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REVIEW

GLP-1 Analogues as a Complementary Therapy in Patients after Metabolic Surgery: a Systematic Review and Qualitative Synthesis

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Abstract

The evidence is strong that bariatric surgery is superior to medical treatment in terms of weight loss and comorbidities in patients with severe obesity. However, a considerable part of patients presents with unsatisfactory response in the long term. It remains unclear whether postoperative administration of glucagon-like peptide-1 analogues can promote additional benefits. Therefore, a systematic review of the current literature on the management of postoperative GLP-1 analogue usage after metabolic surgery was performed. From 4663 identified articles, 6 met the inclusion criteria, but only one was a randomized controlled trial. The papers reviewed revealed that GLP-1 analogues may have beneficial effects on additional weight loss and T2D remission postoperatively. Thus, the use of GLP-1 analogues in addition to surgery promises good results concerning weight loss and improvements of comorbidities and can be used in patients with unsatisfactory results after bariatric surgery.

Keywords GLP-1 · GLP-1 analogues · metabolic surgery · Bariatric surgery

Introduction

Surgical Treatment of Obesity Bariatric surgery is gaining popularity worldwide, and the total number of procedures continues to rise. The most common procedures are the laparoscopic Roux-en-Y gastric bypass (LRYGB) and the laparoscopic sleeve gastrectomy (LSG). Additionally, less common techniques are available as bariatric options, such as the biliopancreatic diversion with or without duodenal switch (BPD/BPD-DS), the adjustable gastric band (AGB), one-

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anastomosis gastric bypass (OAGB), and single anastomosis duodeno-ileal bypass (SADI). LRYGB provides excellent evidence-based results in terms of weight loss and a decrease in obesity-related comorbidities in the long term [1, 2]. LSG represents an alternative to LRYGB and provides comparable results concerning weight loss and comorbidities [3]. Revised guidelines from the Diabetes Surgery Summit (2015) recommend consideration of surgical treatment for patients suffering from type 2 diabetes (T2D) with a body mass index (BMI) of >35 kg/m^2. Additionally, the evaluation of patients with a BMI <35 kg/m^2 with insufficiently controlled blood sugar levels was suggested to be implemented [4, 5].

Pharmacological Alternatives for the Treatment of Obesity Pharmaceutical methods for weight loss in the population with obesity represent an alternative to surgery [6–8]. Besides the long-term effects of bariatric surgery, changes in glucose metabolism and gut hormones can be measured immediately in the first postoperative days [9]. For example, the gut-derived glucagon-like peptide-1 (GLP-1) secreted by L-cells located primarily in the distal ileum and colon but also in the jejunum and duodenum [10] increases after LRYGB [9]. GLP-1 secretion is stimulated by intraluminal carbohydrates, proteins, and fat [11, 12]. In the pancreatic islets, GLP-1 acts as a glucose-dependent stimulator of insulin secretion, slows gastric emptying while increasing satiety, and reduces postprandial glucagon and food intake [13–15]. These functions suggest that drug-induced GLP-1 stimulation might be efficient in weight control and metabolic changes (Fig. 1). Consequently, a GLP-1 analogue named Liraglutide achieved almost 8.4 kg of weight loss and improved glycemic control compared with placebo in randomized controlled trials [6]. Additionally, GLP-1 analogues improved glucose homeostasis in patients already treated with insulin [30]. Nevertheless, bariatric surgery still provides better results concerning weight evolution and comorbidities compared with medical treatment [31].

GLP-1 and Metabolic Surgery Former literature showed that fasting levels of GLP-1 increase after LRYGB [9]. Nonetheless in comparative trials, GLP-1 analogues did not achieve the same satisfying results as in the surgical treated groups [32, 33]. Besides the single use of GLP-1 analogues in patients with impaired glucose metabolism or overweight, a combination of GLP-1 analogues with metabolic surgery might offer improved outcomes in patients fitting the criteria for a surgical approach. Due to the growing demand of more efficient surgery and management of secondary weight regain or insufficient weight loss in the long term [34, 35], therapeutic adjunctions to surgery may continue to emerge.

