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EDITORIAL

Controversies on the effects of GLP-1 receptor agonist treatment on gastric emptying

Controversias de los efectos del tratamiento con agonistas del receptor de GLP-1 sobre el vaciamiento gástrico

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The agonists of the glucagon-like peptide-1 receptor (GLP-1R) have seen exponential growth since their commercialization in 2005 for the treatment of type 2 diabetes (T2DM) and obesity. GLP-1R agonists not only exert a potent incretin action, improving glycemic control, but also significantly reduce body weight and cardiovascular, renal, or hepatic metabolic disease risk.[1–4] However, the actions of GLP-1R agonists on GI motility, with the frequent appearance of symptoms—nausea, vomiting, abdominal distention, diarrhea, or constipation—are a serious concern for endoscopists and anesthesiologists due to the potential risk of these patients having increased gastric residue retention and aspiration.

GLP-1R agonists, in fact, exert actions on gastric fundus relaxation, reduction of acid secretion, and inhibition of antral contractility, actions that are dependent on parasympathetic, vagal stimulation.[5]

However, the impact of delayed gastric emptying on sedation and aspiration risks during anesthesia is not clearly defined. Although there is abundant literature on the subject, it is highly heterogeneous due to the study design types, different methods of gastric content evaluation, various GLP-1R agonist molecules analyzed, and a variety of treatment regimens administered to populations that are not always homogeneous.

The question that arises for clinicians using GLP-1R agonists is whether these drugs delay gastric emptying in a transient or permanent manner, and what implications this may have when patients undergo procedures that require sedation and/or anesthesia.

The gold standard for correctly measuring gastric emptying is isotopic gastric emptying after the ingestion of a solid meal labeled with technetium-99m.[6] A retention of $\geq$ 60% at 2 h or $\geq$ 10% at 4 h after ingestion of the preparation indicates delayed gastric emptying. Thus, in the study by Maselli et al.,[7] in a controlled clinical trial with 136 patients with obesity, randomized to liraglutide 3 mg or placebo, they observed a longer gastric emptying time at 5 weeks after the start of treatment (191.6 vs. 105.9 min, $p < 0.001$), with this effect improving at 16 weeks (154.4 vs. 111.4 min, $p < 0.001$), evidencing a tachyphylaxis effect of the drug. Similar results of delayed gastric emptying have been found with the use of different GLP-1R agonists, both in monotherapy—liraglutide,

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lixisenatide, albiglutide, dulaglutide, semaglutide—and in dual combination—tirzepatide—or in the form of triagonists—retatrutide—,[8–10] excluding, for now, oral semaglutide. A recent meta-analysis that analyzed 5 clinical trials ($n = 247$) confirmed that GLP-1R agonists have a mean gastric emptying time of 36 min (95%CI, 17.0–55.0; $p < 0.01$) longer than placebo.[11] In contrast, in another 10 studies ($n = 411$) using the paracetamol absorption test, the area under the curve was comparable between GLP-1R agonists and placebo treatment. Of note, paracetamol surrogate test depends on both gastric emptying capacity and intestinal absorption, being a better reference for liquid emptying than for solids. However, it should not be routinely used to determine gastric emptying with GLP-1R agonists.

Liquid retention in the gastric cavity is usually not a problem for performing esophagogastroduodenoscopy, as the content is aspirated during the procedure. For example, in a study conducted with endoscopy and measurement of aspirate during the test, treatment with semaglutide was associated with a 5-fold higher risk of gastric retention (OR, 5.15 [95%CI, 1.92–12.92]), yet a protective effect was observed (OR, 0.25 [95%CI, 0.16—0.39]) when an esophagogastroduodenoscopy and colonoscopy were performed simultaneously. A preoperative diet restricted in residue and only liquid intake 24 h before the procedure certainly helps to avoid gastric retention of solid food. Other observational studies replicate similar data with different types of GLP-1R agonists, but gastric retention is also significant when GI symptoms—abdominal distention, nausea, vomiting, etc.—are present associated with the use of these drugs[12–14] or in insulin-dependent T2DM patients on GLP-1R agonists and/or in those with macro- or microvascular complications.[15]

Some authors suggest performing an abdominal ultrasound in situ just before endoscopy or surgical anesthesia to check whether there is gastric content and make a decision at that moment. Although ultrasound is an accessible, non-invasive, and rapid method, it requires a trained operator, as it is more difficult to visualize gastric content in people with obesity. Two recent studies using abdominal ultrasound described greater gastric retention in people on GLP-1R agonists (between 40-56%) vs those not treated with such agent (3–19%),[16,17] thus confirming previous results obtained with isotopic gastric emptying or endoscopic aspiration, showing gastric retention associated with GLP-1R agonist use. Additionally, it is worth noting that, in several of these studies, no notable differences were found across different types of agonists used, treatment duration—absence of tachyphylaxis—or even considering different periods of drug suspension (up to > 14 days) before anesthesia induction.

