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Review Article

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Effectiveness of Glucagon-like Peptide-1 Receptor Agonists in Patients with Obesity and Type 2 Diabetes vs Metabolic Surgery for Weight Loss Achievement

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Abstract

The purpose of this literature review is to investigate the effectiveness of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) compared with metabolic surgery in achieving weight loss among individuals living with obesity and type 2 diabetes (T2D) mellitus. A total of 498 citations were retrieved from previous studies that met prespecified inclusion criteria focusing on adult populations with obesity and T2D. Our findings indicate that bariatric/metabolic surgery results in the greatest reductions in body weight and body mass index (BMI). Both treatment modalities are effective in reducing glycosylated hemoglobin (HbA1c) levels, cardiovascular (CV) risk, morbidity, and mortality. GLP-1 RAs appear to represent a promising therapeutic option for individuals with obesity and diabetes who meet the criteria for bariatric surgery (BS). Ultimately, the individualization of treatment remains the cornerstone for providing the best possible care in managing this population.

Keywords: Glucagon-like peptide-1 receptor agonists, Bariatric surgery, Obesity, Type 2 diabetes

Introduction

The obesity epidemic has evolved during the past decades and has been one of, if not, the most stigmatized epidemics in our society, evidencing an increase in prevalence since the 1980s [1]. There is clear evidence correlating the rise in obesity prevalence with the increasing prevalence of T2D. Complex cellular and physiological mechanisms underlying this disease and associated with obesity include adiposity-induced alterations in β-cell function, changes in adipose tissue biology, and multi-organ insulin resistance (IR). Achieving adequate weight loss has been shown to mitigate or even normalize these pathophysiological processes [2]. Different treatment options have been used for several decades, but a paradigm shift has occurred with the emergence of new pharmacotherapeutic agents targeting weight loss. These agents have led to subsequent improvements in disease-related comorbidities and have positively impacted overall morbidity.

GLP-1 RAs have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of individuals with T2D since 2005, and they have subsequently been shown to improve obesity-related outcomes as well. They are considered a first-line pharmacologic option for glycemic control, particularly in individuals at risk for or with pre-existing CV disease (CVD), due to their cardioprotective properties. In recent years, GLP-1 RAs have also emerged as an effective pharmacologic option for weight loss. These developments have established GLP-1 RAs as a preferred next-generation treatment for individuals with both diabetes and obesity, given their superior efficacy and safety profile [3].

On the other hand, metabolic surgery as a treatment for individuals living with obesity, particularly those with T2D, has been regarded by the medical community as the most effective and safest long-term intervention. Although metabolic surgery continues to generate debate due to the complexity of its procedures, detailed analyses of long-term complication and mortality rates indicate that these risks have significantly declined over time. Consequently, the overall benefits of the surgery now outweigh its potential drawbacks. This improvement has contributed to the increasing adoption of BS each year as a preferred treatment option for individuals with morbid obesity [4].

Worldwide, approximately 700,000 metabolic procedures are performed each year, with about 250,000 of these taking place in the United States. Consequently, the use of surgical treatment has shown significant growth over the past two decades [5].

The aim of this article is to review the most recent literature and determine which of the two approaches demonstrates greater effectiveness in achieving weight loss. We hope that this analysis will contribute to advancements in the management of individuals living with obesity and T2D, as well as help refine the indications for BS. Furthermore, it may highlight the potential for pharmacological treatments to achieve comparable results with a lower risk of adverse outcomes and morbidity associated with surgical procedures.

Methods

Eligibility criteria

During our review of the literature, we used the PICOS tool which stands for population, intervention, comparison, outcomes, and study design approach to establish the inclusion criteria (Table 1). We took into account articles that explored the effects of GLP-1 RAs and/or metabolic surgery on the obese adult population with T2D were chosen according to the following criteria: (1) articles published during 2018 and 2023; (2) adults of both genders; (3) T2D disease (4) compared metabolic surgery outcomes or; (5) undergoing or finished treatment with GLP-1 RAs; and (6) weight loss achievement as a parameter. Exclusion criteria consisted of studies that (1) embraced interventions other than or in addition to GLP-1 RAs or metabolic surgery; (2) patients with BMI less than 30 kg/m^2; (3) age less than 18 years old; and (4) publications before the year 2018. An exception was made for 3 articles regarding the period (2013) as they were manually selected because of the evidence they provided concerning specific therapies.

