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Pharmacological Rescue After Bariatric Surgery Failure: The Role of GLP-1 Receptor Agonists in Weight Regain Management

Authors:
Gabriela Piotrowska, https://orcid.org/0009-0009-1283-7135
piotrowskagabi24@gmail.com
Gabriel Narutowicz Municipal Specialist Hospital in Kraków, Poland

Agnieszka Anna Gaczoł, https://orcid.org/0009-0008-9020-7123
agnieszkagaczol1@gmail.com
Gabriel Narutowicz Municipal Specialist Hospital in Kraków, Poland

Paulina Kopcińska, https://orcid.org/0009-0006-1495-1968
pjkopcinska@gmail.com
Gabriel Narutowicz Municipal Specialist Hospital in Kraków, Poland

Magdalena Mortka, https://orcid.org/0009-0009-0403-0008
magdalenamortka2@gmail.com
Medical University of Lublin, Lublin, Poland

Hubert Bednarz, https://orcid.org/0009-0003-1639-0699
hubertb7809@gmail.com
Medical University of Lublin, Lublin, Poland

Michał Kawa, https://orcid.org/0009-0001-8083-291X
michal.kawa2000@gmail.com
Murcki Hospital in Katowice, Poland

Kamil Idzik, https://orcid.org/0009-0000-7532-9255
kamilidzik99@gmail.com
Murcki Hospital in Katowice, Poland

Dominika Grzybowska, https://orcid.org/0009-0002-0599-8896
dominika.grzybowska996@gmail.com
St. Luke's Provincial Hospital in Tarnow, Poland

Aleksander Urbaś, https://orcid.org/0009-0004-5347-7192
urbas41@gmail.com
Murcki Hospital in Katowice, Poland

Zuzanna Lechowska, https://orcid.org/0009-0008-0430-3996
zuzalechu@gmail.com
Gabriel Narutowicz Municipal Specialist Hospital in Kraków, Poland

Tomasz Kilian, https://orcid.org/0009-0000-3161-6914
kilianowskipl@gmail.com
Murcki Hospital in Katowice, Poland

Michał Kurnik, https://orcid.org/0009-0008-4791-0630
michalkurnik95@gmail.com
Megrez Provincial Multi-Specialist Hospital in Tychy, Poland
Weronika Grzyb-Kurnik, https://orcid.org/0009-0001-7622-281X
wrgrzyb@gmail.com
Megrez Provincial Multi-Specialist Hospital in Tychy, Poland

Corresponding Author
Gabriela Piotrowska, piotrowskagabi24@gmail.com

Abstract
Background:
Obesity is a chronic, multifactorial disease with rapidly growing global prevalence. Bariatric surgery remains the most effective intervention for long-term weight reduction and improvement of obesity-related comorbidities; however, 16 - 37% of patients experience inadequate weight loss or weight regain, prompting the search for less invasive pharmacological strategies.
Aim:
To review the efficacy and safety of GLP-1 receptor agonists in adults after bariatric surgery presenting with insufficient weight loss or weight regain.
Material and methods:
A narrative literature review was conducted using medical databases and current guidelines, including original and review articles in English involving adult post-bariatric patients treated with GLP-1 receptor agonists, reporting weight-related outcomes and safety data.
Results:
Liraglutide 3.0 mg achieved additional weight loss of approximately 5 - 6% over 6 - 8 months, with early onset of effect and comparable efficacy across surgical techniques. Once-weekly semaglutide (0.5 mg) demonstrated weight loss of 10.3% at 6 months. After 12 months of

GLP-1 receptor agonist therapy (liraglutide or semaglutide combined), median total body weight loss reached 11.2%. Preliminary data on tirzepatide suggest superior efficacy: 15.5% weight loss at 6 months versus 10.3% with semaglutide after sleeve gastrectomy. Adverse events were predominantly mild to moderate gastrointestinal symptoms.
Conclusions:
GLP-1 receptor agonists represent a promising, less invasive option for post-bariatric weight management and should be considered before revisional surgery in appropriately selected patients. Larger randomised studies - particularly with tirzepatide - are needed to define optimal drug choice, timing, and patient selection.

Key words:
bariatric surgery; GLP-1 receptor agonists; obesity; post-bariatric weight regain; insufficient weight loss after bariatric surgery; pharmacotherapy of obesity

1. Introduction

Obesity is recognised as a chronic, multifactorial metabolic disease characterised by excessive accumulation of adipose tissue, leading to significant deterioration of quality of life and overall health status. It currently represents one of the most serious public health challenges worldwide, having reached the proportions of a global epidemic [1, 2], as its prevalence continues to rise across all age groups and regions of the world, and this trend has thus far not been reversed despite the implementation of broad preventive measures [1, 24].

