

## Starving for a Cure

Among the myriad of non-communicable diseases plaguing mankind, diabetes mellitus has established itself as the important if not the most prominent disorder. Diabetes mellitus brings with it the spectre of serious often life-threatening micro- and macrovascular complications. Diabetes mellitus hardly spares any organ systems—some are impacted more than others. While the more prominent complications, such as cardiovascular disease, nephropathy and retinopathy, have taken centre stage in terms of early diagnosis and treatment, some equally distressing complications have been left in relative neglect. One of these lesser-known complications is diabetic gastroparesis (DGP).

The prevalence of DGP is quite high. A recent meta-analysis looking at the global prevalence of DGP reported an overall prevalence of 9.3%.<sup>[1]</sup> The data from the United States indicate that this disease is not very common in North America, which indirectly implies that other areas of the world have a much higher prevalence of gastroparesis.<sup>[2]</sup> The prevalence of DGP was reported to be 19% in Brazil, 13.79% in Thailand and an astonishingly high 40% in a study from China.<sup>[1]</sup> In a larger study from the UK, Asians formed the second-largest ethnic group among patients with gastroparesis.<sup>[3]</sup> The data on DGP from Asian countries, however, are limited. It is suspected that the DGP has a high prevalence in Asia but is being under-reported due to a lack of awareness among physicians, a paucity of diagnostic equipment and a dearth of effective treatment options.<sup>[4]</sup> In a survey of gastroenterologists from various Asian countries, only 24.2% and 54.2% could correctly identify the definition and diagnostic gold standards of gastroparesis, respectively.<sup>[5]</sup> The probable high prevalence and lack of awareness in healthcare workers indicate that a lot needs to be performed to improve the diagnosis and management of this disease.

The typical symptoms of DGP include early satiety, bloating, nausea, vomiting, postprandial fullness and weight loss. Interestingly, persistent nausea and vomiting seen in gastroparesis may not always result in weight loss. Many patients with idiopathic gastroparesis expend much fewer calories than they consume, resulting in weight gain.<sup>[6]</sup> Whether this is also true in DGP is not yet known. Still, patients with DGP and type 2 diabetes mellitus (T2DM) are more likely to be overweight or obese when compared to those with type 1 diabetes mellitus (T1DM) or idiopathic gastroparesis.<sup>[3]</sup> The presence of obesity or lack of weight loss should not deter the physician from suspecting DGP.

DGP, apart from these typical symptoms, also impairs the quality of life in patients with diabetes.<sup>[7]</sup> Furthermore, the mortality rates of patients with DGP are higher than those without it.<sup>[8]</sup> It is unclear whether this is entirely due to

comorbidities or due to a direct effect of DGP. Therefore, timely diagnosis of DGP has potential benefits beyond mere symptom control.

Although autonomic neuropathy is considered to be the chief mechanism behind DGP, there is enough evidence to suggest that other mechanisms, such as loss of enteric neurons, intestinal pacemaker cells (interstitial cells of Cajal) and smooth muscle dysfunction, also play a role in DGP. These events are mediated by a variety of pathways, including apoptosis, ischaemia and inflammation.<sup>[9]</sup> This implies that the mere absence of autonomic neuropathy should not prevent the clinician from considering a diagnosis of DGP.

The definitive diagnosis of DGP requires delayed gastric emptying by scintigraphy, but the limited availability of this investigation in primary- and secondary-level healthcare facilities hinders the diagnosis. The categorisation used by Jung *et al.*,<sup>[8]</sup> which proposed entities such as “possible gastroparesis,” “probable gastroparesis” and “definitive gastroparesis,” may be useful in increasing the recognition of these disorders and helping direct referral to higher centres in selected cases.