Literature search strategy

PubMed and Scopus were the two electronic databases we used to search for this literature review. The following key terms (and synonyms searched for by the MeSH database) were included and combined using operators "AND" and "OR" such as: "GLP RAs" or "GLP-1" and "obesity" or "weight loss", and "bariatric surgery" or "sleeve gastrectomy". Additionally, indexed keywords that we used were: {GLP} and {obesity} and {weight loss} and {bariatric surgery}. We manually accomplished the search for the reference list of key papers. Our decision to perform a research review vs a meta-analysis was determined by the selected scoop, which was large in terms of outcome dimensions.

Results and Discussion

The total number of articles that we selected to be analyzed after applying inclusion and exclusion criteria was 378 for the Scopus search and 120 for the PubMed search. Screening of abstracts was based on evidence of citations that showed any potential relevance. Consequently, when abstracts indicated potential inclusion, full-text articles were reviewed (Figure 1).

GLP RAs on T2D and weight loss

Currently, the landscape of T2D management has evolved due to the continuous emergence of new pharmacologic therapies, leading to changes in previous treatment guidelines. These developments have created a challenging situation for clinicians and patients when selecting the most appropriate management strategy from a wide range of available options (Figure 2). GLP-1 RAs have proven to be an excellent therapeutic option, not only for treating individuals with diabetes but also for promoting weight loss, with some patients achieving complete remission [6, 7].

The impact of GLP-1 RAs on weight loss varies depending on the specific agent used. Dulaglutide and liraglutide demonstrate an average weight reduction of 3 - 4%, compared to lixisenatide, exenatide, and albiglutide, which show a 1 - 3% reduction. All assessments have been conducted in individuals with T2D. One of the most recent GLP-1 RAs approved by the FDA, in 2022, is tirzepatide. This medication has been administered to patients with T2D at doses ranging from 5 - 15 mg once weekly, resulting in weight reductions of approximately 8 - 12%. Moreover, tirzepatide has also been developed as a weight loss therapy for individuals with BMI ranging from overweight to obese [7].

Table 1: PICOS criteria for the inclusion of studies.

	Parameters	Inclusion criteria
PICOS criteria for the inclusion of studies	Population	Adults with T2D and obesity
	Intervention	GLP RAs for weight loss
	Comparator	Metabolic surgery
	Outcomes	Weight loss, metabolic parameters
	Study design	Review of the literature

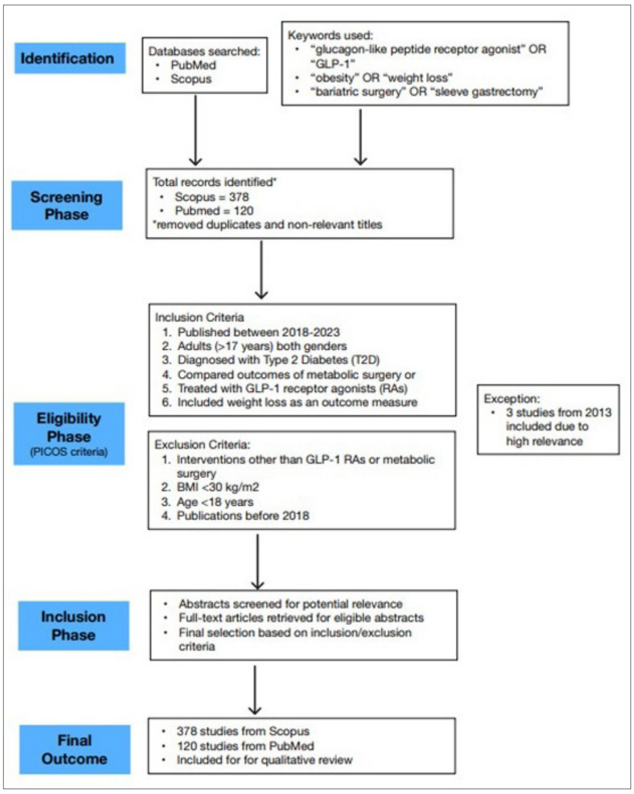

Figure 1: Flowchart of database search algorithm.

