Editorial

Challenges in defining, diagnosing, and treating diabetic gastroparesis

Authors:
Timothy R. Angeli[1] and Gregory O'Grady[1,2]

Author Affiliations:
[1]Auckland Bioengineering Institute, University of Auckland, New Zealand.
[2]Department of Surgery, University of Auckland, New Zealand.

Correspondence:
Dr. Timothy R. Angeli, PhD
Auckland Bioengineering Institute
Level 6, 70 Symonds Street
Auckland 1010
New Zealand
t.angeli@auckland.ac.nz

Gastroparesis is a highly symptomatic, multi-factorial disorder characterized by nausea, vomiting, early satiety, abdominal pain, and bloating, in combination with delayed gastric emptying without obstruction.[1] Although the incidence is relatively low in the general population, individuals with diabetes have a substantially increased risk of developing gastroparesis, reported as being over 7-times higher risk for type 2 diabetes, and 30-times higher risk for type 1 diabetes.[2] These associations are explained by several factors, including oxidative stress on the interstitial cells of Cajal (ICC), autonomic neuropathy and impaired neurotransmission, smooth muscle atrophy, and impaired antropyloric / duodenal coordination.[3] The complications of diabetes in combination with gastroparesis cause considerable compounded morbidity and increased risk for patients, creating a compelling need for improved understanding of the prevalence and clinical impact of diabetic gastroparesis, and for new diagnostic and therapeutic strategies.

In this issue of the *Journal of Diabetes and Its Complications*, Dr. Aleppo and colleagues present an excellent analysis of a large cohort study on the prevalence and impact of gastroparesis in patients with type 1 diabetes.[4] Their study included data from over 7,000 participants from 45 clinics through the use of the 'T1D Exchange Clinic Registry', which encompasses clinical data from over 25,000 total patients across 67 U.S.-based centers.[5] This impressive large-scale network collaboration enabled a substantial improvement in cohort size compared to previous studies,[6] and also enabled interesting clinical data associations to be achieved with statistical adjustment for confounders, including important analysis of HbA1c and hypoglycemia.[4] This study highlights the particular benefits and opportunities of large-scale coordinated networks and collaborations in enabling large datasets to be collected, linked, and collated, particularly when participating centers are able to use consistent methodologies. The rapid emergence and growth of such networks over recent years is becoming an ever-more powerful trend in clinical research, especially in the context of less-common disorders that may be otherwise difficult to accurately research. In gastroparesis, the power of large-scale collaborations has been exemplified by the successful National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Gastroparesis Clinical Research Consortium (GpCRC).[7–9] The large datasets generated from such cooperative networks, and the coordinated research efforts they are leading, hold great promise for being a major source of clinical discovery.

Rates of gastroparesis in diabetics have previously been incompletely defined, with a wide range of incidence reported in smaller cohort studies. The results of this new study by Aleppo *et al.* present similar rates of gastroparesis as a previous notable community-based study from a single county (Olmstead) in Minnesota,[6] with similar patient demographics of age, sex, and BMI, providing valuable concordance. Importantly, Aleppo *et al.* present and discuss the association of higher risk of severe hypoglycemia in participants with gastroparesis compared to participants without gastroparesis, despite higher HbA1c levels. These data highlight the fact that individuals with type 1 diabetes and gastroparesis experience poorer glycemic control than non-gastroparetics, which, as the authors state, results from a "mismatch between insulin kinetics and nutrient absorption," related to the unpredictability induced by delayed gastric emptying. Compounding matters further, hyperglycemia itself can contribute to gastric dysrhythmias and delayed gastric emptying.[10,11] Attempts to re-establish more optimal glycemic control can become frustrating for patients and clinicians in this context. Furthermore, the authors identified clear associations between lower socioeconomic status and type 1 diabetes with gastroparesis, including lower household incomes, lower education levels (likely also signifying a lower health literacy), and decreased usage of private health insurance. These socioeconomic factors are clearly causal to the genesis of

gastroparesis, with reduced access to optimal medical care, modern therapies, and quality diets contributing to poorer control.