According to the World Health Organization, obesity in adults is classified on the basis of the body mass index (BMI), calculated as the ratio of body weight in kilograms to the square of height in meters (kg/m²) [28]. Overweight is defined as a BMI ≥ 25.0 kg/m², while obesity is diagnosed at a BMI ≥ 30.0 kg/m², with further classification into class I obesity (30.0 - 34.99 kg/m²), class II obesity (35.0 - 39.99 kg/m²), and class III obesity (≥ 40.0 kg/m²) [28]. According to the WHO 2022 report, approximately 60% of the European population is affected by overweight or obesity, with a higher prevalence among men, and a peak incidence observed in the 50 - 65 age group [2]. The consequences of obesity include a significantly elevated cardiovascular risk, premature mortality, disability, chronic impairment of physical functioning, and deterioration of quality of life [1], as well as a substantial financial and resource burden on healthcare systems due to the necessity of treating numerous associated complications. Based on current epidemiological trends, it is projected that the total number of individuals aged 18 years and older living with overweight or obesity will reach 3.80 billion (95% UI 3.39 - 4.04) by the year 2050, representing more than half of the probable global adult population at that time [3].

For these reasons, obesity is now regarded not merely as a risk factor for other conditions - such as insulin resistance and type 2 diabetes, arterial hypertension, atherosclerosis and ischemic heart disease, dyslipidemia, metabolic dysfunction-associated steatotic liver disease [32] (formerly known as non-alcoholic fatty liver disease), and obstructive sleep apnea [1] - as well as an increased risk of certain malignancies, including colorectal cancer, breast cancer, renal cell carcinoma, and ovarian cancer [2] - but as an independent disease entity requiring long-term, multidirectional management aimed at body weight reduction and comprehensive metabolic profile modification, necessitating an interdisciplinary approach.

Given the growing scale of the problem, lifestyle modification alone often proves insufficient in the treatment of obesity [29], and as a result, both surgical bariatric treatment [4] and modern pharmacological approaches - including GLP-1 receptor agonists [5] - are being increasingly utilised, as numerous clinical trials have demonstrated significant body weight reduction and improvement of metabolic parameters in patients with obesity. Of particular clinical relevance, however, is the management of patients following bariatric surgery who did not achieve adequate weight loss or who experienced weight regain in the years following the procedure [6, 7]. In this context, there is growing interest in the potential use of GLP-1 receptor agonists as an adjunctive treatment modality in this patient population [6], given that approximately 16 - 37% of patients undergoing bariatric surgery are estimated to experience weight regain or insufficient weight loss in subsequent years [8], which significantly undermines the long-term efficacy of surgical obesity treatment.

This phenomenon serves as the starting point for the present study, the aim of which is to evaluate the potential role of GLP-1 receptor agonists as adjunct therapy in this patient group.

2. Materials and methods

2.1 Research materials and methods

This study is a narrative literature review on the use of GLP-1 receptor agonists in patients following bariatric surgery who did not achieve satisfactory weight loss or experienced subsequent weight regain. To identify relevant studies, a search of medical databases (PubMed, Google Scholar) was conducted using the following terms: "bariatric surgery", "obesity", "GLP-1 receptor agonists", "liraglutide", "semaglutide", "tirzepatide", "post-bariatric weight regain", "insufficient weight loss after bariatric surgery", "pharmacotherapy of obesity", "anti-obesity medications". Additionally, current guidelines from scientific societies and reports from public health institutions regarding the treatment of obesity and post-bariatric management were included. The analysis primarily incorporated original and review articles published in English that met the predefined inclusion criteria: adult patients (aged 18 years and older) following bariatric procedures, use of GLP-1 receptor agonists, and reported data on treatment efficacy and safety.

2.2 Research results

The literature search identified a total of several observational, retrospective, and prospective studies evaluating the efficacy and safety of GLP-1 receptor agonists - liraglutide, semaglutide, and tirzepatide - in adult patients following bariatric surgery who experienced insufficient weight loss or weight regain. The identified studies varied with respect to study design, sample size, type of bariatric procedure, GLP-1 receptor agonist used, dose, and duration of follow-up. The key findings from the included studies are presented in the sections below.

