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Effectiveness and safety of liraglutide for weight loss failure after bariatric interventions – a systematic review

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Resumo

Introdução: Os procedimentos bariátricos são o tratamento mais eficaz para a obesidade e comorbilidades relacionadas em doentes que não conseguiram obter uma perda de peso significativa ou sustentada após abordagens conservadoras. Apesar de serem altamente eficazes, uma percentagem não negligenciável de doentes não atinge uma perda de peso significativa ou recupera o peso perdido. Para estes doentes são necessárias estratégias de tratamento alternativas que podem incluir intervenções no estilo de vida, fármacos, ou cirurgia revisional. A liraglutida é um agonista de longa duração do recetor do péptido semelhante ao glucagon 1, aprovado para o tratamento da obesidade. No entanto, a eficácia da liraglutida na perda de peso em doentes bariátricos não foi ainda testada em ensaios clínicos randomizados.

Objetivo: O objetivo foi realizar uma revisão sistemática dos dados disponíveis sobre a eficácia e segurança dq liraglutida para perda de peso em doentes com resposta inadequada a intervenções bariátricas (perda de peso insuficiente ou recuperação de peso), ou manutenção da perda de peso pós-bariátrica.

Métodos: Foi realizada uma pesquisa de artigos em inglês nas bases de dados PubMed, Scopus e Web of Science, sem limite de datas, para estudos controlados ou observacionais que tivessem como objetivo avaliar a eficácia e segurança do tratamento com liraglutida na perda de peso em adultos previamente submetidos a intervenções bariátricas. A qualidade de cada artigo foi avaliada através de escalas adequadas a cada tipo de estudo.

Resultados: Nesta revisão sistemática foram incluídos treze artigos (n=13). Dez artigos (n=10) avaliaram a percentagem de perda de peso total atingida após o tratamento com liraglutida em doentes com falência da perda de peso pós-bariátrica, que variou entre 3,20% e 17,60%. Dois artigos (n=2) compararam a percentagem de excesso de peso perdida pelo tratamento com liraglutida após intervenção bariátrica com a intervenção bariátrica isolada, e relataram uma maior percentagem de perda de excesso de peso no grupo da liraglutida. O único artigo que avaliou o efeito do tratamento com liraglutida na manutenção da perda de peso e na prevenção do reganho de peso produziu resultados neutros. Não foram observados eventos adversos graves associados ao tratamento com liraglutida após intervenções bariátricas, e a ocorrência de eventos adversos não graves foi semelhante à da população em geral.

Conclusões: A eficácia e a segurança da liraglutida em doentes bariátricos parece ser semelhante ao que foi relatado para a população não-bariátrica e independente do tipo de procedimento de cirurgia bariátrica realizado.

Palavras-chave: Obesidade; Liraglutida; Cirurgia Bariátrica; Perda de peso

Abstract

Background: Bariatric procedures are the most effective treatment for obesity and related disorders in patients who have failed to achieve significant or sustained weight loss after conservative interventions. Despite being highly effective, a non-negligible proportion of patients either fails to achieve significant weight loss or regains weight after weight loss. Therefore, alternative treatment strategies are required for these patients, which may include lifestyle interventions, weight loss drugs or revisional surgery. Liraglutide is a long-acting human glucagon-like peptide 1 receptor agonist that has been approved for obesity treatment. However, liraglutide weight loss efficacy in post-bariatric patients has not been tested in randomized controlled trials.

Purpose: Our aim was to conduct a systematic review of the available data on the effectiveness and safety of liraglutide for weight loss, in patients with inadequate response to bariatric interventions, i.e. non-sufficient weight loss or weight regain, or post-bariatric weight loss maintenance.

Methods: We searched PubMed, Scopus, and Web of Science for publications in English, with no date limits, for controlled or observational studies that aimed to evaluate the weight loss effectiveness and safety of liraglutide treatment in adults previously submitted to bariatric interventions. The quality of each study was assessed with corresponding scales.

Results: Thirteen papers (n=13) were included in this systematic review. Ten papers (n=10) evaluated the percentage of total weight loss (WL) attained after liraglutide treatment in patients with post-bariatric weight loss failure, which ranged between 3.20% and 17.60%. Two papers (n=2) that compared the percentage of excess WL with liraglutide treatment after bariatric intervention with bariatric intervention alone reported a higher percentage of excess WL in the liraglutide group. The single paper that evaluated the effect of liraglutide treatment on weight loss maintenance and prevention of weight regain, yielded neutral weight loss outcomes. No serious adverse events were associated to liraglutide treatment after bariatric interventions, while the occurrence of non-serious adverse events was similar to the general population.

Conclusions: The weight loss effectiveness and safety of liraglutide in post-bariatric patients seems to be similar to what has been reported for the non-bariatric population and independent of the type of bariatric surgery procedure performed.

