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Sex specific responses to oral vs. subcutaneous semaglutide in type 2 diabetes mellitus: A 12-month real-world study

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ABSTRACT

Background and aim: Semaglutide therapy improves glycaemic control, weight loss, and cardiovascular risk reduction in patients with type 2 diabetes mellitus (T2D). Sex-specific differences in the response to oral versus subcutaneous formulation remain unexplored in real-world settings. This interventional pilot study compares the 12-month effectiveness of oral and subcutaneous semaglutide in a real-world cohort of T2D patients, with focus to sex-based differences in treatment outcomes.
Methods and results: Two-hundred and twelve T2D patients, equally assigned to oral or subcutaneous semaglutide (n = 106 per group), were enrolled. The primary endpoint was the change in HbA1c. Secondary endpoints included variations in anthropometric and metabolic parameters, analysed both in the overall cohort and through a sex-stratified approach. Two-hundred and eight patients completed the study. In men, subcutaneous semaglutide resulted in significant reductions in delta(Δ)_weight ($p = 0.010$), Δ_HbA1c ($p = 0.037$), and Δ_LDL ($p = 0.038$) compared to the oral formulation. In women, subcutaneous semaglutide led to significantly lower Δ_hepatic steatosis index ($p = 0.024$). Additionally, women treated with subcutaneous semaglutide showed a significantly greater reduction in Δ_GOT ($p = 0.035$) compared to men.
Conclusions: This real-world study suggests that subcutaneous semaglutide provides greater metabolic benefits than the oral formulation, particularly in men. Women treated with subcutaneous semaglutide experience more favorable liver responses, emphasizing the personalization of T2D treatment.

1. Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are among the most effective treatments for type 2 diabetes (T2D), lowering HbA1c and body weight, carrying a low risk of hypoglycaemia. Some GLP-1 RAs have also demonstrated cardiovascular (CV) benefits [1,2]. They are recommended to achieve adequate HbA1c control and/or high cardiovascular risk or known cardiovascular disease, to lower the likelihood of major adverse cardiovascular events (MACE) [3] and are a preferred option for chronic weight management in individuals with T2D who are overweight or obese.

Among GLP-1 RAs, semaglutide is the only one available in two formulations for the treatment of T2D: a once-weekly subcutaneous injection and a once-daily oral tablet. Extensive clinical research has confirmed its efficacy and safety, with both formulations demonstrating substantial reductions in HbA1c and body weight in comparison to other treatments in pivotal phase 3 trials (SUSTAIN and PIONEER) [4–8]. An interesting metanalysis on 24 trials showed the superiority of both subcutaneous and oral formulation compared to placebo and other anti-diabetic drugs in reducing HbA1c and weight [9].

Furthermore, semaglutide significantly reduces the risk of cardiovascular death, MACE, chronic kidney disease progression and improves cardiovascular parameters and peripheral vascular function in patients with type 2 diabetes mellitus [10–16].

The oral formulation of semaglutide offers a suitable option for those who refuse to start injectable treatment. Anxiety around injections and the perceived burden of injectable therapies are well-documented barriers to adherence in individuals with T2D [17,18]. Consequently, oral

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semaglutide may encourage earlier adoption of GLP-1 RA therapy and support better long-term treatment compliance. Additionally, its oral form may be more convenient for primary care practitioners to prescribe. A recent metanalysis showed that oral semaglutide was non-inferior to injectable semaglutide and superior to placebo and other comparators (liraglutide, dulaglutide and exenatide) in reducing HbA1c and body weight [19]. In addition, it demonstrated superior outcomes compared to injectable semaglutide but was less favorable than other comparators and placebo in terms of adverse event frequency, reinforcing its relevance for patients who are opposed to the subcutaneous formulation [19].

Sex differences have been shown in weight loss and glycaemic control combined with different GLP-1 responses to intraduodenal glucose [20]. However, there are limited clinical data available on sex differences in patients treated with oral and subcutaneous semaglutide.

The primary endpoint of the current study is to assess the change in HbA1c in patients treated with oral vs. subcutaneous semaglutide both in the entire cohort of patients and stratified by sex, over a 12-month period in a real-world setting. Secondary endpoints included changes in anthropometric and metabolic parameters.

2. Methods

This interventional study investigated a population of 1500 adult outpatients with T2D diagnosed for at least 1 year, followed at the Endocrinology and Metabolism Division of the University Hospital of Palermo from January 2024 to April 2024. Two-hundred and twelve out of 1500 patients were included and consecutively initiated on subcutaneous (N = 106) or oral (N = 106) semaglutide (Fig. 1), matched for gender. The route of semaglutide administration was determined by factors unrelated to clinical effectiveness, such as drug availability at the time of prescription and patient preference.

Exclusion criteria were: pregnancy, known allergy or hypersensitivity to semaglutide, participation in another clinical trial during the treatment period.

Inclusion criteria were age over 18 years, diagnosis of T2D at least one year before the recruitment, no treatment with prior GLP-1 RA, baseline HbA1c >6.5 % (48 mmol/mol).

Patients were instructed to titrate semaglutide according to label information as following: oral semaglutide was started at 3 mg/day for a month, followed by 7 mg/day for all the duration of the study. Subcutaneous semaglutide was started at the dose of 0.25 mg/week for a month, followed by 0.5 mg/week. Only if clinically indicated (patients not reaching an adequate glycaemic control) the dose could be further increased to 14 mg/day for oral semaglutide and 1 mg/week for subcutaneous semaglutide.

Patients were instructed to take semaglutide at least 30 min before eating, at fasting. Clinical visits were performed according to good clinical practice.

The study was conducted in accordance with the ethical standards of the institutional and national research committees, and with the 1964 Helsinki declaration and its later amendments. Ethical approval was obtained from the Ethics Committee of the Policlinico Paolo Giaccone (Protocol number: 01/2024) and written informed consent was signed from all individual participants included in the study. Clinical trial number: not applicable.

