

Characterization of Safety and Efficacy of GLP-1 Receptor Agonists in Weight Reduction

Alaa M. Sadiq*, Alaa MA. Albayaty*, Ali SJ. Al Qaissi*

ABSTRACT

The outstanding impact of glucagon-like peptide-1 (GLP-1) receptor agonists on the management of obesity over a short period of time has become commonly applied in clinical settings. However, safety and efficacy data from multicenter studies are lacking. We sought to characterize the comparative safety and efficacy of semaglutide (SGT), liraglutide (LGT), and tirzepatide (TZT) for weight reduction over a short-term treatment duration. This prospective comparative study enrolled 129 participants with obesity, subdivided equally into three groups (n=43 each) treated with standard doses of SGT, LGT, and TZT over a 12-week period. Body mass index (BMI) decreased in all groups; however, a significant reduction in BMI was only associated with TZT (from 42 ± 7.3 to 35.3 ± 3.8 kg/m²; $P=0.0001$), whereas reductions were non-significant with SGT ($P=0.07$) and LGT ($P=0.13$). Moreover, TZT was associated with the lowest rate of adverse effects (headache: 17%; GIT symptoms: 16%) compared to SGT (42%; 37%) and LGT (35%; 42%). TZT has shown better positive outcomes compared to SGT and LGT. TZT induced higher weight reduction, less negative effect, and greater positive outcomes compared to SGT and LGT within the first 12 weeks of treatment.

Keywords: GLP-1 receptor agonists, tirzepatide, semaglutide, liraglutide, obesity, Weight reduction efficacy.

INTRODUCTION

Obesity has arisen as one of the most serious public health problems of this century, reaching epidemic global prevalence¹. Global epidemiological reports have confirmed that the rate of obesity is 1 in 8 people worldwide, with the rate having tripled since 1975². In the USA alone, the rate of obesity reached two-thirds, carrying a risk of developing chronic diseases, such as type 2 diabetes, cardiovascular disease, apnea, and neoplasm³. This increasingly escalating rate necessitates searching for effective and well-tolerated approaches for weight management⁴.

Lifestyle modifications incorporating corrected nutrition and improved physical exercise are the gold standard option for obesity management^{5,6}, their long-term effectiveness is frequently limited by physiological adaptations that promote weight regain^{7,8}. This limitation has driven substantial interest in pharmacological interventions that target the underlying neurohormonal pathways regulating appetite, satiety, and energy homeostasis^{9,10}. Among these, glucagon-like peptide-1 (GLP-1) receptor agonists have transformed the therapeutic landscape for obesity¹¹.

GLP-1 is an incretin hormone ubiquitously secreted by L-cells of the intestine in reaction to eating¹². It encourages glucose-dependent insulin release, blocks glucagon release, postpones gastric emptying, and encourages satiety via CNS effects on the hypothalamus and brainstem¹¹. GLP-1 receptor agonists mimic these physiological effects, resulting in diminished appetite, decreased food desires, and consequently weight loss¹¹. The GLP-1 receptor agonist officially approved for weight loss was liraglutide (2014), semaglutide (2021), and the dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist tirzepatide (2023)^{13,14}.

The GIP receptor agonist is supposed to encourage insulin release and block appetite, leading to greater weight loss than GLP-1 receptor agonism alone^{15,16}. This dualistic mechanism has placed TZT as a

distinctive, promising agent^{17,18}. Indeed, the landmark SURMOUNT-1 trial demonstrated mean weight loss of up to 20.9% at 72 weeks with tirzepatide 15 mg weekly, compared to 2.4% with placebo¹⁹. Similarly, the STEP-1 trial reported a 14.9% weight reduction with semaglutide 2.4 mg weekly at 68 weeks²⁰, while the SCALE trial showed an 8.0% mean weight loss with liraglutide 3.0 mg daily²¹. A recent network meta-analysis of randomised controlled trials in adults without diabetes confirmed the superiority of tirzepatide, particularly at higher doses, followed by semaglutide 2.4 mg and liraglutide 3.0 mg¹². Retatrutide, a triple GLP-1/GIP/glucagon receptor agonist, has shown even greater weight loss potential²².

It is recommended to use SGT and TZT as first-line therapy for weight reduction alongside lifestyle modifications for obesity (BMI ≥ 30 kg/m²) and overweight (BMI ≥ 27 –30 kg/m²) adult subjects who have one comorbidity; LGT could be used as an alternative. TZT is the preferred agent over SGT and LGT; however, comparative safety and efficacy remain less well characterized. Hence, the present study was designed to undermine the safety and efficacy of SGT, LGT, and TZT for weight reduction when used for up to three months at therapeutic doses.