Keywords: Obesity; Liraglutide; Bariatric Surgery; Weight Loss; Weight Regain

Abbreviation List | Lista de abreviaturas

BMI	Body Mass Index
BPD	Biliopancreatic diversion
ESG	Endoscopic Sleeve Gastroplasty
GB	Gastric Banding
GLP-1	Glucagon-like peptide I
IGB	Intragastric Balloon
IWL	Insufficient weight loss
LAGB	Laparoscopic Adjustable Gastric Banding
LSG	Laparoscopic sleeve gastrectomy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International prospective register of systematic reviews
RYGB	Roux-en Y Gastric Bypass
SADI	Single anastomosis duodeno–ileal bypass
SG	Sleeve gastrectomy
VBG	Vertical banded gastroplasty
WR	Weight regain

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Introduction | Introdução

Bariatric surgery is an effective treatment for obesity that is recommended for patients with a body mass index (BMI) over 35kg/m^2, which can also be considered for individuals with a BMI range between 30 and 34.9kg/m^2 in the presence of concomitant obesity-related disorders[1]. The bariatric surgery techniques most frequently used are Roux-en-Y Gastric Bypass (RYGB) and Sleeve Gastrectomy (SG)[2]. Bariatric surgery results in significant weight loss with long-term maintenance, while this is rarely attained or sustained beyond 2 years with conservative medical interventions[3]. Moreover, bariatric surgery is also more effective at improving obesity-related morbidities than nonsurgical weight loss approaches, and most particularly at achieving greater type 2 diabetes remission rates[4].

Despite the majority of patients presenting successful weight loss and maintenance after bariatric surgery, 25% to 35% of the patients experience significant weight regain (>15% of weight gain after initial weight loss) 2 to 5 years after surgery[5–7], and in 20-23.1% of patients surgery fails at producing significant weight loss[8,9]. However, these figures can be highly variable, since there is no universal definition for weight loss failure after bariatric surgery, neither primary, i.e. insufficient weight loss (IWL), nor secondary, i.e. weight regain (WR), therefore different weight loss cut-off points are used, as well as different timeframes for weight loss targets[10,11].

Liraglutide is a long-acting agonist of the human glucagon-like peptide 1 receptor (GLP-1RA), which increases glucose-dependent insulin secretion, decreases inappropriate glucagon secretion, and decreases food intake. Liraglutide at a 3.0 mg daily dose, was shown to be safe and effective at achieving significant weight loss and is now licenced for obesity treatment[12]. However, the evidence on the safety and effectiveness of liraglutide as adjunctive obesity treatment in post-bariatric surgery patients is limited, since these patients have been systematically excluded from phase III clinical trials, so the outcomes of therapy in this specific population is largely unknown[12].

Thus, our aim was to conduct a systematic review in order to compile in a comprehensive way the available data on the weight loss effectiveness of liraglutide treatment in patients with poor weight loss response after bariatric interventions.

Methods | Métodos

Protocol and registration

This protocol was registered at PROSPERO (registration number CRD42022371697), and is accessible at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022371697.
The literature review protocol was conducted in compliance with the PRISMA guidelines.

Search strategy

Original papers evaluating the efficacy of liraglutide in patients submitted to bariatric interventions were included in this systematic review. This search was conducted on three different bibliographic databases: PubMed, Scopus, and Web of Science, in October 2022. The search criteria for each database can be consulted in the Supplementary File 1.

Selection process and criteria

Pre-established conditions for publications retrieval were: only original studies (controlled and observational), only human species, and only in English language. No date restrictions were applied. The inclusion and exclusion criteria were designed following the PICOS (Patient, Intervention, Comparison, Outcome, Study) format. Only studies conducted on adult individuals, subjected to bariatric interventions (any technique either endoscopic or surgical) were included. The exclusion criteria included studies conducted in children (under 18 years old), pregnant women, meeting or conference abstracts, unpublished studies, or study designs other than controlled and observational.

Records screening

References were retrieved from the bibliographic databases and imported into an EndNote library. After duplicates were removed, references were analysed by two independent reviewers (JFCF, SPP) based on titles and abstracts, to screen for the eligibility of each study. In some cases, full text examination was required. A third member was available to solve any disagreements (MPM). On a second phase, the full text of the resulting records was assessed for study inclusion.

Quality assessment

A different scale according to the nature of each study was used to determine the quality and risk of bias of the selected papers: the Jahad scale for randomized controlled trials, the Newcastle-Ottawa scale for Cohort Studies (retrospective or prospective), and the Joanna Briggs Institute Critical Appraisal Checklist for Case Series. Only studies judged to be at least of moderate quality in each of the scales were included.

Data extraction, synthesis and analysis

From the studies included, a spreadsheet was created to summarize the following information: author(s), study name, reference, experimental design, country/region, inclusion and exclusion

criteria, subgroups, number of subjects enrolled, most relevant patient characteristics (age, gender proportion, patients' comorbidities, weight and BMI before the intervention), type of bariatric intervention, time span between bariatric intervention and liraglutide treatment, criteria use to define weight loss failure or weight regain, weight variation after the procedure, liraglutide dosage and duration of treatment, weight variation after treatment with liraglutide, side effects, and comparison with other groups and control, if applicable. Data retrieval was reviewed by a second author in a cross-over manner (SPP).

The papers included were subdivided into two groups: (i) studies that focused on patients with defined weight regain or inadequate weight loss following weight loss interventions and (ii) studies that compared weight loss after liraglutide as adjunctive therapy with bariatric surgery alone.

Data is described in the results section in a qualitative and narrative manner, focusing on the weight loss and side effects of liraglutide treatment. Ultimately, this review summarizes the best available evidence on the use of liraglutide in post-bariatric patients.

