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EDITORIAL

Diabetic Gastroparesis

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ABSTRACT

This editorial addresses the importance of diabetic gastroparesis as a marker of poor glycemic control, other vascular complications, and suboptimal therapeutic outcomes. Highlighting the need to prevent and manage gastroparesis, it tries to understand why the condition has not received its due share of attention. Complexities in screening, diagnosis, and management all contribute to the lack of focus on this autonomic neuropathy. The editorial reinforces the need to enhance awareness about diabetic gastroparesis and utilize good clinical sense and rational prescription writing in order to limit the impact of this complication.

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UNDER-ADDRESSED COMPLICATIONS

The syndrome of diabetes is characterized by myriad complications, ranging from biomedical to psychological, acute to chronic, vascular to inflammatory. As the science of diabetology has evolved, so has diabetes care. From a firefighting approach, concerned with minimizing hyperglycemia and managing hypoglycemia, we have become more proactive and planned in our attitude towards diabetes.

Modern diabetes management lays emphasis not only on acute treatment or symptomatic relief but also on the prevention of long-term complications. Traditionally, such focus has concentrated mostly on macrovascular complications such as cardiovascular disease (CVD) and its outcomes [1]. In recent years, however, attention has also been paid to macrovascular complications such as diabetic kidney disease, and complex comorbidities like erectile dysfunction [2, 3].

Many aspects of diabetes, unfortunately, continue to be ignored. These complications, even though they cause significant morbidity,

do not receive adequate attention from researchers or clinicians. Some examples include conditions such as diabetic autonomic neuropathy, frozen shoulder or periarthritis, diabetic cheiroarthropathy, and diabetic dermopathy, for which no specific disease-modifying therapy has been developed so far [4, 5].

Yet another vascular complication, which is often ignored, is diabetic gastrointestinal autonomic neuropathy.

DIABETIC GASTROPARESIS

The comprehensive review by Krishnasamy and Abell describes diabetic gastroparesis in detail [6]. Defined as delayed gastric emptying with associated upper gastrointestinal symptoms in the absence of any mechanical obstruction [7], diabetic gastroparesis may present with a variety of symptoms. These include postprandial fullness, nausea, vomiting, anorexia, and weight loss, with or without abdominal pain. The long list of complaints is accompanied by an equally exhaustive list of differential diagnoses, including iatrogenic or drug-induced delay in gastric emptying. Diabetic gastroparesis is accoutered by poor glucose control, suboptimal nutritional and hydration status, greater risk of CVD, hypertension and retinopathy, frequent need for hospitalization, and poor quality of life [6]. Thus, diabetic gastroparesis is not only a marker of poor current control but also a predictor of poor future outcomes.

THE VICIOUS GASTRO-GLYCEMIC CYCLE

Glucose metabolism is characterized by close cross talk between the gut and the pancreas [8]. This is specifically true for gastric emptying. Sustained ambient hyperglycemia retards the process of emptying, while hypoglycemia hastens it. This seems to be a homeostatic adaption, geared towards early achievement and maintenance of euglycemia. While hyperglycemia leads to gastroparesis, gastroparesis may also worsen the former by creating a mismatch between nutrient or calorie absorption on the one hand and endogenous insulin release (whether spontaneous or insulinotropic drug facilitated) on the other.

Gastroparesis is also linked with fluctuations in glycemic control due to variable nutrient absorption. Such glycemic variability causes endothelial injury and is an independent risk factor for adverse cardiovascular outcomes [9]. Thus, the gastro-glycemic connection, once disrupted, sets in motion a vicious cycle of poor metabolic control and inadequate gastric function, which feed on each other. This vicious cycle, which characterizes diabetic gastroparesis, may be difficult to break (Fig. 1).

TROJAN HORSE

A timely diagnosis and early, intensive, multifactorial cardiovascular risk mitigation strategy has been shown to delay the onset and progression of cardiac autonomic neuropathy in persons living with type 2 diabetes [10]. It stands to reason, therefore, that a similar strategy may reduce the risk of diabetic gastroparesis as well. In fact, the prevalence of diabetic gastroparesis has been shown to be related to severity of hyperglycemia, measured as HbA1c, but not to duration of diabetes [11].

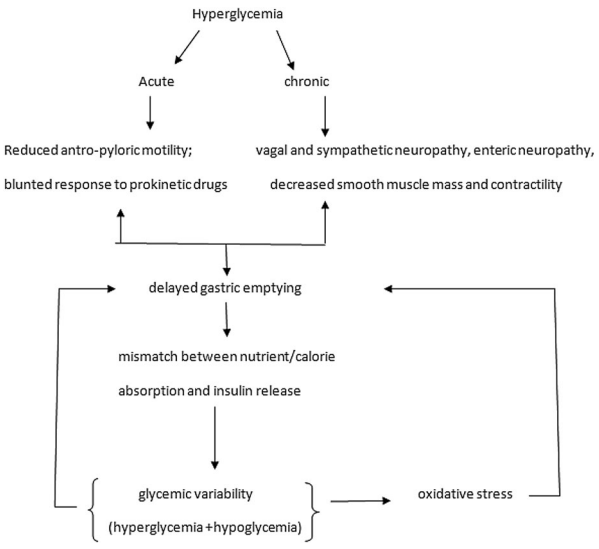

Fig. 1 The vicious gastro-glycemic cycle of diabetic gastroparesis

However, gastroparesis can also be termed the Trojan horse of diabetes care. Once it occurs, it makes management of diabetes more challenging and difficult. Relatively less emphasis is paid to diabetic gastroparesis as compared to other complications of diabetes. The American Diabetes Association standards of care 2018 devote a total of 113 words to gastrointestinal neuropathies, and 155 words to the management of diabetic gastroparesis, out of a total of 14 pages focusing on microvascular complications [12].