2.1. Outcomes

The primary endpoint of this study was to evaluate the change in

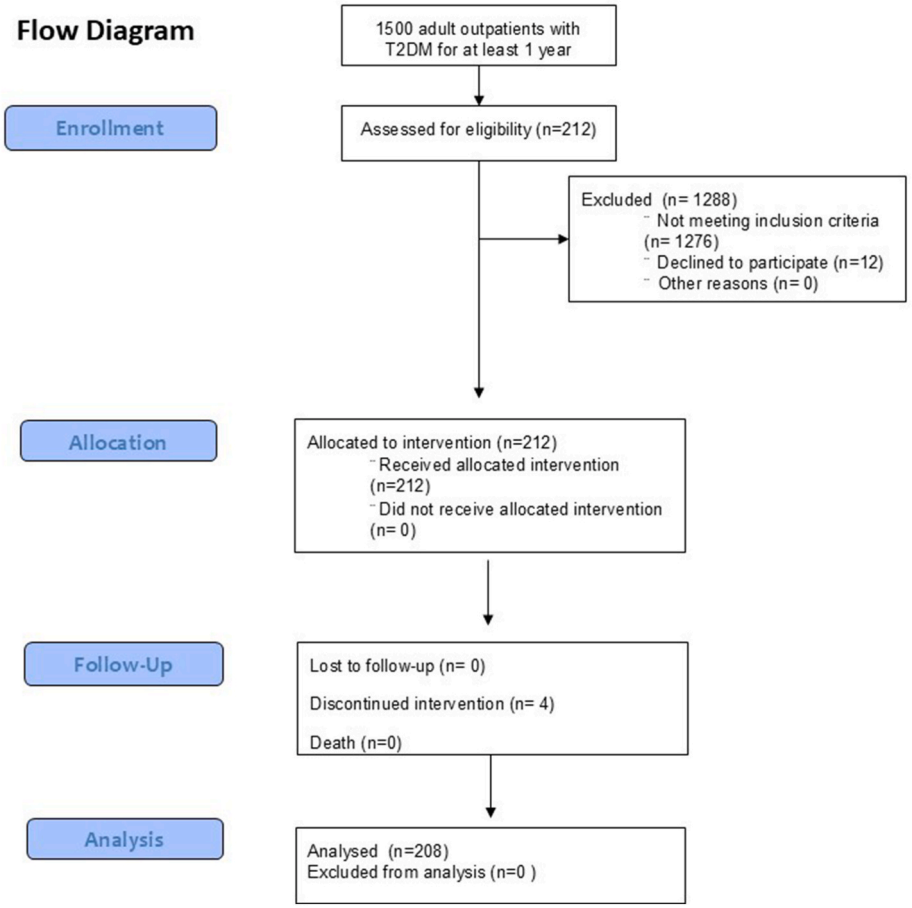

Fig. 1. caption. Study flowchart.

HbA1c among patients treated with oral versus subcutaneous semaglutide, both in the overall cohort and stratified by sex, over a 12-month follow-up in a real-world setting. Secondary endpoints included changes in anthropometric and metabolic parameters.

As anthropometric and metabolic parameters, we assessed BMI, systolic and diastolic blood pressure (SBP and DBP) and waist circumference (WC), total cholesterol (TC), HDL cholesterol (HDL-C), LDL cholesterol (LDL-C) and triglycerides (TG), creatinine, HbA1c, glutamic-oxalacetic transaminase (GOT), glutamic-pyruvate transaminase (GPT) and blood count. We also evaluated fibrosis-4 index (FIB-4) and hepatic steatosis index (HSI) as tools to determine the presence of hepatic fibrosis and steatosis, respectively. In addition, we also evaluated the neutrophil to lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR) as inflammatory markers.

We also evaluated the frequency of diabetic chronic microvascular complications including retinopathy classified as absent, non-proliferating and proliferating and nephropathy evaluated by creatinine measurement, estimated glomerular filtrate rate (GFR), calculated according to CDK-EPI, and microalbuminuria (positive definite for values > 30 mg/g in at least two consecutive measurements). The categories of diabetic kidney disease were based on the current classification proposed by the US National Foundation Kidney Disease Outcomes Quality Initiative (NFK-KDOQI).

2.2. Assays

HbA1c, lipids, creatinine, blood count, GOT and GPT were measured with standard methods (Modular P800, Roche, Milan). LDL-C levels were calculated using the Friedewald formula [TC – (HDL + (TG/5)].

The conversion factors for the International System (SI) were as follows: TC and HDL-C mg/dl vs. mmol/l: 0.0259; TG mg/dl vs. mmol/l: 0.0113; HbA1c % vs. mmol/mol: 10.93 % - 23.5.

2.3. Sample size calculations

Assuming a standard deviation of 1 % in HbA1c variation, we estimated that 104 participants per group would be required to detect a difference in HbA1c variation of 0.35 % between groups, with an alpha value of 0.05 and a power of 0.8.

2.4. Statistical analysis

The Statistical Packages for Social Science SPSS version 26 (SPSS, Inc., IBM, New York, USA) were used for data analysis. The normality of quantitative variables was tested by the Shapiro-Wilk test. The baseline characteristics of the groups were presented as mean ± SD for continuous variables, while the rates and proportions were calculated for categorical data. The comparison between the two groups was performed with an independent Student's t-test for continuous variables or chi-squared test for categorical variables.

3. Results

3.1. Entire cohort

Two patients treated with oral semaglutide and 2 treated with subcutaneous semaglutide interrupted the treatment due to poor adherence. At 12 months the range of doses used was similar in the two groups. Among patients treated with oral semaglutide, 95 patients maintained the dose of 7 mg/day and 9 increased up to 14 mg/day. Among patients treated with subcutaneous semaglutide, 92 patients maintained the dose of 0.5 mg/week and 12 increased up to 1 mg/week.

Baseline characteristics of patients included in the study are shown in Table 1. All patients in our cohort were receiving antihypertensive treatment.

After 12 months of observation, patients treated with subcutaneous semaglutide had significant decrease in weight (p = 0.007), WC (p = 0.013) and triglycerides (p = 0.013) compared to patients treated with oral formulation (Table 2). Evaluating the difference from 12 months to baseline (Δ), significant lower Δ_weight (p = 0.008), Δ_HbA1c (p = 0.015) and Δ_HSI (p = 0.029) was found in patients treated with subcutaneous semaglutide compared to oral formulation (Table 2).

