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Review Article

Semaglutide and Obesity: Real-World Clinical Applications and Outcomes

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Abstract— Obesity, a chronic and complex disease, is projected to have a prevalence of 49% by 2030 and is linked to various comorbidities, including type 2 diabetes, hypertension, dyslipidemia, stroke, coronary heart disease, and cancers, resulting in a substantial economic burden. Effective weight management is crucial to reduce morbidity and mortality. Semaglutide, initially developed as a GLP-1 receptor agonist for treating type 2 diabetes, is now being explored for its potential in addressing obesity. Its utilization is expanding to chronic weight management as it mimics the effects of GLP-1, regulating blood sugar levels and appetite. The FDA approved the use of a 2.4 mg injection of semaglutide once weekly for chronic weight management. Semaglutide proves efficacy for weight loss in obesity, endorsed by STEP trial findings and real-world data, with safety akin to GLP-1RA class, promoting long-term adherence. Its notable effects on albuminuria, HbA1c, heart failure, and quality of life herald a transformative paradigm in obesity and associated comorbidity management. Through a review of existing literature and clinical studies, this article provides a nuanced overview of the diverse real-world scenarios where semaglutide has been applied, elucidating its impact on weight management and associated health outcomes.

Keywords— Obesity, Weight loss, Semaglutide, Real-world, GLP-1RA.

1. Introduction

Obesity, a non-communicable disease, refers to the excessive accumulation of fat in the body, potentially leading to adverse health effects. Obese individuals are prone to major risk factors that lead to increased mortality. Risk factors for obesity include cardiovascular diseases (CVD), diabetes mellitus, musculoskeletal disorders, and specific cancers. Obesity is commonly recognized by measuring body mass index (BMI) $\geq$ 30 kg/m^2 in adults. The global prevalence of obesity has increased three-fold between 1975 and 2016. The World Health Organization (WHO) estimated 650 million adults with obesity in 2016, approximately 13% of the global adult population. Over 124 million children and young adults worldwide were reported obese in 2016 **[1].**

Apart from associated risk factors, obesity can detrimentally affect one's quality of life and lead to psychological challenges like depression, anxiety, and diminished self-esteem **[2].** The foremost causes of obesity are imbalances in calorie consumption and expenditure, intake of processed foods, and physical inactivity. Environmental and societal changes are the underlying reasons for diet and physical activity changes. These contribute to the increase in the global prevalence of obesity, creating a pressing need for efficacious therapies to reduce the disease burden and mortality associated **[1]**.

Weight loss management is a long-term process as weight gain occurs gradually **[3]**. Management of obesity includes dietary therapy, physical exercise, pharmacotherapy, and surgical intervention **[4]**. Most of the conventional anti-obesity medications (AOMs) have demonstrated modest weight loss but are linked to increased adverse effects, including major cardiovascular adverse events. Semaglutide is the only AOM linked to a diminished likelihood of major cardiovascular events. Semaglutide received approval from the Food and Drug Administration (FDA) in 2017 for managing type 2 diabetes mellitus (T2DM). Later, in 2021, the FDA approved it as a novel drug therapy for sustained weight reduction along with a calorie-deficit diet and regular exercise regimen **[3]**.

Semaglutide is an efficacious drug belonging to the glucagon-like peptide-1 receptor agonist (GLP-1 RA) analog. It has shown major weight loss compared to surgical interventions such as gastric bypass surgery. It acts centrally in the brain to decrease appetite and ease the sensation of feeling more satiated for a longer period, thereby promoting weight loss. Additionally, it improves insulin secretion and glycemic control and delays gastric emptying **[3]**.

Randomized clinical trials (RCT) and real-world evidence (RWE) studies have noticeably described Semaglutide's efficacy in treating obesity **[5]**. Moreover, RWE studies provide essential information on weight loss outcomes in more diverse patient populations than RCTs, which are beneficial in clinical practice **[6]**. This review primarily focuses on exploring the role of semaglutide in real-world clinical settings to provide comprehensive insights into its efficacy and safety profile in managing obesity beyond diabetes. In addition to this objective, this review provides valuable insights into its growing use in clinical practice as a potent alternative to other AOMs, complement therapy after treatment failure with surgery, and managing comorbid conditions.

2. Method

This review aims to review the effectiveness of semaglutide in managing obesity within real-world clinical settings. A narrative review of recent literature searches was performed on PubMed and Google Scholar using the following Medical Subject Headings (MeSH) terms: "semaglutide" and "obesity management" in conjunction with "real-world." The literature searches were performed without a predefined research question or specific search strategy but focused on the topic of interest. Only articles written in English were included, and relevant studies and reviews were searched manually.

3. Results and discussion

3.1 Recent evidence on the real-world effectiveness of semaglutide in patients with obesity

The FDA approved a once-weekly (OW) semaglutide 2.4 mg subcutaneous injection for chronic weight management. While lower doses (0.5 mg and 1 mg) of semaglutide were indicated for managing T2DM, these doses were occasionally used off-label to reduce weight **[3]**. In real-world settings, semaglutide across different patient populations has yielded similar results as reported in RCTs. The study characteristics of the included studies are in **Table 1.**

In a recent study, Xiang *et al.* evaluated the effectiveness of 24-week semaglutide (1 mg) treatment and lifestyle modifications in 43 Chinese patients with a BMI ≥28 kg/m^2. The mean weight loss was 9.9 ± 3.9 kg, and the weight loss percentage was 11.2% after 24 weeks of treatment with semaglutide. 93% of patients have shown clinically meaningful weight loss of ≥ 5%, and 53% lost ≥ 10% weight. This study also assessed the impact of semaglutide on muscle mass and muscle strength, wherein muscle mass and muscle strength did not differ considerably. However, there was a slight reduction in skeletal muscle mass (8.1 vs. 7.9), muscle mass (calf circumference: 42.6 cm vs. 3.8 cm), and muscle strength (handgrip strength: 33.3 kg vs. 32.3 kg) from baseline to 24-week, respectively. These data indicate that semaglutide can effectively reduce weight in real-world settings consistent with clinical trial settings **[7]**

Another retrospective study evaluating 1 mg (escalated dose) semaglutide in 350 patients with obesity reported mean weight loss of 6.6% (82% patients) and 12% (64% patients) after 3 and 6 months of treatment, respectively. The percentage of patients who achieved ≥5%, ≥10%, and ≥15% weight loss after three months was 65.5%, 13.5%, and 2.4%, respectively. Noticeably, a higher percentage of weight was reduced in patients after six months of treatment. About 89.7% of patients experienced ≥5% weight loss, 60.3% experienced ≥10% weight loss, and 24.1% experienced ≥15% weight loss. These results were similar to that observed in RCTs **[8], [9]**.