Results | Resultados

1. Literature Search

The search identified 1237 papers (161 from PubMed, 790 from Scopus, and 286 from Web of Science). After removal of 310 duplicates, a total of 927 papers were submitted for screening. By reading the titles and abstracts, 743 papers were excluded for not being full papers with original data (e.g. reviews, guidelines, editorials and abstracts published at proceedings), 76 original papers that did not include patients submitted to bariatric interventions and 84 papers that didn't evaluate the weight loss effect of liraglutide, resulting in 20 papers to be considered for inclusion.

A second screening to assess eligibility was performed after reading the full papers, which resulted in 7 additional papers being excluded, 4 papers for not including a population submitted to any bariatric intervention or not providing information on weight outcomes after liraglutide treatment and 3 papers for reporting aggregated weight loss outcomes of several drug treatments, rendering impossible to separate the effects of liraglutide. The authors of these 3 papers[13–15] were contacted by email, to request the data pertaining to liraglutide treatment only, but after 3 months, no answer was obtained.

This resulted in 13 papers to be included in the systematic review (Figure 1) – 2 were randomized controlled trials, 3 were Cohort studies, and 8 were Case Series (Table I). All papers included passed the quality assessment and the scores are described in Table II, III, and IV.

2. Weight loss efficacy

2.1 Efficacy of liraglutide in weight loss failure after bariatric intervention

Eight of the selected papers aimed to study the efficacy of liraglutide in post-bariatric patients with weight loss failure, manifesting as WR or IWL[16–23]. The criteria used to define WR or IWL varied, and all studies used different definitions. WR was defined by regaining more than 5 to 25% of body weight from the post-intervention body weight nadir achieved. IWL was defined by losing less than 20 to 50% of the total body weight/excess weight, or not achieving a BMI of less than 35kg/m^2.

Studies were performed in different countries: Qatar[16], Spain[17,18], Canada[19,20], Italy[22], Switzerland[23] and Brazil[21]. The number of patients included per study ranged between 15 and 145, totalling 431 post-bariatric patients that underwent liraglutide treatment. Participants were aged between 43 and 56 years, and were predominantly females. The majority of patients had performed Roux-en Y Gastric Bypass (RYGB)[16,17,19–24], although patients who underwent Single anastomosis duodeno–ileal bypass (SADI)[16], Biliopancreatic diversion (BPD)[17,21], Vertical banded gastroplasty (VBG)[17,19], Sleeve gastrectomy (SG)[16,17,19,21,22,25], and Gastric Banding (GB)[17,19–22] were also included. Time between surgery and liraglutide treatment varied between 1 year[16] and 8 years[20]. Except for two studies, a

therapeutic dosage of liraglutide 3mg daily was aimed[17,21]. The duration of liraglutide treatment ranged between 16 weeks to 5 years.

Table V summarizes the outcomes of liraglutide treatment expressed as %TWL. The studies found that liraglutide treatment at the different doses used resulted in a mean %TWL that varied between 3.20% and 17.60%, with a corresponding %TWL per month between 0.13% and 2.68%. Considering only the studies that achieved the 3mg daily dosage, the %TWL range was 4.10% - 17.60%, and 0.58% - 2.18% %TWL per month.

Data analysis from studies that measured the weight loss outcomes at different time points[16,18,19], showed that the majority of the weight loss occurred in the first 6 months of treatment. Of note, in the study with higher % of TWL, liraglutide was administrated 72 months after bariatric surgery and more than 85% of patients loss the regained weight, within 12 months of liraglutide treatment[18]. In the same study the authors divided the patients that received liraglutide in two groups – patients with daily liraglutide treatment for 12 months and another with daily liraglutide treatment for 6 months and for the remaining 6 months with on demand liraglutide treatment[18]. The authors concluded that after the first 6 months, every other day dosing was as effective as the daily dosing for 12 months'.

Muratori *et al* and Wharton *et al* found that the type of bariatric surgical procedure before liraglutide (LSG, LAGB, RYGB, and SG) did not influence the liraglutide weight loss [20,22]. Of particular note, Elhag & El Ansari *et al* compared the efficacy of liraglutide treatment in patients submitted to primary and revisional surgeries (RYGB, LSG, and SADI) and found that liraglutide was equally effective for the management of WR and IWL on both groups[16].

Finally, a prospective cohort study divided patients into 4 groups – lifestyle intervention, liraglutide treatment, revisional endosurgery and Fobi-ring with pouch resizing surgery. This study recommended liraglutide as a first line therapy for WR after RYGB, and to reserve revisional surgery for non-responders or patients in whom liraglutide is contraindicated[23].

In two other studies[24,26], post bariatric weight loss failure was not formally defined. Miras *et al* conducted a randomized, double-blind, placebo-controlled trial that enrolled patients submitted to RYGB or SG with persistent or recurrent type 2 diabetes, with body weight changes being one of the secondary outcomes. The liraglutide treated group had a significant weight loss, and 46% patients lost more than 5% of their baseline weight, versus 9% of patients in the placebo group[24]. Haase *et al* is a case series that reported the outcomes of liraglutide treatment in an outpatient obesity clinic, including a subgroup who had previously been submitted to a bariatric intervention.

The authors found that liraglutide treatment was as effective in bariatric patients as in patients with no previous surgery (%TWL of 4.1% and 4.2%, respectively)[26].