The traditional treatment options for DGP include the use of anti-emetic and gastric motility-enhancing drugs, along with dietary modifications. Better glycaemic control may also help in improving the symptoms of DGP. The use of a small-particle low-fat and fibre diet or a liquid diet can help alleviate symptoms. The commonly used drugs are metoclopramide, domperidone, levosulpiride and erythromycin. While these drugs do reduce symptoms, their use is limited by adverse effects.<sup>[10-12]</sup>

Ghrelin receptor analogues, such as ulimorelin, have been tried in DGP but have met with little success.<sup>[13,14]</sup> A newer ghrelin agonist, relamorelin, has shown better results and is currently undergoing phase 3 trials.<sup>[15]</sup> A trial of 5-hydroxytryptamine 4 (5HT-4) agonist (velusetrag) reported improvement in gastric emptying although only the lowest dose showed improvement in symptoms.<sup>[16]</sup> More studies with ghrelin receptor analogues are underway. A neurokinin-1 antagonist (trapiditant) is also under investigation.<sup>[17]</sup> Camicinal, a small-molecule motilin agonist, has also shown promise in initial studies.<sup>[18]</sup>

These ongoing investigations, notwithstanding the search for safer and more potent therapies for DGP, are far from over. In this issue, Singh *et al.*<sup>[19]</sup> have furthered this search by studying an indigenous plant called *Pistacia lentiscus*. *Pistacia lentiscus* has been earlier reported to have some benefits in gastrointestinal disorders, including improvement in gut motility.<sup>[20,21]</sup> Singh *et al.* have found that the stem extract of *Pistacia lentiscus* improved gastric emptying and symptoms

of DGP to an extent comparable to levosulpiride without causing any significant adverse effects. Metabolic parameters such as glycaemia and low-density lipoprotein (LDL) levels were improved in the *Pistacia lentiscus* group as compared to levosulpiride. The findings of Singh *et al.* are promising and open up a new avenue for the therapy of DGP. If the results are replicated in other studies, *Pistacia lentiscus* stem extract can become a safe yet effective agent in the present armamentarium against DGP.

The increased recognition of DGP by doctors involved in the care of patients with diabetes mellitus is the need of the hour. It will not only enable patients to get access to the available treatment options but also fuel research in this relatively neglected area. It would be prudent to hope that more effective and safe therapeutic options for DGP emerge in the future.

#### S. V. Madhu, Nishant Raizada

Department of Endocrinology, Centre for Diabetes Endocrinology and Metabolism, University College of Medical Sciences and Guru Teg Bahadur Hospital, New Delhi, India

**Address for correspondence:** Dr. S. V. Madhu,  
Department of Endocrinology, Centre for Diabetes Endocrinology and Metabolism, University College of Medical Sciences and Guru Teg Bahadur Hospital, New Delhi - 110 095, India.  
E-mail: drsvmadhu@gmail

