

Original Research Article

Comparative effectiveness of semaglutide and tirzepatide in patients with type 2 diabetes mellitus

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Sent for review: 31 May 2026

Revised accepted: 15 August 2026

Abstract

Purpose: To investigate the effectiveness of semaglutide (Ozempic) and tirzepatide (Mounjaro) on weight reduction, glycaemic control, insulin resistance, and cardiometabolic parameters over 24 weeks in Iraqi patients with T2DM.

Methods: This was a prospective, randomised, open-label, parallel-group study conducted at Al-Fayhaa Teaching Hospital in Basra, Iraq, comprising 60 patients with T2DM (HbA1c: 7 – 10 %, BMI $\geq$ 30 kg/m²). The patients were randomised equally into 2 groups (n = 30). Group 1 received subcutaneous semaglutide (0.5 – 1.0 mg/week), and group 2 received tirzepatide (5 – 15 mg/week) for 24 weeks. Body weight, BMI, waist circumference, HbA1c, fasting plasma glucose (FPG), Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), lipid profile, and adverse events were evaluated at baseline, week 12, and week 24.

Results: Tirzepatide significantly reduced body weight, HbA1c, fasting plasma glucose (FPG), low-density lipoprotein (LDL), triglycerides, and systolic pressure compared to semaglutide ($p < 0.05$). Furthermore, HOMA-IR was significantly reduced following treatment with tirzepatide ($p < 0.05$). There was no significant difference in overall adverse effects following treatment with tirzepatide and semaglutide ($p > 0.05$).

Conclusion: Tirzepatide significantly reduces body weight, FPG, LDL, triglycerides, systolic pressure and decreases HOMA-IR with mild adverse effects.

Keywords: Glycaemic control, HOMA-IR, Insulin resistance, Semaglutide, Tirzepatide, Type 2 Diabetes Mellitus (T2DM)

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterised by a combination of insulin resistance and loss of insulin secretory function leading to persistent hyperglycaemia, and if poorly managed, microvascular disease and macrovascular disease [1]. The International Diabetes Federation (IDF) estimated that there are

currently around 537 million adults with diabetes worldwide and that this number will rise to 783 million by 2045, mostly in low- and middle-income countries [2]. The association of adiposity and metabolic dysfunction is key to the pathophysiology of T2DM, in which an increase in visceral fat leads to peripheral insulin resistance and a compensatory increase in peripheral insulin levels. This results in

progressive loss of pancreatic beta-cell function [3].

Epidemiological burden of type 2 diabetes mellitus (T2DM) has intensified across the Arab region. In Iraq, population-based surveys have reported T2DM prevalence rates ranging from 16 to 20 %, largely attributed to the combined effects of high consumption of high-glycaemic-index foods, declining levels of physical activity, and rapid urbanisation [4]. Clinical audits undertaken in outpatient clinics in Baghdad have also demonstrated that majority of these outpatients with T2DM were not maintaining their glycaemic (HbA1C) or weight goals with the standard oral antidiabetic drug, indicating a clear need for more effective drugs [5]. The GLP-1 receptor agonists are one of the agents used to treat hyperglycaemia and obesity-related weight gain, thus playing a central role in modern T2DM treatment [6].

