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Getting to Know Gastroparesis

Dr. Buch:
Welcome to *GI Insights* on ReachMD. I'm your host, Dr. Peter Buch. Joining us today to help us better understand gastroparesis is Dr. Madhu Grover. Dr. Grover is an Associate Professor of Medicine at the Mayo Clinic and develops and conducts clinical trials on gastroparesis. Dr. Grover is also the lead author of "Gastroparesis: a turning point in understanding and treatment," published in Gut in 2019.

Welcome to the program, Dr. Grover.

Dr. Grover:
Thanks, Dr. Buch. It's exciting to be here and to have this opportunity to discuss gastroparesis with you.

Dr. Buch:
Dr. Grover, to start us off, can you please tell us what we should know about the different etiologies of gastroparesis?

Dr. Grover:
Thank you for that question. So, when we think about gastroparesis, there are two broad, you know, etiologies, one being diabetic, you know, both for type 1 and type 2 diabetes, but more and more we are recognizing that a large proportion of gastroparesis patients are idiopathic in nature. So diabetic and idiopathic gastroparesis are the two major buckets followed by some rare entities, such as postviral or postinfectious gastroparesis, which sometimes, you know, can get lumped with idiopathic. Then there's medication-induced gastroparesis, particularly in the setting of opioid use. And then there is gastroparesis associated with connective tissue disorders like, you know, scleroderma, and so on and so forth. So, those would be the secondary causes of gastroparesis. However, I would say that close to 85 percent of gastroparesis are either diabetic or idiopathic in nature.

Dr. Buch:
And just to make it clear for our audience, idiopathic is cause No. 1. Is that correct?

Dr. Grover:
That is correct, although there is a little bit of a disconnect based on where the studies are coming from. If you look at studies from tertiary care practices, idiopathic is the leading cause, whereas if you look at some of the more recent population-based studies, it appears that diabetic gastroparesis may be equally common.

Dr. Buch:
Thank you for that clarification. So let's get to the cutting edge stuff right now. How do we distinguish gastroparesis from functional dyspepsia?

Dr. Grover:
That's a great question, Dr. Buch, and that's an area which is of significant interest. It has been of interest for last number of years, but more recently, it has gained sort of a resurgence in the interest. So just to set the stage, functional dyspepsia, it is a condition, which is defined by Rome criteria, so these are symptom-based classification, you know, metrics where we try to fit patients based on symptoms of a particular kind happening for a set amount of duration or more. So, when we think about functional dyspepsia, the symptoms of dyspepsia are very much overlapping with the symptoms of gastroparesis to the point that they can be indistinguishable. So what really differentiates gastroparesis is the presence of objective, you know, slowness of gastric emptying, and this is a test where we give the patients a standardized meal, and we are trying to understand, how much of that meal or those contents have been emptied over, a course of three to four hours. So, we use that objective measure to diagnose gastroparesis. However, at the clinical level or at the

symptom, you know, level, these, these, you know, conditions can have fairly overlapping symptoms.

Dr. Buch:
And is it true that gastroparesis can go and become functional dyspepsia and functional dyspepsia can become gastroparesis over time?

Dr. Grover:
That's a great question. It also tells me you have been keeping up with some of the more recent literature. So this was a study that we recently published as a part of the NIH Gastroparesis Clinical Research Consortium where we took a cohort of patients that either gastroparesis or functional dyspepsia, and we did gastric emptying on all of them, and that's why we know who had gastroparesis and who had dyspepsia, and then several weeks later we repeated gastric emptying study on them. And anywhere from 35 to 45 percent of patients, you know, came out of their original category, so if they were gastroparetic to begin with, they now do not have that delayed gastric emptying at a subsequent time point. However, if their gastric emptying was normal to begin with, now they seemed to fit that gastric emptying delay criteria. So it's very true that if you measure symptoms over time or if you follow patients over time, a subset of patients can come and go out of these strict definitions. So that sort of really opened our eyes to this understanding where these conditions may lie on a physiological spectrum.

And as you can imagine, you know, gastric emptying is a physiological test, and we know by doing several studies in patients as well as in animal models, physiology is not something that's static or that's sealed in an envelope. It's something that is influenced by a lot of factors: hormones, stress levels and so on and so forth. So physiology can really change over time, so we are doing more work to understand this cohort that is sort of, you know, coming in and out of these definitions.

Dr. Buch:
Thank you for that clarification. So let's move on now to scintigraphy for a moment. And what can you tell us about false positives and negatives that occur when evaluating gastroparesis?

Dr. Grover:
That's a great question. Thank you for asking. So, as we think about gastric emptying scintigraphy here at least at Mayo Clinic, we use a standardized meal that has around 300 kilocalories as the nutrient composition, and it has around 30 percent fat, so it's a little bit fat-rich diet, but we think that amount of fat more closely approximates the fat intake of the U.S. population. So we administer this meal, and we, you know, measure gastric emptying over the 4 hours, and we like to see at least a 20 percent or more retention of contents at 4 hours to classify somebody as gastroparetic. And there are some variances between men and women when it comes to that normative data.