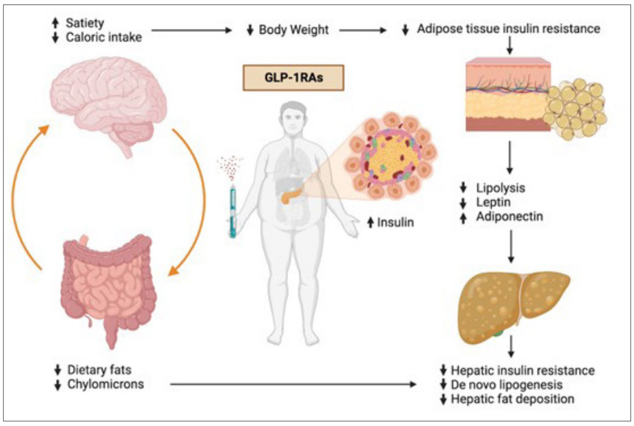

Figure 2: Potential targets of GLP-1 RAs include a decrease in caloric intake through central regulation of satiety, a reduction of hepatic and adipose tissue IR due to a decrease in body weight, a modified intestinal lipoprotein metabolism, a resolution of dysfunctional adipose tissue, and an enhancement of insulin release.

Two studies investigated the implementation of GLP-1 RAs treatment for people with obesity. The semaglutide treatment effect in people with obesity (STEP) study consisted of a step 1 - 4 trial duration of 68 weeks + 7 week follow-up and step 5 trial consistent of 104 weeks + 7 week follow-up. The treatment period in the following STEP trials was followed by a 7 week period of treatment to account for the long half-life of semaglutide. The observation of pharmacological therapy with semaglutide dosed at 2.4 mg once a week and reported a mean weight loss of 16.9% in the patients studied vs a 2.4% mean weight loss in the placebo group. Furthermore, satiety and clinical adiposity - liraglutide evidence maintenance study consisted of a 52 week trial applied to overweight patients and individuals with a BMI > 27 who presented at least one comorbid condition or obesity I or higher (BMI > 30). Individuals were exposed to liraglutide dosed at 3 mg daily to evaluate its efficiency, optimal dosage, and its effect on weight loss. The study evidenced a mean weight loss achievement of 8.4 kg after 56 weeks of treatment. Additionally, it also revealed that 33.1% of trial participants lost more than 10% of their body weight [7].

GLP-1 RAs and their effect on HbA1c

GLP-1 RAs constitute suitable options for treating individuals with T2D because of their efficiency at lowering HbA1c and weight loss. After a close review of Phase III clinical trials, eight peer-reviewed studies were identified. Studies included medications such as two times a day administration of exenatide, and once-weekly administration of exenatide, liraglutide, albiglutide, lixisenatide, and dulaglutide. From the above, safety and efficacy active comparison parameters were evaluated. The primary efficacy endpoint consisted of a change in baseline of HbA1c with a non-inferiority margin of 0.4%. Phase III studies (DURATION-1, DURATION-5, HARMONY-7, LEAD-6, and AWARD-6), reported higher margin efficacy endpoints than 0.4% [8].

GLP-1 RA's CV effects

Most recent studies that focus on CV evaluation are conducted in very high-risk populations to increase its impact on risk reduction of major CVD and to complete the studies in a short period. These parameters limit data on CV safety and potential advantages in lower-risk patients. Exceptions to high-risk patient studies include any investigation involving drug liraglutide and investigations such as the glycemia reduction approaches in diabetes: a comparative effectiveness study, a cohort in patients with low CV risk [9].

A meta-analysis of trials comparing GLP-1 RAs (lixisenatide, albiglutide, liraglutide vs placebo, once weekly exenatide), reported that GLP-1 RAs confer a reduction in the probability of mortality (39 vs 44 events per 1000 persons; odds ratio (OR) 0.87, 95% confidence interval (CI): 0.79 - 0.95) and fatal or non-fatal stroke (26 vs 29 per 1000 persons; OR 0.87, 95% CI: 0.77 - 0.98) caused by CV antecedents [10].