MATERIALS AND METHODS

Study design: This prospective study enrolled a total of 129 patients and assigned them to three treatment groups (n=43): the SGT group (semaglutide), the LGT group (liraglutide), and the TZT group (tirzepatide). All patients in the three groups were standardized for lifestyle interventions with no actual changes in their diet, physical activity, or caloric intake during the study period.

Eligible participants were adults aged 18–65 years with a body mass index (BMI) ≥ 30 kg/m² or ≥ 27 kg/m² with at least one obesity-related comorbidity (e.g., prediabetes, hypertension, dyslipidemia). Pregnant or lactating mothers were excluded. Eligible patients were asked for informed consent before enrollment.

* College of Medicine, Ninevah University
Mosul, Iraq.
Email: alaa.ali@uoninevah.edu.iq

Dosing regimens: The drugs were injected subcutaneously based on FDA-approved dosing intervals. The doses were titrated steadily across the study period to diminish the gastrointestinal adverse effects. The dosing intervals of SGT were initiated at 0.25 mg once weekly for the first month, titrated to 0.5 mg over 8 weeks, reaching a dose of 1.0 mg over the subsequent 3 months. The dosing intervals of LGT were initiated at 0.6 mg once weekly for the first month, titrated to 3 mg over 5 weeks, and continued over the subsequent 3 months. The dosing intervals of TZT were initiated at 2.5 mg once weekly for the first month, titrated to 5 mg over 5 weeks, reaching a dose of 7.5 mg over the subsequent 3 months.

Outcome measures: Patients' height was recorded, and initial and final weight after 3 months if drug use was recorded. Body mass index (BMI, kg/m²) was calculated for both time points. Moreover, adverse effects and positive expected outcomes (sleep, movements, and mood) were recorded.

Statistical analysis: Data were collected through a questionnaire and then presented as a spreadsheet in Excel 2026. Age and BMI were expressed as mean $\pm$ standard deviation. Sex, negative effects, and positive outcomes were expressed as frequencies and percentages. p-value less than 0.05 was considered significant when BMI was compared between groups using One-Way ANOVA or a t-test when before and after were compared.

RESULTS

A total of 129 participants were enrolled in the present study. They were subdivided into three groups: SGT group, LGT group, and TZT group. The groups were matched regarding participants' demographic and baseline clinical characteristics (Table 1). Age showed non-significant differences between groups, with the majority of participants being young adults and female.

Regarding comorbid conditions, no chronic diseases were present, apart from polycystic ovarian syndrome, apnea, and gastric symptoms. Family history was positive in the TZT (77%) and SGT (72%) groups. Smoking was reported in a minority of participants, and non-smokers were alcoholics.

The lowest rates of adverse effects were observed with TZT: headache in the SGT group 42% and LGT group 35%, versus TZT group 17% ($p=0.019$); GIT symptoms 42% in the LGT group, 37% in the SGT group versus 16% in the TZT group ($p=0.037$ and $p=0.012$, respectively) (Table 2).

In addition to weight reduction, the enrolled subjects demonstrated improvements in movement, sleep, and mood (Table 3). The TZT group demonstrated the highest rate of positive outcomes. In TZT, the improvement rate was 65% of the studied group, versus 51% in SGT and 49% in LGT. The rate of improvement in sleep quality was higher

Table 1. Demographic parameters of the studied groups

Demographic parameters, each group: 43 participants		SGT, n(%)	LGT, n(%)	TZT, n(%)
Age, mean $\pm$ SD		28 $\pm$ 7	29 $\pm$ 5	31 $\pm$ 6
Sex	Female	27(63)	25(58)	30(70)
	Male	16(27)	18(42)	13(30)
Compiling diseases	Diabetes mellitus	0(0)	0(0)	0(0)
	Prediabetes	4(9)	2(5)	6(14)
	Hypertension	3(7)	1(2)	3(7)
	Hyperlipidemia	1(2)	2(5)	3(7)
	Liver steatosis	2(5)	2(5)	3(7)
	Polycystic ovarian syndrome	9(21)	7(16)	10(23)
	Apnea	6(14)	8(19)	3(7)
	Gastroesophageal reflux diseases	4(9)	10(23)	8(19)
	Gastric symptoms	7(16)	11(26)	6(14)
	Pancreatitis	0(0)	0(0)	0(0)
	Thyroid diseases	1(2)	0(0)	0(0)
	Cardiovascular diseases	0(0)	0(0)	0(0)
	Anxiety	0(0)	1(2)	0(0)
Family history	Positive	31(72)	25(58)	33(77)
	Negative	12(28)	18(42)	10(23)
Smoking	Yes	6(14)	8(19)	5(12)
	No	37(86)	35(81)	38(88)
Alcoholism	Yes	0(0)	0(0)	0(0)
	No	43(100)	43(100)	43(100)