What We Do Not Know Instead of looking at GLP-1 agonists and metabolic surgery as two concurrent treatments, these two treatment modalities could be seen as two main pillars of one interdisciplinary approach. However, whether the combination of metabolic surgery with postoperative use of GLP1 analogues promotes additional health benefits needs to be further investigated. Those considerations prompted us to perform a review combined with a systematic literature research of possible beneficial effects of GLP-1 analogues, authorized in Switzerland, as an addition after bariatric surgery.

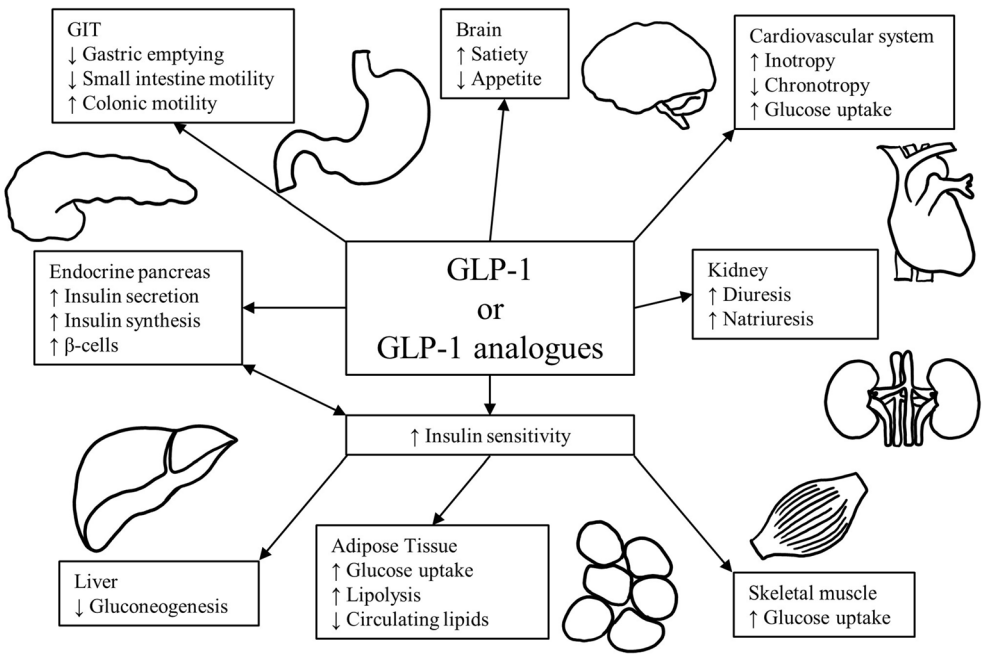

Fig. 1 Mechanisms by which GLP-1 analogues may have beneficial effects after metabolic surgery: GIT [16, 17], brain [14, 18, 19], cardiovascular system [20, 21], kidneys [22], skeletal muscle [23], adipose tissue [24, 25], liver [26, 27], and endocrine pancreas [15, 28, 29]. GLP-1, glucagon-like peptide-1; GIT, gastrointestinal tract

Materials and Methods

Literature Search and Study Selection

A systematic literature research was performed without consideration of date or language on the following MEDLINE search terms according to PRISMA guidelines [36, 37]:

> "metabolic surgery[Title/Abstract]) OR bariatric surgery[Title/Abstract]) OR gastric bypass[Title/Abstract]) OR sleeve gastrectomy[Title/Abstract]) OR BPD[Title/Abstract]) OR biliopancreatic diversion[Title/Abstract]) OR bilio-pancreatic diversion[Title/Abstract]) OR vertical banded gastroplasty[Title/Abstract]) OR vertical-banded gastroplasty[Title/Abstract]) OR one anastomosis gastric bypass[Title/Abstract]) OR mini gastric bypass[Title/Abstract]) AND GLP-1 analogues[Title/Abstract]) OR GLP-1 agonists[Title/Abstract]) OR glucagon-like peptide-1 analogues[Title/Abstract]) OR glucagon-like peptide-1 agonists[Title/Abstract]) OR liraglutide [Title/Abstract]) OR lixisenatide[Title/Abstract]) OR dulaglutide[Title/Abstract]) OR exenatide[Title/Abstract]) OR semaglutide[Title/Abstract]"

Citations of relevant articles were screened as well.