Table 1
General characteristics of all patients included in the study.

	Baseline			
	Overall (N = 208) Mean ± SD	Subcutaneous (N = 104) Mean ± SD	Oral (N = 104) Mean ± SD	*p*
Age (years)	61.4 ± 11.1	59.5 ± 11.4	63.1 ± 10.5	**0.018**
Duration of disease (years)	11.5 ± 9.91	11.0 ± 8.85	11.9 ± 10.8	0.525
	N (%)	**N (%)**	**N (%)**	
Sex				
Female	82 (39.4 %)	41 (39.4 %)	41 (39.4 %)	1
Male	126 (60.6 %)	63 (60.6 %)	63 (60.6 %)	
Smoking	32 (15.4 %)	18 (17.3 %)	14 (13.5 %)	0.357
Arterial hypertension	162 (77.9 %)	79 (76 %)	83 (79.8 %)	0.837
Dyslipidemia	165 (79.3 %)	84 (80.7 %)	81 (77.9 %)	0.153
Cerebrovascular disease	12 (5.7 %)	6 (5.7 %)	6 (5.7 %)	1
Cardiovascular disease	37 (17.8 %)	15 (14.4 %)	22 (21.1 %)	0.445
Diabetic neuropathy	14 (6.7 %)	9 (8.6 %)	5 (4.8 %)	0.308
Diabetic nephropathy	96 (46.1 %)	40 (38.4 %)	56 (53.8 %)	0.116
Diabetic retinopathy	23 (11 %)	15 (14.4 %)	8 (7.7 %)	0.132
Visceral obesity	119 (57.2 %)	62 (59.6 %)	57 (54.8 %)	0.236
Hepatic steatosis	66 (31.7 %)	38 (36.5 %)	28 (26.9 %)	0.061
Carotid artery disease	69 (33.2 %)	38 (36.5 %)	31 (29.8 %)	0.128
Diabetic foot	8 (3.8 %)	6 (5.8 %)	2 (1.9 %)	0.227

3.2. Sex stratification

We included 82 women (41 treated with subcutaneous semaglutide and 41 with oral semaglutide) and 126 men (63 treated with subcutaneous semaglutide and 63 treated with oral semaglutide).

At baseline female patients assigned to subcutaneous semaglutide showed higher SBP value (p = 0.026) and triglycerides (p = 0.006) compared to those assigned to oral formulation. After 12 months, female patients treated with subcutaneous semaglutide maintained higher SBP (p = 0.026) and triglycerides (p = 0.006) compared to oral formulation (Table 3).

At baseline, male patients assigned with subcutaneous semaglutide showed higher weight (p < 0.001), BMI (p = 0.044), WC (p < 0.001), DBP (p = 0.005) and triglycerides (p = 0.032), compared to oral formulation (Table 3). After 12 months, male patients treated with subcutaneous semaglutide had higher weight (p = 0.009) and WC (p < 0.001) compared to oral semaglutide (Table 3).

Further, we compared the changes from 12 months to baseline of all parameters. Evaluating the subcutaneous vs oral therapies effects in male patients we found a significantly greater change in Δ_weight (p = 0.010), Δ_HbA1c (p = 0.037) and Δ_LDL (p = 0.038) in subcutaneous group compared to oral group (Table 4). In female patients we found a significantly greater change in Δ_HSI (p = 0.024) in patients treated with subcutaneous, than oral formulation (Table 4).

Table 2
Metabolic parameters at baseline and after 12 months of treatment with subcutaneous vs. oral formulations.

	Baseline			After 12 months			Change from 12 monts to baseline		
	Subcutaneous (N = 104) Mean ± SD	Oral (N = 104) Mean ± SD	*p*	Subcutaneous (N = 104) Mean ± SD	Oral (N = 104) Mean ± SD	*p*	Subcutaneous (N = 104) Mean ± SD	Oral (N = 104) Mean ± SD	*p*
Weight (Kg	97.5 ± 21.9	86.5 ± 17.7	**<0.001**	93.2 ± 22.3	85.0 ± 18.4	**0.007**	−4.3 ± 5.69	−1.51 ± 6.74	**0.008**
BMI (kg/m2)	33.9 ± 6.48	31.4 ± 6.08	**0.008**	32.6 ± 6.72	32.4 ± 12.6	0.857	−1.3 ± 2.16	1.1 ± 10.8	0.122
WC (cm)	120 ± 26.0	109 ± 21.1	**0.005**	115 ± 23.4	106 ± 20.0	**0.013**	−5.5 ± 14.0	−3.01 ± 6.07	0.181
Systolic blood pressure (mmHg)	130 ± 12.2	127 ± 10.3	0.135	127 ± 7.87	126 ± 7.86	0.350	−2.9 ± 10.3	−1.09 ± 8.93	0.749
Diastolic blood pressure (mmHg)	83.8 ± 7.08	80.1 ± 8.22	**0.008**	82.1 ± 8.30	80.5 ± 7.52	0.278	−1.7 ± 4.45	−0.4 ± 5.87	0.567
Fasting glucose (mmol/L)	11.5 ± 6.93	9.99 ± 3.44	**0.039**	8.65 ± 3.68	7.88 ± 2.55	0.093	−2.85 ± 5.3	−2.11 ± 2.99	0.663
HbA1c (mmol/mol)	73.5 ± 19.8	68.1 ± 17.4	**0.027**	52.4 ± 17.1	54 ± 14.8	0.525	−21.1 ± 21.5	−14.1 ± 16.7	**0.015**
Total cholesterol (mmol/L)	4.39 ± 1.41	4.29 ± 1.11	0.631	3.93 ± 1.08	3.95 ± 1.03	0.783	−0.46 ± 1.05	−0.35 ± 0.92	0.257
HDL cholesterol (mmol/L)	1.12 ± 0.61	1.19 ± 0.28	0.329	1.13 ± 0.31	1.17 ± 0.25	0.229	−0.01 ± 0.63	−0.02 ± 0.23	0.945
Triglycerides (mmol/L)	2.12 ± 1.16	1.64 ± 0.85	**0.002**	1.76 ± 1.02	1.43 ± 0.71	**0.013**	−0.36 ± 1.12	−0.21 ± 0.79	0.418
LDL cholesterol (mmol/L)	2.48 ± 1.19	2.35 ± 1.07	0.44	2.09 ± 0.92	2.13 ± 0.95	0.778	−0.39 ± 1.06	−0.22 ± 1.01	0.060
GOT (U/L)	26.2 ± 18.6	23.9 ± 14.4	0.342	22.3 ± 14.5	20.2 ± 8.18	0.229	−3.9 ± 14.5	−3.7 ± 12.0	0.854
GPT (U/L)	34.5 ± 29.8	29.0 ± 22.5	0.162	24.9 ± 14.1	24.4 ± 26.2	0.887	−9.69 ± 26.4	−4.6 ± 24.0	0.225
FIB4	0.999 ± 0.472	1.12 ± 0.533	0.174	0.979 ± 0.490	1.05 ± 0.420	0.368	0.02 ± 0.378	−0.07 ± 0.404	0.102
HSI	48.5 ± 14.5	43.1 ± 7.69	**0.005**	44.5 ± 7.69	43.7 ± 12.7	0.770	−3.99 ± 12.4	0.59 ± 10.6	**0.029**
Creatinine (mg/dL)	0.925 ± 0.319	0.950 ± 0.325	0.586	0.936 ± 0.325	0.954 ± 0.372	0.711	−0.011 ± 0.322	0.004 ± 0.348	0.811
eGFR (ml/min)	87.1 ± 21.4	82.2 ± 24.5	0.124	85.3 ± 20.7	82.1 ± 24.3	0.307	−1.8 ± 13.4	0.001 ± 16.1	0.380
NLR	2.32 ± 1.40	2.37 ± 1.15	0.824	2.28 ± 0.921	2.64 ± 2.80	0.381	−0.04 ± 0.543	0.27 ± 1.06	0.254
PLR	1.9 ± 2.1	1.42 ± 0.57	0.307	1.55 ± 0.98	1.8 ± 1.48	0.281	−0.35 ± 0.76	0.38 ± 0.87	0.641

