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Navigating Gastrointestinal Impacts of GLP-1 Receptor Agonists

Dr. Buch:
This is *GI Insights* on ReachMD. I'm Dr. Peter Buch, and today I'm joined by Dr. Michael Camilleri, who is a Professor of Medicine at the Mayo Foundation for Medical Education and Research in Rochester, Minnesota. He is also the lead author of "Effects of GLP-1 and Other Gut Hormone Receptors on the Gastrointestinal Tract and Implications in Clinical Practice," which was published in the *American Journal of Gastroenterology* in June of 2024.

Dr. Camilleri, you are an inspiring educator. Welcome back to the program.

Dr. Camilleri:
Thank you for having me back on the program.

Dr. Buch:
So, Dr. Camilleri, let's get started off with our discussion by asking how we can minimize GI side effects in patients taking GLP-1 agonists.

Dr. Camilleri:
So the best way to minimize the GI adverse effects in patients taking GLP-1 receptor agonists is to reduce the dose—to reduce the dose to a level that is tolerated. Now, we had experience with this in an NIH-funded clinical trial that we did with liraglutide compared to placebo, and we had about 65 patients who were on liraglutide. And what we found was that, as we followed the dose escalation recommended by the FDA, many times patients had nausea or nausea and vomiting. But we learned that if we slowed down the dose escalation, we were able to keep the patient on the medication, and they all achieved the maximum dose that was permitted by the FDA—which is 3 milligrams subcutaneous injection per day. It's just that some people took five weeks to get there and some people took seven or eight weeks, but they were all able to stick to the medication and get the benefit and weight loss with liraglutide in that study. So we learned that titrating the dose a bit slower is one of the ways to resolve the problem, particularly of nausea and vomiting.

Dr. Buch:
Thank you for that. And moving ahead, does the use of GLP-1 agonists increase the risk of pancreatitis?

Dr. Camilleri:
So this is still quite a controversial point. I'm going to make basically three points around this. The first is there are animal models that have been tried to see whether GLP-1 receptor agonists can induce pancreatitis, and certainly, the GLP-1 is able to stimulate the release of pancreatic amylase from the acinar cells in the pancreas. And also, there's been some evidence in animals that there is hyperplasia within the duct glands in the pancreas itself, so conceivably, at least theoretically, there could be a risk of pancreatitis. And then you see in the literature two different studies which came to completely opposite conclusions in experimental animals. So in older glucose-intolerant rats, there was an increased risk of pancreatitis, but when a separate group did a study in mice, they didn't see an increase in pancreatitis. So the first point is the experimental animals do not tell us necessarily a definite conclusion as to whether pancreatitis is induced by GLP-1 receptor agonists.

Now, the second bit of information I'm going to give you is that if you look at the FDA's Adverse Event Reporting System, there was a paper published in 2024 that showed that, in the FDA reporting system, there are more than 6,700 cases reported of pancreatitis. But I want to remind you that sometimes those reports may only have an increase in serum amylase or serum lipase, so it's not necessarily

fully proven that they had the full-blown picture of acute pancreatitis.

And indeed, the third point I'll make on this issue is that there have been at least two very large systematic reviews and meta-analyses, and they have shown no increased risk of acute pancreatitis. And these were done in more than 14,000 patients in 17 randomized controlled trials who received three different doses of tirzepatide, and in the other study, in patients who were receiving GLP-1 receptor agonists for cardiovascular outcomes. And there, among 56,000 participants with the diverse range—the full range of GLP-1 receptor agonists—there was no increased risk of acute pancreatitis.

So how do I summarize all of this? I actually don't think at the present time that there is evidence that would support the presence of acute pancreatitis with GLP-1 treatment. On the other hand, there could be an increase in serum amylase, and that is part of the effect of the GLP-1 stimulating the pancreatic cells, just like the GLP-1 also stimulates the beta cells in the pancreas to produce insulin. So at the present time, that's how I would summarize the current state of affairs.

Dr. Buch:
Thank you for clarifying that. So, Dr. Camilleri, if we hone in on endoscopies in particular, what is the best approach to preventing aspiration when managing GLP-1 agonists?

Dr. Camilleri:
So I think the first really important point is these are very good medications. They improve diabetes, they help with obesity, they have tremendous effects on cardiovascular and cerebrovascular adverse effects of obesity, so these are good medications. We shouldn't arbitrarily just stop them, okay? The most important points I will make are two points. The first is please ask your patients, do they have symptoms suggesting gastroparesis? Do they have nausea, vomiting, early satiety, or postprandial fullness, which suggests that the stomach is emptying slowly? If you do identify that, then that's the sort of patient where you might stop a weekly administered GLP-1 agent like semaglutide or tirzepatide. You might stop that seven days before the endoscopy or before a procedure—elective procedure. If, on the other hand, the patients are on a daily injected agent, like liraglutide, then you would stop it one or two days before the procedure.

