

Perioperative Management of Patients Taking Glucagon-like Peptide-1 Receptor Agonists: Applying Evidence to Clinical Practice

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Glucagon-like peptide-1 (GLP-1) receptor agonists, introduced in clinical practice in 2005, have revolutionized the treatment of type 2 diabetes, and their use represents a paradigm shift. GLP-1 receptor agonists have allowed for better control of glycemia when compared to basal insulin with minimal risk of hypoglycemia.¹ The number of prescriptions for this medication class have risen sharply, with introduction of new pharmacologic agents and the wide adoption of GLP-1 receptor agonists for treatment of obesity. Clinicians frequently care for patients prescribed GLP-1 receptor agonists and need to be familiar with perioperative considerations. The anesthetic plan needs to be tailored based on the specific drug, the dosing schedule, fasting time, gastrointestinal symptoms, and the planned procedures. In this article, we discuss the pharmacokinetics of GLP-1 receptor agonists, mitigating factors affecting risks of aspiration, and risks and benefits of stopping or continuing GLP-1 receptor agonists perioperatively. We also propose a framework for periprocedural management of patients taking GLP-1 receptor agonists.

Perioperative Concerns and Currently Recommended Management

The clinical benefits of GLP-1 receptor agonists are derived partly through their propensity to slow down gastrointestinal motility. In the outpatient setting, reported gastrointestinal adverse events related to GLP-1 receptor agonists have risen as their utilization has surged.² Most commonly reported side effects are abdominal pain (57.6%), nausea and vomiting (23.4%), constipation (30.4%), and diarrhea (32.7%).³ Gastrointestinal side effects occur for both short- and long-acting preparations, and for subcutaneously and orally administered preparations. Typically, these adverse effects are not serious, are self-limited, and are more pronounced at the initiation of the drug or during dose escalation phases. They often subside when maintenance doses are reached.

GLP-1 receptor agonists' ability to slow gastric emptying to a gastroparesis level has translated into concerns for perioperative aspiration.^{4,5} Multiple case reports, case series, and studies have been published since 2022.^{6–21} These concerns led the American Society of Anesthesiologists (ASA; Schaumburg, Illinois) to publish a consensus-based guidance suggesting that patients discontinue GLP-1 receptor agonists for 1 day for short-acting preparations and 1 week for long-acting preparations, while observing the current ASA fasting guidelines without any modifications.²² However, the ASA recommendations have been questioned because of the lack of data supporting them and new data that are rapidly emerging.

GLP-1 Receptor Agonists and Their Pharmacologic Properties

There are several GLP-1 receptor agonists currently available (table 1). Short-acting preparations include lixisenatide and exenatide. The lixisenatide-alone formulation was withdrawn from the United States market in January 2023 but remains available in Europe. Lixisenatide is currently available only in combination with long-acting insulin in the United States. Exenatide is available as a short-acting twice-daily subcutaneous preparation or as a long-acting weekly formulation with the drug slowly released from a matrix. Other long-acting GLP-1 receptor agonists include liraglutide, dulaglutide, and semaglutide. Liraglutide is mostly albumin-bound, thus having a reservoir for prolonged release, which accounts for its long half-life.²⁶ Dulaglutide is a GLP-1 molecule coupled with an immunoglobulin Fc fragment leading to slow degradation. Semaglutide is available in two forms: a weekly long-acting preparation, which is albumin-bound, and an oral form with low bioavailability after ingestion leading to the need for daily dosing.²⁶

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Table 1. GLP-1 Receptor Agonist Medications, Their Pharmacologic Properties, and Indications

Medication (Brand Name)	Administration	Half-life	Time to Peak Effect	Steady State	Dose Escalation	Indication
Short-acting GLP-1 receptor agonist						
Exenatide (Byetta; AstraZeneca, UK)	Subcutaneous twice daily	3.3–4 h	3 h		5 µg for 1 mo, 10 µg (maximum dose)	Diabetes
Lixisenatide (Lyxumia; Sanofi, France)	Subcutaneous once daily	2.6 h	2 h		10 µg for 2 wk, 20 µg (maximum dose)	Diabetes
Long-acting GLP-1 receptor agonist						
Exenatide (Bydureon BCise; AstraZeneca)	Subcutaneous once weekly		4–8 h	6–7 wk ²³	2 mg weekly	Diabetes
Liraglutide (Victoza, Saxenda; Novo Nordisk, Denmark)	Subcutaneous once daily	12.6–14.3 h	12 h	3 d ²⁴	0.6 mg for 1 wk, 1.2 mg for 1 wk, 1.8 mg (maximum dose)	Diabetes (Victoza) Obesity (Saxenda)
Dulaglutide (Trulicity; Eli Lilly, USA)	Subcutaneous once weekly	4.7–5.5 d	48 h	2–4 wk ²⁵	0.75 mg for 4 wk, 1.5 mg for 4 wk, 4.5 mg (maximum dose)	Diabetes
Semaglutide (Ozempic, Wegovy; Novo Nordisk)	Subcutaneous once weekly	5.7–6.7 d	24 h	4–5 wk	0.25 mg for 4 wk, 0.5 mg for 4 wk, 1 mg for 4 wk, 1.7 mg for 4 wk (Wegovy)	Diabetes (Ozempic) Obesity (Wegovy, Rybelsus)
Semaglutide (Rybelsus; Novo Nordisk)	Oral once daily	5.7–6.7 d	1–4 h		2.4 mg (Wegovy maximum dose); 2 mg (Ozempic maximum dose) 3 mg for 4 wk, 7 mg for 4 wk, 14 mg (maximum dose)	
Dual GLP-1/GIP receptor agonist						
Tirzepatide (Mounjaro, Zepbound; Eli Lilly)	Subcutaneous once weekly		8–72 h	4 wk	2.5 mg for 4 wk, escalate by 2.5 mg every 4 wk up to 15 mg (maximum dose)	Diabetes (Mounjaro) Obesity (Zepbound)

GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1.

Tirzepatide is a dual GLP-1 receptor agonist and glucose-dependent insulinotropic polypeptide (GIP) dosed weekly and approved for treatment of diabetes mellitus and obesity. The various GLP-1 receptor agonists and their pharmacologic properties are presented in table 1. Orforglipron, a daily oral GLP-1 receptor agonist, and retatrutide, a triple GLP-1, GIP, and glucagon receptor agonist administered subcutaneously, are in late phases of development.^{27–29}

Perioperative Considerations

General principles guiding perioperative medication management include a thoughtful assessment of the risks and benefits of continuing or discontinuing a medication based on the indication, pharmacokinetics, and potential interactions with anesthetic agents. In certain circumstances, the planned procedure and the anesthetic are important considerations. Medications are withheld perioperatively in select circumstances when risks are perceived to outweigh benefits and no alternative measures can mitigate the periprocedural risks.

Benefits versus Risks of Continuing GLP-1 Receptor Agonists

In patients with diabetes mellitus, GLP-1 receptor agonists reduce glycemia through multiple mechanisms such as

slowing gastric emptying, increasing pancreatic insulin secretion, decreasing glucagon release, and decreasing appetite.^{30,31} In the outpatient setting, cardiovascular outcome trials and meta-analyses demonstrate that GLP-1 receptor agonists reduce major adverse cardiovascular events, including acute myocardial infarction, stroke, and mortality in individuals with multiple cardiovascular risk factors and either type 2 diabetes or obesity.^{32–34} The American Diabetes Association (Arlington, Virginia) and the American Association of Clinical Endocrinology (Jacksonville, Florida) recommend GLP-1 receptor agonists as first-line drugs along with metformin for patients with type 2 diabetes with an established or high risk of atherosclerotic cardiovascular disease, stroke, transient ischemic attacks, or chronic kidney disease.^{35,36}

There are emerging data of the *benefits* of continuing GLP-1 receptor agonists during the perioperative period specifically in patients with diabetes mellitus.

- Studies in cardiac surgery show glycemia benefit of GLP-1 receptor agonists (liraglutide and exenatide) when compared to insulin, and delayed initiation and lower doses of insulin needed for glycemic control^{37–42} (table 2).
- Benefits of GLP-1 receptor agonist such as better glycemia control and fewer prosthetic joint infections have been described in patients having noncardiac surgeries. These effects are possibly explained by the

immunomodulatory and anti-inflammatory effects of GLP-1 receptor agonists^{43,44} (table 2).

- There is a lack of data on the benefits of continuing GLP-1 receptor agonists in patients with obesity, because all the studies to date have been performed in patients with diabetes mellitus.

The perioperative *risks* of continuing GLP-1 receptor agonists pertain to their propensity to delay gastric emptying, and concerns for perioperative aspiration of gastric contents. Self-reported symptomatology such as nausea and vomiting suggests delayed gastric emptying.⁴⁵ However, lack of symptoms correlate poorly with gastric emptying. Data show that even when patients report no symptoms, they can still have significantly altered gastric emptying times.⁴⁵ Evidence of delayed gastric emptying from GLP-1 receptor agonist comes from case reports and case series (table 3) and from outpatient gastric emptying studies (table 4).^{6–21,46–88}

A summary of studies and case reports of aspiration events and residual gastric contents assessed by ultrasonography or endoscopy is shown in table 3.

- It is notable that in these reports, the patients followed current recommendations for fasting (*i.e.*, 8 h fasting time for solids and 2 h for liquids).⁸⁹
- Although the number of aspiration events is small, the vast majority occurred in patients receiving monitored anesthesia care. In a retrospective database review of patients having esophagogastroduodenoscopy, the only two aspiration events occurred in patients receiving monitored anesthesia care, and aspiration rates were comparable to those seen in the general population of patients receiving anesthesia.¹⁹
- The risk of aspiration does not appear to be increased in patients having emergency surgeries who have not had time to stop their GLP-1 receptor agonist, which may be partly due to the use of rapid sequence induction and intubation.²⁰ Also, general endotracheal anesthesia seems to protect against the risk of aspiration.⁴⁸

While the risk of aspiration is present and should not be underappreciated, the evidence for delayed gastric emptying primarily comes from outpatient data. The data on gastric emptying in patients on GLP-1 receptor agonist are heterogeneous in nonprocedural and nonsurgical settings (table 4), and interpretation is nuanced.