The Semaglutide Real-world Evidence (SURE) study in Germany investigated the effectiveness of once-weekly semaglutide in a real-world population of patients with T2DM. The study revealed substantial improvements in glycated hemoglobin and body weight among participants, with estimated mean changes from baseline to end-of-study of –1.0% point (–10.9 mmol/mol; P<0.0001) and –4.5kg (–4.2%; P<0.0001), respectively. These results strongly support using once-weekly semaglutide as a viable treatment option in everyday clinical settings for adult T2DM patients **[10]**.

In a recent study from March 2017 to April 2022, 3,555 eligible patients were included, with 539 individuals observed for 52 weeks post-exposure. On average, participants achieved a weight reduction of 4.44%. Specifically, females experienced a loss of 5.08% of their initial weight, while males saw a decrease of 3.66%. Prediagnosis of diabetes mellitus was linked to reduced weight reduction, while prediabetes and the use of linaclotide were linked to more apparent weight loss **[11]**.

A US-based study comprising 175 patients with overweight or obesity investigated the real-world effectiveness of semaglutide doses used in RCTs (1.7 mg and 2.4 mg). The overall patient cohort achieved an average weight loss of 6.7 kg, approximately 5.9% of the average weight lost after three months. Meanwhile, 12.3 kg of average weight was lost after six months, corresponding to 10.9% of average weight lost. 53.7% and 14.9% of patients experienced ≥5% and ≥10% weight loss after three months, which increased to 87.3% and 54.9% after six months, respectively. Although the percentages of ≥5% and ≥10% weight loss were higher at six months, only 102 patients who completed treatment for six months were included in the analysis. Nonetheless, the authors described that the results were equivalent to those reported in the RCTs **[6]**.

3.2 Impact of semaglutide on weight regain after bariatric surgery in a real-world clinical setting

Surgical interventions, including bariatric surgery (BS), are beneficial in managing obesity, especially in patients with a BMI of ≥ 40 kg/m^2 **[3]**. Although BS is an effective intervention, some patients may remain unresponsive, may not achieve target weight loss, or may encounter weight regain, creating an obligation for complement therapy **[12]**. The role of semaglutide remains to be characterized in patients experiencing weight regain after BS. Recently, studies in real-world settings have explored the weight loss outcomes of semaglutide in patients undergoing treatment failure with BS.

Bonnet *et al.* evaluated the weight loss potential of semaglutide in 132 patients with severe obesity experiencing weight recurrence or ineffective weight loss after BS compared to patients with similar obesity criteria who never underwent BS. At the end of the 24-week treatment, about 9.8% of patients in the BS group and 8.7% in the non-BS group experienced mean weight loss. Almost 72% and 32% of patients in the BS group reduced >5% and >10% body weight at 24 weeks, respectively. While only 62% and 31% of patients in the non-BS group reduced >5% and >10% body weight at 24 weeks, respectively. The mean body weight differences between the two groups were comparable, proving that semaglutide is a substantial alternative to BS, particularly for managing obesity in patients with greater BMI **[12]**.

Another study conducted a retrospective analysis utilizing electronic health records (EHR) from 207 patients who underwent metabolic and bariatric surgery (MBS) to examine the effectiveness of two GLP-1 RA agents (semaglutide versus liraglutide). Amongst the overall cohort, 115 patients were treated with semaglutide OW dose of 1 mg and 92 patients with liraglutide daily dose of 3 mg over 12 months. The mean weight loss was 12.9% in the semaglutide group and 8.8% in the liraglutide group from baseline to 12-month with 4.2% mean weight loss differences between the groups ($p<0.001$). In the semaglutide group, 77.4%, 50.4%, and 27.8% of patients reduced ≥5%, ≥10%, and ≥15% of body weight, respectively, compared to 67.4%, 32.6%, and 15.2% in the liraglutide group. Semaglutide demonstrated a nearly two-fold increase in ≥10% and ≥15% body weight reduction compared to liraglutide. This study also found a positive correlation between the percentage of weight lost before MBS and the percentage regained after MBS with GLP-1 RA ($r=0.206$, $p=0.035$). The results suggest that semaglutide and liraglutide effectively reduce weight regain after MBS. Furthermore, the results imply the magnitude of weight loss experienced after MBS in a real-world clinical setting, demonstrating the applicability of GLP-1 RA in treating obesity **[13]**.

In a real-world patient setting, Jensen *et al.* assessed the effects of semaglutide and liraglutide in managing weight regain in patients after BS. The study investigated 1 mg subcutaneous (SC) and 14 mg oral semaglutide with 3 and 1.8 mg SC liraglutide. After six months of treatment, changes in total body weight occurred in 9.8% and 7.3% of patients treated with semaglutide and liraglutide, respectively. About 85.7%, 47.6%, and 23.8% of patients on semaglutide and 69%, 31%, and 3.5% of patients on liraglutide attained ≥5%, ≥10%, and ≥15% weight loss, respectively. Furthermore, a significant reduction in BMI was reported in semaglutide compared to liraglutide (3.9 kg/m^2 vs. 2.5 kg/m^2, $p<0.001$). With six months of GLP-1 RA treatment, patients have reduced 67.4% of weight regained after BS, which is approximately two-thirds of weight regained lost. This study also reflected the effectiveness of semaglutide and liraglutide, emphasizing these GLP-1 RA agents' extensive effects in managing weight regain, wherein their role is yet to be defined **[14]**.

Lautenbach *et al.* investigated the efficacy of semaglutide OW in nondiabetic patients with weight recurrence or insufficient weight loss after BS. This German-based study involved a weekly off-label dose of 0.5 mg semaglutide and lifestyle modification. The weight loss response was significant from baseline to 6 months of treatment (10.3%, $p<0.001$). Six months after treatment, 85% of patients experienced >5% weight loss, and 45% experienced >10% weight loss. This study also assessed the efficacy of semaglutide between the gender-based populations, where females experienced increased weight loss than males (11.04% vs. 5.90%). Notably, the weight loss outcomes between the gender-based populations were statistically significant ($p=0.005$). The findings from this study add up to the limited evidence of GLP-1 RA in managing weight gain recurrence post-BS, suggesting semaglutide is a considerable option to reduce weight recurred after BS **[15]**.

3.3 Real-world prospects of semaglutide in diabetic patients with obesity and its role in economy

The impact of semaglutide on glycemic indices has been well established in RCT trials such as SUSTAIN trials and others. In real-world clinical settings, recently published studies have found improved glycemic control in terms of decreasing HbA1c besides body weight reduction. Interestingly, two real-world studies were driven to seek efficacious alternatives to address the economic crisis.