3. Results

3.1 Bariatric Surgery

Bariatric surgery is recognised as the most effective treatment for obesity, providing patients with long-term weight loss and greater control over obesity-related comorbidities, and in some cases even their remission [9, 13, 15]. In accordance with the current 2022 ASMBS and

IFSO guidelines [30], metabolic and bariatric surgery is recommended for patients with a BMI ≥ 35 kg/m² regardless of the presence of comorbidities, representing a significant change from the 1991 NIH guidelines [31], which required a BMI ≥ 40 kg/m² in the absence of such conditions. Additionally, surgery should be considered in patients with a BMI of 30.0 - 34.9 kg/m² in whom conservative treatment has not yielded lasting results or in whom metabolic disease is present.

In clinical practice, the most commonly performed bariatric procedures remain sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) [10, 14]. The 2024 report of the Global Registry of the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) indicates that sleeve gastrectomy is the most frequently performed bariatric procedure worldwide, accounting for 60% (331,000 out of 547,959) of all primary bariatric procedures globally, making it the leading surgical technique (IFSO Global Registry, 2024) [26, 27].

In a meta-analysis evaluating outcomes by bariatric surgical technique, significant weight loss was demonstrated across all analysed groups, with the greatest reduction achieved following Roux-en-Y gastric bypass, a somewhat smaller reduction after sleeve gastrectomy, and a markedly lower reduction after gastric banding [15]. A substantial proportion of patients undergoing bariatric surgery experience weight regain in subsequent years. Insufficient weight loss is defined as failure to achieve ≥ 50% excess weight loss (%EWL), whereas weight regain is defined as the recovery of more than 50% of previously lost body weight [6, 7, 12, 14]. In practice, this means that the outcome of the procedure does not meet the expectations of either the patient or the treating team. Such a scenario can be particularly demotivating, as it is preceded by a lengthy qualification process, numerous specialist consultations, lifestyle modifications, and extensive preoperative preparation [11, 14]. As a consequence, patients often perceive their prior efforts and sacrifices as futile, which may lead to a decline in motivation to continue obesity treatment, avoidance of postoperative follow-up visits, and even abandonment of further interventions, despite the availability of additional effective methods to support weight reduction.

Table 1. Selected adverse events according to bariatric surgery technique [15]

Complication	Characteristics by surgical technique
Small bowel obstruction (adhesions / hernias)	Most common after RYGB; less frequent after SG and GB
Anastomotic leak / fistula / ulceration / stenosis	More frequent after RYGB than SG
Bleeding	Slightly more common after GB (gastric banding) than after RYGB and SG
Gastric sleeve stenosis	Reported almost exclusively after SG
Band slippage / device dysfunction	Predominantly associated with GB
Dumping syndrome	Markedly more frequent after RYGB; very rarely after SG
GERD (Gastroesophageal reflux disease)	Most common after SG; less frequent after GB; relatively rare after RYGB
Cholelithiasis	Similar incidence across all surgical groups
Mortality	Single reported case after RYGB

A summary of selected adverse events according to bariatric surgical technique is presented in Table 1. Small bowel obstruction and anastomotic complications are reported more frequently following RYGB, whereas gastric stenosis and gastroesophageal reflux disease (GERD) are predominantly associated with SG, and band-related complications are characteristic of GB. Dumping syndrome occurs markedly more often after RYGB, while the incidence of cholelithiasis appears comparable across all surgical modalities [15].

Revisional and conversional procedures are associated with a higher rate of complications compared to primary bariatric surgery [6, 7, 11, 12], thereby limiting their widespread application in patients who experience weight regain or suboptimal weight loss. In light of the above, increasing attention is being directed toward pharmacotherapy as a less invasive and potentially safer approach, particularly in patients burdened with numerous comorbidities or at high perioperative risk. The introduction of modern pharmacological agents, including GLP-1 receptor agonists [16], represents an important alternative to revisional surgery in this patient population, potentially allowing for further weight reduction without the need for repeat surgical intervention [5].