- These data are mixed with respect to the method used to assess gastric emptying; the studied population, which included patients with obesity, diabetes, or healthy volunteers; the reported results; and perioperative relevance.
- The most accurate assessment of gastric emptying is the nuclear scintigraphic method, which evaluates solid food retention in the stomach. The gastric motility breath test is another infrequently used study to measure solid content transit times. However, few studies have assessed gastric emptying in patients taking GLP-1 receptor agonist

using these methods. A recent metaanalysis of studies looking at GLP-1 receptor agonist effects on gastric emptying reported prolonged times required for 50% of ingested gastric contents to leave the stomach. Patients taking GLP-1 receptor agonist had a time required for 50% of ingested gastric contents to leave the stomach of 138.4 min (95% CI, 74.5 to 202.3) *versus* 95.0 min (95% CI, 54.9 to 135.0) for the placebo group, with a pooled mean difference of 36.0 min ($P < 0.01$).⁸⁸ This evidence supports a delayed gastric emptying of solid foods being decreased in patients taking GLP-1 receptor agonists.

- The majority of studies have used an acetaminophen absorption test, which assesses gastric emptying of liquids rather than solids. Consequently, many experts consider data obtained from acetaminophen absorption studies inadequate to base clinical decisions for patients on GLP-1 receptor agonists.⁸⁸ A metaanalysis of 10 studies with 411 individuals using an acetaminophen test showed no significant delay in gastric emptying at 1, 4, and 5 h in patients taking GLP-1 receptor agonist.⁹⁰ These data point toward normal emptying of liquids in these patients.
- There is a difference between short- and long-acting drugs and their effects on gastric emptying. The plasma concentration of short-acting drugs peaks and decreases rapidly. This intermittent stimulation of the GLP-1 receptor may impact gastric emptying more than occurs with long-acting drugs, which continuously stimulate receptors, resulting in tachyphylaxis. It may take weeks to months for patients on short-acting medications to develop tachyphylaxis compared to 4 to 5 weeks for long-acting preparations.⁷³
- Data on tachyphylaxis for long-acting preparations are mixed as well, with some studies showing that even long-acting preparations (liraglutide, weekly semaglutide, long-acting exenatide) significantly delay gastric emptying.^{62,65,67} These data are corroborated by a metaanalysis reporting that the type of GLP-1 receptor agonist did not correlate with the gastric emptying effects regardless of the type of assessment (scintigraphy or acetaminophen absorption).⁹⁰
- Gastric emptying studies have not assessed effects beyond 4 to 6 h. The limited evidence from emptying studies using scintigraphy have detected a prolongation (138 *vs.* 95 min) of gastric emptying measured at 4 h, which is much less than the recommended fasting time for solids, but longer than that recommended for liquids.
- Gastric emptying effects are more pronounced in the first few weeks after initiating GLP-1 receptor agonists or escalating doses. During this time, gastric emptying for liquids can be prolonged as assessed by acetaminophen tests.^{13,87}

Overall, while the current gastric emptying studies may be difficult to interpret and extrapolate to the perioperative setting, the data point toward a prolonged

Table 2. Studies on Perioperative Benefit of GLP-1 Receptor Agonists

Reference	Type of Study	GLP-1 Receptor Agonist	Study Protocol	Results
Cardiac surgery				
Polderman ³⁷ 2018	Randomized controlled trial	Liraglutide	Liraglutide 0.6 mg subcutaneously the evening before procedures and 1.2 mg the day of the procedures vs. insulin by infusion or bolus.	<ul style="list-style-type: none"> • Mean plasma glucose concentrations 1 h postoperatively were significantly lower in the liraglutide group (6.6 mM) vs. the insulin infusion (7.5 mM; $P = 0.026$) and bolus groups (7.6 mM; $P = 0.006$) • No difference in the incidence of hypoglycemia and postoperative complications between groups
Hulst ³⁸ 2020	Randomized controlled trial	Liraglutide	Liraglutide 0.6 mg subcutaneously the evening before procedures and 1.2 mg after anesthesia induction in patients with low nausea scores vs. insulin protocol.	<ul style="list-style-type: none"> • Mean blood glucose concentrations, and dose and number of insulin injections, were lower in liraglutide group vs. insulin protocol group • No difference in the incidence of hypoglycemia, mortality, and postoperative complications between groups
Makino ³⁹ 2019	Randomized controlled trial	Liraglutide	Liraglutide 0.3 mg subcutaneously on days -2 and -1, and 0.6 postoperative days 1 to 10 in addition to insulin.	<ul style="list-style-type: none"> • Glucose concentrations closer to target range in the combination group vs. insulin-only group • Lower incidence of hypoglycemia in the liraglutide group
Lipš ⁴⁰ 2017	Randomized controlled trial	Exenatide	Exenatide or placebo, continuous 72-h IV infusion plus standard perioperative insulin therapy starting 12 h before surgery.	<ul style="list-style-type: none"> • Improved perioperative glucose control with exenatide, with average glucose 6.4 mM (exenatide) vs. 7.3 mM (placebo); $P < 0.001$ • Glucose concentration in the target range of 4.5 to 6.5 mM in the exenatide group 54.8% of the time vs. 38.6% in the control group ($P = 0.001$) • No difference in hypoglycemia risk between groups • Exenatide failed to show superior glycemia values in patients having coronary artery bypass grafting, but exenatide reduced overall consumption of and delayed time to initiation of insulin compared to controls
Besch ⁴¹ 2017	Randomized controlled trial	Exenatide	Exenatide infusion.	<ul style="list-style-type: none"> • Exenatide failed to show superior glycemia values in patients having coronary artery bypass grafting, but exenatide reduced overall consumption of and delayed time to initiation of insulin compared to controls
Noncardiac surgery				
Kaneko ⁴³ 2018	Randomized controlled trial	Liraglutide	Liraglutide 0.6 mg subcutaneously at least a week before procedures; dose doubled every 1 to 2 days if no reported gastrointestinal symptoms. Liraglutide reduced by 0.6 mg on the day of surgery and postoperative day 1, and then increased to the previous maximum on postoperative day 2.	<ul style="list-style-type: none"> • More stable glucose concentrations with liraglutide, fewer patients requiring additional insulin ($P = 0.005$), and a significant reduction of the insulin dosage on day of surgery ($P = 0.004$) in patients having orthopedic, thoracic, otolaryngological, urological, hepatic, gynecological, and breast surgeries
Magruder ⁴⁴ 2024	Observational	Semaglutide	Semaglutide vs. no GLP-1 receptor agonist.	<ul style="list-style-type: none"> • In patients with diabetes mellitus having primary hip arthroplasties, semaglutide had lower rates of readmissions within 90 days of surgery (6.2% vs. 8.8%; $P < 0.01$) and fewer prosthetic joint infections (1.6 vs. 2.9%; odds ratio, 0.56; $P < 0.01$) compared to patients with diabetes mellitus not on a GLP-1 receptor agonist

GLP-1, glucagon-like peptide-1; IV, intravenous.

gastric emptying time for solids. In addition, the presence of residual gastric contents directly observed *via* endoscopy in patients fasting for solids between 8 and 18 h provides irrefutable evidence that gastric emptying time for solids is affected, regardless of the duration of therapy or patients being in a maintenance phase.^{12,21} While effects on gastric emptying for solids are more pronounced with short-acting preparations and long-acting GLP-1 receptor agonists during therapy initiation or dose escalation, some studies show delays in gastric emptying even during the maintenance phase. Emptying time for liquids may not be as significantly impacted with long-acting preparations during steady state due to tachyphylaxis. However, liquid emptying remains slightly prolonged with short-acting preparations, and during start of therapy or dose escalation periods with long-acting GLP-1 receptor agonists.^{13,86}

Benefit versus Risks of Stopping GLP-1 Receptor Agonists

The potential *benefit* of stopping GLP-1 receptor agonists for only one pharmacologic half-life has come under scrutiny. There are several considerations that counter the benefit of stopping the GLP-1 receptor agonist, including the following:

- Pharmacokinetic data demonstrate that there is residual circulating drug after missing one dose of both short- and long-acting GLP-1 receptor agonists.
 - ◆ Pharmacokinetic modeling of liraglutide shows that at the end of one half-life of elimination, the blood concentration is higher in patients taking 1.8 mg compared to the peak concentration of liraglutide 0.6 mg²⁴ (fig. 1).
 - ◆ The simulated semaglutide concentration dosed at 1 mg showed that when missing one dose, there was

Table 3. Clinical Evidence of Decreased Gastric Emptying in Patients Taking GLP-1 Receptor Agonists

