EDITORIAL

Are We Moving in the Right Direction by Altering Gastric Motility for Weight Loss?

Though adoption of bariatric surgery is poor, it provides insights into the influence of the gastrointestinal tract on eating behavior and metabolism. Mechanisms of action of bariatric surgery are no longer simply considered limited to restricting oral intake or inducing malabsorption. Indeed, if this were true, patients who underwent bariatric surgery would be voracious and miserable, a situation not observed, despite patients losing 20%–25% of their total body weight by 6 months.[1,2] Identifying the cellular and molecular alterations after bariatric surgery are critical to developing techniques that are well tolerated, effective, safe, and appealing to patients. While these are being identified and subsequently validated, the most suitable alternative is to alter the gastrointestinal tract in an appealing manner to induce the physiologic effects (not simply the physical effects) of bariatric surgery.[3]

Endoscopic bariatric therapies, such as intragastric balloons and endoscopic sleeve gastroplasty, induce clinically significant weight loss.[4–7] However, they have not matched the degree of weight loss nor the weight independent benefits observed with bariatric surgery.[2,8] This may be the result of physicians and industry focusing efforts on developing endoscopic procedures that imitate the restrictive aspects of bariatric surgery rather than mimicking the changes in metabolic signaling. The physiological changes may be the result of alterations in the microbiome, bile acid metabolism, accelerated nutrient flow as well as gastric emptying, and loss of nutrient exposure to the gastric and small bowel mucosa. This has now been recognized and in the last decade several promising techniques emulating the physiologic changes of bariatric surgery are emerging. These include approaches targeting the neurohormonal aspects of proximal luminal gastrointestinal tract: mucosal surfaces of the stomach and duodenum.[9–12]

In this issue of *Clinical Gastroenterology and Hepatology*, Vargas et al,[13] through a systematic review and meta-analysis, interrogate the changes in time of gastric emptying after surgical and endoscopic bariatric procedures. This metanalysis includes 320 patients from 15 studies. The authors determine that across the various different devices and therapies, the change in gastric emptying correlates with weight loss. In brief, their findings suggest that fluid-filled gastric balloons substantially decrease gastric emptying and laparoscopic sleeve gastrectomy may increase gastric emptying. The authors conclude from their findings that patients should undergo a standard gastric emptying of solids assessment in order to personalize their therapy. They suggest that those with rapid gastric emptying would gain superior benefit from a fluid filled intragastric balloon and those with slow gastric emptying would have a superior benefit with laparoscopic sleeve gastrectomy.

With regard to the study's methodology, the authors have meticulously reviewed the literature and collected all available data on gastrointestinal motility post bariatric procedures. The a priori study protocol and rigorous methodology led to a small number of studies suitable for inclusion, demonstrating a paucity of available data. The decision to analyze fluid- and gas-filled balloons separately was important due to the significantly different influence they have on gastric emptying.

The metaregression was performed evaluate the association between gastric emptying time and weight loss in this study; however, there are 2 concerns with regard to its appropriateness. First, although the authors did not find any association between "change" in emptying time and weight loss after gastrectomy, they proceed to repeat the same analysis using only the "postprocedure" emptying times as the predictor, while for each individual patient it is really the change in emptying times that is a meaningful indication of their altered physiology after gastrectomy. The interpretation of isolated postprocedure emptying times depends on each patient's baseline preprocedure times, as these vary among individuals. Second, and more importantly, metaregression in principle is appropriate for evaluating the association between "study-level" variables and the outcomes and not a valid statistical method to look at the association between "individual-level" variables and study outcomes, such as association between gastric emptying times and weight loss. Using metaregression in this manner can result in "ecological fallacy," a well-known bias that occurs when analysis of aggregate data is used for making inferences about individual-level associations. Even if it is true that studies that on "average" showed more decrease in emptying time also showed more "average" weight loss, it would be unwarranted to assume that the same will be true about "individual" patients in each of these studies.[14]

Fluid-filled intragastric balloons, although deployed in the fundus or proximal gastric body, have a propensity to migrate and reside in the distal gastric body. This raises the question: is the delay in gastric emptying due to the balloon acting as a barrier preventing the transit of solid food? Previous studies have demonstrated that intragastric balloons delay gastric emptying of solids but not liquids.[15,16] Do fluid filled intragastric balloons simply cause a mechanical obstruction preferentially to solids, and could it even interfere with the grinding of food into smaller particles and disruption of normal gastric propagation? Interestingly, a study comparing the outcomes of antral placement of balloons to fundal placement found that antral placement of a fluid-filled balloon led to greater weight loss.[17] Furthermore, the delay in gastric emptying in fluid-filled balloon continues despite a plateau in weight loss.[15] One could therefore argue that the mechanism for weight loss is not the delay itself, but rather the mechanical obstruction. This can be further demonstrated with the transpyloric shuttle device in which the device itself causes a delay in gastric emptying, which is simply the result of intermittent gastric outlet obstruction.[18]

The controversy of whether fluid-filled balloons cause intermittent gastric outlet obstruction vs delayed gastric emptying is tested when considering the clinical outcomes of patients who undergo placement of serial fluid-filled balloons. In 2 separate studies examining serial balloon insertions,[19,20] patients lose the maximum amount of weight after the first balloon, with minimal weight loss after the second and third balloons, suggesting that intermittent obstruction with decreased accommodation may play more of an effect, and that with subsequent balloons, the obstructive effect no longer plays a part, as the stomach has enlarged.