Table 2. Comparison of adverse effects after using different groups of weight reduction drugs

Adverse effects	SGT, n(%)	LGT, n(%)	TZT, n(%)	Chi-square p-value		
				SGT vs LGT	SGT vs TZT	LGT vs TZT
Headache	18(42)	15(35)	8(17)	0.486	0.019	0.088
GIT	16(37)	18(42)	7(16)	0.658	0.037	0.012

Data are expressed as frequencies and percentages. The Chi-square test was used to compare between groups, and p-values less than 0.05 were considered significant at the 95% confidence interval.

Table 3. Comparison of expected positive outcomes after using different groups of weight reduction drugs

Positive outcomes	SGT, n(%)	LGT, n(%)	TZT, n(%)	SGT vs LGT	SGT vs TZT	LGT vs TZT
Movement	22(51)	21(49)	28(65)	0.822	0.174	0.115
Sleep	16(37)	18(42)	22(51)	0.658	0.164	0.362
Mood	11(26)	12(28)	20(47)	0.799	0.034	0.058

Data are expressed as frequencies and percentages. The Chi-square test was used to compare between groups, and p-values less than 0.05 were considered significant at the 95% confidence interval.

Table 4. Comparison of BMI before and after in different groups of weight reduction drugs

Weigh indices		SGT	LGT	TZT	P value*
BMI, kg/m2	Before	41±6.7	39.7±5.6	42±7.3	0.27
	After	38.3±6.9bc	37.9±5.4ca	35.3±3.8a	0.026
	P value#	0.07	0.13	0.0001	
BW reduction, kg		-5	-7	-15	

*p value less than 0.05 using one-way ANCOVA, #p value less than 0.05 using paired t-test at 95% confidence interval. Similar letters indicate non-significant differences between groups, while different letters indicate significant differences between groups. BMI=Body mass index

in the TZT group 51%, compared to 37% in SGT and 42% in LGT. The rate of enhancement in mood was higher in the TZT group 47%, compared to 26% in SGT and 28% in LGT. Despite these numerical variations among groups, no significant differences ($p>0.05$) existed between groups, except that mood improvement was significantly higher in TZT versus SGT ($p=0.034$).

At baseline, the BMI was similar between groups (SGT: 41 ± 6.7 kg/m², LGT: 39.7 ± 5.6 kg/m², TZT: 42 ± 7.3 kg/m²; $P=0.27$), demonstrating non-significant differences at the initiation of the study. There was a reduction in BMI in all groups after therapy; this reduction was only significant in TZT (from 42 ± 7.3 to 35.3 ± 3.8 kg/m²; $P=0.0001$, t-test), compared to non-significant reductions in the SGT ($P=0.07$) and LGT ($P=0.13$). The post hoc test revealed that TZT induced better weight reduction compared to SGT and LGT, with no significant differences between SGT and LGT. In parallel, the actual body weight reduction in kg was greater in TZT (-15kg) compared to SGT (-5kg) and LGT (-7kg), when weight before therapy was subtracted from weight after therapy (Table 4).

DISCUSSION

The present study demonstrated that TZT induced higher weight reduction, a better safety profile, and remarkable improvement in patient outcomes compared to SGT and LGT; this improved overall profile facilitates clinicians in selecting agents with improved efficacy and better safety.