## REFERENCES

- Li L, Wang L, Long R, Song L, Yue R. Prevalence of gastroparesis in diabetic patients: A systematic review and meta-analysis. *Sci Rep* 2023;13:14015. doi: 10.1038/s41598-023-41112-6.
- Syed AR, Wolfe MM, Calles-Escandon J. Epidemiology and diagnosis of gastroparesis in the United States: A population-based study. *J Clin Gastroenterol* 2020;54:50-4.
- Ye Y, Jiang B, Manne S, Moses PL, Almansa C, Bennett D, *et al.* Epidemiology and outcomes of gastroparesis, as documented in general practice records, in the United Kingdom. *Gut* 2021;70:644-53.
- Hsu K-J, Liao C-D, Tsai M-W, Chen C-N. Effects of exercise and nutritional intervention on body composition, metabolic health, and physical performance in adults with sarcopenic obesity: A meta-analysis. *Nutrients* 2019;11:E2163. doi: 10.3390/nu11092163.
- Lee KN. Gastroparesis in Asia: An area still unfamiliar to Asian gastroenterologists. *J Neurogastroenterol Motil* 2021;27:5-7.
- Homko CJ, Zamora LC, Boden G, Parkman HP. Bodyweight in patients with idiopathic gastroparesis: roles of symptoms, caloric intake, physical activity, and body metabolism. *Neurogastroenterol Motil* 2014;26:283-9.
- Talley NJ, Young L, Bytzer P, Hammer J, Leemon M, Jones M, *et al.* Impact of chronic gastrointestinal symptoms in diabetes mellitus on health-related quality of life. *Am J Gastroenterol* 2001;96:71-6.
- Jung H, Choung RS, Locke GR, Schleck CD, Zinsmeister AR, Szarka LA, *et al.* The incidence, prevalence and outcomes of patients with gastroparesis in Olmsted County, Minnesota from 1996 to 2006. *Gastroenterology* 2009;136:1225-33.
- Bharucha AE, Kudva YC, Prichard DO. Diabetic gastroparesis. *Endocr Rev* 2019;40:1318-52.
- Patterson D, Abell T, Rothstein R, Koch K, Barnett J. A double-blind multicenter comparison of domperidone and metoclopramide in the treatment of diabetic patients with symptoms of gastroparesis. *Am J Gastroenterol* 1999;94:1230-34.
- Lanning RK, Zai CC, Müller DJ. Pharmacogenetics of tardive dyskinesia: An updated review of the literature. *Pharmacogenomics* 2016;17:1339-51.
- Silvers D, Kipnes M, Broadstone V, Patterson D, Quigley EM, McCallum R, *et al.* Domperidone in the management of symptoms of diabetic gastroparesis: Efficacy, tolerability, and quality-of-life outcomes in a multicenter controlled trial. DOM-USA-5 study group. *Clin Ther* 1998;20:438-53.
- McCallum RW, Lembo A, Esfandyari T, Bhandari BR, Ejksjaer N, Cosentino C, *et al.* Phase 2b, randomized, double-blind 12-week studies of TZP-102, a ghrelin receptor agonist for diabetic gastroparesis. *Neurogastroenterol Motil* 2013;25:e705-17.
- Ejksjaer N, Dimceviski G, Wo J, Hellström PM, Gormsen LC, Sarosiek I, *et al.* Safety and efficacy of ghrelin agonist TZP-101 in relieving symptoms in patients with diabetic gastroparesis: A randomized, placebo-controlled study. *Neurogastroenterol Motil* 2010;22:1069-e281. doi: 10.1111/j.1365-2982.2010.01519.x.
- Chedid V, Camilleri M. Relamorelin for the treatment of gastrointestinal motility disorders. *Expert Opin Investig Drugs* 2017;26:1189-97.
- Abell TL, Kuo B, Esfandyari T, Pfeifer ND, Grimaldi M, Renzulli C, *et al.* A randomized, double-blind, placebo-controlled, phase 2b study of the efficacy and safety of velusetrag in subjects with diabetic or idiopathic gastroparesis. *Neurogastroenterol Motil* 2023;35:e14523. doi: 10.1111/nmo.14523.
- Carlin JL, Lieberman VR, Dahal A, Keefe MS, Xiao C, Birznieks G, *et al.* Efficacy and safety of tradipitant in patients with diabetic and idiopathic gastroparesis in a randomized, placebo-controlled trial. *Gastroenterology* 2021;160:76-87.e4.
- Chapman MJ, Deane AM, O'Connor SL, Nguyen NQ, Fraser RJL, Richards DB, *et al.* The effect of camicinal (GSK962040), a motilin agonist, on gastric emptying and glucose absorption in feed-intolerant critically ill patients: A randomized, blinded, placebo-controlled, clinical trial. *Crit Care* 2016;20:232.
- Singh A, Kant R, Raina R, Dhingra V, Nema R, Bairwa MC, *et al.* Efficacy of *Pistacia lentiscus* Plant (Rumi Mastagi) in Comparison to Levosulpiride in Patients with Diabetic Gastroparesis: A Double-Blind Non-Inferior Randomised Control Trial Study. *Indian J Endocr Metab* 2023;28:37-44.
- Al-Said MS, Ageel AM, Parmar NS, Tariq M. Evaluation of mastic, a crude drug obtained from *Pistacia lentiscus* for gastric and duodenal anti-ulcer activity. *J Ethnopharmacol* 1986;15:271-8.
- Mahjoub F, Salari R, Yousefi M, Mohebbi M, Saki A, Rezayat KA. Effect of pistacia atlantica kurdica gum on diabetic gastroparesis symptoms: a randomized, triple-blind placebo-controlled clinical trial. *Electron Physician* 2018;10:6997-7007.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

#### Access this article online

##### Quick Response Code:



##### Website:

<https://journals.lww.com/indjem/>

##### DOI:

10.4103/IJEM.IJEM\_63\_24

**How to cite this article:** Madhu SV, Raizada N. Starving for a cure. *Indian J Endocr Metab* 2024;28:1-2.