Inclusion Criteria

The titles and, if available, abstracts of all retrieved articles were screened. To be included in the review, studies had to have a main group or subgroup of human individuals undergoing bariatric/metabolic surgery. Additionally, at least one group or subgroups had to have a treatment with a GLP-1 analogue after previous bariatric/metabolic surgery. Studies needed to include follow-up information on at least weight evolution. Written works containing only abstracts without further documents were excluded.

The screening for the above-mentioned inclusion criteria was carried out by two experienced researchers (RS and MK) and double-checked by a third researcher when uncertainties occurred (TD).

Data Extraction and Outcomes

Full text articles of the studies that fulfilled the search criteria were retrieved. Data on the following information was extracted: type of operation, type of drug used, number of patients, age, weight loss, comorbidities (if available, T2D [glycated hemoglobin A1C], hypertension, and dyslipidemia), and information on drug side effects and follow-up.

Assessment of Quality

Methodological quality assessment of each study was performed using a checklist of randomized and non-randomized studies of health care interventions [38].

Results

Selection of Eligible Studies and Patient Characteristics

The literature search revealed 4663 potentially suitable publications (Fig. 2). After screening title and abstracts, 4636 studies were excluded and 27 assessed for further eligibility. Of these 27 assessed studies, 1 case report was excluded, 5 studies were excluded because of missing qualitative or quantitative data of interest, 5 studies were excluded because they examined the use of GLP-1 analogues prior to metabolic surgery, and 10 studies were excluded due to other reasons. Consequently, 6 studies were included for further analysis. Due to inhomogeneity of the retrieved data (different operation techniques, different time points of GLP-1 analogue administration, multiple indications) and overall the small numbers of studies, an evaluation in form of a meta-analysis as initially planned was omitted.

Studies, Patients, Type of Surgery, and GLP-1 Analogue Used in Collective

Of the 6 studies included, one was a randomized placebo controlled trial [39], one a prospective cohort trial [40], and 4 retrospective cohort studies [41–44]. Studies were performed between 2011 and 2019 and carried out in Spain, the UK, Brazil, Canada, and the United Arab Emirates. In total, 408 patients were included undergoing metabolic surgery and postoperative treatment with GLP-1 analogue. The performed surgeries included LRYGB, LSG, biliopancreatic diversion (BPD), vertical banded gastroplasty (VBG), and adjustable gastric banding (AGB). No statements can be made about actual exact numbers of each operation technique due to partially incomplete information. In all studies, the GLP-1 analogue Liraglutide was used as complementary treatment. A summary of the available baseline characteristics, surgical techniques, and drugs is presented in Table 1.

Weight Loss in Patients Undergoing Bariatric Surgery and GLP-1 Analogue Treatment

All studies reported on weight loss after different time points [39–44]. The use of Liraglutide achieved an additional weight loss in all studies included. In the paper of