3.2 GLP-1 Receptor Agonists

GLP-1 receptor agonists are drugs originally developed and widely used in the treatment of type 2 diabetes, where they improve glycaemic control by enhancing glucose-dependent insulin secretion, inhibiting glucagon secretion from α-cells, and delaying gastric emptying, thereby significantly reducing postprandial glycaemic fluctuations [17]. In the subsequent years following the introduction of GLP-1 receptor agonists, it was demonstrated that drugs from this group also lead to clinically significant weight loss, which resulted in their approval for the treatment of obesity as well [18]. Liraglutide 3.0 mg received marketing authorisation from the European Medicines Agency (EMA) for chronic weight management in March 2015 [33], followed by semaglutide 2.4 mg, which was authorised by the EMA in January 2022 [34]. Weight reduction achieved with GLP-1 receptor agonists results primarily from central nervous system activity - these agents bind to GLP-1 receptors in the hypothalamus, particularly in the dorsomedial hypothalamus (DMH), suppressing appetite and enhancing satiety, thereby reducing total food intake [35]. Given their documented efficacy in weight reduction and favourable effects on the metabolic profile, GLP-1 receptor agonists are currently regarded as a promising therapeutic option in patients following bariatric surgery who did not achieve satisfactory weight loss or who experienced weight regain in long-term follow-up, representing a less invasive alternative to or adjunct for revisional surgery [36].

3.2.1 Liraglutide

Liraglutide, a long-acting GLP-1 receptor agonist with 97% homology to human glucagon-like peptide-1, was initially introduced for the treatment of type 2 diabetes and subsequently approved at a dose of 3.0 mg as an anti-obesity agent, owing to its documented capacity to induce significant weight loss [12, 33]. In recent years, accumulating evidence has indicated that liraglutide pharmacotherapy may represent an effective strategy in patients following bariatric surgery who experience insufficient weight loss or weight regain [12, 19]. Observational and prospective studies have demonstrated that the use of liraglutide 3.0 mg in this patient population leads to additional weight loss at an acceptable safety profile, regardless of the primary surgical technique employed [12, 19].

In a study by Wharton et al. [12], patients following bariatric procedures were evaluated (RYGB in 43.5% and GB in 42.7% of participants). Prior to bariatric surgery, the mean BMI was 49.7 ± 12.1 kg/m², with a mean post-operative weight loss of 40.7 ± 25.0 kg (28.8%). Before the initiation of liraglutide 3.0 mg, patients had regained 21.2 ± 16.9 kg (58.6% of previously lost body weight), reaching a BMI of 42.5 ± 9.6 kg/m²; treatment was initiated a mean of 7.8 ± 5.7 years after surgery (IQR 4 - 10 years). Over a mean treatment duration of 7.6 ± 7.1 months, a statistically significant weight loss of 5.5 ± 6.2% (6.3 ± 7.7 kg, $p < 0.05$) was achieved. Although patients following RYGB had a lower BMI at treatment initiation compared to those after GB or SG ($p < 0.05$), the magnitude of weight loss achieved with liraglutide was comparable across surgical procedure types ($p > 0.05$). Significant weight reduction was observed as early as 1 - 2 months after treatment initiation and was maintained through month 12 ($p < 0.05$), with no differences between surgical procedure types ($p > 0.05$). Patients who continued therapy through months 11 - 12 lost an average of 2.0 ± 7.4 kg more than at months 5 - 6 ($p = 0.004$), suggesting that longer duration of liraglutide therapy translates into a greater cumulative effect. Notably, patients maintaining treatment for more than one month achieved comparable weight loss regardless of whether the target dose of 3.0 mg was reached (7.4 ± 6.9 vs. 6.8 ± 11.4 kg; $p = 0.81$), indicating that treatment duration may be more clinically relevant than achieving the maximum dose [12].

Supporting these findings, the randomised BARI-OPTIMISE trial by Mok et al. [13] demonstrated that liraglutide 3.0 mg once daily was superior to placebo in patients with poor weight loss following metabolic surgery, providing the only randomised controlled evidence currently available for GLP-1 receptor agonist use in this specific post-bariatric population. Liraglutide therefore represents an important adjunctive therapeutic option following bariatric surgery, allowing for partial correction of suboptimal surgical outcomes without the need for additional, more burdensome revisional procedures [12, 19].

3.2.2 Semaglutide

Semaglutide, a long-acting GLP-1 receptor agonist administered once weekly, has demonstrated documented efficacy in weight reduction in patients with obesity, generally exceeding the effects of standard behavioural and dietary interventions [19, 20]. In recent years, evidence has emerged indicating its therapeutic potential in patients following bariatric surgery who did not achieve satisfactory weight loss or experienced weight regain.

