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COMMENTARY

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Glucagon-like peptide-1 receptor agonists, weight loss, and gastric emptying: have I *gut* news for you

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It has only recently been widely appreciated that gastrointestinal function is central to both the pathogenesis and rational treatment of many metabolic disorders. As our understanding of drug mechanisms and pharmacogenetics increases, the capacity to "personalize" management strategies becomes more feasible. However, this carries the implication that mechanistic studies, using the best available techniques, represent an essential component of drug-development programs.

In this issue of *Obesity*, Maselli et al. report the outcomes of a randomized, parallel-group, placebo-controlled trial of the glucagon-like peptide-1 receptor agonist (GLP-1RA) liraglutide in adults with obesity [1], evaluating weight loss, gastric emptying, satiation, satiety, and body composition. Contrary to the widespread expectation that the effect of the long-acting GLP-1RAs to slow gastric emptying would be abolished with persistent use, liraglutide (up-titrated to 3 mg daily) was shown to slow gastric emptying following 16 weeks of treatment when evaluated using the "gold-standard" method of scintigraphy [1]. The magnitude of the slowing was less than what was evident after 5 weeks but was, nevertheless, still substantial. Accordingly, it is now clear that both short- and long-acting GLP-1RAs slow gastric emptying with sustained use, although the effect of short-acting GLP-1RAs (exenatide BD and lixisenatide) is greater [2, 3]. Liraglutide induced moderate weight loss (mean = 5.8 kg vs. no change with placebo), associated with increased satiation and satiety, and induced reductions in truncal and total fat [1]. Importantly, both the magnitude of the slowing of gastric emptying with liraglutide, and a rate of gastric emptying that was relatively more rapid at baseline, were predictive of greater weight loss [1]. These observations parallel what we now know about the effects of GLP-1RAs on gastric emptying and glycemic control in type 2 diabetes, in which postprandial glucose-lowering has been shown to be strongly related to the magnitude of slowing of gastric emptying as well as the baseline rate of emptying [3]. The latter is known to exhibit a substantial inter-, but much less intra-, individual variation. Accordingly, this supports the concept of selecting GLP-1RA therapy, particularly for those individuals in whom gastric emptying is more rapid, which is often the case in both obesity [1] and uncomplicated type 2 diabetes [4].

Scintigraphy, although being the optimal technique to measure gastric emptying, is not widely accessible. However, stable isotope breath tests (which, unlike scintigraphy, are not associated with a radiation burden and which have been validated against scintigraphy) have been shown to be a suitable alternative, particularly in large-scale clinical trials [4]. Suboptimal methods of evaluating gastric emptying, such as the paracetamol absorption test, should be avoided but they are unfortunately still used widely by the pharmaceutical industry in clinical trials. Accurate measurement of gastric emptying is important, particularly as the potential for a GLP-1RA to slow gastric emptying has major clinical implications, e.g., regarding the duration of fasting required before surgery/endoscopic procedures, as well as the timing of administration of oral medications when the rate of absorption determines their onset of action. Whether persistent slowing of gastric emptying with GLP-1RAs influences the propensity for gastrointestinal symptoms and the

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frequent treatment discontinuation in the longer term is uncertain and is an important question that should be addressed.

That slowing of gastric emptying could induce weight loss and symptoms makes intuitive sense, but its contribution should not be overestimated. In the study by Maselli et al., gastric emptying accounted for only 20% of the variance in weight loss [1]. This is analogous to symptomatic diabetic gastroparesis, in which the relationship between symptom improvement and accelerating gastric emptying with prokinetic drugs is now recognized to be weak at best. Slowing of gastric emptying is also inevitably associated with changes in the intragastric distribution of a meal. In health, the content of the distal (presumably, indicative of antral distension), but not proximal, stomach is a major determinant of subsequent food intake. However, this has not appeared to contribute to the reduction in energy intake with GLP-1RAs [5]. Therefore, it is likely that other factors unrelated to gastric emptying, including genetic variation, play a role. Accordingly, Maselli et al. evaluated single-nucleotide polymorphisms (SNPs; rs6923761 and rs7903146) implicated in GLP-1 signaling. Whereas the rs7903146 CC genotype was indeed associated with greater weight loss after 16 weeks of liraglutide treatment, the magnitude of this effect was modest. Accordingly, predictors of weight loss with GLP-1RAs remain poorly understood; central effects of GLP-1RAs are highly likely to be important. Further evaluation, particularly with the long-acting GLP-1RAs and dual GLP-1/gastric inhibitory polypeptide (GIP) receptor agonists (e.g., dulaglutide, semaglutide, tirzepatide), is required.

In conclusion, Maselli et al. have demonstrated, in an excellent study, that the degree of weight loss with liraglutide in individuals who have obesity but do not have type 2 diabetes is related to the following: 1) the baseline rate of gastric emptying; and 2) the degree of GLP-1RA-induced sustained slowing of gastric emptying. These observations attest to the importance of incorporating optimal measurement of gastric emptying into the design of studies evaluating GLP-1RAs.O

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CONFLICT OF INTEREST

Ryan J. Jalleh declared no conflict of interest. Christopher K. Rayner has participated in advisory boards for Allergan plc and Glyscend, Inc., for which honoraria were paid, and has received research funding from Merck & Co., Inc., Eli Lilly and Company, Sanofi S.A., AstraZeneca plc, and Novartis International AG. Karen L. Jones has participated in advisory boards for Glyscend, Inc., and has received research funding from Sanofi S.A. and AstraZeneca plc. Michael Horowitz has participated in advisory boards and/or symposia for Novo Nordisk A/S, Sanofi S.A., Novartis International AG, Eli Lilly and Company, Merck & Co., Inc., Boehringer Ingelheim, AstraZeneca plc, and Glyscend, Inc., and has received honoraria.

REFERENCES

1. Maselli D, Atieh J, Clark MM, et al. Effects of liraglutide on gastrointestinal functions and weight in obesity: a randomized clinical and pharmacogenomic trial. *Obesity (Silver Spring)*. 2022;30:1608-1620.
2. Jones KL, Huynh LQ, Hatzinikolas S, et al. Exenatide once weekly slows gastric emptying of solids and liquids in healthy, overweight people at steady-state concentrations. *Diabetes Obes Metab*. 2020; 22:788-797.
3. Linnebjerg H, Park S, Kothare PA, et al. Effect of exenatide on gastric emptying and relationship to postprandial glycemia in type 2 diabetes. *Regul Pept*. 2008;151:123-129.
4. Watson LE, Xie C, Wang X, et al. Gastric emptying in patients with well-controlled type 2 diabetes compared with young and older control subjects without wiabetes. *J Clin Endocrinol Metab*. 2019;104: 3311-3319.
5. Jalleh R, Pham H, Marathe CS, et al. Acute effects of lixisenatide on energy intake in healthy subjects and patients with type 2 diabetes: relationship to gastric emptying and intragastric distribution. *Nutrients*. 2020;12:1962. doi:10.3390/nu12071962

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