Clinically, the effective diagnosis and treatment of gastroparesis remains a key unmet challenge.[12] Gastroparesis exists as a poorly defined, highly symptomatic disorder, with an ongoing lack of well-defined pathophysiological mechanism(s). In the study by Aleppo *et al.*, the presence of gastroparesis was taken directly from medical records, but the specific method of diagnosis was not specified and may have varied between the many centers included in the T1D Exchange Clinic Registry.[4] The presence of gastroparesis was an all-or-none criteria, whereas previous studies have used a graded classification of 'definite', 'probable', and 'possible' gastroparesis.[6] Up to 75% of diabetic patients may experience gastrointestinal symptoms to some degree.[13] Other patients with symptoms may have been missed if not screened, and/or subclinical presentations of the disorder may not have been captured, as only the cases severe enough to be labeled as gastroparesis were included. The reported incidence may therefore actually be an under-representation of the true impact of the disorder. Complicating this matter is the fact that the diagnostic criteria for gastroparesis are available but not yet comprehensively applied,[14] with variable diagnostic methods used across different clinics.

The nomenclature is also an area of current interest, with several authors recently suggesting an updated nomenclature is required.[9,15,16] Recent studies and commentaries have suggested that gastroparesis may likely be part of a clinical spectrum that overlaps with or includes other functional gastrointestinal disorders.[15,17,16] This concept has recently been pathophysiologically supported by high-resolution electrical mapping data of spatially complex electrical abnormalities and ICC loss in patients with both gastroparesis[18] and 'chronic unexplained nausea and vomiting' (similar symptoms and epidemiology, but with normal gastric emptying).[16] These data not only propose that the two disorders may likely exist as a spectrum of the same disease state, but also present spatial analysis of bioelectrical abnormalities as a potential future adjunctive diagnostic mechanism.[16,18] As Aleppo *et al.* also point out in their current paper, there is relatively poor correlation between symptoms and gastric emptying time, further highlighting the need for improved diagnostic technology.

There is a current lack of effective therapeutic options for gastroparesis, highlighting the need for future development of new medications, like the promising emerging drug Relamorelin,[19] and increased research into emerging treatment options.[20] The low rates of medication usage reported by Aleppo *et al.* are concerning, and need to be a focus of improvement.[4] High-frequency electrical stimulation by the Enterra device by Medtronic has also shown promise for medically-refractory disease in a range of preliminary studies,[21] but has not yet shown efficacy in a large-scale double-blind randomized controlled trial and lacks a defined mechanisms of action, limiting its FDA approval under a humanitarian device exemption.[22] Future improvements to insulin pumps may help improve glycemic control and address the current disparity between insulin kinetics and nutrient absorption in diabetic gastroparetics, but the barrier to access of expensive technologies for this patient cohort must also be addressed to achieve successful clinical outcomes.

Defining, diagnosing, and treating diabetic gastroparesis is a critical challenge that causes substantial increased risk and frustration for patients and clinicians alike. Clinical breakthroughs for this disorder require the current and ongoing discovery and expansion of clinical data, supported by the research and development of novel

technological diagnostics and therapeutics. The study by Aleppo *et al.* is a welcome addition to our knowledge of this significant problem.

Acknowledgements
TRA is supported by the Edith C. Coan Research Fellowship from the Auckland Medical Research Foundation. Both authors also thank the Health Research Council of New Zealand for support.