In a study by Lautenbach et al. [20], the efficacy of semaglutide at a dose of 0.5 mg administered once weekly via subcutaneous injection was evaluated in 44 patients without type 2 diabetes who experienced weight regain or insufficient weight loss following bariatric surgery. Treatment was initiated a mean of 64.7 ± 47.6 months after bariatric surgery, at a baseline BMI of 38.3 ± 6.4 kg/m². After 3 months of treatment, a mean weight loss of 6.0 ± 4.3% was achieved ($p < 0.001$), with 61% of patients losing ≥ 5% and 16% losing ≥ 10% of body weight. After 6 months, mean weight loss increased to 10.3 ± 5.5% ($p < 0.001$), with 85% of patients achieving ≥ 5% and 45% achieving ≥ 10% weight loss. No significant differences in weight loss were observed between patients following SG and RYGB ($p = 0.7$ at 3 months; $p = 0.8$ at 6 months) [20].

In a study by Jensen et al. [19], the efficacy of liraglutide and semaglutide was compared in patients following bariatric surgery with weight regain. Across all participants, after 12 months of GLP-1 receptor agonist treatment, a median weight loss of 10.5 kg (IQR 6.1 - 14.7 kg) was observed, corresponding to a reduction in BMI of 3.7 kg/m² (IQR 2.5 - 5.3 kg/m²)

and a loss of 11.2% (IQR 7.4 - 15.2%) of total body weight. This translated into a reduction of excess body weight by 41.7% (IQR 22.1 - 70.5%) and an almost complete reversal of post-bariatric weight regain - on average 99.3% (IQR 61.0 - 135.4%) of previously regained body weight ($p < 0.0001$). The majority of the effect was already observed at 6 months of therapy (weight loss of 7.8 kg [IQR 5.6 - 11.4 kg] and 3.0 kg/m² [IQR 2.3 - 3.8 kg/m²]); however, between months 6 and 12, a further additional loss of 3.2 kg (IQR 0.4 - 5.5 kg) and 1.3 kg/m² (IQR 0.1-2.0 kg/m²) was observed in the same subgroup. A statistically significant difference between GLP-1 receptor agonist analogues was demonstrated - the reduction in BMI was significantly smaller in patients treated with liraglutide (-3.1 kg/m²; IQR -4.7 to -2.0) than in those receiving semaglutide (-4.7 kg/m²; IQR -6.0 to -3.7; $p = 0.04$) [19].

These findings suggest that semaglutide demonstrates greater efficacy in weight reduction than liraglutide and may represent a particularly attractive therapeutic option in patients with weight regain following bariatric surgery [19, 20].

3.2.3 Tirzepatide

Tirzepatide is a novel dual GIP/GLP-1 receptor agonist, originally developed for the treatment of type 2 diabetes. Unlike classical GLP-1 receptor agonists, tirzepatide combines the actions of two incretin hormones - GLP-1, released from L-cells in the ileum, and GIP, secreted from K-cells in the duodenum and jejunum. GLP-1 slows gastric emptying, enhances satiety, and increases glucose-dependent insulin secretion while suppressing glucagon release. GIP, in turn, enhances insulin secretion, influences insulin sensitivity in adipose tissue, and - as suggested by preclinical studies - may participate in appetite regulation [21]. Preliminary analyses suggest that tirzepatide may be more effective than classical GLP-1 receptor agonists (e.g. liraglutide) and even newer agents such as semaglutide, including in patients following bariatric surgery. However, the number of studies in this specific post-bariatric population remains very limited, with data frequently derived from single, small-scale studies, precluding robust meta-analysis and necessitating larger, well-designed randomised controlled trials.

In an indirect treatment comparison conducted by le Roux et al. [22], tirzepatide at doses of 10 mg and 15 mg was compared with semaglutide 2.4 mg, demonstrating that tirzepatide, regardless of the dose used, led to a significantly greater percentage reduction in body weight. For the 10 mg dose, the mean difference was -4.67% (95% CI -5.91% to -3.43%; $p < 0.001$), and for the 15 mg dose -5.92% (95% CI -7.16% to -4.68%; $p < 0.001$), indicating that tirzepatide provided an additional approximately 5-6 percentage points of weight loss compared to semaglutide 2.4 mg [22].
In a study by Jamal et al. [23], the efficacy of tirzepatide (starting dose 2.5 mg s.c. once weekly) was compared with semaglutide (starting dose 0.25 mg s.c. once weekly) in patients following sleeve gastrectomy. After 6 months of therapy, the semaglutide group achieved a clinically significant weight loss of 10.3 ± 5.9% (decrease from 90.1 ± 19.6 to 81.0 ± 19.0 kg; $p < 0.05$), while the tirzepatide group achieved a greater reduction of 15.5 ± 6.3% (decrease from 100.2 ± 28.5 to 87.6 ± 28.3 kg; $p < 0.05$). It should be noted that both groups received starting doses of the respective agents, which may have influenced the magnitude of the observed effect.