In routine clinical practice, the non-persistence of medications has been increasing due to the chronic management of diseases such as T2DM. This demands an economically cost-efficient and therapeutically efficacious drug. Alternate-day dosing can prominently reduce medications' increasing cost and non-persistence, demonstrating similar effects as daily dosing. In this context, a real-world study in India assessed the efficacy of alternate-day semaglutide dosing versus daily semaglutide dosing. Eleven patients in this study were given 7 mg once daily semaglutide for a minimum of four weeks, following 14 mg semaglutide on alternate days. The ambulatory glucose profile (AGP) was recorded. An increased average TIR was observed with a 14 mg alternate day dose compared to a 7 mg daily dose (85.9% vs. 75.1%), but this comparison was not considerably different. BMI was reduced considerably with 14 mg alternate day dose than 7 mg daily dose (30 ± 3.9 kg/m^2 vs. 32 ± 4.7 kg/m^2). This study involved shorter duration, a smaller patient cohort, and a lack of comparison of standard glycemic measures, which disadvantages it from intending alternate day dosing as a therapeutically and economically efficient choice. Nonetheless, alternate-day dosing presented effects similar to daily dosing on AGP monitoring **[16]**.

A Spanish study addressed the increasing demand for OW semaglutide and dulaglutide in Europe, resulting in supply issues that may affect routine treatment. This retrospective study included patients with T2DM on GLP-1 RA prescriptions, including semaglutide, liraglutide, exenatide, dulaglutide, or lixisenatide. Four groups were considered for analysis: oral semaglutide, SC semaglutide, dulaglutide, and other GLP-1 RA agents. HbA1c declined by 1.36%, 0.91%,

1.74%, and 1.4% with oral semaglutide, SC semaglutide, dulaglutide, and other GLP-1 RA agents (p=0.383). Almost 50% of patients on GLP-1 RAs attained ≥5% weight loss from starting to three months. Notably, 61.1% of patients on oral semaglutide attained ≥5% weight loss, while 45.8% and 40.6% of patients on SC semaglutide and dulaglutide attained ≥5% weight loss, respectively. Total body weights of 4.9 kg, 4.7 kg, and 5 kg were reduced with oral semaglutide, SC semaglutide, and dulaglutide, respectively. BMI was reduced by 1.87 kg/m^2 with SC semaglutide and 1.82 kg/m^2 with oral semaglutide and dulaglutide. Among the groups, BMI and body weight changes were not meaningfully different. These results suggest that oral semaglutide is a suitable replacement for the likelihood of supply problems **[17]**.

3.4 RWE reflecting the efficacy of semaglutide in GLP-1 RA-naïve patients and switchers from other GLP-1 RAs

Compared to other treatments, the SUSTAIN trials have recorded significant enhancements in glycemic management and decreased body weight in patients with T2DM receiving semaglutide. Outcomes from real-world clinical settings are pivotal to strengthening and supporting RCTs' documentation regarding the marked efficacy of semaglutide.

An Italian study evaluated the efficacy of semaglutide in GLP naïve and switchers from other GLP-1 RAs in 216 patients with T2DM, of which 61.5% were GLP-1 RA naïve and 38.5% were switchers from other GLP-1 RAs. Patients were given a maximum dose of 1 mg SC semaglutide. In both groups, substantial HbA1c and body weight declines were observed after six months of treatment with semaglutide, which also sustained substantially after 12 months. The estimated mean weight difference in GLP-1 RA naïve and switchers from other GLP-1 RA was -5.22 kg and -3.13 kg, respectively, after 12 months. Remarkably, 46.9% and 25.9% of GLP-1 RA naïve patients and switchers from other GLP-1 RAs achieved >5% weight loss, respectively. At 12 months compared to baseline, HbA1c levels also reduced to 7.15 % in GLP-1 RA naïve (p<0.0001) and 7.46% in those changed from other GLP-1 RAs (p=0.0001). The percentage of patients who attained target HbA1c <7% with semaglutide were 52% and 31% in GLP-1 RA naïve and switchers from other GLP-1 RAs, respectively. A more pronounced effect was observed in GLP-1 RA naïve patients than those changed from other GLP-1 RAs. Overall, semaglutide has exhibited substantial benefits in both groups regardless of heterogeneous patient population and diabetic status **[18]**.

Okamoto *et al.* investigated a real-world single-center study of 50 Japanese patients with T2DM and obesity. Amongst the cohort, seven patients were semaglutide-naïve, and 43 patients were changed from other GLP-1 RA. All patients received a loading dose of 0.25 mg weekly for four weeks, followed by either 0.5 mg or 1 mg weekly based on the efficiency of semaglutide after four weeks. HbA1c declined significantly from 7.19 ± 1.21% to 6.36 ± 0.5% in semaglutide-naïve patients (p=0.04) and from 6.72 ± 0.62% to 6.22 ± 0.54% in those changed from other GLP-1 RAs (p<0.01). Also, significant body weight reduction from 95.3 ± 8 kg to 91.5 ± 7.2 kg in semaglutide-naïve patients (p=0.02) and from 86.5 ± 18.8 kilograms to 82.7 ± 19 kg in those changed from other GLP-1 RAs (p<0.01) were observed. Treatment with semaglutide resulted in the de-intensification of other antidiabetic therapies at the end of the study **[19]**.

Marzullo *et al.* investigated the changes in glycemic control and body weight among 258 patients with T2DM and obesity in an Italian cohort after 6 and 12 months of semaglutide treatment. Semaglutide was given to patients who were previously treated with antidiabetic therapies. Males were predominant in this cohort, and the overall population was moderately aged with average diabetic complications. The study findings revealed a significant reduction in glucose levels to 130.2 mg/dL after six months and 128.8 mg/dL after 12 months, compared to baseline (p<0.0001). Similarly, HbA1c levels decreased significantly to 6.9% after 6 and 12 months (p<0.0001). Moreover, a significant decline in BMI was also observed after 12 months (30.9 vs. 32.7, p<0.0001). Total body weights up to 19 kg and 26 kg was lost after 6 and 12 months, respectively. About 25.4% and 18.2% of patients experienced ≥5% and ≥10% weight loss. Semaglutide has extensively improved glycemic controls and reduced body weight irrespective of prior antidiabetic treatments or varying patient demographics **[5]**.

The findings from the studies mentioned above clearly show the potency of semaglutide in considerably reducing HbA1c levels beyond weight loss in diabetic patients. Studies have described semaglutide as a more potent drug than the other GLP-1 RAs, which can be considered in treating T2DM.

3.5 Role of semaglutide in the management of comorbid conditions: RWE perceptions

Almost 43% of T2DM patients have an increasing risk of progression with chronic kidney disease (CKD). Semaglutide's augmented effects on renal function were noted in the post-hoc analysis of the SUSTAIN program. In this analysis, semaglutide showed a positive decline in albuminuria, a pivotal contributor to limiting the progression risk of CKD.