GLP-1 RAs and all-cause mortality

In patients with diabetes and established CVD, GLP-1 RAs appear to reduce all causes of mortality. Patients with diabetes and CVD were evaluated through a meta-analysis composed of seven studies that compared GLP-1 RAs drugs (lixisenatide, exenatide, albiglutide, liraglutide, semaglutide) vs placebo, concluding that GLP-1 RAs minimize all causes of mortality (60 vs 68 events per 1000 people, OR 0.88, 95% CI: 0.82 - 0.95) [10].

GLP-1 RAs and adverse outcomes

One of the disadvantages of GLP-1 RAs is their adverse effects, being the most frequent ones related to gastrointestinal intolerance (nausea, vomiting, and diarrhea). Nausea occurs in up to 57% of patients and is usually transient and dose-dependent with symptoms decreasing after approximately 4 - 8 weeks depending on the drug consumed [11]. Hypoglyce-

Table 2: GLP-1 RA drugs: classification according to pharmacokinetic characteristics and approval status by FDA and European medicines agency (EMA).

Drug	Duration/action	Predominant glycemic effect	FDA approval	EMA approval
Exenatide	Short	Prandial	2005	2006
Lixisenatide	Short	Prandial	In process	2013
Liraglutide	Intermediate	Fasting	2014	2009
Exenatide long-acting release	Prolonged	Fasting	2012	2011
Albiglutide	Prolonged	Fasting	2014	2014
Dulaglutide	Prolonged	Fasting	2014	2014

Table 3: GLP-1 RAs are currently available and developing.

Drug	Brand name	Dosing frequency	US FDA approval status	EMA approval status	Phase III clinical trial program
Exenatide	Byetta®	Twice daily	Approved 28 April 2005	Approved 20 November 2006	AMIGO
Liraglutide	Victoza®	Daily	Approved 25 January 2010	Approved 30 June 2009	LEAD
Exenatide	Bydureon®	Weekly	Approved 26 January 2012	Approved 17 June 2011	DURATION
Lixisenatide	Lyxumia® (Europe)	Daily	Submitted withdrawn 12 September 2013	Approved 1 February 2013	GetGoal
Albiglutide	Tanzeum® (US) Eperzam® (Europe)	Weekly	Approved 15 April 2014	Approved 23 January 2014	HARMONY
Dulaglutide	-	Weekly	Submitted	Submitted	AWARD

mia may also occur if co-administered with other hypoglycemic agents (e.g., basal insulin, sulfonylureas, meglitinides). The assessment of GLP-1 RAs in producing pancreatitis as an adverse outcome of treatment was particularly analyzed in a board insurance database. This typically refers to a specialized insurance system that covers board-certified physicians, healthcare providers, or medical liability cases. Insurance databases often contain patient treatment records and adverse event reports. In this case, the database was used to track how often pancreatitis occurred in patients treated with GLP-1 RAs and to determine whether there was a statistically significant link between the drug and the condition. Sitagliptin and exenatide were linked to incrementing the rate of hospitalization due to acute pancreatitis (adjusted OR 2.07, 95% CI: 1.36 - 3.13) [12]. Yet, there are still some retrospective cohort studies and meta-analyses of randomized trials that were not indicative of rising rates of hospitalization due to pancreatitis secondary to medical treatment with GLP-1 RA. In general, the incidence of presenting pancreatitis is minimal (16 cases in 14,562 patients in randomized trials of GLP-1 RA) [13].

In conclusion, while the overall incidence of clinically apparent pancreatitis from GLP-1 analogs remains low and hospitalizations have not increased, the consistent rise in pancreatic enzyme levels observed in many treated patients suggests subclinical exocrine pancreatic stress that may be overlooked in large epidemiological studies. Although the long-term clinical significance of these enzyme elevations is uncertain, they may represent an underrecognized risk, especially in individuals with additional predisposing factors [14].

