (0.0)	Not estimable	—
Acute gallbladder event, n (%)	0 (0.0)	0 (0.0)	Not estimable	—

CI: confidence interval; RR: relative risk. Effect estimates are unadjusted. Severe hypoglycemia, confirmed pancreatitis, and acute gallbladder events were not observed in either group.

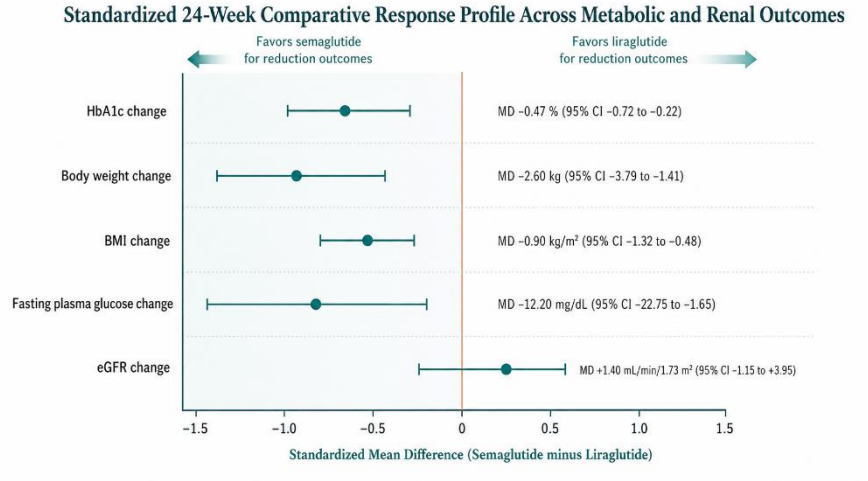

Figure 1 Standardized 24-week comparative response profile across metabolic and renal outcomes.

The figure presents standardized mean differences for continuous outcomes comparing semaglutide with liraglutide at 24 weeks, with horizontal error bars representing 95% confidence intervals and the vertical reference line indicating no between-group difference. Negative values favor semaglutide for reduction outcomes, showing greater improvement in HbA1c change, body weight change, BMI change, and fasting plasma glucose change, with mean differences of -0.47%, -2.60 kg, -0.90 kg/m², and -12.20 mg/dL, respectively. The eGFR estimate crossed the null line, with a mean difference of +1.40 mL/min/1.73 m², indicating no clear short-term renal function difference between groups. Overall, the response profile demonstrates that semaglutide was associated with stronger glycemic and anthropometric improvement, while renal function remained broadly comparable between treatment arms.

DISCUSSION

This prospective non-randomized comparative study found that once-weekly semaglutide was associated with greater 24-week improvement in glycemic and anthropometric outcomes than once-daily liraglutide among adults with type 2 diabetes mellitus and overweight or obesity. The mean additional HbA1c reduction with semaglutide was 0.47 percentage points, while the mean additional body weight reduction was 2.60 kg. These differences are clinically meaningful in a population requiring improvement in both glycemic control and excess body weight. The direction of effect was consistent across HbA1c, final HbA1c, body weight change, BMI change, fasting plasma glucose change, and the

categorical endpoint of at least 5% body weight reduction. At the same time, the findings should be interpreted in the context of the study design because treatment allocation was systematic rather than concealed randomization, and residual confounding cannot be fully excluded despite broadly comparable baseline characteristics.

The glycemic findings are consistent with international head-to-head evidence comparing semaglutide and liraglutide. In the SUSTAIN 10 trial, once-weekly semaglutide 1.0 mg produced greater HbA1c and body weight reduction than once-daily liraglutide 1.2 mg in adults with type 2 diabetes mellitus inadequately controlled on oral antidiabetic drugs (4). The magnitude of HbA1c reduction observed in the present study also aligns with the broader semaglutide trial program, including SUSTAIN 1, SUSTAIN 2, and SUSTAIN 4, where semaglutide produced significant glycemic improvement across different treatment backgrounds, including monotherapy, add-on oral therapy, and comparison with insulin glargine (11–13). Although the present study was conducted in routine hospital practice rather than under randomized trial conditions, its findings support the clinical impression that semaglutide may offer stronger glycemic lowering than liraglutide in patients who require both glucose reduction and weight-related benefit.

The greater body weight and BMI reduction associated with semaglutide is biologically plausible and clinically relevant. Glucagon-like peptide-1 receptor agonists reduce appetite, enhance satiety, slow gastric emptying during early treatment, and influence central pathways involved in food intake and reward-related eating behavior (2,3). Comparative evidence suggests that semaglutide has a stronger weight-lowering effect than several other agents in the same class. In SUSTAIN 7, semaglutide produced greater HbA1c and body weight reduction than dulaglutide, while SUSTAIN FORTE showed additional glycemic and weight benefit with semaglutide 2.0 mg compared with 1.0 mg in patients requiring intensified therapy (5,14). SUSTAIN 9 also demonstrated clinically relevant HbA1c and weight reduction when once-weekly semaglutide was added to sodium-glucose cotransporter-2 inhibitor therapy, which is relevant because combination cardiometabolic therapy is increasingly used in contemporary diabetes practice (15).