Bueno *et al.* evaluated the effectiveness of OW SC semaglutide in 122 Spanish patients with T2DM and CKD. The primary outcomes were HbA1c <7% and weight loss > 5%, while the estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR) were secondary outcomes. After 12 months, HbA1c reduced to 6.83% from baseline (p<0.001), with 57.4% of patients attaining a target HbA1c level of <7%. An average body weight of 6.95 kg was reduced after 12 months, with 59% of patients achieving >5% weight loss. Similarly, a 53% reduction in UACR with a mean UACR difference of 162.2 ± 365.8 mg/g from baseline to 12 months (p<0.001) was observed. The mean eGFR was unchanged after 12 months. In the subgroup analyses, the microalbuminuria group (UACR 30-300 mg/g) experienced more weight loss, and the macroalbuminuria group (UACR >300 mg/g) showed a substantial decline in albuminuria at 12 months compared to baseline. The authors speculated that semaglutide exhibits nephroprotective effects through a direct mechanism on the renal system rather than an indirect way through weight loss, glucose, or blood pressure control based on the sub-group analyses. In this real-world study, notable effects of semaglutide on albuminuria reduction indicate that it may delay the progression of CKD **[20]**.

Heart failure (HF) is the most common comorbid CVD associated with T2DM. HF has a two-fold increased incidence than other CVDs (e.g., stroke) and with increased mortality compared to non-diabetic patients. The influence of semaglutide in HF patients has not been entirely outlined until now.

A real-life study in Spain explored the clinical response of OW semaglutide in obese T2DM patients with HF. The study evaluated the HF health status of patients by assessing the Kansas City Cardiomyopathy Questionnaire (KCCQ), New York Heart Association (NYHA) classification, and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels. Noteworthy changes were noted with the KCCQ symptom score (79.9 points vs. 59 points), NYHA functional class III (40.4% vs. 16.2%), and NT-pro-BNP levels (969.5 ± 653.5 vs. 577.4 ± 322.1) at 12-month compared to baseline ($p<0.01$ for all comparisons). Target HbA1c of <7% was achieved in 64.5% compared to 16.2% at baseline ($p<0.001$). In the 12^{th} month, patients experienced major weight loss (12.7 kg) and BMI decline (7.1 kg/m^2). As a result of improved glycemic control, de-intensification of T2DM treatment was observed, while no changes were observed with HF treatment. Semaglutide improved the overall HF status, as well as the quality of life **[21]**.

Another investigation presents the efficacy of GLP-1 RAs in monogenic obesity in 72 adult patients diagnosed with Alström syndrome (ALMS), a form of monogenic obesity in the United Kingdom in real-world settings. Thirty patients, ranging in age from 31 ± 11 years, underwent a six-month course of GLP-1 RA therapy in the form of exenatide or semaglutide. Body weight was reduced by 5.4 ± 1.7 kg and HbA1c by 12 ± 3.3 mmol/mol on average when GLP-1 RAs were used; this equates to 6% weight loss ($P <0.01$) and 1.1% absolute reduction in HbA1c ($P < 0.01$). Additionally, there were notable improvements in triglycerides, alanine aminotransferase levels, low-density lipoprotein cholesterol, high-density lipid profile, and serum total cholesterol. Regardless of weight reduction, the improvement in metabolic indicators in monogenic syndromic obesity was equivalent to results for polygenic obesity **[22]**.
Early diagnosis plays a crucial role in enhancing metabolic parameters. Clinical epigenetics presents a prospective avenue for diagnosing multifaceted disorders like obesity and type 2 diabetes mellitus (T2DM) **[23]**. Furthermore, machine learning algorithms can expedite diagnostic procedures, aiding in the comprehensive management of comorbidities associated with obesity and complementing interventions such as semaglutide **[24]**.

3.6 Long-term persistence of AOMs: A real world scenario

Non-persistence with AOMs is an uprising concern, given the impact of treatment discontinuation. Weight may occur, as witnessed in the participants of the STEP 1 extension study, wherein an average of two-thirds of weight was recovered at 12 months of discontinuation of semaglutide and lifestyle modifications. Additionally, the cardiometabolic benefits declined in those participants. The determinants of non-persistence are not entirely known, and focusing on such factors would be necessary in following treatment plans for substantial benefits.

A US-based study analyzed the initial fills of AOM prescriptions and refills over a specific period to explore the persistence of AOMs and the determinants related to long-term persistence. The study included 1911 patients with obesity on various AOMs, of which only 19% of patients were persistent with AOMs after one year. Patients on semaglutide were more persistent than other AOMs, especially naltrexone-bupropion, after one year (40% vs. 10%, $p<0.001$). Weight loss and insurance carriers were the critical determinants of persistence. This was mainly attributed to the fact that most patients were privately insured (84%) for AOM coverage. The odds of persistence differed in privately insured patients based on the type of insurance carriers. Additionally, an increased weight loss after six months was associated with 6% increased odds of persistence after one year. Higher odds of long-term persistence to AOMs are possibly associated with the insurance carriers covering AOM costs, given the high monthly costs of AOMs ($200-$1300). Furthermore, patients prescribed new and more productive agents such as semaglutide are likely to persist long-term **[25]**.

3.7 Safety profile of semaglutide: data from real-world studies

Semaglutide has shown similar side effects to those of GLP-1 RA analogs. Gastrointestinal (GI) effects are the side effects most observed in real-world studies **[12]**. GI effects were mainly mild-moderate **[7], [14],** or transient **[14]** and commonly included nausea, vomiting, and diarrhea **[4], [5], [7], [19], [20], [21], [22]**. Injection site reactions were reported less frequently with SC semaglutide [**14], [17]**. Other side effects reported in the studies include weakness, constipation, dyspepsia, headache, flatulence, dizziness, obstipation, and fatigue. Semaglutide was not associated with hypoglycemia **[19]**. Patients with a history of BS compared to non-BS patients did not report any increases in side effects. Moreover, the incidence of side effects, including early discontinuation, was higher in non-BS patients than in BS patients (16.7% vs. 7.7%) **[12]**. Overall, shreds of evidence from real-world studies indicate that semaglutide is an efficacious drug with an excellent safety profile.

4. Conclusion and future scope

In conclusion, semaglutide proves effective for weight loss in individuals with obesity, supporting its use in obesity management. The STEP clinical trial and real-world evidence highlight the efficacy and tolerability of semaglutide in those who are overweight or obese. Semaglutide exhibits a safety profile consistent with the GLP-1RA class. Patients prescribed potent agents like semaglutide are expected to have better long-term adherence. Real-world studies indicate
Semaglutide has significant impacts on reducing albuminuria and HbA1c levels and enhancing quality of life. This shift marks a transformative approach to obesity and obesity-associated comorbidity management.