Author	GLP-1 Receptor Agonist (No. of Patients)	Study Type	Indication for GLP-1 Receptor Agonist	Procedure/ Anesthetic	Length of Fasting	Findings	Comments
Aspiration events or regurgitation of gastric contents							
Gulak and Murphy ⁶	Semaglutide	Case report	Obesity	Breast lumpectomy with general anesthesia	20 h (solids), 8 h (liquids)	Regurgitation of gastric contents upon standard induction	Semaglutide 0.5 mg for 5 mo, taken 2 days before surgery
Klein and Hobai ⁷	Semaglutide	Case report	Obesity	Upper endoscopy with monitored anesthesia care	18 h	Increased residual gastric contents before endotracheal intubation	Semaglutide started 2 mo before procedure, most recent dose 1.7 mg
Avraham <i>et al.</i> ⁹	Semaglutide (n = 2)	Case report	Obesity, type 2 diabetes	General anesthesia for endoscopic retrograde cholangiopancreatography and breast abscess	8–12 h	Regurgitation of gastric contents	Semaglutide 1 mg taken 4 and 6 days before procedure
Weber <i>et al.</i> ⁴⁶	Tirzepatide	Case report	Obesity	General anesthesia with supraglottic airway for hysteroscopy	“Appropriately fasted”	Regurgitation of gastric contents	Tirzepatide recently started
Yeo <i>et al.</i> ⁴⁷	GLP-1 receptor agonist users (n = 46,935) vs. nonusers (n = 916,249)	Retrospective database cohort	Type 2 diabetes, obesity	Upper endoscopies ± colonoscopies	Not reported	Increase in aspiration pneumonia in GLP-1 receptor agonist users vs. nonusers (hazard ratio, 1.33; P= 0.036)	-GLP-1 receptor agonist users defined as taking medication for more than 6 mo and two refills within 6 mo before procedures -Increased hazard ratio for propofol-assisted endoscopies (hazard ratio, 1.49; P=0.014) vs. no propofol (hazard ratio, 1.31; P= 0.310) GLP-1 receptor agonist users at increased risk with upper endoscopy (hazard ratio, 1.48; P=0.002) and combined upper and lower endoscopies (hazard ratio, 2.26; P= 0.007) but not lower endoscopy (hazard ratio, 0.56; P=0.160)
Anazco <i>et al.</i> ¹⁹	GLP-1 receptor agonist users (n = 4,134)	Retrospective	Type 2 diabetes, obesity	Upper endoscopies	Not reported	Two episodes of aspiration pneumonia, both with monitored anesthesia care	Rates of aspiration similar to historical cohort 4.6 per 10,000 vs. 4.8/10,000
Dixit <i>et al.</i> ²⁰	GLP-1 receptor agonist users (n = 3,502) vs. nonusers (n = 20,177)	Retrospective database	Type 2 diabetes	Emergency surgeries	Not reported	Aspiration events 3.5% in GLP-1 receptor agonist users vs. 4.0% in nonusers (adjusted odds ratio, 1.03; P= 0.80)	No increased aspiration with emergency surgeries
Klonoff <i>et al.</i> ⁴⁸	GLP-1 receptor agonist users (n = 2,256) vs. nonusers (n = 11,405)	Retrospective database, 1:1 matching cohorts	Type 2 diabetes	Surgeries with general endotracheal anesthesia	Not reported	GLP-1 receptor agonist users vs. nonusers had lower risk for postoperative decelerated gastric emptying outcomes (odds ratio, 0.81) and aspiration/pneumonitis (odds ratio, 0.78)	
Barlowe <i>et al.</i> ⁴⁹	274,211 upper endoscopies, 15,119 GLP-1 receptor agonist users, 14,407 DPP4 inhibitor users	Retrospective database	Type 2 diabetes	Upper endoscopy	Not reported	When comparing GLP-1 receptor agonist users to DPP4 inhibitor users, crude relative risks of aspiration (0.67), aspiration pneumonia (0.95), pneumonia (1.07), or respiratory failure (0.75) were not higher in patients prescribed GLP-1 receptor agonist	

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Table 3. (Continued)

Author	GLP-1 Receptor Agonist (No. of Patients)	Study Type	Indication for GLP-1 Receptor Agonist	Procedure/ Anesthetic	Length of Fasting	Findings	Comments
Residual gastric content by ultrasound or upper endoscopy							
Fujino <i>et al.</i> ⁸	Semaglutide	Case report	Obesity, type 2 diabetes	Upper endoscopy with monitored anesthesia care Second endoscopy	10 h 36 h (liquids only)	Residual gastric contents present after overnight fast No residual gastric contents	Semaglutide 0.25 mg started 1 mo before procedure Semaglutide 0.25 mg started 2 mo before procedure, last dose 7 days before procedure
Queiroz <i>et al.</i> ⁵⁰	Semaglutide	Case report	Obesity	Computer tomography	9 h (solids and liquids)	Solid gastric contents seen on computed tomography	Semaglutide 0.5 mg started 6 days before procedure
Hodgson <i>et al.</i> ⁵¹	Semaglutide	Case report	Type 2 diabetes	Gastric ultrasound	10 h	Residual gastric contents present after overnight fast	Semaglutide 2 mg 3 days before procedure
Kittner <i>et al.</i> ¹⁰	Semaglutide (n = 3)	Case series	Obesity, type 2 diabetes	Gastric ultrasound preinduction of general anesthesia	10 h	Residual gastric contents by gastric ultrasound after 10 h fast	Semaglutide taken 1–6 days before procedure
Stark <i>et al.</i> ¹¹	GLP-1 receptor agonist users (n = 59) vs. nonusers (n = 118)	Retrospective, single-center	Type 2 diabetes	Upper endoscopy	Not reported	Residual gastric contents in 4.6% of GLP-1 receptor agonist users and 1.7% in no GLP-1 receptor agonist users; <i>P</i> = 0.08	
Silveira <i>et al.</i> ¹²	Semaglutide (n = 33) vs. no semaglutide (n = 371)	Retrospective, single-center	Obesity, type 2 diabetes	Upper endoscopy	9 h for clear fluids and 14 h for solids	Residual gastric contents in semaglutide (24.2%) vs. non-semaglutide (5.1%) users; <i>P</i> < 0.001	Colonoscopy found to protect against residual gastric contents
Sherwin <i>et al.</i> ¹³	Semaglutide (n = 10) vs. no semaglutide (n = 10)	Prospective, single-center	Obesity	Gastric ultrasound	8 h	Residual gastric contents in semaglutide (70%) and no semaglutide (20%) users; <i>P</i> = 0.005	90% taking semaglutide < 8 wk
Kobori <i>et al.</i> ¹⁴	GLP-1 receptor agonist users (n = 205) vs. nonusers (n = 205)	Retrospective, single-center	Type 2 diabetes	Upper endoscopy	>12 h	Residual gastric contents in GLP-1 receptor agonist (5.4%) vs. no GLP-1 receptor agonist (0.49%) users; <i>P</i> = 0.004	Residual gastric contents with liraglutide once daily 1.8 mg (n = 2), dulaglutide 0.75 mg (n = 5), semaglutide 0.5 mg (n = 2), and semaglutide 1.0 mg (n = 2)
Nadeem <i>et al.</i> ¹⁵	GLP-1 receptor agonist users (n = 933) vs. nonusers (n = 34,261)	Retrospective, single-center	Obesity, type 2 diabetes	Upper endoscopy	Not reported	Residual gastric contents with GLP-1 receptor agonist 13.6% vs. no GLP-1 receptor agonist 2.3%; <i>P</i> < 0.0001 Aborted endoscopic gastroduodenoscopy 1.5% with GLP-1 receptor agonist vs. 0.3% if no GLP-1 receptor agonist; <i>P</i> < 0.0001	
Firkins <i>et al.</i> ¹⁶	GLP-1 receptor agonist users (n = 1,512)	Single-center, retrospective	Obesity, type 2 diabetes	Upper endoscopy ± colonoscopy	Not reported	Residual gastric contents in 9.4% of patients, mostly solids (7.4%)	Colonoscopy associated with reduced residual gastric contents (adjusted odds ratio, 0.34; <i>P</i> < 0.001)
Garza <i>et al.</i> ¹⁷	GLP-1 receptor agonist users (n = 306) vs. nonusers (n = 306)	Retrospective, case-control	Obesity, type 2 diabetes	Upper endoscopy ± colonoscopy	Not reported	Residual gastric contents with GLP-1 receptor agonist 14% vs. 4% for nonusers, (<i>P</i> < 0.01), especially in patients with type 2 diabetes (14% vs. 4%; <i>P</i> < 0.01), taking insulin (17% vs. 5%; <i>P</i> < 0.01), and with type 2 diabetes complications (15% vs. 2%; <i>P</i> < 0.01)	Less residual gastric contents after prolonged fasting and clear liquids for concurrent colonoscopy (2% vs. 11%; <i>P</i> < 0.01) and in patients with afternoon procedures (4% vs. 11%; <i>P</i> < 0.01)
Wu <i>et al.</i> ¹⁸	GLP-1 receptor agonist users (n = 90) vs. nonusers (n = 102)	Retrospective	Obesity, type 2 diabetes	Upper endoscopy	16 h in both groups	Residual gastric contents 19% in GLP-1 receptor agonist users vs. 5% in nonusers (adjusted odds ratio, 5.8; <i>P</i> = 0.004)	

(Continued)

Table 3. (Continued)

Author	GLP-1 Receptor Agonist (No. of Patients)	Study Type	Indication for GLP-1 Receptor Agonist	Procedure/ Anesthetic	Length of Fasting	Findings	Comments
Sen <i>et al.</i> ²¹	GLP-1 receptor agonist users (n = 62) vs. nonusers (n = 62)	Prospective, single-center	Obesity, type 2 diabetes	Ultrasound before induction of anesthesia	13–15 h for solids (both groups) 3–6 h for liquids (both groups)	Residual gastric contents 56% in GLP-1 receptor agonist users vs. 19% in nonusers	No association between duration of discontinuation and increased residual gastric contents (adjusted odds ratio, 0.86), risk elevated even after 7-days discontinuation No association between GLP-1 receptor agonist type and increased residual gastric contents
Chapman <i>et al.</i> ⁵²	GLP-1 receptor agonist users (n = 84) vs. nonusers (n = 84)	1:1 matched controlled	Obesity, type 2 diabetes	Upper endoscopy	> 10 h for solids > 2 h for liquids	Residual gastric contents in the GLP-1 receptor agonist group (13.1%) vs. nonusers (4.8%); adjusted odds ratio, 4.62 ($P = 0.025$)	Mostly monitored anesthesia care No aspiration events
Maselli <i>et al.</i> ⁵³	GLP-1 receptor agonist users (n = 57)	Retrospective	Obesity, type 2 diabetes	Upper endoscopy	> 24 h for solids > 12 h for liquids	No residual gastric contents, pulmonary aspiration, gastroesophageal regurgitation, or hypoxia	All patients continued GLP-1 receptor agonist

DPP4, dipeptidyl peptidase 4; GLP-1, glucagon like peptide-1.

a 48% decrease in minimum concentration expected before the next planned dose 7 days later. Delaying the dose 5 days causes minimum semaglutide concentrations to be 37% lower and the maximum concentration after the next dose to be 14% higher compared with the same subject at a normal weekly steady state. In both cases, the nadir of the semaglutide concentrations is higher than the mean concentration at steady state of a similar patient taking 0.5 mg weekly, and closer to regular steady state after 3 weeks⁹¹ (fig. 2).