Now, there are some other protocols out there for gastric emptying measurement that do not have such a high fat content that have more in the range of 3 to 4 percent fat. And, as you know, fatty food is difficult to empty from the stomach, or it takes longer, so in those protocols, one can imagine, with a low fat content, one is much more likely, uh, to have a false recording of gastric emptying. Another area where a lot of false testing, both false positives and negatives are happening, when gastric emptying is not measured for at least three hours. So, as you might have seen in the most recent American College of Gastroenterology recommendations—and we have been talking about this for a while now—that we should really be doing scintigraphies for at least three hours, if not the total of four hours. But a lot of practices even to date been doing these half-baked studies. These are studies that get completed within a span of about two hours, and then the curve is extrapolated to understand where that gastric emptying may lie, but what we have realized doing studies is that that may not give us the correct representation of how the gastric emptying might really actually perform over the three to four hours.

Dr. Buch:
All extremely useful information. So, moving on from there, are there any limitations that come to mind when we're using isotope breath test or motility capsules?

Dr. Grover:
That's again a good question. So, as we think about the isotope breath test, these are particularly carbon 13 spirulina breath tests. And carbon 13, as you know, is a stable isotope, so it's not radioactive. It's, you know, constitutes around 1 to 2 percent of carbon in nature. And this test is actually a really good test. It's approved by FDA. It's also particularly advantageous in, you know, kids where we do not want to subject them to radiation and to imaging. So I, you know, personally feel that if a practice is aligned to do a carbon 13 spirulina breath test, it's actually a very good test with very high sensitivity in that 85–90 percent when it's compared to gastric emptying scintigraphy.

As we think about the wireless motility capsule—that's your second modality you mentioned—then we have a little bit of a problem, and

the problem being although a number of studies have looked at the wireless motility capsule and how it might compare with the scintigraphy, one has to understand the way our stomach processes food. A capsule has a very different dynamics emptying the stomach. It, it doesn't have quite the dynamics that a meal would have, and hence you know, often, capsules are hanging out in the stomach for a longer duration. So we at least do not feel that wireless motility capsule is a particularly good test for detection of gastroparesis. I think it leads to too many false positives when the capsule, it's just floating in the stomach going back and forth because it's not seen its actual dynamics of being emptied the way a meal would get emptied.

Dr. Buch:
Thank you for that insight. For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Madhu Grover about gastroparesis.

So, let's move on to this one. What are some key advancements in our understanding of the pathophysiology of gastroparesis?

Dr. Grover:
So, you know, this is an area where I feel really proud of the gastroenterology and the research community in general for making a lot of progress. So, if you even look back 10 to 15 years ago, gastroparesis used to be this black box disease where patients would have symptoms, they would lose a ton of weight, and we would have very little to understand why they're having those symptoms. Now, over the last decade or so, work done by the Gastroparesis Clinical Research Consortium, which is a large NIH-funded effort, as well as by other groups have shed a lot of light on our understanding of pathophysiology.

What we have learned over the last decade or so, that a lot of these patients have identifiable cellular changes in their gastric muscle. So, as you think about the muscle layers, refreshing your sort of memory on the anatomy, we have the mucosal lining, but underneath that mucous lining the stomach we have the muscle layers, and these are the layers that house the enteric nervous system, and the enteric nervous system is the one that regulates this motility in the stomach and in the GI tract in general. So, what we have learned based on the work looking at biopsy specimens from patients with gastroparesis, that over half of these patients have a loss of, these pacemaker cells called interstitial cells of Cajal in their gastric muscle. And if you look more closely using sophisticated techniques like electron microscopy, close to 90 percent of patients have, you know, changes or signs of damage to these pacemaker cells. Some of the patients would have fibrosis in the muscle. Others would have damage to the enteric nerve fibers. So that's really shifted the paradigm in us now thinking about this as a true cellular problem affecting these specialized cells in the muscle layers of the stomach.

Then over the last 5 to 7 years we started understanding or, started answering the question: Why are these cells damaged? And what we have learned, again, these are based on, you know, studies coming from patients who have given biopsy specimens—is that there is an evidence of immune dysregulation in these stomachs, you know, particularly with imbalance between the pro and the anti-inflammatory macrophages, and we believe this imbalance results in an injury to these specialized cells of the enteric nervous system.

So we and others, we are heavily engaged in learning more about how these interactions between immune system and the enteric nervous system take place, and we are really excited for the next, I would say, 4 to 5 years, to really try to get to a stage where we just don't treat gastroparesis symptomatically, but we can try to treat it at more of a root cause, try to use some of the disease-modifying strategies to essentially cure this disease.

Dr. Buch:
With those final thoughts in mind, I want to thank my guest, Dr. Madhu Grover, for sharing his insights on gastroparesis.

Dr. Grover, it was great having you on the program today.

Dr. Grover:
Thank you, Dr. Buch.

Dr. Buch:
For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit ReachMD.com/GIInsights where you can be Part of the Knowledge. Thanks for listening.