Semaglutide (Ozempic; Novo Nordisk), a once-weekly subcutaneous injection, is 94 % identical in amino acid sequence with endogenous GLP-1, and has a long circulating half-life due to high affinity binding to albumin. In each of the SUSTAIN trial programs, treatment with semaglutide resulted in an HbA1c lowering of 1.5 – 1.8 %, and a body weight loss between 4 – 6 kg [7,8]. Further analysis of the data from SUSTAIN-6 also identified beneficial cardiovascular risk profile and renal protective effect, expanding the clinical potential of the drug [9]. Unlike traditional incretin therapy, tirzepatide (Mounjaro; Eli Lilly) is the first drug to target both the GIP and GLP-1 receptors in a single once-weekly molecule, representing a significant step forward [8,10]. Stimulating both receptor subtypes leads to coordinated metabolic effects, including increased insulin secretion, decreased glucagon secretion, decreased appetite, and favourable remodelling of adipose tissue function, which is superior to stimulation of the GLP-1 pathway alone [10]. In SURPASS-2 (the first prospective head-to-head comparison study with semaglutide), weight loss was greatest with tirzepatide at 5 mg, 10 mg and 15 mg, with reductions of 3.5 kg, 5.8 kg and 11.2 kg, and HbA1c changes of -0.9 %, -1.4 % and -2.1 %, respectively [8]. These results were independently validated by subsequent studies conducted in SURPASS-1, SURPASS-4 and the SURMOUNT-1 study of obesity [11,12]. Although there is increasing evidence from multinational clinical trials, there are still some key knowledge gaps. Data on these agents come from Western, East Asian, or Latin American populations and may not be directly applicable to patients in the Middle East, who may be genetically more

susceptible to insulin resistance, have different diets, metabolic phenotypes and access to health care [4]. Also, there is little published literature on real-world evidence from Iraq-specific studies, and the diabetic population of Iraq is still understudied regarding modern incretin-based therapeutics [5]. Although SURPASS-2 showed superior activity of tirzepatide over semaglutide in an international population, there are no studies that replicated or validated this result in a patient population from the Arab world or Iraq. Furthermore, impact of these therapies on clinically important surrogate markers of insulin resistance, such as Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), remains inadequately investigated in real-world populations within the region and has not been studied among Iraqi patients with T2DM [11,12]. Also, key cardiometabolic outcomes, including lipid profile parameters and blood pressure changes, have not been comparatively evaluated despite the high prevalence of dyslipidaemia and hypertension among Iraqi individuals with T2DM [5].

There is a huge evidence-to-practice gap for Iraqi health care providers working with patients with T2DM due to lack of local comparative evidence. Currently, the use of semaglutide compared to tirzepatide is extrapolated from trial data worldwide without validation in the study population. This is an unacceptable assumption of therapeutic responsiveness, tolerability, and patient adherence that may differ significantly between ethnic groups and healthcare settings in Iraq [4,5]. Thus, there is a great need for the development of a carefully planned prospective comparative study within the Iraqi healthcare system.

This study therefore investigated the effect of semaglutide administered once weekly compared to tirzepatide in T2DM patients who attended outpatient endocrinology clinic at Al-Fayhaa Teaching Hospital in Basra, Iraq, for over 24 weeks. Mean change in body weight, BMI, HbA1c, FPG, insulin resistance (HOMA-IR), fasting serum insulin, waist circumference, lipid profile, BP, patients with ≥ 5 % body weight loss, HbA1c < 7.0 %, safety and tolerability profile following treatment with semaglutide, and tirzepatide were compared.

METHOD

Study design and setting

This study was a prospective, open-label, randomised, and parallel-group trial. The recruitment and follow-up of patients were

conducted in the Diabetes and Endocrinology Center of Al-Fayhaa Teaching Hospital, Basra, Iraq, from March 2025 to December 2025. The method followed the CONSORT 2010 guidelines for reporting randomised trials.

Ethical approval

Ethical approval was obtained from the Institutional Review Board (IRB). The study was approved by the College of Pharmacy, University of Basra (approval no. EC133). All participants signed an informed consent form in accordance with the Principles of the Declaration of Helsinki [13].

Inclusion criteria

Adults aged 18 to 70 years, with an established T2DM diagnosis of at least one year, BMI ≥ 30 kg/m² or BMI ≥ 27 kg/m² with at least one comorbid condition associated with obesity. All participants must have been on a stable dose of metformin (at least 1000 mg per day) for at least 3 months.

Exclusion criteria

Diagnosis of type 1 diabetes, personal or family history of medullary thyroid carcinoma, multiple endocrine neoplasia type 2, prior attack of pancreatitis, eGFR < 30 mL/min/1.73 m², active liver disease and pregnancy/breastfeeding at screening.