The presentation of acute renal failure in patients with GLP-1 RAs is usually associated with serious gastrointestinal adverse events leading to dehydration and has been evidenced particularly in patients who have received exenatide two times a day. Hence, the need to evaluate patients' renal function in those who present with severe gastrointestinal symptomatology [15].

In studies comparing once-weekly insulin with GLP-1 RAs, local reactions were more common, particularly with albiglutide and exenatide (10%) compared to insulin (1% - 5%) [16]. Comparative studies showed that injection site reactions occurred significantly greater with exenatide weekly [17]. Among the most frequent reactions, the presence of abscesses, cellulitis, and necrosis with or without subcutaneous nodules have been reported.

BS on T2D and weight loss

Patients with T2D have exhibited a major benefit from BS in recent evidence in controlling the glucose blood level as well as benefits in a vast scope of CV and renal aspects [18]. There are currently 2 main approaches described and widely performed: Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy.

The diabetes surgery study (DSS) and the surgical treatment and medications potentially eradicate diabetes efficiently (STAMPEDE) trial [19] are two clinical trials in which evidence of weight loss is attributed to alterations in the body's physiology to regulate body weight. According to their analysis, these two procedures have no relation with patient mechanical restriction nor the presence of macronutrient malabsorption [20].

On further assessment of the DSS study, 120 patients were submitted to a randomized trial consisting of lifestyle and pharmacological therapy as independent variables with the presence or absence of performing RYGB as the dependent variable. Endpoint achievements in this trial consisted of a HbA1c < 7.0%, low-density lipoprotein-cholesterol < 100 mg/dL, and systolic blood pressure < 130 mmHg. At 12 months 11 participants in the pharmacological-only therapy group achieved endpoints exposed previously with a 19% (95% CI: 10 - 32%) vs a 28% within the pharmacological therapy plus RYGB arm (19%, 95% CI: 10 - 32%) [19].

On the other hand, the STAMPEDE trial evaluated 150 participants with T2D with no evidence of glycemic control and BMI ranges between 27 - 43 kg/m^2. The study contrasted the results between the implementation of standard medical therapy vs standard medical therapy plus RYGB or laparoscopic sleeve gastrectomy (LSG). The primary endpoint of HbA1c at 1 year was established to be 6.0%. Results disclosed achievements of endpoints in the medical therapy-only group at 12%, 42% in the RYGB group, and 37% in the SG group. Furthermore, secondary endpoints that were reported to improve after surgery consisted of the evaluation of BMI, total body weight, waist circumference, and the homeostatic model assessment for IR is a technique used to evaluate IR and beta-cell activity based on fasting levels of glucose and insulin (or C-peptide). It is mainly employed in clinical and epidemiological research to estimate IR using a single fasting blood sample and is often applied to populations at risk for metabolic syndrome and T2D [19].

The Swedish obese subjects, a study centered around a prospective multicenter evaluation of individuals with obesity and T2D, adequately matched groups that compared outcomes of various types of bariatric surgeries vs conservative management. Patients with T2D status of remission were based on glycemic levels < 100 ml/dl and no requirement of drugs for the treatment of individuals with diabetes [20]. Results after two years reported a reach of the endpoint of remission in 72% of patients undergoing surgery, in contrast to 21% in medically treated patients alone. A 10 year follow-up of the Swedish obese subject's study evidenced recovery rates more than three times higher in patients who underwent surgery in comparison to the control group. Finally, the association of relative risk of T2D in surgical patients was three times lower than the control group.

Several authors have hypothesized that the hormone incretin plays a key role in the metabolic outcomes associated with BS. Incretins, particularly GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), mediate postprandial insulin secretion and account for nearly 70% of insulin release after meals. Physiologically, GLP-1 secretion is stimulated by accelerated gastric emptying and by the interaction of nutrients with intestinal L cells located on the apical surface. These processes are markedly enhanced following BS, which involves resection of the gastric fundus and body [21]. Consequently, surgery induces a significant postprandial rise in incretin levels-especially GLP-1 (up to tenfold)-reaching concentrations comparable to those in individuals without obesity. This increase contributes to weight loss and improved glycemic control.