Abbreviations: HSI, hepatic steatosis index; NLR, neutrophyl to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

A further comparison between female vs. male patients treated with subcutaneous formulation showed significantly greater change in Δ_GOT ($p = 0.035$) in female patients compared to males (Table 4). No differences were found for male and females treated with oral semaglutide (Table 4).

4. Discussion

This 12-month, real-world observational study comparing oral and subcutaneous semaglutide in GLP-1 RA–naïve patients with T2D demonstrates that the subcutaneous formulation leads to greater improvements in HbA1c, HSI and body weight compared to the oral formulation. Notably, sex-disaggregated analysis revealed distinct patterns, men treated with subcutaneous semaglutide exhibited significantly greater reductions in weight, HbA1c, and LDL cholesterol than those treated with oral formulation. Further, women treated with subcutaneous formulation showed more pronounced hepatic benefits, particularly in HSI decrease, compared to those treated with oral formulation. Among patients treated with subcutaneous semaglutide, women had greater decrease in GOT, than men.

Our findings about the entire cohort are consistent with those from other observational studies which suggest a modest superiority of subcutaneous semaglutide. Kwon et al. reported a significant weight loss in patients receiving the subcutaneous formulation compared to oral users, especially among older individuals [21]. Similarly, Formichi et al. observed significant reductions in HbA1c, weight, BMI, and WC with subcutaneous semaglutide versus the oral formulation [22].

Conversely, pivotal trials and clinical studies have reported equal efficacy between the subcutaneous and oral formulations. A post hoc analysis of data from the SUSTAIN-6 and PIONEER-6 trials demonstrated consistent effects of both formulations on cardiovascular risk factors, including weight and glycaemic control [23]. Fadini et al. found similar efficacy between oral and subcutaneous formulations, although patients on subcutaneous semaglutide experienced a ≥5 % weight loss, likely attributed to more stable drug exposure and simplified dosing schedules [24]. Chowdhury et al. found no significant differences in either HbA1c or weight reduction between oral and subcutaneous semaglutide in a 6-month study [25]. Similarly, Conti et al. observed equivalent reductions in glycaemic and anthropometric parameters over 18 months, although a slightly higher proportion of patients in the injectable group achieved HbA1c <7.0 % [26]. A network meta-analysis reported that oral semaglutide 14 mg was non-inferior to subcutaneous GLP-1 RAs, including semaglutide itself, in both glycaemic and weight outcomes [27]. Another meta-analysis indicated that oral semaglutide was non-inferior to injectable semaglutide and superior to placebo and other comparators (liraglutide, dulaglutide, and exenatide) in reducing HbA1c and body weight [19].

These discrepancies across studies may reflect heterogeneity in patient populations, trial conditions, or adherence patterns.

A strength of our study is the high persistence and adherence observed in both treatment arms, with only four patients discontinuing therapy. This contrasts with prior real-world evidence, which reported lower persistence with oral semaglutide due to gastrointestinal adverse events and complex administration [24,26,28]. Interestingly, Horii et al. noted better average adherence and greater persistence at 12 months in oral users than in subcutaneous users, despite higher early discontinuation with oral therapy [29].

A central and novel aspect of our study is the exploration of sex-specific responses to semaglutide formulations, an area that has been largely underreported in the literature. We found no significant differences between males and females treated with oral semaglutide, except for women on subcutaneous semaglutide who experienced a significantly greater decrease in GOT compared to men. Another noteworthy finding was the differential male response to the semaglutide formulations. Specifically, men treated with the subcutaneous formulation exhibited a greater mean reduction in weight, HbA1c, and LDL cholesterol compared to those treated with oral formulation. In addition, women treated with subcutaneous formulation showed lower HSI, than oral users. The HSI is a validated, simple, and efficient screening tool for metabolic dysfunction-associated steatotic liver disease (MASLD), with values above 36 suggestive of hepatic steatosis [30].

These findings, although not previously highlighted in randomized controlled trials, may be attributed to a complex interplay of pharmacokinetic, hormonal, and physiological differences between sexes and routes of administration.