Treatment

A total of 60 individuals were randomly and equally assigned into 2 groups containing 30 patients per group, using a computer-generated randomisation sequence. Group 1 received weekly subcutaneous injections of semaglutide starting at 0.5 mg and then slowly increased to 1.0 mg. Group 2 received subcutaneous injections of tirzepatide once weekly, starting at 5 mg, increasing by 10 mg to 15 mg (Table 1). Baseline antidiabetic therapy was maintained throughout the study, except for reductions in sulfonylurea dosage when symptomatic hypoglycaemic episodes occurred.

Outcome measures

Primary outcome is the change in body weight (kg) from baseline to week 24. Secondary outcomes included BMI, waist circumference, HbA1c, FPG, fasting serum insulin, HOMA-IR (Matthew's formula), systolic blood pressure, LDL cholesterol, triglycerides, proportion of subjects meeting prespecified glycaemic and weight targets, and incidence of adverse events.

Evaluation of parameters/indices

Venous blood was drawn at each assessment (fasting ≥ 8 h). HbA1c was determined by HPLC, FPG by enzymatic hexokinase method, fasting serum insulin by electrochemiluminescence immunoassay, lipids by standard enzymatic photometric assay, and HOMA-IR was determined using Eq 1.

HOMA-IR = fasting glucose (mmol/L) x fasting insulin (μ U/mL) / 22.5..... (1)

Statistical analysis

Participants in each arm were calculated to be 30 to detect a difference of 2.5 kg between the arms (SD 5 kg) with 80 % power ($\alpha = 0.05$, independent t-test). Data were analysed using Statistical Packages for Social Sciences (SPSS) version 26.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as mean $\pm$ standard deviation (SD), and compared using paired t-test for within-group comparisons and independent t-test for between-group comparisons. Categorical variables were expressed as frequency (%). $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

A total of 68 patients were screened, and 60 were eligible and randomised (30 to each arm; Figure 1). There was no significant difference in baseline characteristics between the two groups ($p > 0.05$; Table 2).

Table 1: Dose titration schedule and study protocol

Week	Phase	Semaglutide	Tirzepatide
1–4	Initiation	0.5 mg once weekly	5 mg once weekly
5–8	Escalation	1.0 mg once weekly	10 mg once weekly
9–24	Maintenance	1.0 mg once weekly	15 mg once weekly*
Follow-up	Assessment	Baseline, week 12, and 24	Baseline, week 12, and 24

*Tirzepatide titration to 15 mg was at investigator's discretion based on tolerability. All assessments were performed at baseline, week 12, and 24