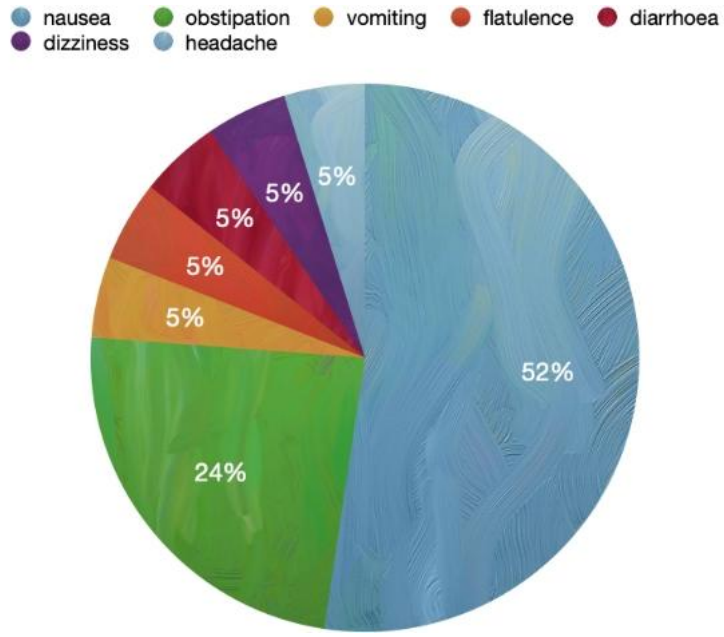
Currently, the number of studies evaluating tirzepatide in the post-bariatric patient population remains limited, and available data are derived primarily from small retrospective studies, precluding robust meta-analysis. Nevertheless, the available evidence suggests that tirzepatide may lead to greater weight loss than previously established GLP-1 receptor agonists such as

liraglutide and semaglutide, and warrants further evaluation in larger, well-designed randomised controlled trials [5, 22, 23].

3.2.4 Adverse Effects of GLP-1 Receptor Agonists

Adverse effects of GLP-1 receptor agonists are generally mild to moderate and transient, most commonly affecting the gastrointestinal tract and including nausea, vomiting, diarrhoea, bloating, and postprandial fullness [12, 19]. These symptoms are most pronounced during the initial period of therapy and typically resolve spontaneously with continued treatment; the risk of their occurrence can be minimised through gradual dose titration. In clinical studies, some patients chose to discontinue therapy due to gastrointestinal intolerance, insufficient weight loss response, or lack of reimbursement [8]. Isolated cases of transient, asymptomatic increases in pancreatic enzyme activity, such as lipase, have been reported, which resolved spontaneously during long-term follow-up without the need for permanent treatment discontinuation [20]; clinical pancreatitis remains a rare event.

Figure 1. Pie chart showing the distribution of adverse events during GLP- 1 RA therapy after bariatric surgery [8]



In the study by Jensen et al. [8], nausea was the most frequently reported adverse event during treatment with liraglutide and semaglutide for post- bariatric weight regain, accounting for 52% of all recorded side effects. Constipation represented 24% of events, whereas vomiting, flatulence, diarrhoea, dizziness and headache were each reported in 5% of cases. This distribution, illustrated in the pie chart, underlines that the safety profile of GLP- 1 receptor agonists in this post- bariatric population is dominated by mild to moderate gastrointestinal symptoms.

4. Discussion

Bariatric surgery remains the most effective long-term treatment for obesity, providing substantial weight loss and improvement, and sometimes remission, of obesity-related comorbidities. Nevertheless, a considerable proportion of patients experience inadequate weight loss or weight regain after surgery, estimated in long-term follow-up at approximately 16-37% [6-8]. This phenomenon undermines the perceived efficacy of bariatric surgery and often leads to frustration, loss of motivation and avoidance of follow-up visits, despite the availability of additional therapeutic options. In this context, pharmacological rescue strategies are gaining increasing importance, especially those that can provide clinically meaningful weight loss without exposing patients to the higher complication risk associated with revisional or conversional procedures [6, 7, 11, 12].
The evidence reviewed in this paper indicates that GLP-1 receptor agonists represent a valuable and increasingly well-documented option for the management of weight regain or insufficient weight loss after bariatric surgery. Across the studies evaluated, additional weight loss ranged from approximately 5% to more than 15% of baseline body weight over 6 - 12 months of pharmacotherapy - a magnitude considered clinically significant both from the perspective of obesity control and cardiometabolic risk reduction. Importantly, these effects were achieved in patients who had already undergone a major surgical intervention and remained obese, highlighting the potential of GLP-1 receptor agonists as an effective second-line strategy in post-bariatric care.