Although the three drugs led to reductions in BMI, only TZT has reached significant reduction limits after 3 months of use. In line with this study, a meta-analysis found that TZT induced greater weight loss compared to other agents, especially at higher doses, with a better safety profile¹². Alternatively, a meta-analysis using GLP-1 agonists has confirmed that TZT has scored the highest weight loss in 6 months compared to SGT and LGT drugs²³. The effectiveness was low with the three drugs and lower with SGT and LGT; perhaps this might be due to the short duration of treatment of 12 weeks. This aligns with a systematic review collected from earlier studies, which have confirmed that short use of weight reduction medication results in reduced effectiveness²⁴. In obese Asian populations, the use of weight reduction agents for more than 10 months achieved remarkable effectiveness; effectiveness was absent initially during the first few weeks²⁵. In an alternative clinical trial, LGT reduced weight effectively after prolonged use for more than 56 weeks²⁴. The superiority of TZT over other agents could be explained in the context that SGT and LGT are selective GLP-1 receptor agonists,

compared to TZT, which serves as a biarmed agonist of both the GLP-1 and glucose-dependent insulintropic polypeptide (GIP) receptors¹²; moreover, TZT has been shown to increase insulin sensitivity and improve β -cell function independently, resulting in weight reduction²⁶.

The incidence of adverse effects was lower in the TZT group compared to SGT and LGT. This finding aligns with earlier studies that have reported a high incidence of adverse effects with SGT and LGT. The lower rate in TZT might be due to balanced GLP-1/GIP agonism improving GIT intolerance compared to GLP-1 monotherapy^{11,12}. On the other hand, improvement in movement, sleep, and mood. These positive improvements have been reported earlier, with TZT showing better positive outcomes regarding daily activities¹². Moreover, GLP-1 receptors have been expressed in the brain and regulate appetite and mood¹². Moreover, SGT and LGT have shown similar rates of gastrointestinal symptoms²⁷.

Limitations of this study include the short duration of treatment, which may not reflect the long-term benefit or adverse effects. Patients' reported outcomes are subjective, which could reflect patients' perception rather than the drug's real impact. However, these drugs carry important clinical impacts, reducing weight and improving patients' daily activities; particularly, TZT has shown the highest positive therapeutic and expected outcomes with the lowest downside features. Longer studies are required to completely identify the effectiveness of these drugs and their side effects. We also further acknowledge that the doses prescribed are much lower than those indicated for diabetic and/or maximum FDA-approved maintenance doses for obesity treatment: SGT 2.4 mg and TZT 10–15 mg.

CONCLUSION

In this comparative study, TZT has shown moderate effects in reducing participants' weight, with well-tolerated adverse effects, and slightly improved outcomes compared to SGT and LGT. Hence, TZT was associated with greater short-term BMI reduction in this study; however, a long-term study with a larger sample size in a multicentre setting is recommended to prove the effects.

Authorship Contribution: All authors share equal effort contribution towards (1) substantial contributions to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes.