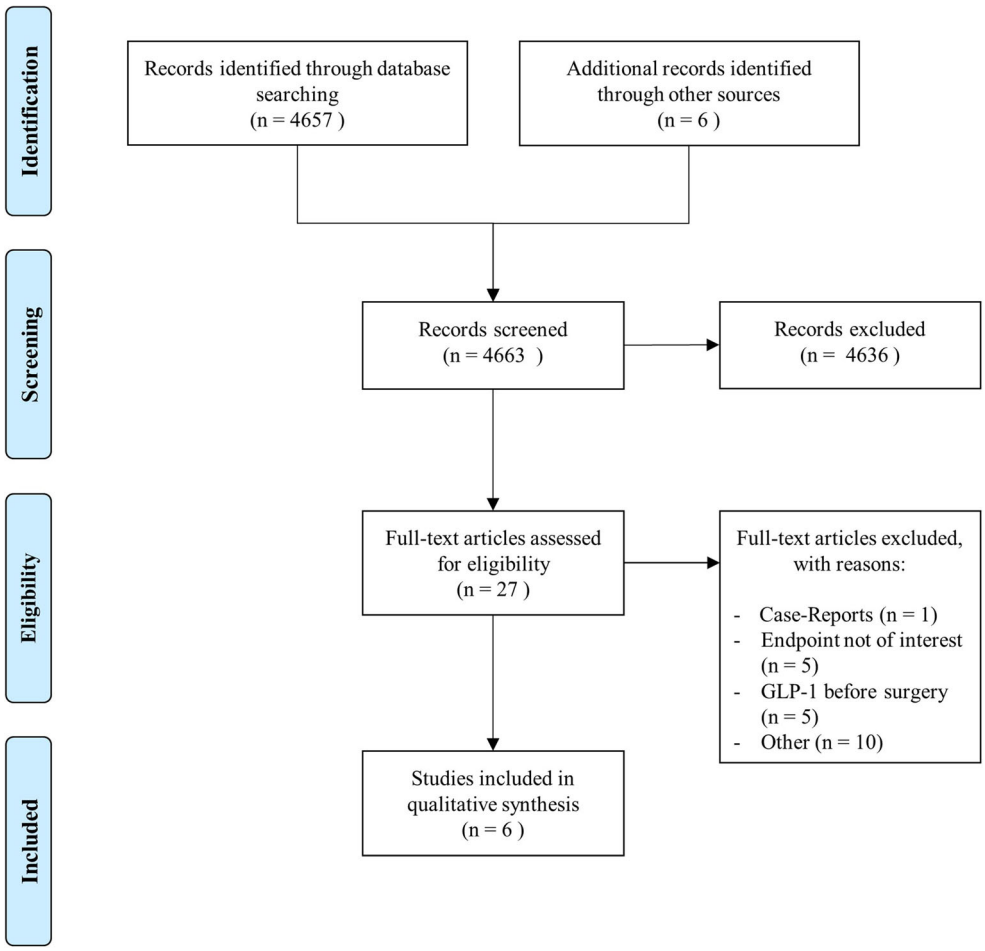

Fig. 2 PRISMA Flowchart; GLP-1 = glucagon-like peptide-1

Table 1 Study characteristics

Study	Design	Surgery	Medical therapy	Administration interval *	Outcomes	Follow-up
Gorgojo et al. [41]	Retrospective cohort	LRYGB ($n = 8$), BPD ($n = 3$), VBG ($n = 2$), LSG ($n = 1$), AGB ($n = 1$)	Liraglutide 1.6 ± 0.2 mg	5.2 years (IQR 2.4–9.2)	Weight, comorbidities, side effects	12–24 months
Miras et al. [39]	Randomized controlled trial	LRYGB ($n = 42$), LSG ($n = 11$)	Liraglutide 1.8 mg	3.8 ± 2.0 years	Weight, comorbidities, side effects	26 weeks
Pajecki et al. [42]	Retrospective cohort	LRYGB ($n = 9$), BPD ($n = 1$), LSG ($n = 1$), AGB ($n = 4$)	Liraglutide 1.2 to 3.0 mg	5.6 years (2 to 13 years range)	Weight, side effects	8.6 ± 7.3 months
Rye et al. [43]	Retrospective cohort	LRYGB ($n = 7$), VBG ($n = 3$), LSG ($n = 7$), AGB ($n = 3$)	Liraglutide 2.9 ± 0.2	76.3 ± 72.9 months	Weight, side effects	4 to 7 months
Suliman et al. [40]	Prospective cohort	LRYGB, LSG, and others (amount unknown), total $n = 188$	Liraglutide 3 mg	4 years (median)	Weight	–
Wharton et al. [44]	Retrospective cohort	LRYGB ($n = 53$), AGB ($n = 50$)	Liraglutide 3 mg	8 years (7.8 ± 5.7)	Weight, side effects	8.0 ± 7.6 months

*time interval between metabolic surgery and the first administration of the GLP-1 analogue; *LRYGB* laparoscopic Roux-en-Y gastric bypass, *BPD* biliopancreatic diversion, *VBG* vertical banded gastroplasty, *LSG* laparoscopic sleeve gastrectomy, *AGB* adjustable gastric banding