Data on liraglutide 3.0 mg demonstrate a consistent and early weight-loss response in post-bariatric patients, irrespective of the primary surgical technique employed. The comparability of outcomes across Roux-en-Y gastric bypass, sleeve gastrectomy and gastric banding - despite the markedly different anatomical and hormonal alterations produced by each procedure - suggests that the weight-loss effect of liraglutide in this population is mediated predominantly through central appetite suppression rather than procedure-specific neuro-hormonal adaptations, consistent with the known hypothalamic mechanism of action of GLP-1 receptor agonists [35]. Of particular practical relevance is the finding by Wharton et al. that treatment duration appears more important than attainment of the maximum dose: patients who did not reach the full 3.0 mg target but maintained therapy beyond one month achieved weight loss comparable to those titrated to the maximum dose [12]. This supports a tolerability-guided titration approach in clinical practice, which may improve long-term adherence in this patient population.

Semaglutide appears to be more effective than liraglutide in the post-bariatric setting, a finding that is consistent with its documented superior efficacy in non-surgical obese populations [19, 20]. The near-complete reversal of post-bariatric weight regain reported by Jensen et al. [19] represents a clinically striking outcome that positions semaglutide as a particularly promising pharmacological rescue option. However, an important methodological caveat must be acknowledged when interpreting the comparative data: the study by Lautenbach et al. [20] administered semaglutide at a once-weekly dose of 0.5 mg - substantially below the 2.4 mg dose approved by the EMA for chronic weight management [34]. The outcomes reported in that study therefore likely represent an underestimate of the effect achievable at the full therapeutic dose. While this reinforces rather than undermines confidence in semaglutide's efficacy, it means that a direct comparison with liraglutide 3.0 mg on the basis of available post-bariatric data should be interpreted with caution.

Tirzepatide's dual GIP/GLP-1 receptor agonism provides a mechanistic rationale for its apparently superior efficacy, as simultaneous activation of both incretin pathways produces additive effects on appetite regulation and insulin sensitivity [21]. The preliminary post-

bariatric data are consistent with this prediction. However, the comparative efficacy results require careful contextualisation: the head-to-head study by Jamal et al. [23] compared starting doses of both agents (tirzepatide 2.5 mg vs. semaglutide 0.25 mg once weekly) rather than their respective therapeutic maintenance doses, and the observed difference at six months may reflect differences in titration kinetics rather than true ceiling efficacy. Furthermore, the indirect treatment comparison by le Roux et al. [22] was conducted in a non-surgical obese population, and its results cannot be directly transposed to post-bariatric patients whose altered anatomy and incretin physiology may modify drug response. Given these limitations, definitive conclusions about the superiority of tirzepatide over semaglutide in the post-bariatric setting would be premature; the available data are best interpreted as generating a strong hypothesis for testing in dedicated randomised trials.

Across the analysed studies, adverse events were predominantly mild to moderate and transient, mainly involving the gastrointestinal tract. In the study by Jensen et al. [8], nausea accounted for 52% of reported adverse events, constipation for 24%, and vomiting, flatulence, diarrhoea, dizziness and headache each occurred in 5% of cases - a profile that is generally manageable through gradual dose titration. Isolated and transient asymptomatic elevations in pancreatic enzyme activity were described by Lautenbach et al. [20], while clinical pancreatitis remained rare. In the post-bariatric context, gastrointestinal complaints may mask or mimic surgical complications such as gastric stenosis, anastomotic leakage or dumping syndrome, and careful clinical evaluation is therefore required before attributing symptoms exclusively to drug intolerance. Additionally, delayed gastric emptying induced by GLP-1 receptor agonists carries perioperative relevance: current anaesthetic guidelines recommend temporary discontinuation of these agents before elective procedures under general anaesthesia to reduce the risk of pulmonary aspiration, and close coordination between the treating teams is essential [25].