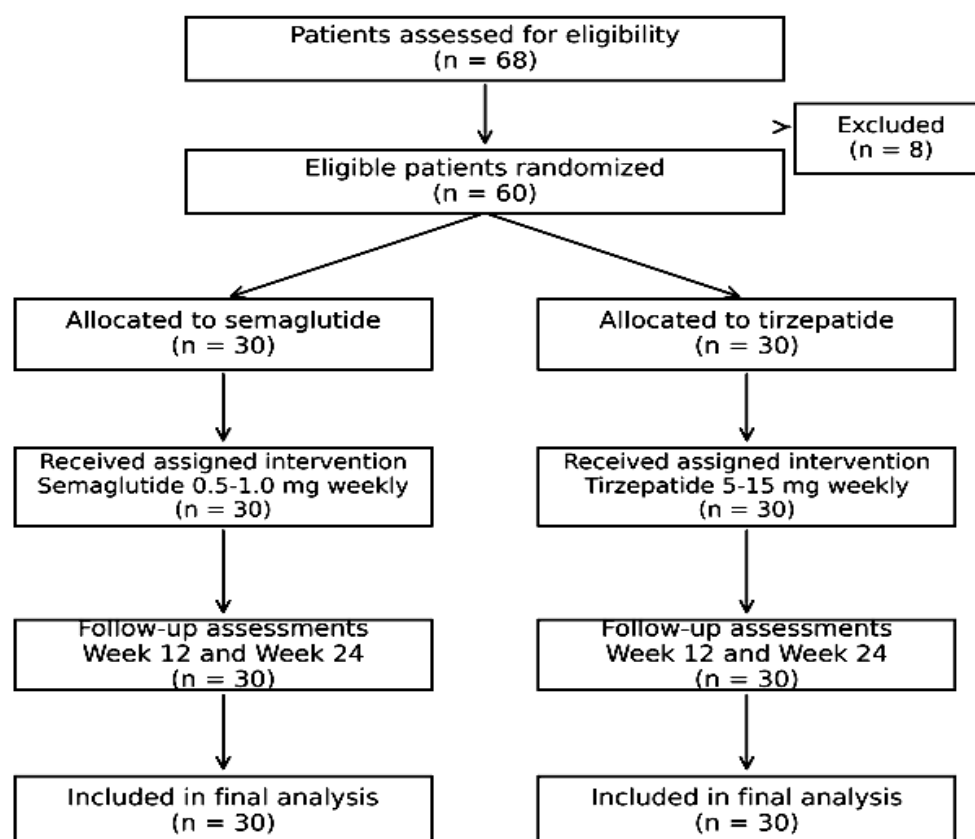


Figure 1: CONSORT flow diagram of patient recruitment and randomization

Table 2: Baseline characteristics

Variable	Semaglutide (n = 30)	Tirzepatide (n = 30)	P-value
Age (years)	54.3±9.1	53.8±8.7	0.78
Sex: Male/Female	17/13	16/14	0.81
Weight (kg)	93.4±11.2	94.2±12.1	0.71
BMI (kg/m ²)	33.6±3.4	34.1±3.8	0.44
Duration of T2DM (years)	7.2±4.3	7.5±4.1	0.68
HbA1c (%)	8.4±0.9	8.5±1.0	0.58
FPG (mg/dL)	178.5±34.2	181.3±37.6	0.66
Fasting insulin (μU/mL)	21.6±6.4	22.1±6.8	0.70
HOMA-IR	4.82±1.61	4.91±1.58	0.75
Waist circumference (cm)	102.4±8.7	103.1±9.2	0.66
Systolic BP (mmHg)	134.2±12.1	135.6±11.8	0.53
LDL cholesterol (mg/dL)	112.4±28.7	114.1±30.2	0.74
On metformin (%)	86.7	83.3	0.69
On sulfonylurea (%)	36.7	40.0	0.77
Hypertension (%)	53.3	56.7	0.79
Dyslipidemia (%)	50.0	53.3	0.79

Data expressed as mean ± SD or n (%). FPG (fasting plasma glucose), HOMA-IR (homeostatic model assessment of insulin resistance), BP (blood pressure), LDL (low-density lipoprotein). No significant difference between the groups ($p > 0.05$)

Efficacy outcomes at week 12 and week 24

Body weight

Treatment with tirzepatide significantly reduced mean body weight (-10.5 ± 3.2 kg, -11.1 %) at week 12 and week 24 compared to semaglutide ($p < 0.05$; Figure 2).

Glycaemic control

Glycated haemoglobin (HbA1c; Figure 3 A) and fasting plasma glucose (FPG; Figure 3 B) were significantly reduced following treatment with tirzepatide compared to semaglutide ($p < 0.05$).

Homeostatic model assessment of insulin resistance (HOMA-IR) and fasting plasma glucose (FPG)

Treatment with tirzepatide significantly improved HOMA-IR (Figure 4 A), and reduced FPG (Figure 4 B) compared to semaglutide ($p < 0.05$).

Efficacy and adverse effects

Treatment with tirzepatide showed a significantly higher proportion of patients with HbA1c $< 7.0\%$ compared to semaglutide ($p < 0.05$; Table 3). Body weight loss of $\geq 10\%$ was achieved by 73.3% of patients following treatment with tirzepatide compared to semaglutide ($p < 0.05$).