References

1. Hasler WL. Gastroparesis: pathogenesis, diagnosis and management. Nat. Rev. Gastroenterol. Hepatol. 2011;8:438–453.
2. Choung RS, Locke GR, Schleck CD, et al. Risk of gastroparesis in subjects with type 1 and 2 diabetes in the general population. Am. J. Gastroenterol. 2012;107:82–88.
3. Kashyap P, Farrugia G. Diabetic gastroparesis: what we have learned and had to unlearn in the past 5 years. Gut 2010;59:1716–1726.
4. Aleppo G, Calhoun P, Foster NC, et al. Reported gastroparesis in adults with type 1 diabetes (T1D) from the T1D exchange clinic registry. J. Diabetes Complicat. 2017;In Press:[E-pub ahead of print].
5. Beck RW, Tamborlane W V., Bergenstal RM, et al. The T1D exchange clinic registry. J. Clin. Endocrinol. Metab. 2012;97:4383–4389.
6. Jung HK, Choung RS, Locke GR, et al. The incidence, prevalence, and outcomes of patients with gastroparesis in Olmsted County, Minnesota, from 1996 to 2006. Gastroenterology 2009;136:1225–1233.
7. Parkman HP, Yates K, Hasler WL, et al. Similarities and differences between diabetic and idiopathic gastroparesis. Clin. Gastroenterol. Hepatol. 2011;9:1056–1064.
8. Grover M, Bernard CE, Pasricha PJ, et al. Clinical-histological associations in gastroparesis: Results from the Gastroparesis Clinical Research Consortium. Neurogastroenterol. Motil. 2012;24:531–539, e249.
9. Pasricha PJ, Colvin R, Yates K, et al. Characteristics of patients with chronic unexplained nausea and vomiting and normal gastric emptying. Clin. Gastroenterol. Hepatol. 2011;9:567-576–4.
10. Coleski R, Hasler WL. Coupling and propagation of normal and dysrhythmic gastric slow waves during acute hyperglycaemia in healthy humans. Neurogastroenterol. Motil. 2009;21:492–9, e1-2.
11. Schvarcz E, Palmér M, Aman J, et al. Physiological hyperglycemia slows gastric emptying in normal subjects and patients with insulin-dependent diabetes mellitus. Gastroenterology 1997;113:60–66.
12. Tack J. The difficult patient with gastroparesis. Best Pr. Res. Clin. Gastroenterol. 2007;21:379–391.
13. Schvarcz E, Palmér M, Ingberg CM, et al. Increased prevalence of upper gastrointestinal symptoms in long-term type 1 diabetes mellitus. Diabet. Med. 1996;13:478–481.
14. Abell TL, Camilleri M, Donohoe K, et al. Consensus recommendations for gastric emptying scintigraphy: a joint report of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine. Am. J. Gastroenterol. 2008;103:753–763.
15. Harer K, Pasricha P. Chronic unexplained nausea and vomiting or gastric neuromuscular dysfunction (GND)? An update on nomenclature, pathophysiology and treatment, and relationship to gastroparesis. Curr. Treat Options Gastroenterol. 2016;14:410–419.
16. Angeli TR, Cheng LK, Du P, et al. Loss of interstitial cells of Cajal and patterns of gastric dysrhythmia in patients with chronic unexplained nausea and vomiting. Gastroenterology 2015;149:56–66.e5.

17. Lacy BE. Functional Dyspepsia and Gastroparesis: One Disease or Two? Am. J. Gastroenterol. 2012;107:1615–1620.
18. O'Grady G, Angeli TR, Du P, et al. Abnormal initiation and conduction of slow-wave activity in gastroparesis, defined by high-resolution electrical mapping. Gastroenterology 2012;143:589-598–3.
19. Chedid V, Camilleri M. Relamorelin for the treatment of gastrointestinal motility disorders. Expert Opin. Investig. Drugs 2017;26:1189–1197.
20. Stevens JE, Jones KL, Rayner CK, et al. Pathophysiology and pharmacotherapy of gastroparesis: current and future perspectives. Expert Opin. Pharmacother. 2013;14:1171–1186.
21. O'Grady G, Egbuji JU, Du P, et al. High-frequency gastric electrical stimulation for the treatment of gastroparesis: a meta-analysis. World J. Surg. 2009;33:1693–1701.
22. Camilleri M. Clinical practice. Diabetic gastroparesis. N. Engl. J. Med. 2007;356:820–829.