The second and a really important point is, of course, apart from looking after the symptoms, can we do things for patients who are not symptomatic just to make sure we keep them safe and make sure they don't have aspiration? And what we have learned over the last two or three years is that if we give the patient a full liquid diet—not for just the evening meal before but for at least 24 hours before the procedure—then the risk of aspiration drops. And so that's another thing which I think is very useful. And we learned this because it turns out that retained gastric content is much less frequent in patients who have colonoscopy preparation and patients on GLP-1 receptor agonists who are being prepared for colonoscopy where usually we tell patients, "Take a liquid diet for 24 hours, then take your bowel preparation," which is a lot of liquids.

So in summary, three important points. Number one, see whether the patient has any symptoms; number two, you might need to consider stopping the medication if they have symptoms; and number three, give them 24 hours of liquid diet prior to the procedure, and then, of course, fasting for eight hours before the procedure is performed.

Dr. Buch:
Thank you. Dr. Camilleri, when will this be codified among the various societies?

Dr. Camilleri:
What I've just said has recently been summarized as the most appropriate approach among the different societies: the prolonged period of fasting or the prolonged liquid meals—liquid diet for 24 hours before—and also avoiding or stopping medications unless there is a very good indication. So a recent guideline was produced by the different societies, and they've come to a very similar conclusion.

Dr. Buch:
And as a further note on that, are the anesthesiologists agreeing with us as well?

Dr. Camilleri:
I think in general the anesthesiologists are agreeing, except that they've also suggested point-of-care ultrasound to be done. Now, the problem is that most GI practices do not have point-of-care ultrasound where you can actually check to see whether the patient has food remaining in the stomach. The other thing I will tell you is that when we did that study of liraglutide, two-thirds of the patients who were on 16 weeks of liraglutide did not have delayed gastric emptying, and so it seems unreasonable to me to think of doing a point-of-care ultrasound on a hundred percent of patients just because they're on a GLP-1 receptor agonist. That's why I emphasized the importance of asking the patient whether they have those symptoms that suggest the stomach is not emptying at the right rate.

Dr. Buch:

Thank you for that. For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Michael Camilleri about the GI consequences of using GLP-1 agonists.

So, Dr. Camilleri, let's go back to colonoscopy. Should we be adjusting the colonoscopy preps in those patients who are on GLP-1 agonists?

Dr. Camilleri:
So this is a very important point, and there's now been a systematic review meta-analysis of six trials that has shown that if you're on a GLP-1 receptor agonist, it's more likely that there will be inadequate bowel preparation, so I do think that we might need to extend the period of liquid diet in patients on GLP-1 receptor agonists. Maybe instead of 24 hours, you might need to go to 48 hours. And also, we've got to make sure that the patient takes the full bowel preparation so that we can cleanse the colon as best we can. So those are the two precautions I would take.

Dr. Buch:
Thank you, and good luck with talking about being on a liquid diet for some of these patients for 48 hours. So I wish us all strength in that one. Moving on to liver disease, what should we know about the effects of GLP-1 agonist on liver fibrosis?

Dr. Camilleri:
This is a great question. And even this past week there was yet another paper in *The New England Journal of Medicine* showing—I think it was with either tirzepatide or semaglutide—two really important things that happened with the GLP-1 receptor agonists. Number one is they reduce the AST and ALT, and number two is they reduce the level of fibrosis without messing up the ALT and AST. And while the GLP-1 receptor agonists are not yet approved for metabolic-associated fatty liver disease—what we used to call NAFLD or NASH in the past—I think it's just a matter of time. At the present time there is a medication called resmetirom, which is approved for liver fibrosis, but we're seeing more and more evidence that these GLP-1 receptor agonists, in addition to all of their other benefits on the comorbidities of obesity and diabetes, are also improving inflammation and fibrosis in the liver. And the *American Diabetes Association* within the last week also made the recommendation that diabetologists should be checking for metabolic-associated fatty liver disease, and that should be one of the goals for improving the overall health of patients with type 2 diabetes or obesity who are receiving these medications. That is the diabetologists need to also start looking at the liver function and improving it.

Dr. Buch:
That certainly makes a lot of sense in patients with type 2 diabetes. As we approach the end of our conversation, Dr. Camilleri, do you have any final takeaways you'd like to share?

Dr. Camilleri:
Well, my final takeaway would be that we as gastroenterologists and hepatologists should embrace the opportunity to treat the obesity when we're seeing patients with other reasons why they're coming to us as gastroenterologists or hepatologists. Obviously, if the patient comes with elevated liver enzymes due to hepatic steatosis, the hepatologists are now becoming more and more attuned to the idea of giving a GLP-1 receptor agonist to treat that, but also, in general gastroenterology, we know that patients with gallstones, patients with inflammatory bowel disease, etc., obesity has an impact on all of those other GI conditions. About a year and a half ago I actually wrote a commentary about this, which appeared in the peer-reviewed literature, and it's called "Ten Reasons Gastroenterologists and Hepatologists Should Be Treating Obesity," and I still think this is an opportunity for us as digestive tract specialists to actually help the whole health situation of our patients.

Dr. Buch:
Amen. I want to thank my guest, Dr. Michael Camilleri, for an incredible review of the impacts of GLP-1 agonists on the GI tract. Dr. Camilleri, it was a pleasure speaking with you today as always.

Dr. Camilleri:
Thank you so much. It was a pleasure participating in this interview.

Dr. Buch:
For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit *GI Insights* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening, and looking forward to learning with you again very soon.