Table 1. Study characteristics semaglutide for obesity/diabetes.

Study ID; Country	Study design	Patient population	N; % Males; Age (± SD)	Background treatment regimen	Intervention		Comparator		Outcomes (Primary, secondary and safety outcomes)
					Dosage	n (no of patients)	Dosage	n (no of patients)	
Ali *et al.*, 2023; UK	Real-world setting	Adult patients with Alström syndrome	30; 63; 31 ± 11	Metformin, sulfonylurea, SGLT2-i, insulin,Pioglitazones	Oral semaglutide 14 mg/once daily Subcutaneous semaglutide 1 mg/week	14	Subcutaneous Exenatide 0.5 mg/twice daily, 4 weeks Subcutaneous Exenatide 1.0 mg/twice daily	9	*Primary outcome:* • Participants achieved an average weight loss of 5.4 ± 1.7 (95% confidence interval [CI] 3.6-7) kg with a 6% mean weight change from baseline ($p < .01$). *Secondary outcome:* • HbA1c decreased by 12 ± 3.3 (95% CI 8.7-15.3) mmol/mol with an absolute reduction of 1.1% from baseline ($p < .01$). • Statistically significant changes were observed in systolic blood pressure ($P \leq .03$) and other metabolic variables, including triglycerides ($p \leq .01$), total cholesterol ($p \leq .03$), low-density lipoprotein cholesterol ($p \leq .03$) and, alanine aminotransferase ($p \leq .04$). • Commonly reported side effects were transient and self-limiting nausea, abdominal discomfort and diarrhoea during the dose titration period in 9 out of 21 patients.
Bonnet *et al.*, 2023; France	Retrospective cohort, real-world evidence study	Adult patients with obesity (BMI ≥40 kg/m^2) and with or without history of BS	129; 45; 51.1 (13.4)	GLP-1-RA	Semaglutide 0.25-2.4 mg/week	129	NA	NA	*Primary outcomes*: BS group vs. non-BS group: • Overall weight loss at week 24: 9.8% ± 5.7% vs. 8.7% ± 5.4% • Patients with >5% weight lost at week 24: 72% vs. 62% • Patients with >10% weight lost at week 24: 36% vs. 31% • Patients with >15% weight lost at week 24: 8% vs. 8% • Change in waist circumference at week 24: 9.2 ± 5.8 cm vs. 7.8 ± 6 cm • EWL at week 24: 23.2% ± 14.9% vs. 19.7% ± 12.4% • HbA1c after 24 weeks: 0.44% vs. 0.42% *Safety outcomes:* • Prevalence of adverse reactions or discontinuation (BS group vs. non-BS group): 7.7% vs. 16.7% • Most common side effects were GI effects
Gasoyan *et al.*, 2023; USA	Retrospective cohort study	Adult patients with obesity (BMI ≥30 kg/m^2)	1911; 25; 44 (12)	NA	Semaglutide 2.4 mg	NA	Naltrexone-bupropion, phentermine-topiramate, liraglutide 3 mg, orlistat	NA	*Primary outcomes*: Early- and late-stage persistence with AOMs: Persistence rates at 3-month ($p<0.001$): • Semaglutide: 63% • Liraglutide: 52% • Phentermine-topiramate: 36% • Naltrexone-bupropion: 34% • Orlistat: 11% Persistence rates at 12-month ($p<0.001$): • Semaglutide: 40% • Liraglutide: 17% • Phentermine-topiramate: 13% • Naltrexone-bupropion: 10% • Orlistat: 0%

Study ID; Country	Study design	Patient population	N; % Males; Age (± SD)	Background treatment regimen	Intervention		Comparator		Outcomes (Primary, secondary and safety outcomes)
					Dosage	n (no of patients)	Dosage	n (no of patients)	
Menzen *et al.*, 2023; Germany	Real-world setting	Adult T2DM patients	779, 56.1, 60.2 (10.16)	OAD, GLP-1RA, Insulin ± OAD without GLP-1RA	Semaglutide 0.25-1 mg/week	779	NA	NA	*Primary outcomes*: • HbA1c Control: At End of Study (EOS), the percentages of patients achieving: HbA1c < 8.0% (64 mmol/mol): 84.2% (n = 550) HbA1c < 7.5% (59 mmol/mol): 71.2% (n = 465) HbA1c < 7.0% (53 mmol/mol): 54.1% (n = 353) Additionally, 39.8% (n = 260) achieved an HbA1c reduction of ⩾ 1 %-point. *Secondary outcomes:* • Weight Loss: Proportion of patients achieving: ⩾ 3% weight loss: 53.3% ⩾ 5% weight loss: 38.1% • Waist Circumference Reduction: Mean change from baseline to EOS: –4.8 cm [95% CI –5.37 to –4.18]. • Blood Pressure (BP) Reduction: Systolic Blood Pressure (SBP) in the EAS decreased from baseline to EOS by 2.7 mmHg [95% CI –3.81 to –1.62]. Diastolic Blood Pressure (DBP) decreased from baseline to EOS by –1.1 mmHg [95% CI –1.78 to –0.37]. • Blood Lipids Changes: Total cholesterol decreased from baseline to EOS: from 180.1 mg/dL to 166.0 mg/dL. Triglycerides decreased from baseline to EOS: –48.0 mg/dL [95% CI –58.22 to –37.84], from 242.4 mg/dL to 194.4 mg/dL. •
Xiang *et al.*, 2023; China	Real-world setting	Adult patients with obesity (BMI ≥28 kg/m^2)	43; 23; 30.4 (8.1)	NA	Semaglutide 0.25-1 mg/week	43	NA	NA	*Primary outcomes:* Change in body weight after 24 weeks: • Overall weight loss: 11.2% ± 4.5%, p<0.001 • ≥5% weight reduced: 93% patients • ≥10% weight reduced: 53% patients • Waist and hip circumference: 6.9 and 7.7 cm, respectively. Alterations in body composition and muscle mass: • Skeletal muscle mass loss at 24-week: 1.4 ± 1.3 kg, p<0.001 • Fat mass loss at 24-week: 5.6 ± 3.7 kg, p<0.001 • SMI (at baseline vs. at 24-week): 8.1 ± 1 kg/m^2 vs. 7.9 ± 1 kg/m^2. Blood metabolic parameters including HbA1c, fasting blood glucose, fasting insulin, HOMA-IR index, blood uric acid, and blood lipid levels reduced after treatment *Safety outcomes:* • Mild-moderate GI disorders: nausea (n=5), diarrhea (n=4), and vomiting (n=4), Weakness (n=1) • No drop-outs due to adverse events