From a pharmacological perspective, subcutaneous semaglutide provides more consistent systemic exposure, with reduced variability and sustained plasma concentrations [31,32], which may be particularly advantageous for men. Unlike the oral formulation, which requires strict adherence to fasting and water-only conditions to ensure optimal

Table 3
Comparison of anthropometric and metabolic parameters after 12 months of treatment in male and female patients.

Parameters	Females						Males					
	Baseline			12 months			Baseline			12 months		
	Subcutaneous (N = 41)	Oral (N = 41)	*p*	Subcutaneous (N = 41)	Oral (N = 41)	*p**	Subcutaneous (N = 63)	Oral (N = 63)	*p*	Subcutaneous (N = 63)	Oral (N = 63)	*p**
Weight (Kg)	91.7 ± 18.5	85.6 ± 18.6	0.174	87.3 ± 18.6	83.1 ± 20.4	0.355	101 ± 23.0	87.2 ± 17.0	**<0.001**	96.8 ± 23.7	86.5 ± 16.9	**0.009**
BMI (Kg/m^2)	35.3 ± 6.84	33.2 ± 6.70	0.217	33.6 ± 6.97	32.2 ± 6.80	0.383	33.1 ± 6.21	29.9 ± 5.16	**0.044**	32.0 ± 6.54	32.5 ± 15.7	0.848
WC (cm)	127 ± 30.4	115 ± 24.8	0.134	117 ± 24.4	112 ± 23.6	0.397	117 ± 22.7	102 ± 13.5	**<0.001**	114 ± 23.1	99.6 ± 13.1	**<0.001**
SBP (mmHg)	131 ± 8.10	126 ± 10.1	**0.042**	128 ± 7.12	124 ± 5.49	**0.026**	129 ± 14.2	128 ± 10.7	0.630	126 ± 8.34	127 ± 9.41	0.715
DBP (mmHg)	82.4 ± 7.36	80.8 ± 8.48	0.458	81.0 ± 8.13	81.3 ± 6.42	0.897	84.8 ± 6.83	79.4 ± 8.03	**0.005**	82.8 ± 8.45	79.7 ± 8.40	0.149
Fasting glucose (mmol/L)	8.43 ± 2.97	7.32 ± 2.2	0.092	8.6 ± 3.14	7.43 ± 2.28	0.078	8.71 ± 3.99	8.21 ± 2.73	0.463	8.71 ± 3.99	8.21 ± 2.73	0.463
HbA1c (mmol/mol)	71.6 ± 19.6	66.1 ± 15.8	0.179	54.4 ± 17.9	53.1 ± 13.7	0.695	75.2 ± 19.8	69.4 ± 18.5	0.098	51.1 ± 16.6	54.4 ± 15.6	0.266
Total cholesterol (mmol/L)	4.83 ± 1.65	4.65 ± 1.25	0.621	4.26 ± 1.28	4.16 ± 1.06	0.721	4.13 ± 1.21	4.08 ± 0.97	0.751	3.8 ± 0.91	3.82 ± 0.99	0.614
HDL-cholesterol (mmol/L)	1.13 ± 0.29	1.24 ± 0.31	0.144	1.19 ± 0.28	1.26 ± 0.29	0.334	1.11 ± 0.73	1.15 ± 0.26	0.678	1.08 ± 0.32	1.11 ± 0.19	0.613
Triglycerides (mmol/L)	2.25 ± 1.23	1.67 ± 0.86	**0.027**	1.85 ± 0.76	1.38 ± 0.56	**0.006**	2.04 ± 1.12	1.63 ± 0.86	**0.032**	1.7 ± 1.14	1.45 ± 0.81	0.188
LDL_cholesterol (mmol/L)	2.76 ± 1.41	2.74 ± 1.28	0.975	2.26 ± 1.04	2.25 ± 0.91	0.947	2.33 ± 1.02	2.1 ± 0.84	0.216	1.99 ± 0.84	2.04 ± 0.98	0.773
GOT (U/L)	30.4 ± 21.4	24.0 ± 13.5	0.145	22.2 ± 12.8	21.2 ± 9.65	0.691	23.8 ± 16.5	23.8 ± 15.0	0.999	22.3 ± 15.4	19.5 ± 7	0.215
GPT (U/L)	35.7 ± 29.1	26.7 ± 17.0	0.129	21.6 ± 11.8	27.3 ± 38.5	0.39	33.9 ± 30.5	30.4 ± 25.2	0.510	26.7 ± 15	22.4 ± 11.9	0.094
FIB4	0.970 ± 0.438	1.12 ± 0.543	0.284	0.89 ± 0.41	1.03 ± 0.41	0.254	1.01 ± 0.494	1.12 ± 0.534	0.368	1.03 ± 0.53	1.07 ± 0.43	0.709
HSI	48.6 ± 8.37	46.3 ± 7.33	0.268	45.7 ± 7.89	45.4 ± 7.31	0.865	48.3 ± 16.7	41.1 ± 7.09	**0.008**	44.1 ± 7.89	43.2 ± 17.2	0.766
Creatinine (mg/dL)	0.762 ± 0.169	0.880 ± 0.370	0.062	0.78 ± 0.16	0.84 ± 0.34	0.343	1.02 ± 0.347	0.999 ± 0.283	0.713	1.03 ± 0.36	1.04 ± 0.37	0.868
eGFR (ml/min)	91.2 ± 20.9	80.8 ± 26.8	0.055	88.4 ± 20.1	82.3 ± 26.8	0.25	84.7 ± 21.5	83.1 ± 22.9	0.685	83.5 ± 21	81.9 ± 22.5	0.693
NLR	2.50 ± 1.98	2.17 ± 0.949	0.495	2.13 ± 0.91	2.29 ± 1.08	0.61	2.24 ± 1.05	2.54 ± 1.28	0.288	2.36 ± 0.93	2.95 ± 3.69	0.427
PLR	2.56 ± 4.61	1.40 ± 0.687	0.267	1.69 ± 1.25	1.36 ± 0.48	0.274	2.15 ± 1.34	1.42 ± 0.573	0.321	1.85 ± 1.61	1.67 ± 1.22	0.626

p* comparison between subutaneous vs. oral formulation at 12 months.
p** comparison between subcutaneous formulations at 12 months in female vs. male patients.
p*** comparison between oral formulations at 12 months in female vs. male patients.