The conclusions drawn from the meta-analysis regarding the change in gastric emptying with fluid-filled balloons compared with gas filled balloons are interesting. The authors conclude gastric emptying is decreased after insertion of fluid-filled balloons but not gas-filled balloons. Is this finding important? Two recent studies of gas-filled balloons show a total body weight loss (TBWL) of 10%, which brings into question the mechanism of weight loss with these balloons. The authors point out that the delay in emptying also explains the difference in weight loss between the gas- and fluid-filled balloons. However, there is not enough evidence to conclude this. A recent registry study of over 1300 patients with gas-filled balloons demonstrated a TBWL of 10.2%.[21] This is similar to other registry data on fluid-filled balloons, which resulted in TBWL of 11.8% with the single balloon and 11.4% with the dual balloon.[7,22] Moreover, when looking at the pivotal sham control trials, the weight loss between the 2 balloons is similar: 7.1% vs 3.6% TBWL in the gas-filled balloon compared with 6.8% vs 3.3% TBWL in the fluid-filled dual balloon trial.[23,24] Given the similar weight loss seen in both real-world experience and the randomized sham trials, one must conclude that other factors are at play, not simply the delay in gastric emptying.

When considering gastric emptying after laparoscopic sleeve gastrectomy, the same inferences can be made. Is the expedited gastric emptying simply a manifestation of the fact that these postsurgical stomachs have a smaller reservoir and as a result solids traverse at a more rapid rate, and the increase in emptying is simply a byproduct and possibly independent of weight loss? It should be noted that the authors suggest both increased and decreased gastric emptying times are associated with weight loss, so it might just be the case that these changes in emptying time are only byproducts of the type of the studied bariatric procedures and not independent pathways leading to weight loss. For example, several studies looking at the mechanism of action of sleeve gastrectomy have demonstrated that this surgery leads to a combination of alternation in GLP1 and PYY, similar to RYGB, as well as a change in bile acid physiology, as potential mechanisms for weight loss.[25]

The influence of fluid-filled intragastric balloons and laparoscopic sleeve gastrectomy on the gastric pacemaker and interstitial cells of Cajal needs to be elicited before it can be stated that the changes in gastric emptying are not simply a matter of physics. Are the results presented robust enough to be translated clinically? We believe that more data pertaining to the gastric emptying story are necessary before drawing the conclusions in this study.

REEM Z. SHARAIHA, MD, MSc
Division of Gastroenterology and Hepatology
Weill Cornell Medicine
New York, New York

VIVEK KUMBHARI, MD
Division of Gastroenterology and Hepatology
Johns Hopkins University School of Medicine
Baltimore, Maryland

References

1. Schauer PR, Kashyap SR, Wolski K, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med 2012;366:1567–1576.
2. Fayad L, Adam A, Schweitzer M, et al. Endoscopic sleeve gastroplasty versus laparoscopic sleeve gastrectomy: a case-matched study. Gastrointest Endosc 2019;89:782–788.
3. Kaplan LM. What bariatric surgery can teach us about endoluminal treatment of obesity and metabolic disorders. Gastrointest Endosc Clin N Am 2017;27:213–231.
4. Fayad L, Cheskin LJ, Adam A, et al. Endoscopic sleeve gastroplasty versus intragastric balloon insertion: efficacy, durability, and safety. Endoscopy 2019;51:532–539.
5. Sharaiha RZ, Kumta NA, Saumoy M, et al. Endoscopic sleeve gastroplasty significantly reduces body mass index and metabolic complications in obese patients. Clin Gastroenterol Hepatol 2017;15:504–510.
6. Agnihotri A, Xie A, Bartalos C, et al. Real-world safety and efficacy of fluid-filled dual intragastric balloon for weight loss. Clin Gastroenterol Hepatol 2018;16:1081–1088.e1.
7. Vargas EJ, Pesta CM, Bali A, et al. Single fluid-filled intragastric balloon safe and effective for inducing weight loss in a real-world population. Clin Gastroenterol Hepatol 2018; 16:1073–1080.e1.
8. Novikov AA, Afaneh C, Saumoy M, et al. Endoscopic sleeve gastroplasty, laparoscopic sleeve gastrectomy, and laparoscopic band for weight loss: how do they compare? J Gastrointest Surg 2018;22:267–273.
9. Haidry RJ, Van Baar AC, Galvao Neto MP, et al. Duodenal mucosal resurfacing: proof-of-concept, procedural

development, and initial implementation in the clinical setting. Gastrointest Endosc 2019 Mar 29 [E-pub ahead of print].