Study ID; Country	Study design	Patient population	N; % Males; Age (± SD)	Background treatment regimen	Intervention		Comparator		Outcomes (Primary, secondary and safety outcomes)
					Dosage	n (no of patients)	Dosage	n (no of patients)	
Alabduljabbar *et al.*, 2023; Ireland	Real-world setting, observational, retrospective study	Adult patients with obesity	350; NA; NA	NA	Semaglutide up to 1 mg	350	NA	NA	*Primary outcomes:* • Weight lost after 3 months in 82% patients: 6.6 ± 3.8% • Weight lost after 6 months in 64% patients: 12 ± 6.1% • Patients with ≥5% weight lost after 3 and 6 months: 65.5% and 89.7% • Patients with ≥10% weight lost after 3 and 6 months: 13.5% and 60.3% • Patients with ≥15% weight lost after 3 and 6 months: 2.4% and 24.1%
RoyChaudhuri *et al.*, 2023; India	Retrospective observational real-world cohort study	T2DM patients	11; 63.6; 58 (11)	NA	Semaglutide 7 mg/day	11	NA	NA	*Primary outcomes:* At the start of 1st AGP monitoring on 7 mg dose vs. at the end of 2nd AGP monitoring on 14 mg dose: • Average TIR: 75.1 ± 23.8% vs. 85.9 ± 12.8% • BMI: 32 ± 4.7 kg/m^2 vs. 30 ± 3.9 kg/m^2
					Semaglutide 14 mg qod	11			
Seijas-Amigo *et al.*, 2023; Spain	Multicenter, prospective, observational, real-world study	T2DM patients with BMI >30 kg/m^2	94; 51; 61.9 (10.9)	NA	Oral semaglutide	28	Dulaglutide, Other GLP-1-RA (liraglutide, exenatide, lixisenatide)	21, 5	*Primary outcomes:* Change in ≥5% weight lost at 3 months: • Oral semaglutide: 61.1% • Subcutaneous semaglutide: 45.8% • Dulaglutide: 40.6% • Other GLP-1-RA: 66.7% Change in body weight at 3 months: • Oral semaglutide: 4.9 kg • Subcutaneous semaglutide: 4.7 kg • Dulaglutide: 5 kg • Other GLP-1-RA: 6.1 kg • Overall body weight reduction: 4.95 kg, p<0.001 Change in BMI: • Oral semaglutide: 1.82 kg/m^2 • Subcutaneous semaglutide: 1.87 kg/m^2 • Dulaglutide: 1.82 kg/m^2 • Other GLP-1-RA: 2.47 kg/m^2 • Overall reduction in BMI: 1.86 kg/m^2, p<0.001 Change in HbA1c: • Oral semaglutide: 1.36% • Subcutaneous semaglutide: 0.91% • Dulaglutide: 1.74% • Other GLP-1-RA: 1.4% • Overall reduction in HbA1c: 1.4%, p<0.001 *Secondary outcomes:* • Overall % of patients' intolerant to maximum dose: 24% • Overall % of patients at maximum dose lost ≥5% of their body weight: 55.8%
					Subcutaneous semaglutide	40			

Study ID; Country	Study design	Patient population	N; % Males; Age (± SD)	Background treatment regimen	Intervention		Comparator		Outcomes (Primary, secondary and safety outcomes)
					Dosage	n (no of patients)	Dosage	n (no of patients)	
									Safety outcomes: Oral semaglutide group vs. subcutaneous semaglutide group vs. dulaglutide group: • GI disorders (nausea, diarrhea, constipation, dyspepsia, etc.): 25% vs. 22% vs. 62% • Headache or injection reactions: 11% vs. 10% vs. 14%
Murvelashvili *et al.*, 2023; USA	Retrospective analysis of real-world data	Adult patients with obesity after MBS (BMI ≥27 kg/m^2)	207; 10.1; 55.2 (10.7)	NA	Semaglutide 1 mg/week	115	Liraglutide 3 mg/day	92	*Primary outcomes:* Change in body weight from baseline to 12-month: • Mean weight change in semaglutide group: LS mean (SE): -12.9%, 95% CI: -14.1% to -11.8% • Mean weight change in liraglutide group: LS mean (SE): -8.8%, 95% CI: -10% to 7.5% • Mean difference between the groups: LS mean (SE): -4.2%, 95% CI: -5.9% to 2.4%; p<0.001 • Patients with ≥5% weight loss (Semaglutide vs. liraglutide): 77.4% vs. 67.4% • Patients with ≥10% weight loss (Semaglutide vs. liraglutide): 50.4% vs. 32.6% • Patients with ≥15% weight loss (Semaglutide vs. liraglutide): 27.8% vs. 15.2% • Patients with ≥20% weight loss (Semaglutide vs. liraglutide): 12.2% vs. 5.4%
Jensen *et al.*, 2023; Switzerland	Retrospective observational, real-world study	Adult patients with obesity after BS	50; NA; 50 (44.3, 57.8)	NA	Subcutaneous semaglutide 1 mg/week	20	Subcutaneous Liraglutide 3 mg/day	28	*Primary outcomes:* • Median weight of patients (at baseline vs. after 6 months of GLP-1-RA): 90.5 kg (83.4, 107.9) vs. 83.1 kg (75, 96.8) • Median BMI of patients (at baseline vs. after 6 months of GLP-1-RA): 34 kg/m^2 (26.6, 32.5) vs. 31.5 kg/m^2 (28.5, 36.2) • Change in total body weight after 6 months of GLP-1-RA (semaglutide vs. liraglutide): 9.8% vs. 7.3%, p<0.05 • ≥5% weight loss of baseline weight (Semaglutide vs. liraglutide): 85.7% vs. 69% patients • ≥10% weight loss of baseline weight (Semaglutide vs. liraglutide): 47.6% vs. 31% patients • ≥15% weight loss of baseline weight (Semaglutide vs. liraglutide): 23.8% vs. 3.5% patients • Change in BMI after 6 months of GLP-1-RA (semaglutide vs. liraglutide): 3.9 kg/m^2 (2.9, 4.8) vs. 2.5 kg/m^2 (1.1,3.3), p<0.001 *Safety outcomes:* • In overall, 36% of patients reported mild and transient adverse events such as, nausea (22%), obstipation (10%), vomiting (2%), flatulence (2%), diarrhea (2%), headache (2%), dizziness (2%), injection site reaction (2%). • No serious adverse events were reported.
					Oral semaglutide 14 mg/day	1	Subcutaneous Liraglutide 1.8 mg/day	1	