- ◆ Similarly, if a dose of dulaglutide or tirzepatide is missed, there is residual circulating GLP-1 receptor agonist. Moreover, if a dose of dulaglutide is not taken within 3 days or if tirzepatide is held for 4 days, there are transient 20% higher concentrations after the subsequent doses of the GLP-1 receptor agonist^{25,92} (figs. 3 and 4).
- ◆ Package inserts advise skipping the missed dose and administering the GLP-1 receptor agonist on the regularly scheduled day if fewer than 3 days remain until the next dose for exenatide, dulaglutide, or tirzepatide, or fewer than 2 days for semaglutide.⁹³
- More importantly, clinical data confirm that even when a GLP-1 receptor agonist dose is omitted, some patients have residual gastric contents on the day of procedure while following standard fasting guidelines.⁸⁹

- ◆ A prospective study of 124 patients presenting for surgeries found ultrasonographic confirmation of increased gastric contents defined by the presence of solids, thick liquids, or more than 1.5 ml/kg clear liquids in patients taking GLP-1 receptor agonists. Interestingly, there was no association between the duration of drug interruption and the prevalence of increased gastric contents, including in some patients who had stopped their drugs more than 7 days before surgery.²¹
- ◆ Another study of 404 patients found no relationship between the interval interruption of semaglutide and the presence of residual gastric contents in patients having endoscopies. The interruption intervals of semaglutide in patients without retained gastric contents were 10 days (6 to 15) compared to 11 days (7.75 to 12.5) in those with delayed emptying ($P = 0.67$).¹²

Considerations of risks associated with stopping GLP-1 receptor agonists are the following:

- In patients with diabetes mellitus prescribed GLP-1 receptor agonists, no glycemic data are available on the effects of stopping GLP-1 receptor agonists. It is likely that glycemia control will deteriorate, especially in those with poor control, requiring multidrug regimens, taking insulin, or on high doses of antihyperglycemics. Moreover, acute hyperglycemia slows gastric emptying, so it is possible that this will negate the benefit of stopping the drugs.⁹⁴

Table 4. Studies Assessing Gastric Emptying in Patients on GLP-1 Receptor Agonists

Reference	Drug	Indication	Design	No. of Patients	Protocol Used	Test Used	Results
Gastric emptying for solids in patients taking short-acting GLP-1 receptor agonists							
Acosta <i>et al.</i> 2015 ⁵⁴	Exenatide	Obesity	Randomized controlled trial, double-blinded, single-center	20	Exenatide 5 µg subcutaneously twice daily vs. placebo for 30 d	Nuclear scintigraphy (solid meal)	Delayed gastric emptying at 30 days in exenatide group compared to placebo. T _{1/2} was 187 min with exenatide vs. 86 min with placebo (<i>P</i> < 0.001).
Linnebjerg <i>et al.</i> 2008 ⁵⁵	Exenatide	Type 2 diabetes	Randomized controlled trial, single-blinded	17	Exenatide 5 µg, exenatide 10 µg, or placebo for 5 d	Nuclear scintigraphy (solid meal)	After 5 d, T _{1/2} of solids was 60 min for placebo, 111 min for exenatide 5 µg, and 169 min for exenatide 10 µg (both vs. placebo; <i>P</i> < 0.01). Delayed gastric emptying for both doses of exenatide.
Kuwata <i>et al.</i> 2021 ⁵⁶	Dulaglutide Liraglutide Lixisenatide	Type 2 diabetes	Single-arm, prospective, observational	18	Lixisenatide 10 µg subcutaneously daily week 1, 15 µg daily week 2, and 20 µg on the day of the meal test at week 2 and thereafter up to 12 wk Liraglutide 0.3 mg daily in week 1, 0.6 mg in week 2, and 0.9 mg on the day of the meal test in week 2 and thereafter up to 12 wk Dulaglutide 0.75 mg weekly for 12 wk	¹³ C-acetate breath test	T _{1/2} extended by lixisenatide, at weeks 2 and 12 (<i>P</i> < 0.05).
Quast <i>et al.</i> 2020 ⁵⁷	Liraglutide Lixisenatide	Type 2 diabetes	Randomized, bicentric, investigator-blinded, parallel-group study	57	Lixisenatide 10 µg subcutaneously daily for 1 wk, followed by 20 µg subcutaneously for 9 wk Liraglutide 0.6 mg once daily for week 1, 1.2 mg once daily for week 2, followed by 1.8 mg once daily for 8 wk	¹³ C-sodium octanoate breath test	At 10 wk, T _{1/2} was delayed by 52 min with lixisenatide (<i>P</i> = 0.0065) compared to baseline.
Lorenz <i>et al.</i> 2013 ⁵⁸	Lixisenatide	Type 2 diabetes	Randomized controlled trial, double-blinded, parallel-group study	43	Lixisenatide 5 µg subcutaneously and increased by 2.5 µg every 5 days to maximum of 20 µg daily vs. placebo for 8 wk	¹³ C-octanoic acid breath test	T _{1/2} from baseline to day 28 was 211.5 min (delayed) for lixisenatide vs. - 24.1 min for placebo (<i>P</i> = 0.0031).
Meier <i>et al.</i> 2020 ⁵⁹	Lixisenatide	Type 2 diabetes	Randomized controlled trial, open-label with two treatment regimens (4 wk of monotherapy with either lixisenatide or glargine insulin and another 4 wk of combination therapy with both medications)	20	Lixisenatide 10 µg (30 min before breakfast) initially, and after 2 wk increased to 20 µg if tolerated Glargine insulin at bedtime titrated to achieve glucose concentrations 4.4–5.6 mM	¹³ C-octanoic acid breath test	T _{1/2} of test prolonged to 187 min for lixisenatide + glargine insulin (<i>P</i> < 0.001) and 168 min for lixisenatide alone (<i>P</i> = 0.002) vs. 87 min at baseline.
Meier <i>et al.</i> 2015 ⁶⁰	Liraglutide Lixisenatide	Type 2 diabetes	Randomized controlled trial, open-label, multicenter	94	Lixisenatide 20 µg subcutaneously daily, liraglutide 1.2 mg subcutaneously or 1.8 mg daily combined with glargine insulin for 8 wk	¹³ C-sodium octanoate breath test	Gastric emptying delayed at 8 wk. T _{1/2} was 537 min for lixisenatide vs. 169 min at baseline (<i>P</i> < 0.001).
Gastric emptying for solids in patients taking long-acting GLP-1 receptor agonists							
Jones <i>et al.</i> 2020 ⁶¹	Exenatide weekly	Obesity	Randomized controlled trial	32	Exenatide 2 mg weekly or placebo for 8 wk	Nuclear scintigraphy (solid meal)	After 8 wk, there was increased retention at 100 min with exenatide vs. placebo (52% vs. 36%; <i>P</i> < 0.02).

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Table 4. (Continued)