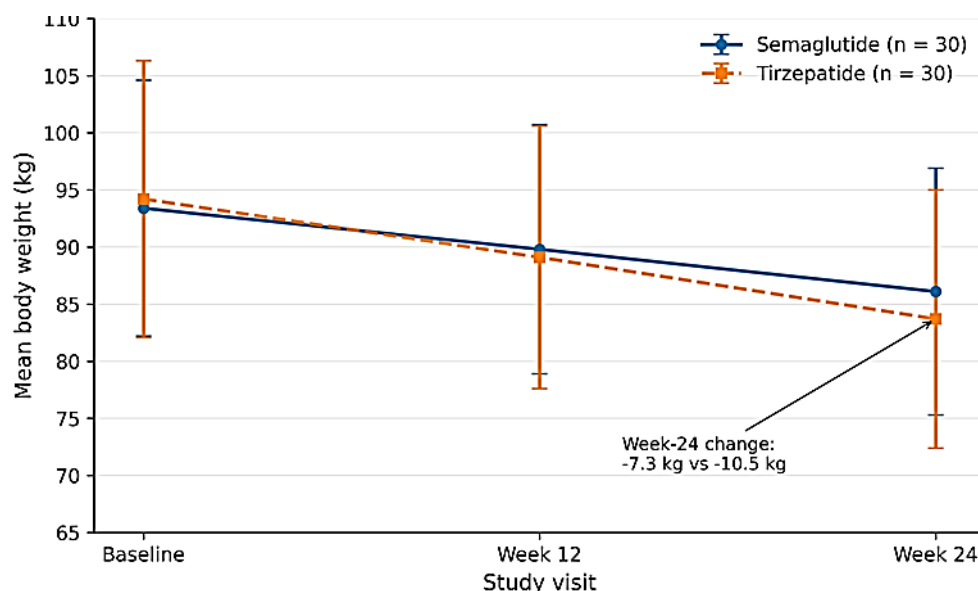


Figure 2: Mean body weight reduction. Mean body weight decreased progressively in both groups, with greater reduction following treatment with tirzepatide at week 24. Data expressed as mean $\pm$ standard deviation (SD)