Study ID; Country	Study design	Patient population	N; % Males; Age (± SD)	Background treatment regimen	Intervention		Comparator		Outcomes (Primary, secondary and safety outcomes)
					Dosage	n (no of patients)	Dosage	n (no of patients)	
Pérez-Belmonte *et al.*, 2022; Spain	Retrospective observational, real-world study	T2DM patients with obesity and HF	136;	Metformin, sulfonylurea, DPP4-i, SGLT2-i, basal insulin, insulin combinations	Semaglutide 0.25-1 mg/week	136	NA	NA	*Primary outcomes:* • KCCQ total symptom score from baseline to 12 months: 59 to 79.9, p<0.01 • NYHA functional class III from baseline to 12 months: 40.4% to 16.2%, p<0.01 • NT-pro-BNP levels from baseline to 12 months: 969.5 ± 653.5 to 577.4 ± 322.1, p<0.01 *Secondary outcomes:* • HbA1c <7% from baseline to 12 months: 16.2% to 64.5%, p<0.001 • BMI from baseline to 12 months: 36.6 ± 7.2 kg to 29.5 ± 4.3 kg, p<0.001 • De-intensification of T2DM treatment from baseline to 12 months: 3.5 ± 1.2 to 2.2 ± 0.8, p<0.05 • No differences in HF medications after treatment with GLP-1-RA *Safety outcomes:* • In overall, 24.2% patients experienced adverse drug reactions (namely GI disorders: nausea, vomiting and diarrhea) • Discontinuation of semaglutide treatment: 8.8% • 3P-MACE at 12 months: 4.8% • Hospitalizations due to HF from baseline to 12 months: 38.2% to 27.4%, p<0.05 • All-cause hospitalizations from baseline to 12 months: 8.8% to 4%, p<0.05 • Emergency departments visits due to HF from baseline to 12 months: 50.7% to 39.5%, p<0.05
Lautenbach *et al.*, 2022; Germany	Retrospective analysis	Adult patients with WR (EWL >50%) and IWL (EWL <50%) after BS	44 NA 46.4 (8.8)	NA	Semaglutide 0.25-0.5 mg/week	44	NA	NA	*Primary outcomes:* Weight reduction at 3 months and 6 months after treatment initiation: • >5% weight loss: 61% and 85% patients • >10% weight loss: 16% and 45% patients • >15% weight loss: 2% and 5% patients • Overall weight loss: -10.3 ± 5.5%, p<0.001 *Secondary outcomes:* • HbA1c (at baseline vs. at 6 months): 5.3 ± 0.4 vs. 5.2 ± 0.2 • BMI (at baseline vs. at 6 months): 38.3 ± 6.4 kg/m^2 vs. 36.2 ± 6.7 kg/m^2 *Safety outcomes:* • Only 2 patients reported nausea and 1 patient showed increase in pancreatic lipase levels, which resolved spontaneously after 6 months of treatment initiation
Ghusn *et al.*, 2022; USA	Retrospective cohort study	Adult patients with overweight or obesity (BMI ≥27 kg/m^2)	175; 24.6 49.3 (12.5)	Insulin with metformin, empagliflozin, glipizide	Subcutaneous semaglutide 0.25 mg/week	6	NA	NA	*Primary outcomes:* • Mean weight loss of 175 patients at 3 months: 6.7 (4.4) kg ≡ 5.9% (3.7%), p<0.001 • Mean weight loss of 102 patients at 6 months: 12.3 (6.6) kg ≡ 10.9% (5.8%), p<0.001 • Mean weight loss with higher doses (1.7 and 2.4 mg) vs. lower doses (0.25, 0.5, and 1 mg) at 3 months: 6.9% (3.9%) vs. 5.1% (3.4%), p=0.002 • Mean weight loss with higher doses (1.7 and 2.4 mg) vs. lower doses (0.25, 0.5, and 1 mg) at 6 months: 12.1% (5.9%) vs. 9.2% (5.2%), p=0.01
					Subcutaneous semaglutide 0.5 mg/week	36			

Study ID; Country	Study design	Patient population	N; % Males; Age (± SD)	Background treatment regimen	Intervention		Comparator		Outcomes (Primary, secondary and safety outcomes)
					Dosage	n (no of patients)	Dosage	n (no of patients)	
					Subcutaneous semaglutide 1 mg/week	56			*Secondary outcomes:* • Patients with ≥5% and ≥10% weight loss at 3 months: 53.7% and 14.9%, respectively • Patients with ≥5% and ≥10% weight loss at 6 months: 87.3% and 54.9%, respectively • Mean % weight loss in patients with T2DM vs. without T2DM at 3 months: 3.9% (3.1%) vs. 6.3% (3.7%); p=0.001 • Mean % weight loss in patients with T2DM vs. without T2DM at 6 months: 7.2% (6.3%) vs. 11.8% (5.3%); p=0.005 *Safety outcomes:* • Adverse effects were experienced by 48.6% patients • Most common effects were GI symptoms: Nausea and vomiting (36.6%), diarrhea (8.6%) and fatigue (6.3%)
					Subcutaneous semaglutide 1.7 mg/week	29			
					Subcutaneous semaglutide 2.4 mg/week	48			
Marzullo *et al.*, 2022; Italy	Retrospective observational cohort study	T2DM patients with obesity (BMI ≥ 32 kg/m^2)	258; 58.5 60.4 (0.5)	Metformin, sulfonylurea, DPP4-i, SGLT2-i, insulin	Semaglutide 0.5 mg/week	258	NA	NA	*Primary outcomes:* • HbA1c at baseline, 6 months, and 12 months: 8 ± 0.6, 6.9 ± 0.1, 6.9 ± 0.1; p<0.0001 • % patients attained target HbA1c (<7%) after 6 months and 12 months: 61% and 57% *Secondary outcomes:* • Overall weight loss after 6 months and 12 months: 73.5% (range 0.5-19 kg loss) and 78.1% (range 0.2-26 kg loss) • BMI at baseline vs. 12 months: 32.7 ± 0.4 kg/m2 vs. 30.9 ± 0.8 kg/m2; p<0.0001 • Patients with ≥5% weight loss at 6 and 12 months: 21.2% and 25.4%, respectively • Patients with ≥10% weight loss at 6 and 12 months: 6.8% and 18.2%, respectively *Safety outcomes* • In overall, 15.1% of patients discontinued semaglutide. Of which 11.2% discontinued due to GI intolerance. • In overall, 18.1% patients reported side effects. Mainly, GI effects such as nausea, diarrhea or constipation, and abdominal cramps. • No patients required hospitalization
					Semaglutide 1 mg/week	NA			
Di Loreto *et al.*, 2022; Italy	Multicenter, observational, retrospective, real-world study	T2DM adult patients	216; 65.7; 64.1 (10.4)	Liraglutide, dulaglutide, exenatide, lixisenatide, basal insulin, OHA, short-acting insulin	Semaglutide 0.25, 0.5, 1 mg	216	NA	NA	*Primary outcomes:* • HbA1c levels at baseline, 6 months, and 12 months in GLP-1-RA naïve patients: 8.4%; 7.09%, p<0.0001; 7.15%, p<0.0001 • HbA1c levels at baseline, 6 months, and 12 months in patients changing from other GLP-1-RA: 8.24%; 7.46%, p<0.0001; 7.42%, p=0.0001 • Estimated mean weight difference after 6 and 12 months in GLP-1-RA naïve patients: -3.92 kg, p<0.0001 and -5.22 kg, p<0.0001 • Estimated mean weight difference after 6 and 12 months in patients changing from other GLP-1-RA: -2.64 kg, p<0.0001 and -3.13 kg, p=0.0003 *Secondary outcomes:* • % GLP-1-RA naïve patient attaining HbA1c <7%: 52% • % patients changing from other GLP-1-RA attaining HbA1c <7%: 31% • Patients with >5% weight loss in GLP-1-RA naïve patients: 46.9% • Patients with >5% weight loss in patients changing from other GLP-1-RA: 25.9%