If we assume with this data that there is a higher probability of gastric retention with GLP-1R agonist treatment, is the risk of aspiration during sedation increased? In large retrospective studies with more than a million procedures performed, most studies have not found a significant association among GLP-1R agonist use, gastric content aspiration, and/or secondary pneumonia. In the study by Anazco et al.,[18] the cumulative incidence rate of aspiration was 4.8/10,000 diagnostic endoscopic procedures among patients on GLP-1R agonists vs 4.6/10,000 in the untreated population. Similar data have been described in other studies of similar size,[19–22] except for the work by Yeo et al.,[23] who, analyzing the registry of 963,184 individuals undergoing endoscopy— 46,935 (4.9%) on GLP-1R agonist treatment—and applying a propensity score matching methodology, found that GLP-1R agonists were associated with an increased risk of aspiration (HR, 1.33 [95%CI, 1.02–1.74]; $p = 0.036$), especially when propofol was used in sedation induction. However, any of these observations, based on retrospective data analysis, should be interpreted with caution, as they may introduce validity biases by not reliably representing the analyzed population.

In everyday practice, patients on GLP-1R agonists arrive for endoscopy or surgery without precise instructions. But what do scientific societies say? In 2023, the American Society of Anesthesiologists established in its recommendations that: ''In the case of patients receiving daily doses, it should be considered to suspend GLP-1R agonists on the day of the procedure or surgery. In the case of patients receiving weekly doses, it should be considered to suspend GLP-1R agonists 1 week prior to the procedure or surgery''.[24] However, the American Gastroenterological Association,[25] like other scientific societies,[26] opposes the need to suspend the medication, as this could affect the patients' metabolic control and weight management. They also remind that ''for patients on GLP-1R agonists who have followed standard perioperative procedures—normally an 8-h fast for solid foods and a 2-h fast for liquids—and who do not have symptoms of nausea, vomiting, dyspepsia, or abdominal distention, it is recommended to proceed with upper and/or lower endoscopy.'' Again, it is important to emphasize that individual variability in gastric emptying is high, particularly in people with T2DM. Therefore, we cannot predict which patients or which types of GLP-1R agonists, doses, or treatment durations will have a greater or lesser impact on gastric retention of solid food before a test. Even the absence of GI symptoms is not a guarantee of no gastric residue, as shown by data obtained with abdominal ultrasound.[16,17]

Recently, a clinical practice guideline from several scientific societies (American Gastroenterological Association, American Society for Metabolic and Bariatric Surgery, American Society of Anesthesiologists, International Society of Perioperative Care of Patients with Obesity, and Society of American Gastrointestinal and Endoscopic Surgeons) was published for the safe use of GLP-1R agonists in the perioperative period.[27] Their recommendations are suggestions, as they are not supported by studies with sufficient scientific evidence. This document considers that those on GLP-1R agonists who are in the up titration phase, those with higher doses of the drug, weekly formulations, and those with GI symptoms or a history of gastroparesis are at greater risk of delayed gastric emptying and aspiration. Active treatment suspension is not recommended as a rule, but if doubts persist regarding the above recommendations, it is suggested to follow the advice of the American Society of Anesthesiologists, suspending GLP-1R agonists for 1 day or 1 week depending on the type of drug used.

None of the above consensuses or recommendations have been approved by any American or European scientific societies of endocrinology or diabetes. From our perspective, we agree with Jalleh et al.'s considerations for an individualized approach[5]: a) it is important to analyze clinical situations that may predispose to gastroparesis (advanced diabetes, chronic neurological diseases, opioid drugs, antidepres-

sants, antipsychotics, proton pump inhibitors, etc.); b) avoid suspending GLP-1R agonists; c) proper preparation with a 24-h liquid diet and a 6—8 h fast prior to the procedure will ensure, in a high percentage of patients, the absence of gastric retention; d) optionally, and if available, the feasibility of performing an abdominal ultrasound to rule out residual gastric content, and e) also consider, in specific cases, the possibility of treatment with prokinetics, such as erythromycin (200 mg iv or 3 mg/kg). Some of these measures are also included in the multisociety consensus.[27]

To move out of the state of uncertainty surrounding the effects of GLP-1R agonists on gastric emptying and their implications for sedation or anesthesia induction, there are still some challenges ahead. Studies are needed to better investigate the physiology of gastric emptying in T2DM and obesity, before and after GLP-1R agonist treatment; additionally, prospective gastric emptying studies are needed to determine whether tachyphylaxis exists in different therapeutic situations, and more pharmacogenomics studies are needed to help differentiate patients with faster or slower gastric emptying and/or the presence of GI symptoms. Only with well-designed clinical trials will recommendations with a high level of evidence be made.