Gorgojo et al., 15 patients undergoing either RYGB, BPD, VBG, LSG, or AGB regained 10.1% ± 8.2% of their weight loss nadir before beginning the medical treatment with Liraglutide (mean time metabolic surgery to Liraglutide 5.2 years). In the study, the mean weight of 106.0 ± 7.2 kg could be reduced to 102.6 ± 6.9 kg by using 1.6 ± 0.2 mg of Liraglutide postoperatively [41]. In a placebo RCT, Miras et al. showed that patients with prior LRYGB or LSG with primary excellent weight loss (126.8 ± 25.1 kg to 85.3 ± 16.2 kg in LRYGB and 132.1 ± 29 kg to 104.3 ± 21.7 kg in LSG) regained weight (12.0 ± 9.4 kg after LRYGB and 9.3 ± 5.7 kg after LSG, respectively). However, 1.8 mg Liraglutide induced greater weight loss compared with the placebo at two different time points (− 3.7 kg, − 4.6 to − 2.8; $p = < 0.0001$ in week 10 and − 5.3 kg, − 6.2 to − 4.4; $p = < 0.0001$ in week 26) [39]. Another paper demonstrated that patients with 16.7 ± 16.2 kg weight regain after LRYGB, LSG, VBG, or AGB achieved additional 7.1% TWL (interquartile range [IQR] 5.1–12.2%) at 16 weeks and 9.7% TWL (IQR 7.8–13.9%) at 28 weeks after implementation of 2.9 ± 0.2 mg of postoperative Liraglutide [43]. Suliman et al. demonstrated 6.1% (3.1–8.7%) additional total weight loss (TWL%) in a cohort of mainly LRYGB and LSG patients adding 3 mg of Liraglutide. In another collective of LRYGB, LSG, and AGB patients, a significant additional weight loss was reached with the use of 3.0 mg Liraglutide (6.6 ± 7.1 TWL% after LRYGB, 3.6 ± 3.0 TWL% after LSG, and 4.9 ± 5.6 TWL% after AGB) [44]. The time points of weight loss displayed range from 6 to approximatively 35 weeks. Details on weight evolution can be found in Table 2.

Table 2 Weight evolution

Study	Group	Size	Sex, male (%)	Age, years ± SD	Weight primary surgery ± SD	Maximum weight change post bariatric surgery ± SD	Weight regain before additional GLP-1 therapy ± SD	Weight change on GLP-1 therapy ± SD (total weight or – weight loss according to paper information)
Gorgojo et al. [41]	RYGB BPD VBG LSG AGB	8 3 2 1 1	5 (33.3%)	53.0 ± 9.0	128.5 ± 26.4 kg	96.7 ± 24.8 kg	107.7 ± 26.3 kg	102.6 ± 6.9 kg ($p = 0.11$)
Miras et al. [39]	RYGB LSG	42 11	15 (36%) 5 (45%)	54 (IQR 49.8–69.0) 57.0 (IQR 51–68)	126.8 ± 25.1 kg 132.1 ± 29.0 kg	85.3 ± 16.2 kg 104.3 ± 21.7 kg	97.2 ± 18.7 kg 114.0 ± 23.2 kg	− 3.71 kg, − 4.59 to − 2.82; $p < 0.0001$ week 10; − 5.26 kg, − 6.15 to − 4.38; $p < 0.0001$ week 26
Pajecki et al. [42]	RYGB BPD LSG AGB	8 1 1 4	5 (33.3%)	47.2 ± 12.5	120.8 ± 22.1 kg	86.7 ± 14.4 kg	100.9 ± 18.3 kg	93.5 ± 17.4 kg (− 7.5 ± 4.3 kg)
Rye et al. [43]	RYGB LSG VBG AGB	7 7 3 3	1 (5%)	49.6 ± 8.3	134.4 ± 30.7 kg	–		3.5 kg/m^2 at 16 weeks (IQR 2.2–4.6 kg/m^2); 4.7 kg/m^2 at 28 weeks (IQR 3.7–5.6 kg/m^2)
Suliman et al. [40]	RYGB and LSG	76	–	–	–	–	–	6.1% (3.1%–8.7%) TWL%
Wharton et al. [44]	RYGB	53	3 (5.7%)	49.9 ± 9.1 BMI	50.8 ± 11.2 BMI	− 51.6 ± 23.5 kg	19.0 ± 23.5 kg	− 7.1 ± 8.7 kg
	AGB	50	8 (16.0%)	52.5 ± 9.5 BMI	47.6 ± 13.1 BMI	− 29.8 ± 23.3 kg	25.4 ± 20.4 kg	− 6.0 ± 7.2 kg
	LSG	14	4 (28.6%)	51.4 ± 10.3 BMI	52.2 ± 11.9 BMI	− 34.7 ± 19.5 kg	15.8 ± 14.1 kg	− 4.5 ± 4.5 kg