Reference	Drug	Indication	Design	No. of Patients	Protocol Used	Test Used	Results
Maselli <i>et al.</i> 2022 ⁶²	Liraglutide	Obesity	Randomized controlled trial	130	Liraglutide 0.6 mg daily, escalated by 0.6 daily every week to 3 mg subcutaneously daily for a total of 16 wk	Nuclear scintigraphy (solid meal)	T _{1/2} increased with liraglutide at 5 and 16 wk (both <i>P</i> < 0.001) vs. placebo and increased fasting gastric volume (<i>P</i> = 0.01) at 16 wk.
Quast <i>et al.</i> 2020 ⁵⁷	Liraglutide Lixisenatide	Type 2 diabetes	Randomized, bicentric, investigator-blinded, parallel-group study	57	Lixisenatide 10 µg subcutaneously daily for 1 wk, followed by 20 µg subcutaneously for 9 wk Liraglutide 0.6 mg once daily for week 1, 1.2 mg once daily for week 2, followed by 1.8 mg once daily for 8 wk	¹³ C-sodium octanoate breath test	At 10 wk, T _{1/2} was increased by 25 min with liraglutide (<i>P</i> = 0.025) compared to baseline.
Kuwata <i>et al.</i> 2021 ⁵⁶	Dulaglutide Liraglutide Lixisenatide	Type 2 diabetes	Single-arm, prospective, observational	18	Lixisenatide 10 µg subcutaneously daily week 1, 15 µg daily week 2, and 20 µg on the day of the meal test at week 2 and thereafter up to 12 wk Liraglutide 0.3 mg daily in week 1, 0.6 mg week 2, and 0.9 mg on the day of the meal test week 2 and thereafter up to 12 wk Dulaglutide 0.75 mg weekly for 12 wk	¹³ C-acetate breath test	T _{1/2} nonsignificantly increased by liraglutide at 2 wk and largely unaffected by liraglutide and dulaglutide at 2 and 12 wk.
Meier <i>et al.</i> 2015 ⁶⁰	Liraglutide Lixisenatide	Type 2 diabetes	Randomized controlled trial, open-label, multicenter	94	Lixisenatide 20 µg subcutaneously daily, liraglutide 1.2 mg or 1.8 mg subcutaneously daily combined with glargine insulin for 8 wk	¹³ C-sodium octanoate breath test	Gastric emptying delayed at 8 wk with liraglutide. T _{1/2} was 259 min for 1.2 mg liraglutide and 209 min for 1.8 mg liraglutide vs. 164 min at baseline (<i>P</i> < 0.001).
Nagai <i>et al.</i> 2014 ⁶³	Liraglutide	Type 2 diabetes	Prospective	16	Liraglutide initiated at 0.3 mg daily, and increased by 0.3 mg every 3 days to maximum 0.9 mg for 7 d	¹³ C-acetate breath test	T _{1/2} after liraglutide increased by 31 ± 4 min vs. baseline (<i>P</i> < 0.01) in some patients (delayers) compared to 2 ± 3 min vs. baseline (<i>P</i> = 0.60) in others (nondelayers).
Halawi <i>et al.</i> 2017 ⁶⁴	Liraglutide	Obesity	Randomized controlled trial, double-blinded, single-center	21	Liraglutide titrated by 0.6 mg/wk for 5 wk to 3.0 mg subcutaneously daily, continued until week 16 or placebo	Nuclear scintigraphy (solid meal)	Gastric emptying of solids from baseline to 5 wk more delayed with liraglutide (median 70 min) vs. placebo (median 4 min; <i>P</i> < 0.0001). Gastric emptying of solids T _{1/2} change from baseline to 16 wk delayed with liraglutide (median 30.5 min) vs. placebo (median -1 min; <i>P</i> = 0.025).
Nakatani <i>et al.</i> 2017 ⁶⁵	Liraglutide	Type 2 diabetes	Single-center, observational	14	Liraglutide 0.3 mg subcutaneously daily for a week, 0.6 mg daily for a week, and 0.9 mg daily for 2 wk	Transit time of capsule endoscopy	Gastric transit time (n = 14) 1:11:53 ± 1:03:17 h at baseline and 1:45:46 ± 1:40:46 h after liraglutide 1 wk after final dose of 0.9 mg (<i>P</i> = 0.16). Patients without diabetic neuropathy (n = 7) had gastric transit of 1:01:30 ± 0:52:59 h at baseline and 2:33:29 ± 1:37:24 h after liraglutide (<i>P</i> = 0.03). Patients with diabetic neuropathy (n = 7) had gastric transit of 1:12:36 ± 1:04:30 h at baseline and 0:48:40 ± 0:32:52 h after liraglutide (<i>P</i> = 0.19).

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Table 4. (Continued)

Reference	Drug	Indication	Design	No. of Patients	Protocol Used	Test Used	Results
Jensterle <i>et al.</i> 2023 ⁶⁶	Semaglutide	Obesity	Single-blinded, placebo-controlled	20	Semaglutide 1.0 mg subcutaneously weekly or placebo for 12 wk	Nuclear scintigraphy (solid food)	Gastric contents increased 3.5% at 1 h, 25.5% at 2 h, 38.0% at 3 h, and 30.0% at 4 h with semaglutide. Four hours after ingestion, 37% of solids retained with semaglutide vs. placebo ($P = 0.002$). $T_{1/2}$ significantly increased with semaglutide vs. placebo (171 vs. 118 min; $P < 0.001$).
Gastric emptying for liquids in patients taking short-acting GLP-1 receptor agonists							
Cervera <i>et al.</i> 2008 ⁶⁷	Exenatide	Type 2 diabetes, obesity	Single-center, placebo-controlled	12	Exenatide IV (0.05 µg/min 15 min before meals, decreased to 0.025 µg/min 45 min after meals) vs. placebo, treatment repeated three times, 2–4 wk apart	Acetaminophen (with solid meal)	Delay in gastric emptying after 6 h with exenatide reflected by a 58% decrease in mean plasma acetaminophen concentration ($P < 0.001$) vs. placebo.
DeFronzo <i>et al.</i> 2008 ⁶⁸	Exenatide	Type 2 diabetes	Randomized controlled trial, double-blinded, crossover, multicenter	95	Exenatide 5 µg twice daily for 1 wk, then 10 µg twice daily for 1 wk or sitagliptin daily for 2 wk	Acetaminophen (with solid meal)	After 2 wk, delayed gastric emptying with exenatide vs. sitagliptin ($P < 0.0001$), measured up to 4 h.
Drucker <i>et al.</i> 2008 ⁶⁹	Exenatide	Type 2 diabetes, obesity	Randomized, open-label	50	Exenatide 2.0 mg subcutaneously weekly in 26 patients or subcutaneously twice daily or exenatide 5 µg subcutaneously twice daily, titrated to 10 µg twice daily after 28 d in 24 patients for 14 wk	Acetaminophen (with solid meal)	Gastric emptying at week 14 delayed compared to baseline with exenatide twice daily measured up to 5 h.
Kolterman <i>et al.</i> 2005 ⁷⁰	Exenatide	Type 2 diabetes	Randomized controlled trial, single-blinded, placebo-controlled	8	Exenatide daily: 0.02 µg/kg, 0.05 µg/kg, and 0.10 µg/kg or placebo on 4 consecutive days	Acetaminophen (liquid meal)	Dose-dependent slowing of gastric emptying compared to placebo ($P = 0.0011$), measured up to 2 h.
Juel <i>et al.</i> 2020 ⁷¹	Lixisenatide	Status post pancreatic resection	Randomized controlled trial, double-blinded, crossover study	24	Lixisenatide 20 µg subcutaneously or placebo, one single dose	Acetaminophen (liquid meal)	Lixisenatide reduced gastric emptying vs. placebo in both the totally pancreatectomized ($P < 0.001$) and the controls ($P < 0.001$).
Becker <i>et al.</i> 2015 ⁷²	Lixisenatide	Healthy	Randomized controlled trial, open-label, crossover, single-center	20	Lixisenatide 2.5, 5, 10, or 20 µg subcutaneously for one dose with 2–7-d washout period	Acetaminophen (liquid meal)	Gastric emptying at 1 h delayed at doses >5 µg ($P < 0.05$).
Jones <i>et al.</i> 2019 ⁷³	Lixisenatide	Healthy, type 2 diabetes	Randomized controlled trial, double-blinded, crossover study	30	Lixisenatide 10 µg subcutaneously or placebo on 2 separate days	Nuclear scintigraphy (25% glucose drink)	Delayed gastric emptying at 3 h in both healthy subjects and subjects with type 2 diabetes with lixisenatide compared to placebo.
Jalleh <i>et al.</i> 2020 ⁷⁴	Lixisenatide	Healthy, type 2 diabetes	Randomized controlled trial, double-blind, placebo-controlled, crossover design	30	Lixisenatide 10 µg subcutaneously or placebo on 2 separate days	Nuclear scintigraphy (25% glucose drink)	Proximal stomach retention in healthy group at 3 h was 6.6% with placebo vs. 40.9% with lixisenatide ($P < 0.001$) and in the type 2 diabetes group was 6.3% with placebo vs. 34.8% with lixisenatide ($P < 0.001$). Distal stomach retention at 3 h in healthy group was 9.4% with placebo vs. 18.6% with lixisenatide ($P < 0.001$) and in type 2 diabetes was 8.2% with placebo vs. 19.6% with lixisenatide ($P < 0.001$).

(Continued)

Table 4. (Continued)