The categorical outcomes reinforce the practical importance of the weight-related findings. A body weight reduction of at least 5% was achieved by 58.7% of participants receiving semaglutide compared with 32.6% receiving liraglutide, indicating a statistically significant advantage for semaglutide in achieving a clinically meaningful weight-loss threshold. This outcome is important because even modest weight reduction can improve insulin resistance, blood pressure, lipid profile, mobility, treatment satisfaction, and long-term cardiometabolic risk. Although semaglutide 2.4 mg was used in the STEP obesity program rather than the diabetes doses used in the present study, STEP 2 confirmed that semaglutide can produce clinically meaningful weight reduction in adults with overweight or obesity and type 2 diabetes mellitus (10). STEP 1 and STEP 5 further support the durability and magnitude of semaglutide-associated weight reduction in adults with overweight or obesity, although those populations and dosing schedules differ from routine diabetes practice (16,17). Therefore, the present findings add locally relevant support for semaglutide use when body weight reduction is a major therapeutic goal in patients with type 2 diabetes mellitus.

The proportion of participants achieving HbA1c below 7.0% was higher with semaglutide than liraglutide, but this comparison approached rather than reached statistical significance. Similarly, the combined endpoint of HbA1c below 7.0% with at least 5% body weight reduction showed a favorable numerical trend for semaglutide but did not reach conventional statistical significance. These findings should not be overinterpreted as definitive superiority for categorical glycemic target achievement because the study had a modest sample size and may have been underpowered for binary secondary outcomes. Nevertheless, the consistency between continuous outcomes and categorical trends strengthens the clinical interpretation that semaglutide was associated with broader metabolic improvement over 24 weeks.

Safety and tolerability findings were broadly consistent with the known adverse-effect profile of glucagon-like peptide-1 receptor agonists. Gastrointestinal symptoms were the most common adverse events in both groups, with nausea being the most frequently reported individual symptom. The rate of any gastrointestinal symptom was numerically higher with semaglutide than liraglutide, but the difference was not statistically significant. Drug discontinuation due to intolerance was uncommon in both groups, and no severe hypoglycemia, confirmed pancreatitis, or acute gallbladder event was observed during follow-up. These findings are compatible with previous glucagon-like peptide-1 receptor agonist trials, where gastrointestinal symptoms were usually the most frequent tolerability issue and hypoglycemia risk remained low unless therapy was combined with insulin or sulfonylureas (4–7,10).

Renal function remained broadly stable over 24 weeks, with no statistically significant between-group difference in eGFR change. This finding should be interpreted cautiously because the study was not powered to evaluate kidney outcomes and excluded patients with advanced renal impairment. However, the absence of a short-term renal safety signal is reassuring in routine clinical practice, particularly in a population receiving endocrine, medical, and nephrology-linked care. Large cardiovascular outcome trials and meta-analyses have shown that glucagon-like peptide-1 receptor agonists reduce major adverse cardiovascular events and may provide favorable kidney-related effects in patients with type 2 diabetes mellitus (8,9,19,20). Oral semaglutide has also demonstrated cardiovascular safety in PIONEER 6, while injectable semaglutide and liraglutide have shown cardiovascular benefit in dedicated outcome trials (8,9,18). Although cardiovascular and renal endpoints were outside the scope of the present study, these broader data support careful selection of glucagon-like peptide-1 receptor agonists in patients with diabetes, excess body weight, and cardiometabolic risk.

The local clinical implications of these findings are important. In Pakistan, treatment selection is influenced not only by efficacy and tolerability but also by medication cost, availability, injection frequency, patient preference, follow-up feasibility, and background therapy. Once-weekly semaglutide may improve convenience compared with once-daily liraglutide, but affordability and uninterrupted access may limit its routine use for many patients. Liraglutide may remain a clinically reasonable option when semaglutide is unavailable, unaffordable, or not tolerated. Therefore, semaglutide may be preferred when greater glycemic and weight reduction is the dominant therapeutic goal and the drug is accessible and tolerated, while final treatment decisions should remain individualized according to clinical profile, renal function, gastrointestinal tolerability, adherence likelihood, and patient preference.

This study has several limitations. It was conducted at a single center with a modest sample size, which limits generalizability and reduces power for secondary categorical and safety outcomes. Treatment assignment was based on systematic alternate allocation rather than concealed randomization, creating potential selection bias and residual confounding. Although baseline characteristics were comparable between groups, unmeasured factors such as socioeconomic status, medication affordability, dietary adherence, physical activity, injection adherence, and clinician preference may have influenced outcomes. Follow-up was limited to 24 weeks, so long-term durability, cardiovascular outcomes, kidney outcomes, pancreatobiliary events, and cost-effectiveness could not be assessed. Adverse-event severity grading and detailed adherence quantification were also limited. Despite these limitations, the study provides useful local comparative evidence from routine hospital practice and supports the need for larger randomized or well-adjusted real-world studies evaluating semaglutide and liraglutide in South Asian populations with type 2 diabetes mellitus and excess body weight.

CONCLUSION

In adults with type 2 diabetes mellitus and overweight or obesity, once-weekly semaglutide was associated with greater 24-week reductions in HbA1c, body weight, BMI, and fasting plasma glucose than once-daily liraglutide, while short-term safety and tolerability outcomes were broadly comparable between groups. Semaglutide showed a statistically significant advantage for achieving at least 5% body

weight reduction and favorable non-significant trends for HbA1c target achievement and the combined glycemic-weight endpoint. Gastrointestinal symptoms were the most frequent adverse events, but drug discontinuation was uncommon, and no severe hypoglycemia, confirmed pancreatitis, or acute gallbladder event was observed. Because the study used systematic alternate assignment rather than concealed randomization, the findings should be interpreted as treatment-associated differences rather than definitive causal effects. Semaglutide may be preferred when greater glycemic and weight reduction is required, provided that cost, availability, renal status, tolerability, adherence, and patient preference support its use.

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