GLP-1 glucagon-like peptide-1, *LRYGB* laparoscopic Roux-en-Y gastric bypass, *BPD* biliopancreatic diversion, *VBG* vertical banded gastroplasty, *LSG* laparoscopic sleeve gastrectomy, *AGB* adjustable gastric banding, *IQR* interquartile range; if possible, all data is displayed as kilogram bodyweight or kilogram weight change (kg); in selected cases, if kg was not available, data is displayed as BMI (body mass index)

Table 3 Short-acting and long-acting GLP-1 analogues in direct comparison

Parameter	Short-lasting GLP-1 analogues	Long-lasting GLP-1 analogues
Agents	Exenatide Lixisenatide	Liraglutide Albiglutide Dulaglutide
Duration of action	2 to 5 h [48, 51, 52]	12 h to up to a week [16, 53, 54]
Weight loss	↑ [50, 55]	↑ [50, 55]
Fasting blood glucose levels	↓ [50, 55, 56]	↓ ↓ ↓ [50]
A1C	↓ [50, 55, 57]	↓ ↓ [50]
Blood pressure	↓ [55]	↓ ↓ [58]
Heart rate	No effect [55]	↑ [59, 60]
Gastric emptying	↓ ↓ [48, 49]	No effect [47]
Nausea	20–50% [55, 61]	20–40% [50]

GLP-1 glucagon-like peptide-1, *A1C* glycated hemoglobin

Note: Arrows should show the effects of the drugs e.g. one arrow: little effect, two arrows: medium effect, three arrows: strong effect.

T2D, Hypertension, and Dyslipidemia in Patients After Bariatric Surgery and GLP-1 Analogues Treatment

Two contributions contained detailed information about obesity-related comorbidities. The study of Gorgojo et al. reported that the amount of patients with a A1C of less than 7% was increased from 66.7 to 81.8% after 1.6 ± 0.2 mg Liraglutide [41], In the randomized controlled trial, the multivariable linear regression demonstrated a decrease of A1C [%] compared with placebo ($R^2 = -1.22$ [− 1.80 to − 0.64]; $p = 0.0001$). [39] However, both contributions did not observe differences in arterial hypertension or dyslipidemia.

Reporting of Side Effects Concerning GLP-1 Analogues in Patients Who Underwent Bariatric Surgery

Information about side effects of the used additive medication was found in 5 out of 6 papers. Most commonly reported side effects were gastrointestinal symptoms like nausea (9–37%), constipation (11–36%), and diarrhea (2–31%) [39, 43, 44]. Rye et al. also showed a high prevalence of gastroesophageal reflux (GERD) in 35% of the patients treated with Liraglutide. Other side effects, reported in small numbers, included fatigue, headache, dizziness, and other general symptoms.

Discussion

This systematic review may show beneficial effect of the postoperative addition of the GLP-1 analogue Liraglutide after metabolic surgery. Although most data had relatively short follow-up and did not allow a quantitative synthesis in form of a meta-analysis nor a statement regarding macrovascular outcomes, the present assessment demonstrates promising results for additional weight loss and improvement of T2D.