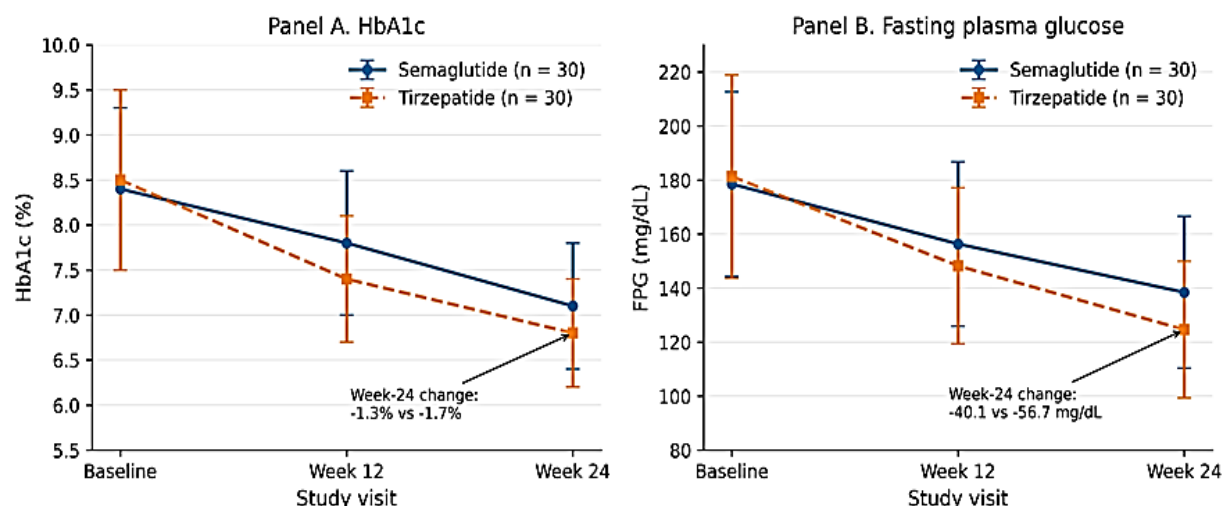


Figure 3: Glycaemic control. HbA1c (A) and fasting plasma glucose (B) reduction. Data expressed as mean $\pm$ standard deviation (SD)

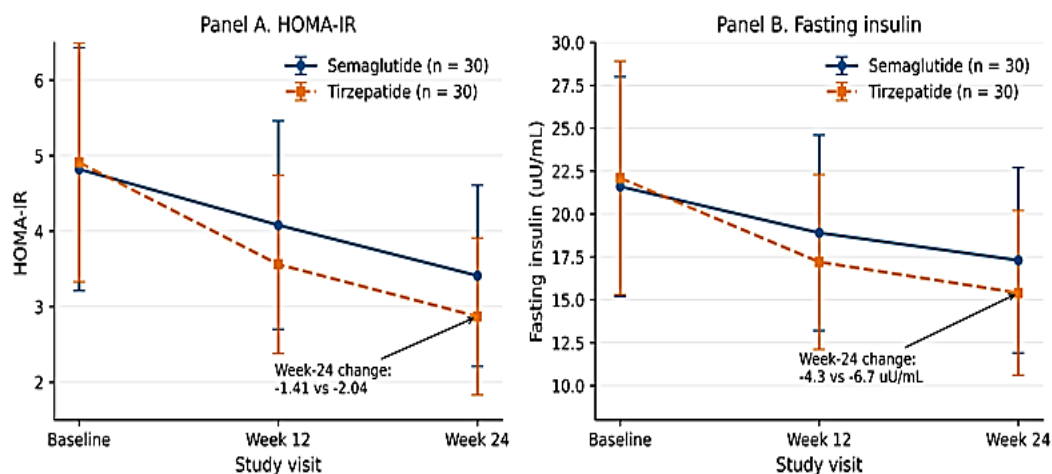


Figure 4: Homeostatic model assessment of insulin resistance (HOMA-IR; A) and fasting plasma glucose (FPG; B). Data expressed as mean $\pm$ standard deviation (SD)

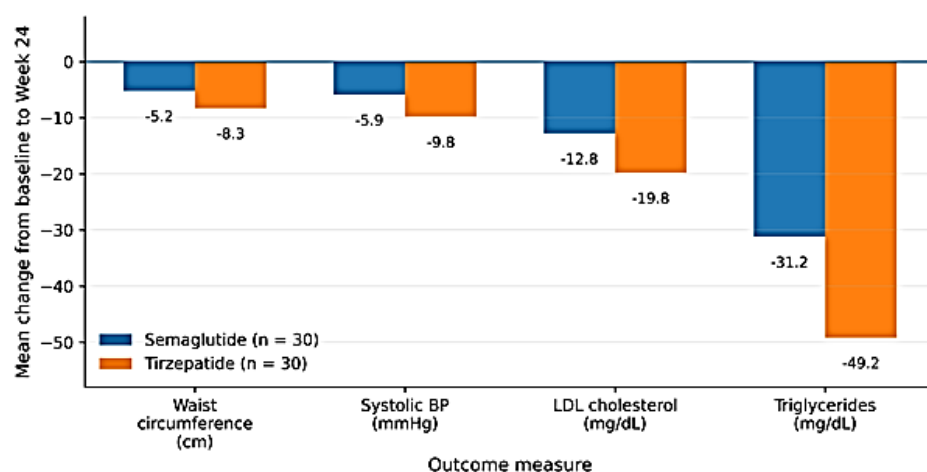


Figure 5: Waist circumference, systolic pressure, LDL cholesterol, and triglyceride levels. Data expressed as mean $\pm$ standard deviation (SD)