Study ID; Country	Study design	Patient population	N; % Males; Age (± SD)	Background treatment regimen	Intervention		Comparator		Outcomes (Primary, secondary and safety outcomes)
					Dosage	n (no of patients)	Dosage	n (no of patients)	
									Safety outcomes: • In overall, 6.5% (n=14) patients discontinued semaglutide treatment. Of which, 6 patients discontinued due to GI effects. • No severe hypoglycemia was reported.
Bueno *et al.*, 2022; Spain	Multicenter, retrospective observational study	T2DM patients with CKD and HbA1c of 7.5-9.5%	122; 62; 65.5 (11)	Metformin, SGLT2-i, basal insulin, rapid-acting insulin, other GLP-1-RA (liraglutide, dulaglutide, exenatide LAR)	Semaglutide 0.25-1 mg/week	122	NA	NA	*Primary outcomes:* • HbA1c from baseline to 12 months: 7.57 ± 1.36% to 6.83 ± 0.85%; p<0.001 • % Patients attaining target HbA1c levels <7%: 57.4% • Mean weight reduced after 12 months: -6.95 ± 6; p<0.001 • BMI from baseline to 12 months: 35.8 ± 4.79 to 33.33 ± 4.77; p<0.001 • Patients with >5% weight lost after 12 months: 59% *Safety outcomes:* • Semaglutide was discontinued in 5.7% of patients. Of which, 65% discontinued due to digestive intolerance. Nausea occurred in 1.6% of patients. • Most frequent effects were digestive problems (0.8%), constipation (0.8%) and diarrhea (0.6%)
Okamoto *et al.*, 2021; Japan	Single-center, retrospective cohort study	T2DM patients (HbA1c ≥6.5%) with obesity (BMI ≥25 kg/m^2)	50; 39.5; 51.3 (11)	Dulaglutide, liraglutide, exenatide, SGLT2-i	Semaglutide 0.25-1 mg/week	50	NA	NA	*Primary outcomes:* • HbA1c from baseline to 6 months in semaglutide-naïve patients: 7.19 ± 1.21% to 6.36 ± 0.5%; p=0.04 • HbA1c from baseline to 6 months in patients changed to semaglutide: 6.72 ± 0.62% to 6.22 ± 0.54%; p<0.01 • Body weight from baseline to 6 months in semaglutide-naïve patients: 95.3 ± 8 kg to 91.5 ± 7.2 kg; p=0.02 • Body weight from baseline to 6 months in patients changed to semaglutide: 86.5 ± 18.8 kg to 82.7 ± 19 kg; p<0.01 *Secondary outcomes:* • % of semaglutide-naïve patients attaining target HbA1c <6.5% at 6 months: 100% (n=7) • % of semaglutide-naïve patients attaining target HbA1c <6.5% at 6 months: 100% (n=7) • Dose of insulin reduced in 19 patients by end of study: 7.9 ± 3.7 units • Dose reduction or interruption was possible in 6 patients receiving sulfonylureas or glinides *Safety outcomes:* • In overall patient cohort, liver-related paraments such as AST, ALT, γ-GTP, and LDH after 6 months of semaglutide improved significantly (p<0.01) • No adverse events related to semaglutide were reported.

Abbreviations: 3-Point major adverse cardiovascular event (3P-MACE); ambulatory glucose profile (AGP); alanine transaminase (ALT); anti-obesity medications (AOMs); antihyperglycemic agents (AHAs); aspartate aminotransferase (AST); body mass index (BMI); bariatric surgery (BS); chronic kidney disease (CKD); centimeter (cm); dipeptidyl peptidase-4 inhibitor (DPP4-i); effectiveness analysis set (EAS); End of study (EOS); excess weight loss (EWL); gastrointestinal (GI); Glucagon-like peptide-1 receptor agonists (GLP-1-RA); glycated hemoglobin (HbA1c); heart failure (HF); Homeostatic Model Assessment for Insulin Resistance index (HOMA-IR index); insufficient weight loss (IWL); Kansas City Cardiomyopathy Questionnaire (KCCQ); kilogram (kg); long-acting release (LAR); lactate dehydrogenase (LDH); least-square mean (LS mean); metabolic and bariatric surgery (MBS); milligram (mg); not available (NA); N-terminal pro-brain natriuretic peptide (NT-proBNP); New York Heart Association (NYHA); oral hypoglycemic agents (OHA); probability (p); every other day (qod); standard error (SE); sodium–glucose cotransporter-2 inhibitor (SGLT2-i); skeletal muscle index (SMI); Systolic blood pressure (SBP); type 2 diabetes mellitus (T2DM); time in range (TIR); United States of America (USA); versus (vs.); weight regain (WR); gamma-glutamyl transpeptidase (γ-GTP); less than (<); greater than or equal to (≥); greater than (>); equivalent (≡).

The future scope for semaglutide in obesity management is poised for significant advancement. Moving forward, personalized treatment regimens tailored to individual patient profiles, integration of digital health solutions for remote monitoring and support, and ongoing safety monitoring will be key areas of focus.

Data Availability (Size 10 Bold)
None.

Conflict of Interest
The authors affirm that they have no conflicts of interest.

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Authors' Contributions
Author 1 was responsible for the concept, design, writing, review, and editing of the manuscript drafts. Author 2 and 3 contributed to the collection of literature, data analysis, and manuscript writing. Author 4 was involved in reviewing the final draft and supervised the coordination of the publication process.

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