Although the elevation of incretin levels appears to play an important role in the mechanisms underlying BS, it is not considered decisive. The secreted hormone has a very short degradation time, acting primarily in a paracrine manner via receptors on vagal afferent fibers (VAF), with minimal systemic influence. This is supported by evidence showing that the effects of GLP-1 are almost completely abolished following bilateral subdiaphragmatic vagotomy or damage to VAF induced by capsaicin, a neurotoxic agent. Moreover, the genetic absence or blockade of GLP-1 receptors does not alter the metabolic benefits of BS. Therefore, the precise nature of the interaction between GLP-1 and BS remains to be fully elucidated.

Many authors have hypothesized that the hormone incretin plays a crucial role in the association with the metabolic outcome of BS. Incretin contributes to the postprandial mechanism of insulin release via the activity of GLP-1 and GIP, accounting for nearly 70% of postprandial insulin release. Physiological release of GLP-1 is stimulated by the increase in the rate at which gastric emptying occurs as well as the interaction of the nutrients with intestinal L cells located in the apical surface. These reactions are increased after BS, which involves the surgical removal of the gastric fundus and its body [21]. Surgery results in a marked post-prandial increase in incretins, particularly GLP-1 (up to 10 times reaching levels similar to those in patients without obesity), which play an essential role in weight loss and diabetes reduction.

The role of increased incretin levels in the mechanisms of BS is certainly important but does not appear to be decisive. In fact, the degradation time of the secreted hormone is a few seconds and, therefore, this effect is mainly paracrine through its receptors on VAF (and minimally systemic). This is confirmed by the observation that the efficacy of GLP-1 is almost completely lost after bilateral subdiaphragmatic vagotomy or the destruction or damage of the VAF by capsaicin (a chemical neurotoxin). Finally, the genetic absence or blockade of the receptors does not modify the effect of surgery. The nature of the GLP-1-BS collaboration remains to be clarified [22].

In fact, a metabolic syndrome program located in Europe entitled: the RESOLVE research, scoped the capacity and the mechanics of endogenous GLP-1 towards insulin sensitivity. Methods of assessment consisted of measuring the levels in the plasma of specific metabolic markers previously and after surgical intervention with RYGB in individuals with obesity with an indication of weight loss. Incretin postprandial release was evidenced to elevate noticeably in the first-year checkup in those who were submitted to BS, something that was previously attributed to the accelerated passage of nutrients throughout the intestine. Therefore, nutrients reaching the intestines produce increased stimulus of neuroendocrine cells that secrete GLP-1. This leads to an association between the secretion of GLP-1 and insulin sensitivity in patients following RYGB surgery. Hence hypothesizing a direct relationship or common cause association between GLP-1 release and insulin sensitivity is a theory that could be applied to insulin-resistant patients with class II/III obesity as well as patients with a better metabolic condition. Eventually, the essence of their collaboration is still yet to be interpreted and clarified [23].

Furthermore, indicators of pancreatic function and insulin sensitivity at a hepatic level were evaluated for 43 patients in a 2019 study in Austria before and after RYGB with a 1 year follow-up of these same indicators. Outcomes reported after the first year showed a 37% decrease in BMI, proinsulin, insulin, and C-peptide levels. Thus, the study suggested that individuals with diabetes who have RYGB surgery influence proinsulin levels and could present a direct relationship with weight loss evidenced after the procedure [24].

Although previously mentioned studies support BS as a possible treatment for individuals with T2D and obesity, many patients have not been reported to reach sustained remission of their diabetes posterior to BS. Subsequently, Liraglutide, a GLP-1 analog, was evaluated vs placebo in a double-blinded randomized trial entitled gauging responsiveness with a verifynow assay—impact on thrombosis and safety. This study exhibited outcomes in which patients who underwent BS alone continued or had recurrent T2D with superior glycemic measurements and lower rates of weight loss vs BS with liraglutide as adjunctive therapy [25].