Several limitations of the current evidence base must be acknowledged. The key clinical studies identified in this review are predominantly observational, retrospective or single-centre, with relatively small sample sizes. Heterogeneous definitions of insufficient weight loss and weight regain, as well as varying time points for GLP-1 receptor agonist initiation after surgery, complicate cross-study comparisons. Follow-up periods are typically limited to 6 - 12 months, which is insufficient to assess long-term durability of effect, impact on comorbidities, or late adverse events. Randomised controlled trials specifically designed for the post-bariatric population remain scarce - to date, only the BARI-OPTIMISE trial [13] has evaluated liraglutide against placebo in this group - and no head-to-head comparisons of liraglutide, semaglutide and tirzepatide are currently available in this setting. Dosing inconsistencies - including the use of a sub-therapeutic semaglutide dose [20] and starting doses of tirzepatide [23] - further limit the interpretation of comparative efficacy data. Finally, cost, reimbursement and drug availability may represent a decisive practical barrier to implementation in everyday clinical practice [8].

Despite these limitations, the available data support the concept of pharmacological rescue after failure of bariatric surgery. GLP-1 receptor agonists, particularly semaglutide and potentially tirzepatide, provide clinically meaningful additional weight loss with a safety profile dominated by transient gastrointestinal symptoms, and should be considered before revisional surgery in appropriately selected patients. Future research should prioritise randomised head-to-head trials of liraglutide, semaglutide and tirzepatide in post-bariatric populations, standardisation of definitions of surgical failure, long-term outcome data

including quality of life and comorbidity control, and cost-effectiveness analyses to define the optimal role of GLP-1 receptor agonists within a multidisciplinary post-bariatric care pathway.

5. Conclusions

GLP-1 receptor agonists represent a rational and effective pharmacological rescue option for patients with obesity who experience insufficient weight loss or weight regain after bariatric surgery. Across the available studies, liraglutide, semaglutide and tirzepatide consistently provided clinically meaningful additional weight loss - typically in the range of 5 - 15% of baseline body weight over 6 - 12 months - with a safety profile dominated by mild to moderate, predominantly transient gastrointestinal adverse events, while serious complications remained rare.

Available data suggest that semaglutide may offer greater efficacy than liraglutide in this setting; however, this conclusion is tempered by the fact that the key semaglutide study [20] used a once-weekly dose of 0.5 mg, substantially below the 2.4 mg dose approved for chronic weight management, which likely underestimates the true therapeutic effect. Similarly, tirzepatide showed promising results in early data, but comparisons were based on starting doses rather than maintenance doses and were partly derived from a non-bariatric population [22], precluding definitive conclusions about its superiority in this specific group.

Taken together, current evidence supports integrating GLP-1 receptor agonists into the post-bariatric treatment pathway as a less invasive alternative or complement to revisional surgery in appropriately selected patients, particularly those at high operative risk or unwilling to undergo repeat surgical intervention. Larger, long-term randomised controlled trials - especially with tirzepatide at therapeutic maintenance doses and in well-defined post-bariatric populations - are needed to establish optimal drug choice, timing of initiation, and patient selection criteria.

Disclosure

Author Contributions

Conceptualization: Gabriela Piotrowska, Agnieszka Anna Gaczoł
Methodology: Gabriela Piotrowska, Agnieszka Anna Gaczoł, Paulina Kopcińska, Magdalena Mortka
Software: not applicable
Check: Hubert Bednarz, Magdalena Mortka, Michał Kawa, Kamil Idzik
Formal analysis: Gabriela Piotrowska, Agnieszka Anna Gaczoł, Paulina Kopcińska, Weronika Grzyb-Kurnik
Investigation: Gabriela Piotrowska, Agnieszka Anna Gaczoł, Zuzanna Lechowska
Resources: Gabriela Piotrowska, Agnieszka Anna Gaczoł, Michał Kawa, Kamil Idzik, Magdalena Mortka
Data curation: Gabriela Piotrowska, Agnieszka Anna Gaczoł
Writing - rough preparation: Weronika Grzyb-Kurnik, Michał Kurnik
Writing - review and editing: Tomasz Kilian, Zuzanna Lechowska, Aleksander Urbaś
Visualization: Dominika Grzybowska, Aleksander Urbaś
Supervision: Paulina Kopcińska, Magdalena Mortka, Hubert Bednarz
Project administration: Gabriela Piotrowska, Agnieszka Anna Gaczoł
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