Reference	Drug	Indication	Design	No. of Patients	Protocol Used	Test Used	Results
Rayner <i>et al.</i> 2020 ⁷⁵	Lixisenatide	Type 2 diabetes	Randomized controlled trial	30	Lixisenatide 20 µg subcutaneously daily or placebo for 8 wk	Nuclear scintigraphy (25% glucose drink)	Delayed gastric emptying at 2 h and 4 h with lixisenatide at 8 wk vs. placebo ($P < 0.001$).
Kovoor <i>et al.</i> 2024 ⁷⁶	Lixisenatide	Type 2 diabetes	Randomized controlled trial	30	Lixisenatide 20 µg subcutaneously daily or placebo for 8 wk	Nuclear scintigraphy (25% glucose drink)	Delayed gastric emptying at 4 h with lixisenatide at 8 wk vs. placebo ($P < 0.0001$).
Gastric emptying for liquids in patients taking long-acting GLP-1 receptor agonists							
Jones <i>et al.</i> 2020 ⁶¹	Exenatide weekly	Obesity	Randomized controlled trial	32	Exenatide 2 mg weekly or placebo for 8 wk	Nuclear scintigraphy (radiolabeled glucose with solid meal)	After 8 wk, exenatide slowed gastric emptying of liquids ($P = 0.01$) measured up to 2 h.
Drucker <i>et al.</i> 2008 ⁶⁹	Exenatide weekly	DM, obesity	Randomized, open-label	50	Exenatide 2.0 mg subcutaneously weekly in 26 patients or subcutaneously twice daily or exenatide 5 µg subcutaneously twice daily, titrated to 10 µg twice daily after 28 d in 24 patients for 14 wk	Acetaminophen (with solid meal)	Gastric emptying at week 14 not delayed with weekly dosing when compared to baseline, suggesting tachyphylaxis, measured up to 5 h.
Barrington <i>et al.</i> 2011 ⁷⁷	Dulaglutide	Type 2 diabetes	Randomized controlled trial, double-blinded, multicenter	43	Weekly placebo vs. dulaglutide subcutaneously 0.05 mg (n = 3), 0.3 mg (n = 6), 1 mg (n = 5), 3 mg (n = 3), 5 mg (n = 9), or 8 mg for 5 wk	Acetaminophen (with solid meal)	Significant delay in gastric emptying with 5 mg dose after recent start of dulaglutide.
Degn <i>et al.</i> 2004 ⁷⁸	Liraglutide	Type 2 diabetes, obesity	Randomized controlled trial, double-blinded, crossover	13	Liraglutide 6 µg/kg subcutaneously or placebo for 9 days	Acetaminophen (with solid meal)	After 8 days, no change in gastric emptying with liraglutide vs. placebo measured up to 2 h.
Dejgaard <i>et al.</i> 2016 ⁷⁹	Liraglutide	Obesity, type 1 diabetes	Randomized controlled trial	10	Liraglutide 0.6 mg subcutaneously daily, increased to 1.2 mg subcutaneously daily after 1 wk, then to 1.8 mg daily after 1 wk or placebo for 3 wk	Acetaminophen (with liquid meal)	Gastric emptying delayed after 3 wk of liraglutide (19.9 min; $P = 0.0412$), but no difference after 24 wk of treatment (−1.5 min; $P = 0.8793$).
Flint <i>et al.</i> 2011 ⁸⁰	Liraglutide	Type 2 diabetes	Randomized controlled trial, double-blinded, single-center	18	Liraglutide 0.6 mg subcutaneously daily, increased to 1.2 mg subcutaneously daily after 1 wk, then to 1.8 mg daily after 1 wk or placebo for 3 wk	Acetaminophen (with solid meal)	Gastric emptying delayed with 1.2 mg dose ($P < 0.001$) but not significant for 0.6 mg or 1.8 mg, measured greater than 5 h vs. placebo at end of each dosing change. Gastric emptying delayed in the first hour, with 1.2 mg ($P < 0.001$) and 1.8 mg ($P = 0.028$).
Horowitz <i>et al.</i> 2012 ⁸¹	Liraglutide	Type 2 diabetes	Randomized controlled trial, double-blinded, incomplete crossover, two centers	46	Participants randomized to two of three arms for 4 wk, with a 3-wk washout; liraglutide followed by placebo, placebo followed by glimepiride, glimepiride followed by liraglutide Liraglutide started at 0.6 mg subcutaneously daily, escalated by 0.6 mg increments weekly to a maximum dose of 1.8 mg daily, maintained for 2 wk; glimepiride started at 1 mg daily for 1 wk, then titrated to 2–4 mg daily per renal function	Acetaminophen (with liquid meal)	At end of 4 wk gastric emptying delayed in liraglutide compared to control groups. ($P < 0.001$), measured at 1 h and 5 h. Acetaminophen maximum serum concentrations 20% lower with liraglutide vs. placebo and 15% lower with liraglutide than glimepiride ($P \leq 0.006$ for both).

(Continued)

Table 4. (Continued)

Reference	Drug	Indication	Design	No. of Patients	Protocol Used	Test Used	Results
van Can <i>et al.</i> 2014 ⁸²	Liraglutide	Obesity	Randomized controlled trial, single-center	49	Two randomly chosen treatment periods of 5 wk each, with 6–8 wk washouts Liraglutide 1.8 mg subcutaneously daily, liraglutide 3.0 mg subcutaneously daily, or placebo	Acetaminophen (with solid meal)	No difference in gastric emptying between either liraglutide doses and placebo, measured at 5 h at the end of each 5-wk period. Delayed gastric emptying from both liraglutide doses over the first hour: 23% less with liraglutide 3.0 mg vs. placebo ($P = 0.007$), 13% less with liraglutide 1.8 mg vs. placebo ($P = 0.14$).
Saxena <i>et al.</i> 2021 ⁸³	Liraglutide	Obesity	Randomized controlled trial	61	Liraglutide initiated at 0.6 mg subcutaneously daily and escalated by 0.6 mg/wk to a maximum of 3.0 mg/d or placebo for a total of 6 wk	Acetaminophen (with solid meal)	Delayed gastric emptying at 3 and 6 wk with liraglutide at 1 h ($P = 0.0348$) and 5 h ($P = 0.0152$).
Hjerpsted <i>et al.</i> 2018 ⁸⁴	Semaglutide	Obesity	Randomized controlled trial, double-blinded, two-period, crossover	30	Semaglutide 0.25 mg subcutaneously weekly for 4 wk, 0.5 mg weekly for 4 wk, then 1.0 mg weekly for 4 wk or placebo	Acetaminophen (solid meal)	Gastric emptying delayed in first hour with semaglutide at 12 wk. No differences in gastric emptying at 5 h for semaglutide vs. placebo.
Dahl <i>et al.</i> 2021 ⁸⁵	Semaglutide oral	Type 2 diabetes	Randomized, double-blinded, single-center	15	Semaglutide daily orally, at 3 mg daily for 4 wk, then 7 mg daily for 4 wk, and then 14 mg daily for 4 wk followed by placebo after 4–9 wash-out weeks, or <i>vice versa</i> , during two consecutive 12-wk periods	Acetaminophen (solid meal)	Gastric emptying delayed by 31% with semaglutide vs. placebo during first postprandial hour, but not significantly different at 5 h.
Friedrichsen <i>et al.</i> 2021 ⁸⁶	Semaglutide	Obesity	Randomized controlled trial	72	Semaglutide subcutaneously 0.25 mg weekly for 4 wk, escalated to 0.5 weekly for 4 wk, 1 mg weekly for 4 wk, 1.7 mg weekly for 4 wk, and 2.4 mg weekly for 5 wk or placebo for 20 wk	Acetaminophen (solid meal)	Gastric emptying not delayed with semaglutide 2.4 mg vs. placebo at week 20 ($P = 0.12$).
Urva <i>et al.</i> 2020 ⁸⁷	Tirzepatide	Healthy, type 2 diabetes	Investigator-blinded, three parts: single-ascending dose and 4-wk multiple-ascending doses in healthy participants, followed by a 4-wk multiple-doses phase 1b proof of concept in participants with type 2 diabetes	86 (n = 33 healthy, n = 53 with type 2 diabetes)	Tirzepatide 0.5 mg, 1.5 mg, 4.5 mg, 5 mg, 10 mg, or 15 mg subcutaneously weekly (4 wk per dose)	Acetaminophen (solid meal)	Gastric emptying delayed with tirzepatide ≥ 4.5 and ≥ 5 mg after a single dose. Effect diminished after multiple doses of tirzepatide in healthy group. Gastric emptying delayed after multiple doses with escalation of tirzepatide 5/5/10/10 or 5/5/10/15 mg in type 2 diabetes group.

Adapted with permission from Maselli and Camilleri, *Adv Exp Med Biol* 2021; 1307:171–92.⁸⁸
GLP-1, glucagon-like peptide-1; IV, intravenous; $T_{1/2}$, time to half gastric emptying.

- Patients taking high doses of GLP-1 receptor agonists (more common in obese patients, but also in patients with diabetes) and those experiencing severe symptoms at initiation or during escalation of treatment are at high risk of adverse gastrointestinal effects when doses are missed and then restarted.⁹³ These patients often need to be started on a lower dose of drug to mitigate side effects. However, this is logistically difficult since some

of these medications (*e.g.*, tirzepatide, dulaglutide) are packaged in prefilled syringes, and patients are provided with precise doses monthly. In contrast, semaglutide pens allow adjustment of doses.⁹³

Both pharmacokinetic and clinical data indicate that short interruptions of long-acting GLP-1 receptor agonist (*i.e.*, one half-life) are not sufficient to ensure complete

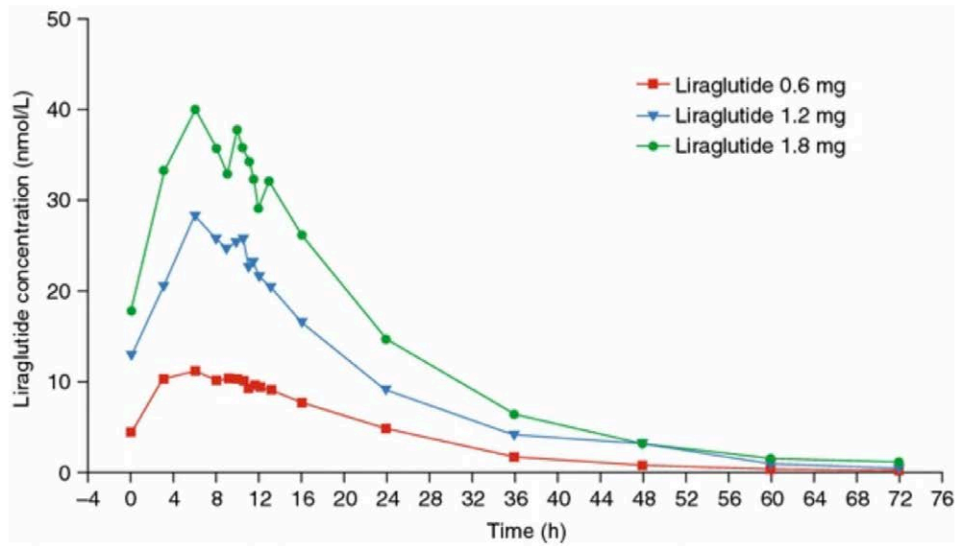


Fig. 1. Steady-state concentration-time curve of liraglutide after last dose (day 21). From Jacobsen *et al.* Clin Pharmacokinet 2016; 55:657–72.²⁴

clearance of the drug. While no data are available on gastric emptying from residual GLP-1 receptor agonist concentrations, it is likely that there is no complete dissipation of the effect. The longer duration of interruption needed (*i.e.*, 4 or 5 half-lives) is impractical, potentially harmful, and not patient-centric.