Potential Conflicts of Interest: None

Competing Interest: None

Acceptance Date: 26 August 2026

REFERENCE

1. Mohammad N, Darweesh O MM. The impact of disease-modifying medications on the lipid profile of patients with ischemic heart disease. *Georgian Med News*. 2025 Jun;(363):175–8.
2. Jaacks LM, Vandevijvere S, Pan A, et al. The obesity transition: stages of the global epidemic. *Lancet Diabetes Endocrinol* [Internet]. 2019 Mar 1;7(3):231–40.
3. Faruque S, Tong J, Lacmanovic V, et al. The Dose Makes the Poison: Sugar and Obesity in the United States - a Review. *Polish J food Nutr Sci*. 2019;69(3):219–33.
4. Chao AM, Taylor S, Moore M, et al. Evolving Approaches for Pharmacological Therapy of Obesity. *Annu Rev Pharmacol Toxicol* [Internet]. 2025;65(Volume 65, 2025):169–89.
5. Wadden TA, Webb VL, Moran CH, et als. Lifestyle Modification for Obesity. *Circulation* [Internet]. 2012;125(9):1157–70.
6. Kushner RF, Ryan DH. Assessment and Lifestyle Management of Patients With Obesity: Clinical Recommendations From Systematic Reviews. *JAMA* [Internet]. 2014;312(9):943–52.
7. van Baak MA, Mariman ECM. Obesity-induced and weight-loss-induced physiological factors affecting weight regain. *Nat Rev Endocrinol* [Internet]. 2023;19(11):655–70.
8. Greenway FL. Physiological adaptations to weight loss and factors favouring weight regain. *Int J Obes* [Internet]. 2015;39(8):1188–96.
9. Koliaki C, Liatis S, Dalamaga M, et al. The Implication of Gut Hormones in the Regulation of Energy Homeostasis and Their Role in the Pathophysiology of Obesity. *Curr Obes Rep* [Internet]. 2020;9(3):255–71.
10. Miller GD. Appetite Regulation: Hormones, Peptides, and Neurotransmitters and Their Role in Obesity. *Am J Lifestyle Med* [Internet]. 2019;13(6):586–601.
11. Drucker DJ. GLP-1 physiology informs the pharmacotherapy of obesity. *Mol Metab* [Internet]. 2022;57:101351.
12. Lim M, Gokhale P, Akosah A, et al. Weight Loss With GLP-1 Agonists in Nondiabetic Adults: Systematic Review and Network Meta-Analysis. *Obesity* [Internet]. 2026;34(6):1210–29.
13. Podder D, Stala O, Miah A, et al. Incretin-Based Multi-Agonist Therapies for Type 2 Diabetes Mellitus and Obesity: Mechanisms, Clinical Efficacy, and Future Directions. *Diabetology* [Internet]. 2026;7(3).
14. Abdelrahman RM, Musa TH, Arbab IA, et al. Adverse effects of GLP-1 receptor agonists: Clinical Implications, regulatory perspectives, and future directions. *Obes Med* [Internet]. 2026;61:100699.
15. Holst JJ, Rosenkilde MM. GIP as a Therapeutic Target in Diabetes and Obesity: Insight From Incretin Co-agonists. *J Clin Endocrinol Metab* [Internet]. 2020;105(8):e2710–6.
16. Liu QK. Mechanisms of action and therapeutic applications of GLP-1 and dual GIP/GLP-1 receptor agonists. *Front Endocrinol (Lausanne)* [Internet]. 2024;Volume 15.
17. Willard FS, Dourous JD, Gabe MB, et al. Tirzepatide is an imbalanced and biased dual GIP and GLP-1 receptor agonist. *JCI insight*. 2020 Sep;5(17).
18. Anastasiou IA, Argyrakopoulou G, Dalamaga M, et al. Dual and Triple Gut Peptide Agonists on the Horizon for the Treatment of Type 2 Diabetes and Obesity. An Overview of Preclinical and Clinical Data. *Curr Obes Rep* [Internet]. 2025;14(1):34.
19. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide Once Weekly for the Treatment of Obesity. *N Engl J Med*. 2022;387(3):205–16.
20. McGowan BM, Houshmand-Oeregaard A, Laursen PN, et al. Impact of BMI and comorbidities on efficacy of once-weekly semaglutide: Post hoc analyses of the STEP 1 randomized trial. *Obesity* [Internet]. 2023;31(4):990–9.
21. Lau DC, Krempf M, Astrup A, et al. Liraglutide 3.0 mg Reduces Body Weight and Improves Cardiometabolic Risk Factors in Adults with Overweight/Obesity: The SCALE Obesity and Prediabetes Randomised Trial. *Can J Diabetes* [Internet]. 2015 Apr 1;39:S48–9.
22. Jakubowska Agnieszka Roux Carel W. le VA. The Road towards Triple Agonists: Glucagon-Like Peptide 1, Glucose-Dependent Insulinotropic Polypeptide and Glucagon Receptor - An Update. *enm* [Internet]. 2024;39(1):12–22.
23. Moiz A, Filion K, Reynier P, et al. Abstract 4365415: Comparative Efficacy of Glucagon-Like Peptide-1 Receptor Agonists and Co-Agonists for Weight Loss Among Patients Without Diabetes: A Network Meta-Analysis. *Circulation* [Internet]. 2025;152(Suppl_3):A4365415–A4365415.
24. Roh E, Choi KM. Hormonal Gut–Brain Signaling for the Treatment of Obesity. *Int J Mol Sci* [Internet]. 2023;24(4).
25. Lim S, Buranapin S, Bao X, et al. Once-weekly semaglutide 2·4 mg in an Asian population with obesity, defined as BMI ≥25 kg/m2, in South Korea and Thailand (STEP 11): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol* [Internet]. 2025;13(10):838–47.
26. Mari A, Stefanski A, van Raalte DH, et al. Tirzepatide treatment and associated changes in β -cell function and insulin sensitivity in people with obesity or overweight with prediabetes or normoglycemia: a post hoc analysis from the SURMOUNT-1 trial. *Diabetes Care*. 2025;48(9):1622-7.
27. Boer GA, Hay DL, Tups A. Obesity pharmacotherapy: incretin action in the central nervous system. *Trends Pharmacol Sci* [Internet]. 2023;44(1):50–63.