Table 4
Changes in Anthropometric and Metabolic Parameters (Δ) from Baseline to 12 Months in female and male patients treated with oral and subcutaneous formulations.

	Female			Male				
	Subcutaneous (N = 41)	Oral (N = 41)	p^*	Subcutaneous (N = 63)	Oral (N = 63)	p^*	p^{**}	p^{***}
Δ_weight	−5.12 ± 6.46	−2.03 ± 9.41	0.108	−3.45 ± 5.17	−1.20 ± 3.54	0.010	0.232	0.599
Δ_BMI	−1.82 ± 2.66	−0.799 ± 2.18	0.092	−1.05 ± 1.79	1.46 ± 14.2	0.215	0.168	0.268
Δ_WC	−9.46 ± 20.9	−3.82 ± 7.84	0.219	−3.44 ± 6.84	−2.35 ± 3.26	0.377	0.184	0.330
Δ_SBP	−2.42 ± 4.38	−1.92 ± 5.50	0.726	−2.18 ± 13.0	−1.46 ± 11.5	0.823	0.924	0.855
Δ_DBP	−0.958 ± 3.37	−1.27 ± 5.63	0.812	−1.36 ± 5.15	0.038 ± 6.14	0.355	0.721	0.427
Δ_Gly	−3.23 ± 10.8	−2.16 ± 3.25	0.594	−2.1 ± 5.17	−2.09 ± 3.97	0.994	0.585	0.929
Δ_HbA1c	−17.1 ± 16.6	−13.1 ± 15.2	0.263	−23.5 ± 23.8	−14.6 ± 22.5	0.037	0.129	0.681
Δ_TC	−0.71 ± 1.28	−0.54 ± 1.19	0.583	−0.42 ± 0.91	−0.23 ± 0.68	0.219	0.277	0.162
Δ_HDL	0.05 ± 0.26	0.02 ± 0.23	0.603	−0.05 ± 0.76	−0.33 ± 0.23	0.844	0.333	0.260
Δ _TG	−0.38 ± 0.88	−0.29 ± 0.74	0.621	−0.31 ± 1.24	−0.18 ± 0.83	0.501	0.758	0.521
Δ_LDL	−0.56 ± 1.28	−0.31 ± 1.34	0.424	−0.44 ± 0.9	−0.11 ± 0.7	0.038	0.657	0.407
Δ_GOT	−8.78 ± 16.0	−2.71 ± 11.2	0.086	−1.59 ± 13.0	−4.52 ± 12.6	0.242	0.035	0.503
Δ_GPT	−14.1 ± 28.5	1.87 ± 47.5	0.114	−7.21 ± 25.0	−7.58 ± 21.8	0.936	0.262	0.304
Δ_FIB4	−0.078 ± 0.455	−0.073 ± 0.362	0.967	−0.026 ± 0.311	−0.108 ± 0.440	0.234	0.199	0.746
Δ_HSI	−3.82 ± 4.72	−1.04 ± 4.25	0.024	−4.06 ± 15.3	1.68 ± 15.9	0.083	0.936	0.382
Δ _NLR	0.038 ± 0.575	0.194 ± 0.470	0.355	0.011 ± 0.533	0.622 ± 3.38	0.379	0.866	0.537
Δ _PLR	−0.779 ± 4.87	−0.0518 ± 0.277	0.524	0.284 ± 1.41	0.276 ± 1.09	0.98	0.364	0.158

p* comparison between subutaneous vs. oral formulations.
p** changes in athropometric and metabolic parameters (Δ) only in female vs male treated with subcutaneous formulation.
p*** comparison between oral formulations at 12 months in female vs. male patients treated with oral formulation.

absorption, the injectable route bypasses gastrointestinal variability, delivering the drug in a reproducible and reliable manner, which may be critical for achieving metabolic targets in male patients.

Furthermore, emerging data suggest that estrogen plays a pivotal role in enhancing GLP-1 receptor signaling, particularly in central and hepatic pathways. As reported by Börchers and Skibicka [20], this estrogen-mediated potentiation may allow women to derive substantial benefit even with lower or fluctuating drug exposure. In contrast, men, who lack this hormonal amplification, may require higher and steadier drug concentrations to achieve comparable or superior clinical outcomes, more easily achieved via subcutaneous delivery.

Sex-based differences in body composition and GLP-1 pharmacodynamics may also contribute. Men typically present with greater visceral adiposity and a more atherogenic lipid profile at baseline. These characteristics, associated with a more insulin-resistant metabolic phenotype, may render them more responsive to the peripheral metabolic actions of GLP-1 RAs when exposure is adequate and sustained.

Currently, sex-related differences in weight loss have been evaluated among patients treated with heterogeneous pharmacological classes of GLP-1 RAs, rather than within a single agent or formulation.

A recent meta-analysis evaluating the efficacy of GLP-1 RA, including subcutaneous semaglutide, exenatide, dulaglutide, and the dual GIP/GLP-1 agonist retatrutide, has provided robust evidence of a sex-specific differential response in weight reduction (in patients with and without diabetes mellitus), with females achieving significantly greater weight loss compared to males [33]. This difference was positively correlated with the extent of weight reduction, suggesting that biological sex may modulate the pharmacodynamic effects of GLP-1 RAs, particularly in the context of obesity-focused interventions.

Further, another meta-analysis assessing sex-stratified cardiovascular outcomes in individuals treated with both subcutaneous and oral formulations of semaglutide revealed a greater relative risk reduction in MACE among males, compared to females [34].

Our study has some limitations. The non-randomized design limits causal inference. While the study was powered for primary outcomes, subgroup analyses, particularly those stratified by sex, require cautious interpretation. In this regard, no adjustment for baseline differences or interaction terms was performed, due to the minimal and non-significant baseline differences observed across groups. The follow-up period, although clinically relevant, does not capture long-term cardiovascular or hepatic events. The selection of patients, even though was not based on clinical criteria, could be represent a bias. Additionally, lifestyle factors such as physical activity and dietary adherence were not systematically assessed.