Adverse outcomes of BS

Literature reports that complications secondary to LSG are roughly 13% with a slightly 0.34% postoperative risk of mortality. Complications tend to spike in the subsequent late postoperative period of LSG making the most common ones involved with the gastrointestinal system: gastroesophageal reflux, stenosis, vomiting, gastric tube stricture, gastro-cutaneous fistula, and weight regain [26]. More complex gastrointestinal complications but at much lower rates of presentation include the presence of internal hernias, which are reported in the early and late postoperative period and are related to defects in the mesentery generating small intestine herniation, frequently towards the upper left abdomen. This event predisposes the patient to develop obstruction, ischemia, infarction, and even perforation. Anastomotic stenosis is another complication that can lead to obstruction as a result of reactional edema in the perioperative period [27].

On the other hand, anemia is one of the major adverse effects of BS. Generally, the presence of underlying anemia is correlated to prolonged length of inpatient stay. Notably, 151 patients were followed during 10 years in Brazil posterior to Guillain-Barré Syndrome. Results marked the presence of anemia in 37.5% of those cases with values of < 15 μg/L in ferritin and 45% of cases evidenced anemia when values of ferritin reached levels below 30 μg/L. Similarly, 1999 patients who were assessed retrospectively in a Portuguese cohort study that included 4 years of follow-up, presented an index of 24.4% of anemia posteriorly to BS. Numerous factors have been correlated with anemia that elevates its prevalence. Two of them that stand out amongst the rest are female sex and RYGB as the type of bariatric procedure, presenting a two-fold increased risk of developing anemia compared to male patients and LSG and gastric band surgery [28]. Finally, the development of anemia in patients who underwent BS may show persistently elevated rates over time even with the presence of iron supplementation.

Hair loss after BS is reported in > 50% of patients as a short-term complication. Similarly, studies also mention the relation between iron and zinc levels with this complication. Eventually, the presence of hair loss is not reported to cause serious morbidity in patients but does correlate to patients expressing an unnecessary deterioration in their quality of life secondary to alterations in their mental health and self-esteem [29].

Post-bariatric non-alcoholic Wernicke encephalopathy (NAWE) usually manifests as soon as 4 - 12 weeks after the procedure even though there have been clinical cases that report its development as late as 18 - 24 months. NAWE is distinct from classic WE, both clinically and in neuroimages. In NAWE, mental status changes, and ocular and cerebellar dysfunctions show up 38 - 65% of the time while in WE only 16 - 38% [30-32].

Conclusion

After our revision of the literature, the acknowledgment of treating individuals living with obesity and diabetes is of great importance due to clear evidence of impacting not solely on their weight loss and T2D control but also the emotional burden patients may experience due to these pathologies. In BS trials compared to subcutaneous injection of GLP-1 RAs, glycemic control was similar after both treatments; however, we evidenced that weight loss was greater after surgery, providing the greatest reduction in body weight and BMI. Furthermore, GLP-1 RAs were shown to carry lower adverse effects compared to BS. As to CV outcomes, we can conclude that GLP-1 RAs as well as BS have been shown to carry a protective effect by reducing all causes of mortality as well as a reduction of cancer risk. Our recommendation is to provide the best treatment available for each patient. Physicians must individualize each case according to the associated comorbidities taking into account ongoing clinical trials and new evidence regarding these new drugs; as well as the possibility of finding their benefits and side effects that have not yet been established. We emphasize the importance surrounding the lack of literature when comparing both treatments including the newly available drugs (tirzepatide) as well as when trying to include non-diabetic patients undergoing GLP-1 RAs therapy for weight loss only. Eventually, we hope that with the evidence shown, there might be a possible breakthrough for a subset of patients trying to achieve weight loss and reduction of comorbidities associated with metabolic syndrome. We emphasize that the current evidence showing greater weight loss with BS compared to GLP-1 analogues is significant from both therapeutic and preventive perspectives, given that metabolic syndrome fundamentally arises from excessive adipose tissue accumulation. The lack of comparative studies between BS and newer GLP-1 analogues represents an important research gap that warrants further investigation. However, including non-diabetic patients may be less critical, as IR is almost universally linked to excess body weight. In conclusion, these findings highlight the superior weight-reduction efficacy of BS and the need for additional comparative research to better define the respective roles of BS and GLP-1 analogues in managing obesity and metabolic syndrome. We encourage continued investigation to determine whether future advancements in GLP-1 therapies might narrow this gap.

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None.

Conflict of Interest

None.

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