2.2 Efficacy of liraglutide used as combination therapy with bariatric interventions

Two studies reported the efficacy of bariatric interventions - Endoscopic Sleeve Gastroplasty (ESG) and Laparoscopic sleeve gastrectomy (LSG) alone or in combination with liraglutide[25–27]. These included 38 patients and the liraglutide treatment duration ranged between 24 weeks and 7 months. In one of the studies the mean liraglutide dose was 1.4mg[28]. Both studies found that the group that received liraglutide had higher %TWL when comparing to the placebo group. Thakur *et al* reported a %TWL of 23.2% and 28.2% (placebo and liraglutide groups, respectively), after 24 weeks of treatment[28]. Badurdeen *et al* reported a %TWL of 20.51% and 24.72% (placebo and liraglutide groups, respectively), after 7 months.[25]

2.3 Efficacy of liraglutide for weight loss maintenance and prevention of weight regain

Badurdeen *et al* in a two-arm study in which patients treated with IGB for 12 months were treated with liraglutide for 9 months immediately after IGB retrieval. The authors found no significant difference in the %TWL with liraglutide after IGB retrieval when compared to placebo, although the absolute weight loss was numerically higher[27].

3. Adverse events associated with liraglutide treatment

None of the studies reported any serious adverse event related to liraglutide. All studies reported the occurrence on non-serious adverse events as expected from liraglutide use and described in clinical trials. The percentage reported by each study is summarized on Table VI. One study did not provide any data describing side effects.[26]

Discussion | Discussão

This review was aimed to compile the available evidence on the efficacy and safety of liraglutide in post-bariatric patients. Ultimately addressing a knowledge gap and unmet need, since the weight loss efficacy of liraglutide treatment in this patient population, classically excluded from clinical trials focused on weight loss drugs, remains to be demonstrated.

Post-bariatric weight loss failure is a condition that requires further intervention in order to treat obesity and related conditions. Revisional surgery is an option available that can be considered and 1.4% to 27.8% of patients are reoperated[29–31]. However, given the increased risk of short and long term complications, surgery should only be considered when other non-invasive options have proven to be ineffective[32,33]. Non-invasive approaches for weight loss failure, include lifestyle interventions and pharmacological treatments, to be used as first and second line therapies[34].

The studies included in this review have shown that liraglutide treatment in patients with weight regain/weight loss failure after bariatric surgery resulted in a mean %TWL between 3.20% and 17.60%. The wide discrepancies in weight loss between studies could be attributed to unprecedented differences in patient populations, timing of treatment initiation, liraglutide dosage and treatment duration. In randomized controlled trials, patients with obesity, excluding individuals with a previous bariatric interventions, treated with liraglutide 3.0mg daily achieved a mean %TWL of 8%[12,35–37]. Therefore, the %TWL interval identified by this systematic review, is consistent with previous data, suggesting that the efficacy of liraglutide treatment in post-bariatric patients may be similar to the general population with obesity. Of notice, the four studies with the best weight loss outcomes[18,19,21,22] had a mean of time since bariatric intervention and liraglutide treatment longer than 60 months. Additionally, except for the Pajecki *et al*[21] study in which 53.3% of patients were treated with liraglutide 1.8mg, and 46.7% less than 1.8mg, in all other studies patients received a 3mg dose of liraglutide.

Concerning the heterogeneous group of studies that evaluated the effects of liraglutide as adjunctive therapy to bariatric interventions, by comparing the weight loss effectiveness of bariatric intervention alone to the combination with liraglutide[25,27,28], the two studies reported a greater %TWL in the liraglutide group[25,28]. The last group, regarding liraglutide effectiveness for weight loss after IGB removal, had neutral results when it comes to the weight loss maintenance and prevention of weight regain[27].

Overall, the weight loss efficacy of liraglutide did not seem to be influenced by the type of bariatric procedure previously performed. Of notice, the most effective dose for treatment of obesity was liraglutide 3.0 mg, indeed lower doses are sub-therapeutic for obesity treatment and are indicated for diabetes, only.

Noteworthy, although the frequent occurrence of mild gastrointestinal symptoms as side effects of GLP-1 RA, for which the patient needs to be informed when initiating the therapy, there were no reports of serious adverse events with the use of liraglutide in this patient population, which lines up with previous available evidence on the safety of this drug from randomized trials conducted in non-bariatric populations[12,35–37].

There are a few limitations that could have hampered the results of this review that must be acknowledged. One of the aforementioned limitations is the fact that there is an inconsistency in the definition of weight loss failure after bariatric surgery, a widely reported limitation that has an overarching impact on the assessment and comparison of bariatric surgery outcomes[10,11]. This is not only a limitation when assessing the post-surgical outcomes, as well as in standardizing new obesity interventions, surgical or non-surgical, but also because as a consequence of the different criteria used to define weight loss failure across studies, inevitably the populations also presented distinctive patient features. An additional limitation found was the inconsistency of the metrics for reporting weight loss outcomes, with the most common being absolute weight loss and total body weight loss percentage, although other being also used, such as BMI change and percentage of excess weight loss, sometimes used as the sole measure of weight loss outcomes, which rendered impossible the establishment of comparisons. The lack of non-computed anthropometric data, such as body weight prior and after liraglutide treatment initiation, precluded further comparisons and interpretation of the results as well. Indeed, a call of action was made for researchers to make an effort to report body weight and BMI to enable data gathering for retrieving more robust real-world evidence[38]. The discontinuation of the therapy is also an uncharted territory, since there are no reports on the effects of liraglutide treatment suspension in post-bariatric patients. As obesity is a chronic disease, requires chronic therapy, and the interruption of liraglutide treatment is usually associated with increased appetite and decreased satiety, and there is subsequent weight regain and a recurrence in comorbidities[39]. At last, but not the least, notwithstanding the weight loss effectiveness of liraglutide treatment has been demonstrated, a cost-benefit analysis should also be taken into consideration when deciding patient treatment for each individual patient. The fact that none of the available studies included a financial cost-effectiveness analysis, also limited our ability to include this factor in the discussion.