10. Rajagopalan H, Cherrington AD, Thompson CC, et al. Endoscopic duodenal mucosal resurfacing for the treatment of type 2 diabetes: 6-month interim analysis from the first-in-human proof-of-concept study. Diabetes Care 2016;39:2254–2261.
11. Oberbach A, Schlichting N, Heinrich M, et al. Gastric mucosal devitalization reduces adiposity and improves lipid and glucose metabolism in obese rats. Gastrointest Endosc 2018; 87:288–299.e6.
12. Kumbhari V, Lehmann S, Schlichting N, et al. Gastric mucosal devitalization is safe and effective in reducing body weight and visceral adiposity in a porcine model. Gastrointest Endosc 2018; 88:175–184.e1.
13. Vargas EJ, Bazerbachi F, Calderon G, et al. Changes in time of gastric emptying after surgical and endoscopic bariatrics and weight loss: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2020;18:57–68.
14. Reade MC, Delaney A, Bailey MJ, Angus DC. Bench-to-bedside review: avoiding pitfalls in critical care meta-analysis–funnel plots, risk estimates, types of heterogeneity, baseline risk and the ecologic fallacy. Crit Care 2008;12:220.
15. Gomez V, Woodman G, Abu Dayyeh BK. Delayed gastric emptying as a proposed mechanism of action during intragastric balloon therapy: results of a prospective study. Obesity (Silver Spring) 2016;24:1849–1853.
16. Mion F, Napoléon B, Roman S, et al. Effects of intragastric balloon on gastric emptying and plasma ghrelin levels in non-morbid obese patients. Obes Surg 2005;15:510–516.
17. Papavramidis TS, Grosomanidis V, Papakostas P, Penna S, Kotzampassi K. Intragastric balloon fundal or antral position affects weight loss and tolerability. Obes Surg 2012; 22:904–909.
18. Marinos G, Eliades C, Raman Muthusamy V, Greenway F. Weight loss and improved quality of life with a nonsurgical endoscopic treatment for obesity: clinical results from a 3- and 6-month study. Surg Obes Relat Dis 2014;10:929–934.
19. Nguyen V, Li J, Gan J, et al. Outcomes following serial intragastric balloon therapy for obesity and nonalcoholic fatty liver disease in a single centre. Can J Gastroenterol Hepatol 2017; 2017:4697194.
20. Alfredo G, Roberta M, Massimiliano C, Michele L, Nicola B, Adriano R. Long-term multiple intragastric balloon treatment–a new strategy to treat morbid obese patients refusing surgery: prospective 6-year follow-up study. Surg Obes Relat Dis 2014; 10:307–311.
21. Moore RL, Seger MV, Garber SM, et al. Clinical safety and effectiveness of a swallowable gas-filled intragastric balloon system for weight loss: consecutively treated patients in the initial year of U.S. commercialization. Surg Obes Relat Dis 2019; 15:417–423.
22. Bukhari M, Kowalski T, Nieto J, et al. An international, multicenter, comparative trial of EUS-guided gastrogastrostomy-assisted ERCP versus enteroscopy-assisted ERCP in patients with Roux-en-Y gastric bypass anatomy. Gastrointest Endosc 2018;88:486–494.
23. Sullivan S, Swain J, Woodman G, et al. Randomized sham-controlled trial of the 6-month swallowable gas-filled intragastric balloon system for weight loss. Surg Obes Relat Dis 2018;14:1876–1889.
24. Ponce J, Woodman G, Swain J, et al. REDUCE Pivotal Trial Investigators. The REDUCE pivotal trial: a prospective, randomized controlled pivotal trial of a dual intragastric balloon for the treatment of obesity. Surg Obes Relat Dis 2015;11:874–881.
25. Bradley D, Magkos F, Eagon JC, et al. Matched weight loss induced by sleeve gastrectomy or gastric bypass similarly improves metabolic function in obese subjects. Obesity (Silver Spring) 2014;22:2026–2031.

Conflicts of interest
Vivek Kumbhari is a consultant for Medtronic, Pentax Medical, Boston Scientific, Apollo Endosurgery, ReShape Life Sciences, and Obalon. He receives research support from ERBE USA and Apollo Endosurgery. Reem Z. Sharaiha is a consultant for Boston Scientific, Olympus America, Medtronic, and Cook Medical.

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