Table 3: Categorical efficacy and adverse effects

Parameter	Semaglutide (n, %)	Tirzepatide (n, %)
Efficacy endpoints		
HbA1c < 7.0 % achieved at week 24	13(43.3)	18(60.0)*
≥ 5 % body weight loss at week 24	23(76.7)	27(90.0)*
≥ 10 % body weight loss at week 24	13(43.3)	22(73.3)*
FPG < 126 mg/dL at week 24	15(50.0)	22(73.3)*
HOMA-IR < 2.5 achieved at week 24	9(30.0)	16(53.3)*
Adverse events		
Nausea	9(30.0)	11(36.7)
Vomiting	5(16.7)	7(23.3)
Diarrhoea	6(20.0)	7(23.3)
Constipation	3(10.0)	3(10.0)
Injection site reaction	2(6.7)	3(10.0)
Hypoglycaemia (mild)	2(6.7)	1(3.3)
Discontinuation due to adverse effects	1(3.3)	2(6.7)

* $P < 0.05$ compared to semaglutide

Furthermore, normal HOMA-IR (< 2.5) level was achieved by 53.3 % with tirzepatide compared to semaglutide ($p < 0.05$). Both drugs were well tolerated and adverse events (AE) were mostly

mild gastrointestinal reactions. No serious adverse events were reported, and there was no significant difference in overall AE rates between groups ($p > 0.05$; Table 3).

DISCUSSION

This prospective, randomised study showed that over a period of 24 weeks, both semaglutide and tirzepatide were clinically effective and significantly reduced body weight, blood glucose levels, insulin resistance, and systolic blood pressure in patients with T2DM from Iraq. However, tirzepatide showed a significantly better effect compared to semaglutide. For example, tirzepatide, significantly reduced weight by 11.1 % (10.5 kg) compared to semaglutide. Previous studies have shown that weight loss >10 % is correlated with remission of T2DM in some patient groups [14]. The significant decrease in insulin resistance achieved with tirzepatide is not attributable to weight reduction alone, but also a direct beneficial effect on glucose metabolism. Such reduction is clinically relevant because insulin resistance plays a pivotal role in the development and progression of T2DM due to the activation of GIP and GLP-1 receptors [10]. Activation of GIP receptor is synergistic with GLP-1 in stimulating glucose-dependent insulin secretion, inhibiting glucagon, regulating adipocyte lipolysis and lipogenesis, and possibly increasing energy expenditure at a hypothalamic level [9,10]. This dual receptor pharmacology is complementary to that of GLP-1 alone, accounting for the consistently improved cardiometabolic outcomes, such as lipids, blood pressure and insulin sensitivity, observed with this combination [8]. Results of the present study compared favourably and supported results of the pivotal head-to-head randomised trial (SURPASS-2) which showed that tirzepatide was more effective than semaglutide 1.0 mg at reducing weight (up to -11.2 kg at 15 mg) and HbA1c (up to -2.1 %) [8]. These results for tirzepatide (-10.5 kg; -1.7 % HbA1C) are very similar to the SURPASS-2 results, providing external validity of the single-centre results. Results of the HOMA-IR also supported the post hoc SURPASS-2 which showed that tirzepatide was superior to semaglutide at improving insulin resistance [10].

For weight outcome specifically, results with semaglutide were comparable to those of STEP-1 trial (-14.9 % in a more overweight population) and SUSTAIN-7 trial (-6.5 kg at 1.0 mg), recognising that the population was less overweight following treatment with the lower approved dose of semaglutide [7]. This study showed that tirzepatide resulted in 11.1 % weight loss, comparable with findings from the SURMOUNT-1 trial (22.5 % weight loss) in non-diabetic obese patients. The smaller weight loss in T2DM patients is consistent with background data showing that T2DM reduced weight

response to GLP-1 drugs. The study data also supported epidemiological findings by Al-Azzawi and Salih [4] and Al-Hamdi et al [5], which emphasised that the burden of uncontrolled T2DM is high in Iraqi outpatients. Improvement in metabolism was quite large, especially normalisation rate of HOMA-IR, which was 53.3 % with tirzepatide, with important implications for a population where insulin resistance is a major phenotypic characteristic [4].