Despite the limitations, this systematic review also holds the major strength of having compiled the best available evidence on the effectiveness and safety of liraglutide in post-bariatric patients, which could be useful to propose an algorithm taking into consideration the weight loss required and expected treatment outcomes. These are important not only to manage patient expectations when discussing the treatment alternatives for weight loss, but most of maximize the probabilities of a successful intervention. Since data showed that the mean TWL achieved by liraglutide treatment

was 8%, a reasonable algorithm to manage weight regain considering the TWL required could be the use of lifestyle interventions for TWL<5% , use of liraglutide 3.0 mg as weight loss drug for a TWL from 5 to 10%, and consider revision surgery whenever a TWL >10% is needed. Notwithstanding, the need to revisit this algorithm in the near future is foreseeable, as novel gut hormone analogue drugs for obesity treatment, such as semaglutide[40] and tirzepatide, reach the market, although the bariatric population continues to be excluded from large clinical trials[41–44].

Conclusion | Conclusão

The weight loss effectiveness and safety of liraglutide in patients with weight loss failure after bariatric interventions seems to be similar to what has been reported for the non-bariatric population and independent of the type of bariatric surgery procedure performed. Despite these findings, randomized controlled trials to test the efficacy and safety of liraglutide 3.0mg in patients with declared weight loss failure after bariatric interventions are still needed. Ultimately, the data gathered by this review provides useful information to decide between weight loss management strategies to treat post-bariatric patients.

Appendix | Apêndice

Table I Summary of the included studies

	Experimental Design	N	Type 2 Diabetes	Bariatric Intervention	Time since bariatric intervention	IWL or WR Definition	Liraglutide Dose after titration	Liraglutide treatment duration (months)	Main outcomes
Elhag & El Ansari, 2022	Case Series	145	20.7%	RYGB - 11.7% LSG - 85.5% SADI - 2.8%	54.1 months	WR: >10kg from nadir IWL: <50% of excess weight lost at 18 months after intervention	3mg daily	12	Primary Surgery: TWL 5.97% and 6.93% (6 and 12 months, respectively). At 12 months, 60% of patients lost at least 5% of total body weight. Revision Surgery: TWL 6.41% and 4.99% (6 and 12 months, respectively). At 12 months, 48% of patients lost at least 5% of total body weight.
Muratori et al., 2022	Case Series	62	ND	LSG - 37% LAGB - 35.6% RYGB - 27.4%	70.7 months	WR: 10-15% from minimum weight IWL: if unsatisfied with WL	3mg daily	10.5	Average BMI loss of 5.1kg/m2. No differences in regards to the type of surgery.
Badurdeen et al., 2021	Cohort	53	28.3%	IGB removal after 12 months - 100%	0 months	ND	3mg daily	9	**Primary Outcome:** weight regain prevention Only IGB group: average WR -0.66kg IGB + Liraglutide group: average WR -1.15kg **Secondary Outcome**: %Body Fat Loss Only IGB group: -7.94% body fat IGB+Liraglutide group: -10.83% body fat
Badurdeen et al., 2021	Cohort	26	ND	ESG - 100%	5 months	ND	3mg daily	7	**Primary Outcome**: %TWL and %EWL Only ESG group: 20.51% and 69.94%, respectively ESG + Liraglutide group: 24.72% and 84.33%, respectively **Secondary Outcome**: Percentage of lost body fat Only ESG group: 7.85% ESG + Liraglutide group: 10.54%

Table I Summary of the included studies (cont.)

Haase et al., 2021	Case Series	52	0%	ND	ND	ND	3mg daily	7	**Primary outcome**: %TWL 4.1% **Secondary outcome**: Percentage of patients achieving >5% and >10% weight loss 33.3% of patients lost more than 5% of baseline weight and 18.2% lost more than 10%
Horber & Steffen, 2021	Cohort	34	5.8%	RYGB - 100%	6 -13 years	WR: >10% from nadir	3mg daily	24	Control group: average BMI change of +0.1kg/m2. Liraglutide group: average BMI change of -4.8kg/m2
Rubio & Ramos-Leví, 2021	Case Series	23	ND	ND	72 months	WR: >15% from nadir	3mg daily or every other day	12	%TWL - 17.6% ± 5.5 >85% of patients lost regained weight Every other day dosing after 6 months of daily administration was as effective as daily dosing
Thakur et al., 2021	RCT	12	33.3%	LSG - 100%	6 weeks	ND	3mg daily Mean daily dose - 1.4mg	6	**Primary outcome**: %TWL and %EWL LSG + Placebo: 23.2% and 44.5%, respectively LSG + liraglutide: 28.2% and 58.7%, respectively **Secondary outcome**: changes in glucose, HbA1c, insulin resistance, among other parameters
Miras et al., 2019	RCT	48	100%	RYGB - 79.2% VSG - 20.8%	3.8 years	ND	1.8mg daily	5.25	**Primary outcome**: change in HbA1c. **Secondary outcome**: changes from baseline in bodyweight, systolic and diastolic blood pressure, among other parameters

Table I Summary of the included studies (cont.)