In conclusion, our study reinforces the importance of tailoring GLP-1 RA therapy to both clinical and biological characteristics, including sex. Subcutaneous semaglutide may be particularly effective in male patients with obesity and atherogenic dyslipidemia and in female patients with steatotic liver. Oral semaglutide remains a valuable alternative for patients who are averse to injections or face logistical barriers, particularly when adherence can be assured.

5. Conclusions

Our findings demonstrate that subcutaneous semaglutide achieves greater metabolic efficacy than the oral formulation over 12 months, with distinct sex-specific patterns: men showed greater glycaemic and lipid improvements, while women experienced greater hepatic benefit. In contrast to preclinical and trial-based data suggesting a female advantage with GLP-1 RAs, our real-world study suggests that formulation type and sex interact in complex ways that warrant further investigation. Ultimately, these results support a sex-informed and formulation-sensitive approach to GLP-1 RA therapy, highlighting the need for future studies to include sex-disaggregated outcomes and explore the biological mechanisms underlying differential drug responses.

Ethics approval and consent to participate:

The study was conducted in accordance with the ethical standards of the institutional and national research committees, and with the 1964 Helsinki declaration and its later amendments. Ethical approval was obtained from the Ethics Committee of the Policlinico Paolo Giaccone (Protocol number: 01/2024) and written informed consent was signed from all individual participants included in the study.

Consent for publication:

Not applicable.

Availability of data and materials:

All data generated or analysed during this study are included in this published article.

Author contributions

Conceptualization, A.P., V.G.; Data curation, A.P., M.B., M.B., M.I.M., E.V.; Formal analysis, A.P., M.B., L.T., V.G.; Investigation, A.P., M.B., E.V., M.I.M., F.P.; Methodology, A.P., V.G., L.M.; Project administration, V.G.; Resources, G.A., V.G.; Software, L.M.; Supervision, G.A., V.G.; Validation, A.P., E.V., V.G.; Writing – original draft, A.P., M.B., V.G.; Writing – review & editing, E.V., M.I.M., F.P., G.A., V.G.

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During the preparation of this work the author V.G used chat gpt in order to revise the scientific language. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Declaration of competing interest

The authors declare that they have no competing interests.

References

[1] Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American diabetes association (ADA) and the European association for the study of diabetes (EASD). Diabetes Care 2022;45:2753–86. https://doi.org/10.2337/dci22-0034.

[2] Trujillo JM, Nuffer W, Smith BA. GLP-1 receptor agonists: an updated review of head-to-head clinical studies. Therapeutic Advances in Endocrinology 2021;12:2042018821997320. https://doi.org/10.1177/2042018821997320.

[3] Caruso I, Di Gioia L, Di Molfetta S, Cignarelli A, Palmer SC, Natale P, et al. Glucometabolic outcomes of GLP-1 receptor agonist-based therapies in patients with type 2 diabetes: a systematic review and network meta-analysis. eClinicalMedicine 2023;64:102181. https://doi.org/10.1016/j.eclinm.2023.102181.

[4] Ahrén B, Masmiquel L, Kumar H, Sargin M, Karsbøl JD, Jacobsen SH, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. Lancet Diabetes Endocrinol 2017;5:341–54. https://doi.org/10.1016/S2213-8587(17)30092-X.

[5] Pratley R, Amod A, Hoff ST, Kadowaki T, Lingvay I, Nauck M, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. Lancet 2019;394:39–50. https://doi.org/10.1016/S0140-6736(19)31271-1.

[6] Lingvay I, Catarig A-M, Frias JP, Kumar H, Lausvig NL, Le Roux CW, et al. Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial. Lancet Diabetes Endocrinol 2019;7:834–44. https://doi.org/10.1016/S2213-8587(19)30311-0.

[7] Capehorn MS, Catarig A-M, Furberg JK, Janez A, Price HC, Tadayon S, et al. Efficacy and safety of once-weekly semaglutide 1.0 mg vs once-daily liraglutide 1.2 mg as add-on to 1–3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). Diabetes Metabol 2020;46:100–9. https://doi.org/10.1016/j.diabet.2019.101117.

[8] Rodbard HW, Rosenstock J, Canani LH, Deerochanawong C, Gumprecht J, Lindberg SØ, et al. Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin: the PIONEER 2 trial. Diabetes Care 2019;42:2272–81. https://doi.org/10.2337/dc19-0883.

[9] Zhong P, Zeng H, Huang M, He G, Chen Z. Efficacy and safety of subcutaneous and oral semaglutide administration in patients with type 2 diabetes: a meta-analysis. Front Pharmacol 2021;12:695182. https://doi.org/10.3389/fphar.2021.695182.

[10] Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–44. https://doi.org/10.1056/NEJMoa1607141.

[11] Bonaca MP, Catarig A-M, Houlind K, Ludvik B, Nordanstig J, Ramesh CK, et al. Semaglutide and walking capacity in people with symptomatic peripheral artery disease and type 2 diabetes (STRIDE): a phase 3b, double-blind, randomised, placebo-controlled trial. Lancet 2025;405:1580–93. https://doi.org/10.1016/S0140-6736(25)00509-4.

[12] Krishnanda SI, Christabelle M, Yausep OE, Sugiharto C, Vincent LD, Agarwal R, et al. The effect of oral semaglutide on cardiovascular risk factors in patients with type 2 diabetes: a systematic review. JCM 2025;14:2239. https://doi.org/10.3390/jcm14072239.

[13] McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. JAMA Cardiol 2021;6:148–58. https://doi.org/10.1001/jamacardio.2020.4511.

[14] Rudofsky G, Amadid H, Braae UC, Catrina S-B, Kick A, Mandavya K, et al. Oral semaglutide use in type 2 diabetes: a pooled analysis of clinical and patient-reported outcomes from seven PIONEER REAL prospective real-world studies. Diabetes Ther 2025;16:73–87. https://doi.org/10.1007/s13300-024-01668-6.

[15] Odigwe C, Mulyala R, Malik H, Ruiz B, Riad M, Sayiadeh MA, et al. Emerging role of GLP-1 agonists in cardio-metabolic therapy - focus on semaglutide. Am Heart J: Cardiol Res Pract 2025;52:100518. https://doi.org/10.1016/j.ahjo.2025.100518.