Moreover, there are data suggesting safety of continuation of GLP-1 receptor agonists perioperatively. A study in patients having endoscopy while continuing their medications and following a modified fasting regimen reported no increased gastric volumes and no aspiration events.⁵³

Symptomatic patients describing severe gastrointestinal symptoms may represent a special category where the medication regimen can be interrupted or dose de-escalated. However, even in these patients, current guidelines recommend dietary interventions such as small frequent meals and consumption of bland foods as a first-line intervention.^{95,96} Medication adjustments are recommended only when symptoms do not resolve.^{95,96}

Role of Fasting

Current guidance suggests that the standard fasting time is sufficient to mitigate aspiration risk in patients taking GLP-1 receptor agonists.²² However, this approach is questionable based on clinical data (table 3).

Considerations for *solid* fasting times are the following:

- Many patients found to have residual gastric contents on the day of their procedures have observed the standard ASA fasting times.^{12,21} In these studies, despite

interrupting GLP-1 receptor agonist for more than 7 days, patients had retained gastric contents.^{12,21}

- Data from a case control study showed lower rates of persistent stomach contents in patients having afternoon procedures with prolonged fasting compared to those having procedures in the morning (4% *vs.* 11%; $P < 0.01$).¹⁷
- Several studies reveal that patients having colonoscopies (with or without upper endoscopies) have a lower incidence of retained gastric contents.^{12,16,17,47} This is most likely due to the fact that patients having colonoscopies typically follow a clear liquid diet the day before the procedure, and less likely due to the concurrent bowel preparation.⁹⁷

The evidence suggests that an extended fasting time for solids should be recommended for patients taking GLP-1 receptor agonists. Perhaps the best data in support of this approach come from a study of 57 patients having endoscopies where GLP-1 receptor agonists were not stopped. All of the patients followed a liquid diet for 24 h or more and were *nil per os* (nothing by mouth; NPO) for more than 12 h before their endoscopies. No patients had detectable residual gastric contents determined by endoscopy, and no aspiration events occurred.⁵³ Overall, there is clear evidence of delayed gastric emptying for solids irrespective of the type of GLP 1 receptor agonist preparation or duration of treatment, suggesting that a clear liquid diet for 24 h or more may be necessary for these patients.

At this time, the best duration of fasting from *liquids* is unclear because data are scarce and heterogeneous.

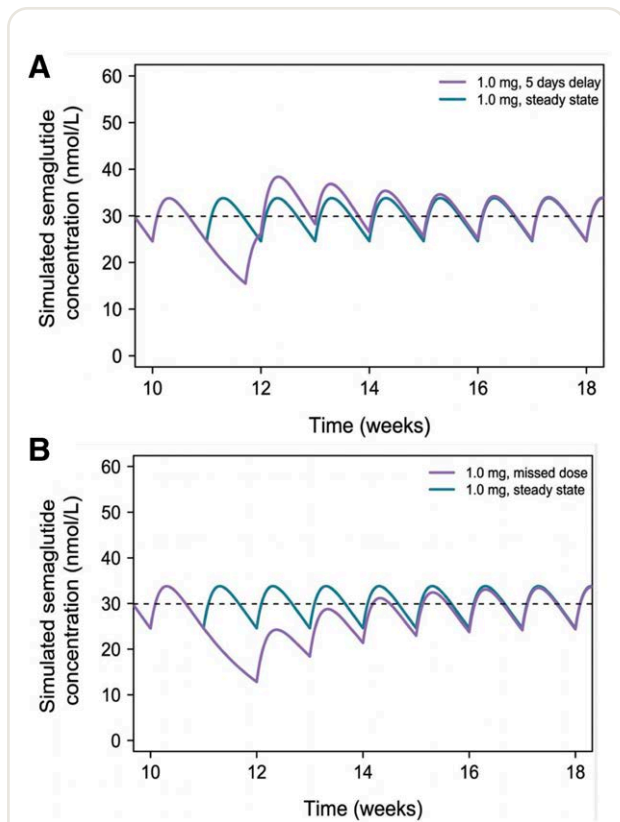


Fig. 2. Simulated semaglutide concentration profiles after missed or delayed doses. Data are simulated concentrations during once-weekly dosing at steady state concentrations with one missed dose at week 11 (A) and for a dose with a delay of 5 days at week 11 (B) compared with a steady state profile for semaglutide dosed at weekly intervals. Simulations are for a reference subject profile (non-Hispanic or Latino, white female, 65 yr, with a body weight of 85 kg, with normal renal function, and dosed in the abdomen with semaglutide 1.0 mg). From Carlsson Petri *et al.* *Diabetes Ther* 2018; 9:1533–47.⁹¹

- Various liquids empty from the stomach at different rates. High-caloric liquids (those containing fat or greater than 10% glucose) empty more slowly than water or low caloric clear liquids (10% glucose or less) in patients with normal gastric emptying.⁹⁸
- Patients on short-acting preparations have delayed gastric emptying for liquids after weeks of treatments. Significant liquid intragastric content has been described at 4 h after 8 weeks of treatment with lixisenatide with consumption of high-caloric glucose-containing liquids.^{73–76}
- In individual studies, patients on long-acting preparations in a maintenance phase at least 4 weeks from initiation seem to have slightly prolonged delays in gastric emptying for liquids in the first 1 to 2 h that normalize by 5 h.^{84–86} However, in the majority of these studies, acetaminophen elixir was given after a solid meal, which likely confounds the data and may overestimate the delay (table 4).

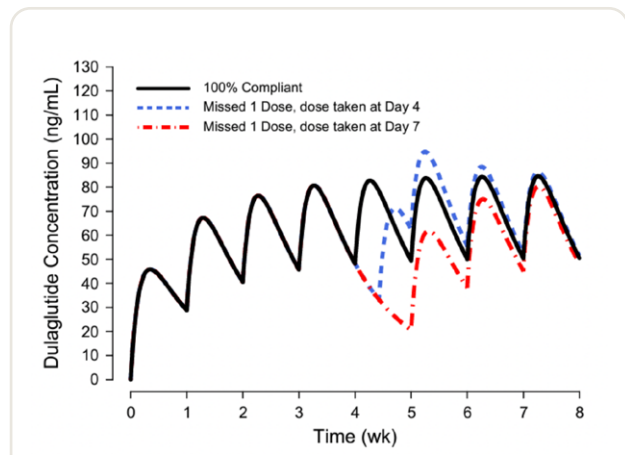


Fig. 3. Effects of missed doses on concentration–time profiles of dulaglutide. The pharmacokinetic model simulated dulaglutide concentration–time profiles after a once-weekly dose of 1.5 mg taken as prescribed (solid black line), with a dose being missed at midweek (blue dashed line) or with a dose being skipped (red dotted–dashed line). From Geiser *et al.* *Clin Pharmacokinet* 2016;55:625–34.²⁵ Used with permission.

- Patients who recently started or dose-escalated long-acting GLP-1 receptor agonist within the previous 4 weeks do not exhibit tachyphylaxis and may need more prolonged NPO fasting times. A study of 20 patients detected that 30% of the semaglutide group (most of whom had been on therapy for less than 4 weeks) compared to 90% of the controls were considered to have empty stomachs 2 h after drinking 12 oz of clear liquids in a supine position.¹³ These findings corroborate other data on gastric emptying assessed by acetaminophen absorption.⁸⁷
- A recently published meta-analysis did not show any significant delay in gastric emptying for liquids regardless of the GLP-1 receptor agonist. However, it did not include all of the studies, and there was heterogeneity in the reported measurements and in the nature of the meals coadministered with the acetaminophen.⁹⁰

There are concerns that prolonged fasting for liquids is not patient friendly and counters the principles of enhanced recovery. High-caloric carbohydrate drinks have been shown to empty slower than water even in patients not taking GLP-1 receptor agonists. They are generally not recommended in patients with diabetes where the risks of hyperglycemia may outweigh their benefits.⁹⁹ They may be restricted for longer than 4 h in patients on GLP-1 receptor agonists for obesity, because their emptying is particularly delayed, especially by short-acting GLP-1 receptor agonist.^{73–76}

Extended restriction periods for other non- or low-caloric clear liquids may not be advantageous or necessary for the majority of patients on maintenance doses of long-acting GLP-1 receptor agonists for more than 4 weeks.

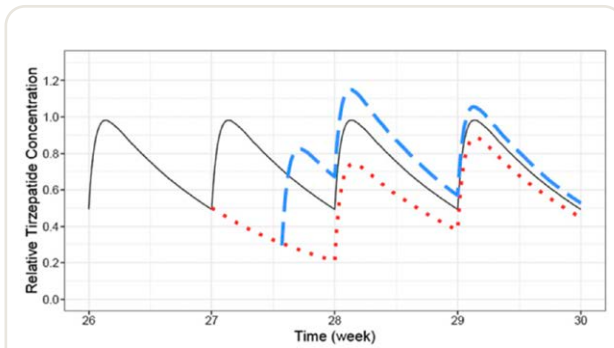


Fig. 4. Effects of delayed or missed dose on the steady-state concentration–time profile of tirzepatide. The pharmacokinetic model simulated tirzepatide concentration–time profiles after a once-weekly dose taken as prescribed (solid black line), with a dose being delayed until midweek (blue dashed line) or with a dose being skipped (red dotted line). From Schneck *et al.* CPT Pharmacometrics Syst Pharmacol 2024;13:494–503.⁹² Used with permission.

However, not all patients exhibit tachyphylaxis.⁶¹ The evidence suggests fasting for non- or low-caloric clear liquids for longer than current recommendations is necessary for patients taking long-acting preparations during initiation and dose escalation periods, and those on short-acting GLP-1 receptor agonists.