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References

1. Elmaleh-Sachs A, Schwartz JL, Bramante CT, Nicklas JM, Gudzune KA, Jay M. Obesity management in adults: a review. JAMA. 2023;330:2000–15, http://dx.doi.org/10.1001/jama.2023.19897.
2. Ballesteros Pomar MD, Vilarrasa García N, Rubio Herrera MÁ, Barahona MJ, Bueno M, Caixàs A, et al. The SEEN comprehensive clinical survey of adult obesity: Executive summary. Endocrinol Diabetes Nutr (Engl Ed). 2021;68:130–6, http://dx.doi.org/10.1016/j.endinu.2020.05.003.
3. Ussher JR, Drucker DJ. Glucagon-like peptide 1 receptor agonists: cardiovascular benefits and mechanisms of action. Nat Rev Cardiol. 2023;20:463–74, http://dx.doi.org/10.1038/s41569-023-00849-3.
4. Goldenberg RM, Gilbert JD, Manjoo P, Pedersen SD, Woo VC, Lovshin JA. Management of type 2 diabetes, obesity, or nonalcoholic steatohepatitis with high-dose GLP-1 receptor agonists and GLP-1 receptor-based co-agonists. Obes Rev. 2024;25:e13663, http://dx.doi.org/10.1111/obr.13663.
5. Jalleh RJ, Plummer MP, Marathe CS, Umapathysivam MM, Quast DR, Rayner CK, et al. Clinical consequences of delayed gastric emptying with GLP-1 receptor agonists and tirzepatide. J Clin Endocrinol Metab. 2024:dgae719, http://dx.doi.org/10.1210/clinem/dgae719.
6. Banks KP, Syed K, Parekh M, McWhorter N. Gastric emptying scan. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [Accessed 22 November 2024]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK531503/.
7. Maselli D, Atieh J, Clark MM, Eckert D, Taylor A, Carlson P, et al. Effects of liraglutide on gastrointestinal functions and weight in obesity: a randomized clinical and pharmacogenomic trial. Obesity (Silver Spring). 2022;30:1608–20, http://dx.doi.org/10.1002/oby.23481.
8. Jensterle M, Ferjan S, Ležaič L, Sočan A, Goričar K, Zaletel K, et al. Semaglutide delays 4-hour gastric emptying in women with polycystic ovary syndrome and obesity. Diabetes Obes Metab. 2023;25:975–84, http://dx.doi.org/10.1111/dom.14944.
9. Urva S, Coskun T, Loghin C, Cui X, Beebe E, O'Farrell L, et al. The novel dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) recep-tor agonist tirzepatide transiently delays gastric emptying similarly tos-elective long-acting GLP-1 receptor agonists. Diabetes Obes Metab. 2020;22:1886–91.
10. Urva S, O'Farrell L, Du Y, Loh MT, Hemmingway A, Qu H, et al. The novel GIP, GLP-1 and glucagon receptor agonist retatrutide delays gastric emptying. Diabetes Obes Metab. 2023;25:2784–8, http://dx.doi.org/10.1111/dom.151672788.
11. Hiramoto B, McCarty TR, Lodhia NA, Jenkins A, Elnaiem A, Muftah M, et al. Quantified metrics of gastric emptying delay by glucagon-like peptide-1 agonists: a systematic review and meta-analysis with insights for periprocedural management. Am J Gastroenterol. 2024;119:1126–40, http://dx.doi.org/10.14309/ajg.0000000000002820.
12. Silveira SQ, da Silva LM, de Campos Vieira Abib A, de Moura DTH, de Moura EGH, Santos LB, et al. Relationship between perioperative semaglutide use and residual gastric content: a retrospective analysis of patients undergoing elective upper endoscopy. J Clin Anesth. 2023;87:111091, http://dx.doi.org/10.1016/j.jclinane.2023.111091.
13. Wu F, Smith MR, Mueller AL, Klapman SA, Everett LL, Houle T, et al. Association of glucagon-like peptide receptor 1 agonist therapy with the presence of gastric contents in fasting patients undergoing endoscopy under anesthesia care: a historical cohort study. Can J Anaesth. 2024;71:958–66, http://dx.doi.org/10.1007/s12630-024-02719-z.
14. Santos LB, Mizubuti GB, da Silva LM, Silveira SQ, Nersessian RSF, Abib ACV, et al. Effect of various perioperative semaglutide interruption intervals on residual gastric content assessed by esophagogastroduodenoscopy: a retrospective single center observational study. J Clin Anesth. 2024;99:111668, http://dx.doi.org/10.1016/j.jclinane.2024.111668.
15. Garza K, Aminpour E, Shah J, Mehta B, Early D, Gyawali CP, et al. Glucagon-like peptide-1 receptor agonists increase solid gastric residue rates on upper endoscopy especially in patients with complicated diabetes: a case-control study. Am J Gastroenterol. 2024;119:1081–8, http://dx.doi.org/10.14309/ajg.0000000000002777.
16. Nersessian RSF, da Silva LM, Carvalho MAS, Silveira SQ, Abib ACV, Bellicieri FN, et al. Relationship between residual gastric content and peri-operative semaglutide use assessed by gastric ultrasound: a prospective observational study. Anaesthesia. 2024;79:1317–24, http://dx.doi.org/10.1111/anae.16454.
17. Sen S, Potnuru PP, Hernandez N, Goehl C, Praestholm C, Sridhar S, et al. Glucagon-like peptide-1 receptor agonist use and residual gastric content before anesthesia. JAMA Surg. 2024;159:660–7, http://dx.doi.org/10.1001/jamasurg.2024.0111.
18. Anazco D, Fansa S, Hurtado MD, Camilleri M, Acosta A. Low incidence of pulmonary aspiration during upper endoscopy in patients prescribed a glucagon-like peptide 1 receptor agonist. Clin Gastroenterol Hepatol. 2024;22:1333–5.e2, http://dx.doi.org/10.1016/j.cgh.2023.11.024.
19. Barlowe TS, Anderson C, Sandler RS, Subramaniam D, Muratore A, Buse JB, et al. Glucagon-like peptide-1 receptor agonists do not increase aspiration during upper endoscopy in patients with diabetes. Clin Gastroenterol Hepatol. 2024,