[16] Mahaffey KW, Tuttle KR, Arici M, Baeres FMM, Bakris G, Charytan DM, et al. Cardiovascular outcomes with semaglutide by severity of chronic kidney disease in type 2 diabetes: the FLOW trial. Eur Heart J 2025;46:1096–108. https://doi.org/10.1093/eurheartj/ehae613.

[17] Kim HS, Jung CH. Oral semaglutide, the first ingestible glucagon-like Peptide-1 receptor agonist: could it be a magic bullet for type 2 diabetes? IJMS 2021;22:9936. https://doi.org/10.3390/ijms22189936.

[18] Giorgino F, Penfornis A, Pechtner V, Gentilella R, Corcos A. Adherence to antihyperglycemic medications and glucagon-like peptide 1-receptor agonists in type 2 diabetes: clinical consequences and strategies for improvement. PPA 2018;12:707–19. https://doi.org/10.2147/PPA.S151736.

[19] Alhindi Y, Avery A. The efficacy and safety of oral semaglutide for glycaemic management in adults with type 2 diabetes compared to subcutaneous semaglutide, placebo, and other GLP-1 RA comparators: a systematic review and network meta-analysis. Contemporary Clinical Trials Communications 2022;28:100944. https://doi.org/10.1016/j.conctc.2022.100944.

[20] Börchers S, Skibicka KP. GLP-1 and its analogs: does sex matter? Endocrinology 2025;166:bqae165. https://doi.org/10.1210/endocr/bqae165.

[21] Kwon J, Thiara D, Watanabe JH. Oral versus subcutaneous semaglutide weight loss outcomes after two years among patients with type 2 diabetes in a real-world database. Expet Rev Endocrinol Metabol 2025;20:163–8. https://doi.org/10.1080/17446651.2025.2462100.

[22] Formichi C, Baronti W, De Gennaro G, Cerrai Ceroni M, Nigi L, Rizzo L, et al. Real-world use of oral versus subcutaneous semaglutide in a cohort of type 2 diabetic patients: which option to which patient? J Endocrinol Investig 2024;47:2679–90. https://doi.org/10.1007/s40618-024-02369-4.

[23] Husain M, Bain SC, Jeppesen OK, Lingvay I, Sørrig R, Treppendahl MB, et al. Semaglutide (SUSTAIN and PIONEER) reduces cardiovascular events in type 2 diabetes across varying cardiovascular risk. Diabetes Obes Metabol 2020;22:442–51. https://doi.org/10.1111/dom.13955.

[24] Fadini GP, Bonora BM, Ghiani M, Anichini R, Melchionda E, Fattor B, et al. Oral or injectable semaglutide for the management of type 2 diabetes in routine care: a multicentre observational study comparing matched cohorts. Diabetes Obes Metabol 2024;26:2390–400. https://doi.org/10.1111/dom.15554.

[25] Roy Chowdhury S, Sadouki F, Collins E, Keen F, Bhagi R, Lim YSJ, et al. Real-world use of oral and subcutaneous semaglutide in routine clinical practice in the UK: a single-centre, retrospective observational study. Diabetes Ther 2024;15:869–81. https://doi.org/10.1007/s13300-024-01551-4.

[26] Conti M, Pontiggia L, Vergani M, Muraca E, Cannistraci R, Perra S, et al. Comparing medication persistence with oral and subcutaneous semaglutide in a real-world setting. Acta Diabetol 2024. https://doi.org/10.1007/s00592-024-02424-9.

[27] Chubb B, Gupta P, Gupta J, Nuhoho S, Kallenbach K, Orme M. Once-daily oral semaglutide versus injectable GLP-1 RAs in people with type 2 diabetes inadequately controlled on basal insulin: systematic review and network meta-analysis. Diabetes Ther 2021;12:1325–39. https://doi.org/10.1007/s13300-021-01034-w.

[28] Bonora BM, Russo G, Leonetti F, Strazzabosco M, Nollino L, Aimaretti G, et al. Effectiveness of oral semaglutide on glucose control and body weight up to 18 months: a multicenter retrospective real-world study. J Endocrinol Investig 2024;47:1395–403. https://doi.org/10.1007/s40618-024-02309-2.

[29] Horii T, Masudo C, Takayanagi Y, Oikawa Y, Shimada A, Mihara K. Adherence and treatment discontinuation of oral semaglutide and once-weekly semaglutide injection at 12 month follow-up: japanese real-world data. J of Diabetes Invest 2024;15:1578–84. https://doi.org/10.1111/jdi.14265.

[30] Lee J-H, Kim D, Kim HJ, Lee C-H, Yang JI, Kim W, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis 2010;42:503–8. https://doi.org/10.1016/j.dld.2009.08.002.

[31] Granhall C, Donsmark M, Blicher TM, Golor G, Søndergaard FL, Thomsen M, et al. Safety and pharmacokinetics of single and multiple ascending doses of the novel oral human GLP-1 analogue, oral semaglutide, in healthy subjects and subjects with type 2 diabetes. Clin Pharmacokinet 2019;58:781–91. https://doi.org/10.1007/s40262-018-0728-4.

[32] Overgaard RV, Delff PH, Petri KCC, Anderson TW, Flint A, Ingwersen SH. Population pharmacokinetics of semaglutide for type 2 diabetes. Diabetes Ther 2019;10:649–62. https://doi.org/10.1007/s13300-019-0581-y.

[33] Yang Y, He L, Han S, Yang N, Liu Y, Wang X, et al. Sex differences in the efficacy of glucagon-like Peptide-1 receptor agonists for weight reduction: a systematic review and meta-analysis. J Diabetes 2025;17:e70063. https://doi.org/10.1111/1753-0407.70063.

[34] Hamayal M, Akhtar CH, Ahmad N, Awwab M, Shahid W, Abbasi HS, et al. Cardiovascular safety profile of semaglutide and variations by sex, race, and kidney function: a systematic review and meta-analysis. Am J Cardiovasc Drugs 2025. https://doi.org/10.1007/s40256-025-00727-y.