Since the implementation of bariatric and metabolic surgery, the trend towards safer and more efficient procedures is essential to the field. The surgical treatment of obesity has been a milestone not only in treating overweight itself but also in treating obesity-related comorbidities. Nevertheless, poor primary response or relapse of obesity and related comorbidities is not uncommon, which is usually addressed by additional nutrition counseling or revisional surgery in highly selected cases. For instance, the present literature shows a relapse of cured diabetes in 35–50% after a median disease-free period of approximatively 8 years [5, 45]. Behavioral and pharmacotherapeutic interventions to address postsurgical weight regain and maintenance of reduced comorbidities are subjects for further investigations [46]. A patient with weight regain, insufficient weight loss, or relapse of comorbidities after surgery needs to be evaluated by an interdisciplinary team. Besides dietary counseling and revisional surgery (e.g., banding or distalization of RYGB, re-sleeve, conversion to RYGB, BPD-DS, or SADI), new medical agents might offer an alternative that has not been considered so far.

Literature search showed an additional weight loss in all studies included; however, different parameters were used for weight loss measurement which may impede the interpretation of the findings. Additionally, there is only one RCT included in the reviewed papers, which influence the quality of the evidence considerably. The lack of a longer follow-up in the present data allows only an assessment of the GLP-1 analogue effect up to maximally 2 years [39–44]. The choice of operation technique had no influence of the response on GLP-1 analogues; however, not all studies included the data on different procedures. Besides

weight loss, reduction of obesity-related comorbidities might be achieved by the new medical treatment addition. For instance, Liraglutide seems to have beneficial effects on A1C after metabolic surgery [39, 41]. In contrast, hypertension and dyslipidemia were not affected by the additive medical treatment, although weight reduction should have a positive effect on these comorbidities as well. To allow us a statement on hypertension and dyslipidemia, and more importantly on macrovascular outcomes as a consequence of additional weight loss, more reliable data is needed. Since literature only provides data on the specific agent Liraglutide and metabolic surgery, the use of other GLP-1 analogues may be of interest for future investigations. Long-lasting GLP-1 analogues such as Liraglutide have no influence on gastric emptying [47]. Comparatively, short-term agents like lixisenatide or exenatide slow down gastric emptying significantly [48, 49]. Nevertheless, the long-lasting agents were superior concerning glucose metabolism in comparative trials [50] [Table 3].

Besides good results in weight loss and comorbidities, high prevalence of gastrointestinal side effects can be found in the corresponding study collectives [39, 43, 44]. In general, GLP-1 analogues showed several typical side effects on the gastrointestinal tract [62]. In contrast, the prevalence of unspecific or specific gastrointestinal symptoms after bariatric surgery is rather high [63]. Abdominal symptoms might be caused by early or late surgical complications [64]. After LRYGB, potential life-threatening internal hernias may cause unspecific gastrointestinal symptoms [65]. Concerning the emerging possible long-term complication of GERD and Barrett after LSG [66, 67], the slowed gastric emptying caused by GLP-1 could be responsible for a deterioration of symptomatic or asymptomatic acid reflux into the lower esophagus [68]. Another decisive question will be the cost and reimbursement of the corresponding medical agents. For instance, insurances in Switzerland do only take over the costs for GLP-1 in a few selected cases (at the moment BMI > 35 or > 28 with comorbidities).

Synoptically, obesity and its comorbidities are chronic diseases that despite an efficient treatment, such as metabolic surgery, can recur. As in any other chronic diseases involving various organ systems, a multidisciplinary treatment approach, similar to oncological patients, may offer the most beneficial outcome in the long-term. Despite the effectiveness of metabolic surgery in the vast majority of patients, poor long-term weight loss and relapse of comorbidities present a commonplace in the daily practice. Addition of promising medical treatments such as GLP-1 analogues may offer improved outcomes concerning weight loss plus resolution of comorbidities in patients with poor response to surgery alone in the future.

Compliance with Ethical Standards

Conflict of Interest Dr. Schneider reports grants from the University of Basel, grants from Department of Surgery, University Hospital Basel, grants from SFCS, grants from Freiwillige Akademische Gesellschaft Basel, and grants from Gebauer Stiftung, outside the submitted work. Dr. Peterli reports grants and other from the Johnson & Johnson, outside the submitted work. Marko Kraljević, Theresa V. Rohm, Jennifer M. Klasen, Claudia Cavelti-Weder, and Tarik Delko have no conflicts of interest or financial ties to disclose. All authors have no ties to GLP-1 analogues producing pharmaceutical companies.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Informed consent does not apply.

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