Role of Gastric Ultrasonography

Point-of-care gastric ultrasonography has been used to identify patients taking GLP-1 receptor agonists who have residual gastric content preoperatively.^{10,13,21,51,99,100,101} Training and achieving proficiency in gastric ultrasonography followed by wide adoption among anesthesiology clinicians will take some time. Most importantly, gastric ultrasonography only identifies those with retained gastric contents after they arrive for their procedures. It does not allow for timely interventions to avoid the risk of perioperative aspiration other than a change in the planned anesthetic or postponement of the procedure. A better approach is needed to ensure a majority of patients taking GLP-1 receptor agonists present without retained gastric contents preoperatively and can avoid unnecessary anesthesia procedures such as rapid sequence induction and intubation, or aspiration on emergence from anesthesia. Gastric ultrasonography may be best suited for patients who are symptomatic or are asymptomatic without having observed prolonged fasting times.

Summary

Emerging data point to the limitations of the current ASA consensus-based guidance for patients taking GLP-1 receptor agonists. It is becoming more obvious that interrupting GLP-1 receptor agonists as currently suggested

may not offer much benefit, since a longer washout time is needed to resolve the effects on gastric emptying. Moreover, the current approach gives clinicians a false sense of security when proceeding with anesthesia, especially when a monitored anesthesia care or a standard general anesthesia induction technique is planned, as residual gastric contents may be present. Furthermore, the glycemia benefit and the perioperative effects of mitigating major adverse cardiovascular events may be lost with drug interruptions in patients with diabetes mellitus. Additionally, there is the possibility of renewed side effects when reinstating a high-dose GLP-1 receptor agonist, and de-escalating may not be feasible due to fixed-dose pre-filled pen preparations.

GLP-1 receptor agonists may need to be interrupted in patients who have recently started these medications or are in dose escalation phases, and have significant symptoms of fullness, nausea, and vomiting. Stopping the drugs or de-escalating doses, when possible, may be beneficial to decrease risks of aspiration in these patients who have not reached a steady state or developed tachyphylaxis to the gastrointestinal side effects. These patients may be referred to their prescribing physician for diet and medication modification before proceeding with elective procedures requiring anesthesia.

However, the first and most important intervention appears to be changing the duration of fasting for solids and possibly for liquids. Prolonged fasting time for solid foods beyond current recommendations is likely more effective than drug interruption to prevent patients from presenting on the day of procedures with residual gastric contents.⁵³ Data from the “real world” and gastric emptying studies support recommending a clear liquid diet for 24 h before anesthesia.⁵³ The fasting duration for liquids is unclear at this time, but it appears that patients who have recently started a long-acting GLP-1 receptor agonist or are in the dose escalation period and those on short-acting preparations may need a more prolonged NPO time than currently recommended. The caloric content of the liquids is important, with high-caloric clear liquids likely needing a longer fasting time than the low- or noncaloric clear liquids (8 h *vs.* 4 h). While these timeframes for liquids may appear arbitrary, data suggest that complete NPO times ranging between 4 and 12 h are more likely to result in lower gastric volumes, thus balancing the risks of aspiration with enhanced recovery principles.

Patients not tolerating the GLP-1 receptor agonist should be advised to follow a bland, low-fat, and low-fiber diet and to eat small meals. Medication changes (*i.e.*, dose de-escalation) are secondarily considered. Elective surgeries should be postponed in patients with significant symptoms refractory to these interventions. Patients who are planning dose escalation should be advised not to do so in the weeks leading up to elective procedures. Collaboration with the prescribing clinicians is important when making decisions.

Proceeding with the planned anesthetic appears safe for asymptomatic patients presenting for elective procedures who are in maintenance phases, and have followed clear liquid diets for 24h. For symptomatic patients or those who have not been on clear liquids for 24h, a gastric ultrasound may help guide decisions.

Since the publication of the ASA consensus-based guidance, a number of studies have been published on the gastric emptying effects of GLP-1 receptor agonists. Therefore, we propose updated recommendations for decision-making during the preoperative period and on the day of surgery (figs. 5 and 6).

Conclusions

Data on the perioperative management of patients taking GLP-1 receptor agonists are sparse, but emerging. There is heterogeneity as to the subjects studied (healthy controls, patients with obesity or diabetes) and the tests and measurements used, which may limit the ability to extrapolate findings across populations. Perioperative clinicians need to consider indications for medication, dosing schedule, concurrent symptoms, and the logistics of access to the medications in specific doses. Dietary recommendations, anesthetic

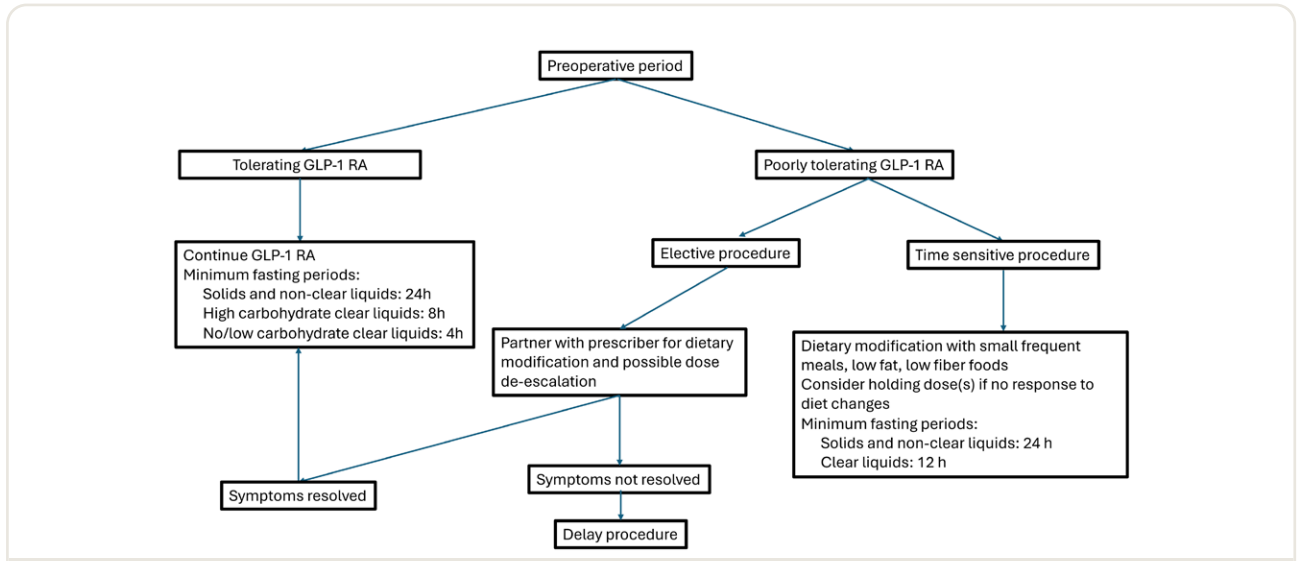


Fig. 5. Proposed recommendations for preoperative visit management of patients on glucagon-like peptide-1 (GLP-1) receptor agonists (RA; summary from current literature).

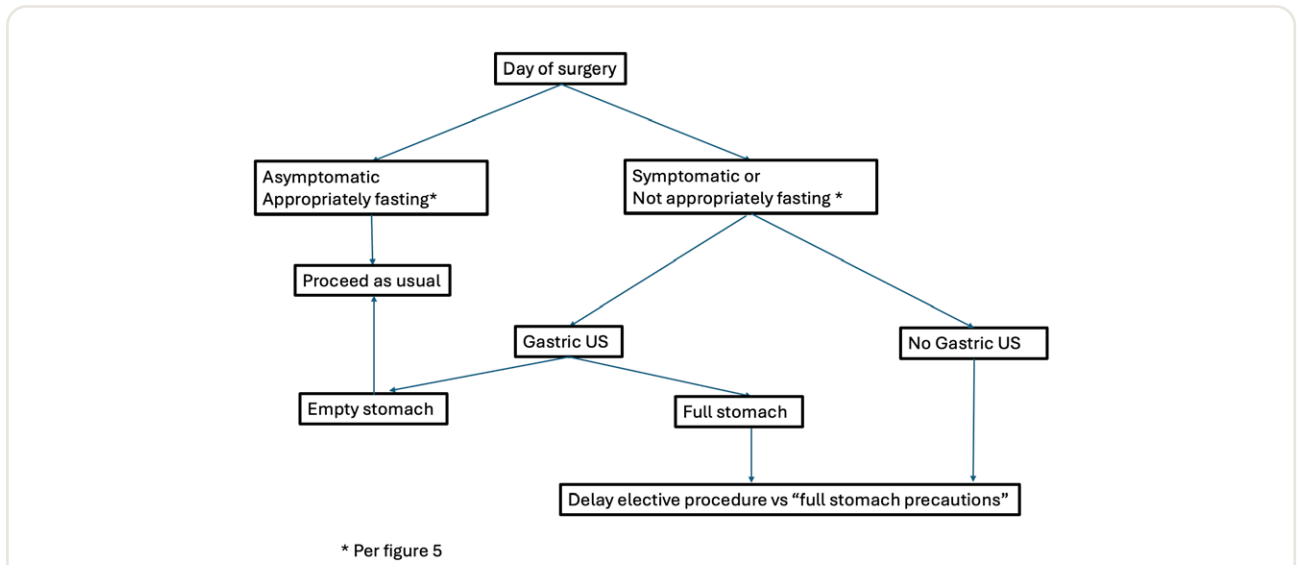


Fig. 6. Proposed recommendations for day of surgery management of patients on glucagon-like peptide-1 (GLP-1) receptor agonists (RA; summary from current literature). US, ultrasound.

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options, and the relative urgency of the proposed procedure are also important factors to review. Indeed, a multidisciplinary, patient-centric approach is needed when caring for these patients.

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Competing Interests

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