Wharton et al., 2019	Case Series	117	ND	RYGB - 45.3% Gbanding - 42.7% Gsleeve - 12%	8 years	WR: + 10-25% of excess weight OR total weight lost	3mg daily	7.6	Average total weight loss - 5.5% (6.3kg) No differences in regards to the type of surgery. Weight loss after 12 months of treatment greater than at 6 months.
Rye et al., 2018	Case Series	20	25%	RYGB - 35% LSG - 35% VBG - 15% LAGB - 15%	76.3 months	WR: >10% from nadir IWL: <20% WL from baseline	2.9mg mean daily dose	6.5	**Primary outcome**: %TWL and median BMI change 9.7% and -4.7kg/m2, respectively 50% of patients attained a body weight lower than nadir.
Gorgojo-Martínez et al., 2016	Case Series	15	100%	RYGB - 53.3% BPD - 20% VBG - 13.3% SG - 6.7% LAGB - 6.7%	5.2 years	WR: >5% from nadir IWL: BMI >35 kg/m^2 or %EWL <50%	1.2mg daily 1.8mg daily if insufficient glycemic response or weight loss (91.7%)	24	Average weight loss of 3.4kg. BMI change of -1.2kg/m^2
Pajecki et al., 2013	Case Series	15	ND	RYGB - 60% LAGB - 26.6% SG - 6.7% BPD - 6.7%	5.3 years	WR: >15% from nadir IWL: <50% of excess weight	1.2 to 1.8mg daily 1.8mg in 53.3% of the participants	2.75	%TWL of 7.38%

IWL – Insufficient weight loss; WR – Weight regain; RCT – Randomized controlled trial; RYGB – Roux-en-Y Gastric Bypass; VSG – Vertical Sleeve Gastrectomy; ND – Not Determined; SC – subcutaneous; LSG – Laparoscopic Sleeve Gastrectomy; %TWL – total weight loss in percentage; %EWL – excess weight loss in percentage; BMI – Body Mass Index; IGB – Intragastric Balloon; ESG – Endoscopic Sleeve Gastroplasty; FP - Fobi-ring with pouch resizing; ES – endosurgery; SADI - Single anastomosis duodeno–ileal bypass; BPD - Biliopancreatic diversion; VBG - Vertical banded gastroplasty; SG - Sleeve gastrectomy; LABG - Laparoscopic Adjustable Gastric Banding.

Table II Summary of the Jahad Scale scores of the randomized controlled trials included in the systematic review

Jahad Scale for randomized controlled trials				
First author and year	**Randomization**	**Blinding**	**An account of all patients**	**Total**
Thakur U., 2021[28]	2	2	1	5
Miras A.D., 2019[24]	2	2	1	5

Table III Summary of the Newcastle-Ottawa Scale scores of the Cohort Studies included in the systematic review

Newcastle-Ottawa Quality Assessment Scale for Cohort Studies									
First author and year	Selection				Comparability	Outcome			Total Score
	1	2	3	4	1	1	2	3	
Badurdeen D., 2021[27]	1	1	1	1	2	1	1	1	9
Badurdeen D., 2021[25]	1	1	1	1	2	1	1	1	9
Horber F.F., 2021[23]	1	1	1	1	0	1	1	1	7

Table IV Summary of the Joanna Briggs Institute Critical Appraisal Checklist scores of the Case Series included in the systematic review

Joanna Briggs Institute Critical Appraisal Checklist for Case Series											
First author and year	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Total**
Elhag W., 2022[16]	x	x	x	x	x	x	x	x		x	9
Rye P., 2018[19]	x	x	x	x	x	x	x	x		x	9
Gorgojo-Martínez J.J., 2016[17]	x	x	x	x	x	x	x	x		x	9
Haase C.L., 2021[26]	x	x	x	x		x	x	x		x	8
Muratori F., 2022[22]	x	x	x			x	x	x		x	7
Rubio M.A., 2021[18]	x	x	x	x		x		x		x	7
Wharton S., 2019[20]	x	x	x			x	x	x		x	7
Pajecki D., 2013[21]		x	x			x	x	x		x	6

1. Were there clear criteria for inclusion in the case series?

2. Was the condition measured in a standard, reliable way for all participants included in the case series?

3. Were valid methods used for identification of the condition for all participants included in the case series?

4. Did the case series have consecutive inclusion of participants?

5. Did the case series have complete inclusion of participants?

6. Was there clear reporting of the demographics of the participants in the study?

7. Was there clear reporting of clinical information of the participants?

8. Were the outcomes or follow up results of cases clearly reported?

9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?