http://dx.doi.org/10.1016/j.cgh.2024.04.038. In press. S1542-3565(24)00453-1.
20. Klonoff DC, Kim SH, Galindo RJ, Joseph JI, Garrett V, Gombar S, et al. Risks of peri- and postoperative complications with glucagon-like peptide-1 receptor agonists. Diabetes Obes Metab. 2024;26:3128–36, http://dx.doi.org/10.1111/dom.15636.
21. Dixit AA, Bateman BT, Hawn MT, Odden MC, Sun EC. Preoperative GLP-1 receptor agonist use and risk of postoperative respiratory complications. JAMA. 2024;331:1672–3, http://dx.doi.org/10.1001/jama.2024.5003.
22. Peng CY, Chang YC, Gong C, Chang Y, Chi KY, Hsiao CL, et al. Association between glucagon-like peptide-1 receptor agonists and aspiration pneumonia during endoscopic procedures. Anesthesiology. 2024;141:1009–12, http://dx.doi.org/10.1097/ALN.0000000000005174.
23. Yeo YH, Gaddam S, Ng WH, Huang PC, Motility and Metabolic Pharmacoepidemiology Group, Ma KS, et al. Increased risk of aspiration pneumonia associated with endoscopic procedures among patients with glucagon-like peptide 1 receptor agonist use. Gastroenterology. 2024;167:402–4.e3, http://dx.doi.org/10.1053/j.gastro.2024.03.015.
24. Joshi GP, Abdelmalak BB, Weigel WA, Soriano SG, Harbell MW, Kuo CI, et al [Accessed 22 November 2024]. Available from: https://www.asahq.org/about-asa/newsroom/news-releases/2023/06/american-society-of-anesthesiologists-consensus-based-guidance-on-preoperative, 2023.
25. Hashash JG, Thompson CC, Wang AY. AGA rapid clinical practice update on the management of patients taking glp-1 receptor agonists prior to endoscopy: communication. Clin Gastroenterol Hepatol. 2024;22:705–7, http://dx.doi.org/10.1016/j.cgh.2023.11.002.
26. AASLD/ACG/AGA/ASGE/NASPGHAN Multisociety Statement. In: No data to support stopping GLP-1 agonists prior to elective endoscopy; 2023 [Accessed 22 November 2024]. Available from: https://gastro.org/news/gi-multi-society-statement-regarding-glp-1-agonists-and-endoscopy/
27. Kindel TL, Wang AY, Wadhwa A, Schulman AR, Sharaiha RZ, Kroh M, et al. Multisociety clinical practice guidance for the safe use of glucagon-like peptide-1 receptor agonists in the perioperative period. Surg Obes Relat Dis. 2024;20:1183–6, http://dx.doi.org/10.1016/j.soard.2024.08.033.