This study has several clinical implications. Tirzepatide is superior in its effects on weight, glycaemic, and cardiometabolic parameters, making it a preferred pharmacological choice for Iraqi patients with obesity-related T2DM who are not achieving target goals on conventional oral therapy [15,16]. The high weight loss (73.3 %) is clinically transformative and may be beneficial for beta-cell rest, attenuation of cardiovascular risk, and reduction of hepatic steatosis within a population at high cardiometabolic burden [17,18]. Also, both agents (especially tirzepatide) have a comprehensive cardiometabolic impact that extends beyond glycaemic control, especially as cardiovascular disease is the predominant cause of death in T2DM [19]. The once-a-week dosing regimen and lack of serious adverse effects found in this cohort have made it feasible to implement these agents in an outpatient clinic. Adherence to both drugs was also achieved with low rates of discontinuation, indicating good tolerability and adequate patient counselling [14]. There are some very interesting strengths to this study. This is the first prospective randomised study of semaglutide compared to tirzepatide in Iraqi health care system, offering locally derived evidence relevant to clinical practice. Rigorous randomization, objective laboratory measurements and standardized assessment intervals were used.

The outcome panel is comprehensive and covers a range of metabolic parameters including HOMA-IR, fasting insulin, lipid profile and blood pressure, in addition to traditional glycaemic parameters, allowing a multidimensional characterization of metabolic response [10,15]. The results are also consistent with those obtained in international trials [8,10]. However, further multicentre randomised trials in various regions and health sectors in Iraq would be required to determine the applicability of these results. Also, longer-term studies (12 - 24 months) with more cardiorenal endpoints are needed to confirm that metabolic improvements seen are a result of lower incidence of cardiovascular effects, progression of nephropathy, and mortality in Iraq [9]. Cost-effectiveness analysis would be extremely useful

as a basis for informing Iraqi national formulary and prescribing guidelines. Molecularly, sub-studies of genetic polymorphisms of GLP-1 and GIP receptor genes may help determine if variants that affect drug action are present in Iraqi population [8,10]. The use of continuous glucose monitoring data in future trials in addition to patient-reported outcome data would further support available evidence. Research into the effects of these agents in combination with SGLT-2 inhibitors is an exciting new area of investigation, especially as this combination has complementary effects and is relevant to the high prevalence of comorbid obesity, hypertension, and chronic kidney disease in the Iraqi population [16,17].

Limitations of the study

This study has some limitations. An open-label clinical design is associated with performance and detection bias, but blinding of the injectable incretin therapies is impractical in the clinic. The six-month follow-up does not reflect longer outcomes such as durability of weight loss or late adverse events or serious cardiovascular effects. Results may not be applicable to primary health care or the rural Iraqi population as they are from a single-centre tertiary healthcare facility. The relatively small sample size ($n = 60$) was sufficient to detect differences in common adverse effects but may be too small to detect differences in less common adverse effects. Also, the study lacked quality of life assessments, patient-reported outcomes and cost-effectiveness analysis which are important limitations in health policy decision-making.

CONCLUSION

Tirzepatide was significantly more effective in improving body weight, glycaemic control, insulin resistance, and cardiometabolic risk factors over a 24-week period in patients with T2DM with predominantly mild and transient gastrointestinal adverse effects.

DECLARATIONS

Acknowledgement/Funding

None.

Ethical approval

Ethical approval was obtained from the Institutional Review Board (IRB), College of Medicine, University of Baghdad (IRB-2023-014).

Data Availability

De-identified data supporting the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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