10. Was statistical analysis appropriate?

Table V Summary of weight loss outcomes of liraglutide treatment in subjects with weight loss failure after bariatric interventions

First Author and Year	N	Dosage (mg)	Months	%TWL	%TWL/Month
Elhag & El Ansari, 2022[16]	145	3	6	5.97% ± 5.71% (sd)	0.995%
			12	6.93%	0.5775%
Muratori et al., 2022[22]	62	3	10.5	14.9%*	1.419%
Haase et al., 2021[26]	52	3	7	4.1% ± 7% (sd)	0.59%
Horber & Steffen, 2021[23]	34	3	24	ND	ND
Rubio & Ramos-Leví, 2021[18]	23	3	6	13.1% ± 4.2% (sd)	2.183%
			12	17.6% ± 5.5% (sd)	1.467%
Miras et al., 2019[24]	48	1.8	5.25	5.22%*	0.99%
Wharton et al., 2019[20]	117	3	7.6	5.5% ± 6.2% (sd)	0.726%
Rye et al., 2018[19]	20	2.9	3.75	7.1% (IQR 5.1–12.2%)	1.893%
			6.5	9.7% (IQR 7.8–13.9%)	1.492%
Gorgojo-Martínez et al., 2016[17]	15	1.8	24	3.2%*	0.133%
Pajecki et al., 2013[21]	15	1.8	2.75	7.38%*	2.684%

*Value calculated by the authors of this review

N= - number of subjects submitted to liraglutide treatment; %TWL – percentage of total weight loss; sd – standard deviation; ND – Not determined; IQR – Interquartile range.

Table VI Summary of adverse events reported to be associated with liraglutide treatment

First Author and Year	Adverse events			
	Total adverse event rate	Mild gastro-intestinal*	Other adverse events**	Discontinuation rate
Elhag & El Ansari, 2022[16]	17.5%	16.1%	3%	NA
Muratori et al., 2022[22]	11.3%	11.3%	0%	0%
Badurdeen et al., 2021[27]	NA	NA	NA	5.7%
Badurdeen et al., 2021[25]	NA	NA	NA	0%
Haase et al., 2021[26]	NA	NA	NA	NA
Horber & Steffen, 2021[23]	NA	50%	NA	0%
Rubio & Ramos-Leví, 2021[18]	65.2%	65.2%	0%	0%
Thakur et al, 2021[28]	NA	NA	NA	0%
Miras et al., 2019[24]	45%	27%	22%	5,6%
Wharton et al., 2019[20]	50.4%	47%	29.1%	15%
Rye et al., 2018[19]	NA	68.9%	32.7%	6%
Gorgojo-Martínez et al., 2016[17]	NA	6.7%	NA	NA
Pajecki et al., 2013[21]	40%	40%	0%	0%

Percentage of patients that had an adverse event.

*nausea/vomiting, constipation, diarrhoea
**fatigue, headache, transient scalp hair loss, other not specified
NA – Not available.

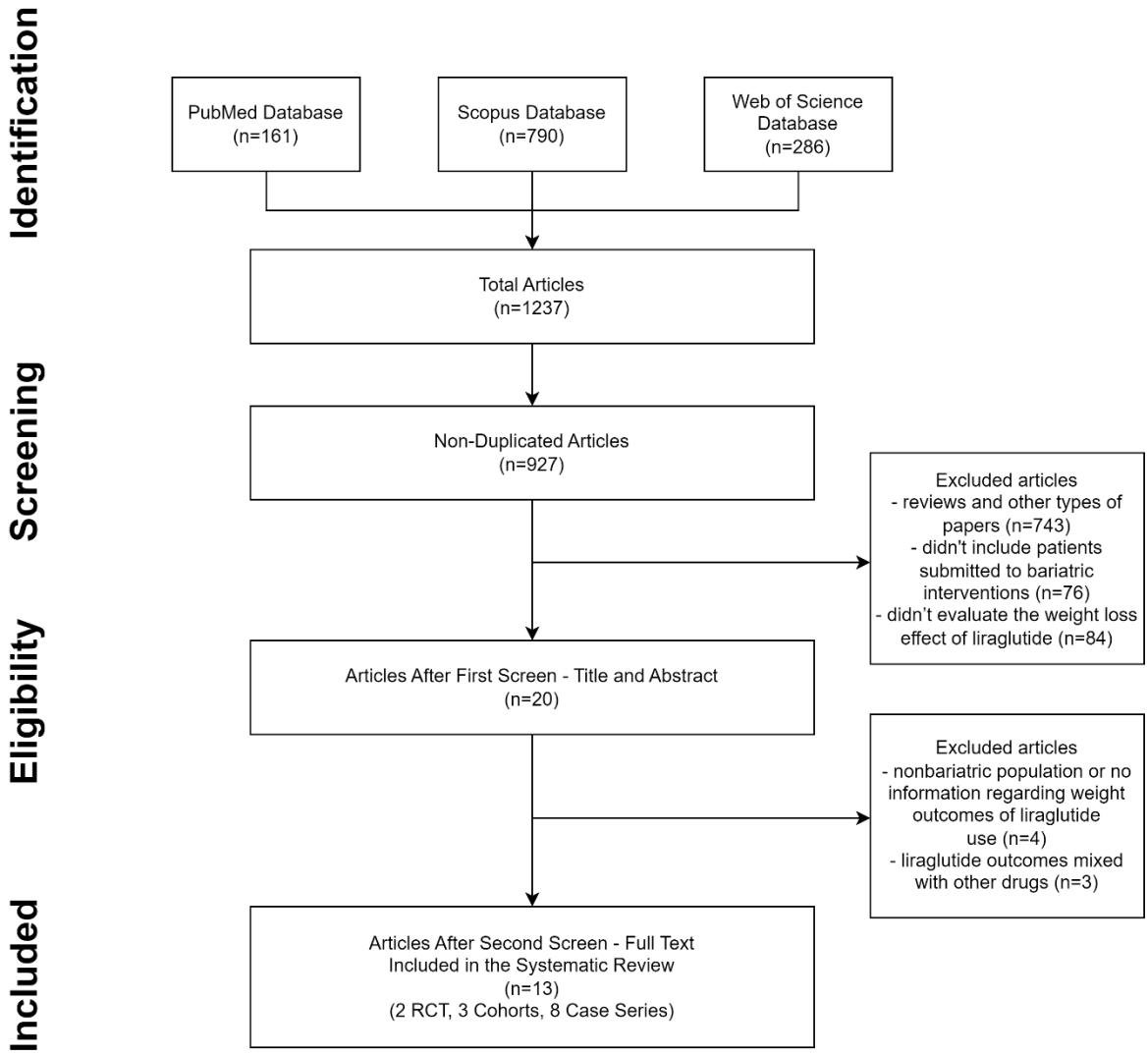

Figure 1 PRISMA Flowchart of the search, eligibility criteria approaches and study inclusion for the systematic review

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Supplementary File 1

DATABASE SEARCH

PubMed:

("bariatric surger*" OR "bariatric intervention*" OR "obesity surger*" OR "bariatric procedur*"OR "gastric bypass" OR "biliopancreatic diversion" OR "RYGB" OR "sleeve gastrectomy" OR "BPD" OR "BPD-DS" OR "duodenal switch" OR "Single anastomosis duodeno–ileal bypass" OR "SADI-S" OR "SADI" OR "SIPS" OR "SASI" OR "gastric plication" OR "endosleeve" or "endobarrier" OR "gastric clip*" OR "endoscopic bariatric therap*" OR "EBT" OR "endoscopic sleeve gastroplast*" OR "ESG" OR "Intragastric balloon*" OR "Endoluminal bypass liner*" OR "gastric band*") AND ("liraglutide" OR "glucagon-like peptide 1 receptor agonist*" OR "glucagon-like peptide-1 receptor agonist*" OR "GLP-1 receptor agonist*" OR "GLP1 receptor agonist*" OR "GLP-1R agonist*" OR "GLP1R agonist*" OR "GLP-1 analogue" OR "GLP1 analogue") NOT ("infant*" OR "child*" OR "gestational" OR "pregnanc*" OR "animal*" OR "rat" OR "rats" OR "mice" OR "mouse")

Scopus:

TITLE-ABS-KEY ("bariatric surger*" OR "bariatric intervention*" OR "obesity surger*" OR "bariatric procedur*"OR "gastric bypass" OR "biliopancreatic diversion" OR "RYGB" OR "sleeve gastrectomy" OR "BPD" OR "BPD-DS" OR "duodenal switch" OR "Single anastomosis duodeno–ileal bypass" OR "SADI-S" OR "SADI" OR "SIPS" OR "SASI" OR "gastric plication" OR "endosleeve" or "endobarrier" OR "gastric clip*" OR "endoscopic bariatric therap*" OR "EBT" OR "endoscopic sleeve gastroplast*" OR "ESG" OR "Intragastric balloon*" OR "Endoluminal bypass liner*" OR "gastric band*") AND TITLE-ABS-KEY ("liraglutide" OR "glucagon-like peptide 1 receptor agonist*" OR "glucagon-like peptide-1 receptor agonist*" OR "GLP-1 receptor agonist*" OR "GLP1 receptor agonist*" OR "GLP-1R agonist*" OR "GLP1R agonist*" OR "GLP-1 analogue" OR "GLP1 analogue") AND NOT TITLE-ABS-KEY ("infant*" OR "child*" OR "gestational" OR "pregnanc*" OR "animal*" OR "rat" OR "rats" OR "mice" OR "mouse")

Web of Science:

#1: ((TS=("bariatric surger*" OR "bariatric intervention*" OR "obesity surger*" OR "bariatric procedur*"OR "gastric bypass" OR "biliopancreatic diversion" OR "RYGB" OR "sleeve gastrectomy" OR "BPD" OR "BPD-DS" OR "duodenal switch" OR "Single anastomosis duodeno–ileal bypass" OR "SADI-S" OR "SADI" OR "SIPS" OR "SASI" OR "gastric plication" OR "endosleeve" or "endobarrier" OR "gastric clip*" OR "endoscopic bariatric therap*" OR "EBT" OR "endoscopic sleeve gastroplast*" OR "ESG" OR "Intragastric balloon*" OR "Endoluminal bypass liner*" OR "gastric band*")) NOT (TS=("infant*" OR "child*" OR "gestational" OR "pregnanc*" OR "animal*" OR "rat" OR "rats" OR "mice" OR "mouse"))) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC
Timespan=All years

AND

#2: ((TS=("liraglutide" OR "glucagon-like peptide 1 receptor agonist*" OR "glucagon-like peptide-1 receptor agonist*" OR "GLP-1 receptor agonist*" OR "GLP1 receptor agonist*" OR "GLP-1R agonist*" OR "GLP1R agonist*" OR "GLP-1 analogue" OR "GLP1 analogue"))) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

Final Search (#3): #1 AND #2