COMPLEXITY OF SCREENING

One reason for this may be the lack of suitable objective, validated, non-invasive, symptom-based tools to screen for and diagnose diabetic gastroparesis. To meet the current definition of gastroparesis, one must demonstrate delayed gastric emptying as well as prove absence of mechanical obstruction or ulceration [13]. This would require invasive investigations that may not always be available, accessible, or affordable.

The existing symptom-based questionnaires, such as the Gastroparesis Cardinal Symptom Index (GCSI) [14], have shortcomings which limit their utility. The GCSI, though based on patient-reported symptom severity, does not measure abdominal pain. Other scoring systems grade the severity of gastroparesis on symptomatology, quality of life, as well as response to therapy, but are not useful for screening of patients [15–17]. The Federal Drug Agency's guidance on symptoms scoring systems is a welcome addition, but does not obviate, the need for invasive diagnostic investigations [18]. This draft suggests evaluation of the five core symptoms of gastroparesis: nausea, vomiting, early satiety, abdominal pain and postprandial fullness. There is no validated tool which can help physicians differentiate between gastroesophageal reflux disorder (GERD) or acid peptic disease (APD) and gastroparesis.

Table 1 Drugs which may mimic diabetic gastroparesis

Glucose-lowering drugs
Glucagon-like peptide 1 receptor agonists (GLP1RA)
Alpha-glucosidase inhibitors (AGIs)
Pramlintide
Metformin
Orlistat
Sodium glucose cotransporter 1 (SGLT1) antagonists, e.g., sotagliflozin
High-fiber diet
Gastrotropic drugs
Proton pump inhibitors
H2 receptor antagonists
Sucralfate
Aluminum hydroxide-containing antacids
Drugs used in painful neuropathy
Tricyclic antidepressants
Opioid analgesics
Other hormones
Progesterone
Octreotide

PYROMANIAC FIREFIGHTING: ADDING FUEL TO FIRE

Another factor which complicates the diagnosis of diabetic gastroparesis is the use of drugs which may alter gastric emptying or cause gastrointestinal symptoms. Many of the iatrogenic causes of gastroparesis are either glucose-lowering agents or tropic medications (Table 1). While it is difficult to differentiate between diabetic gastroparesis and drug-induced gastrointestinal adverse events, a few pointers are listed in Table 2.

Quite frequently, diabetic gastroparesis may be unmasked, precipitated, or worsened by initiation of a glucose-lowering drug with effects on the gastrointestinal tract. This means that the ability to manage glycemia, in a safe and

Table 2 Differential diagnosis of diabetic gastroparesis and drug-induced gastrointestinal symptoms

Clinical parameter	Diabetic gastroparesis	Drug-induced symptoms
Age	More common in elderly	No relation
Gender	More common in women	No difference
Duration of diabetes	May be more common in longer-duration diabetes	No relation with duration of diabetes
Presence of other vascular complications	More common	No relation
Food intake	Usually not impaired	Loss of appetite, metallic taste may occur
Pain	May or may not occur	May be more common
Lower GI (gastrointestinal) symptoms	Less common	More common, e.g., flatulence, oily stool
Relation to initiation of offending drug	No relation	Within few days
Course	Variable, progressive	May be self-limiting; result in self drug discontinuation
Glycemic control	Poor	No relation
Glycemic variability	High	No relation

well-tolerated manner, in a person with diabetic gastroparesis, may be challenged at times.

A similar situation may occur in a misguided attempt to improve gastric health by using the ubiquitously prescribed proton pump inhibitors, H2 receptor antagonists, and sucralfate or aluminum hydroxide-based antacids [19, 20]. These drugs are a cause of delayed gastric emptying. Such "therapeutic adventures", akin to a pyromaniac leading a firefighting operation, may harm rather than improve diabetic gastroparesis. A combination of acid-suppressing and prokinetic drugs is indicated only if dyspepsia and gastroparesis co-exist with each other.

GOOD CLINICAL SENSE

While it is easy to suggest that abdominal imaging endoscopy and scintigraphy be advised for every person complaining of upper gastrointestinal symptoms, it is naïve to expect the health care system to be able to handle this burden. One must therefore fall back upon "good clinical sense" [20] in order to address the problem of diabetic gastroparesis.

A detailed history should be able to identify gastroparesis, and rule out contributory factors, including iatrogenic ones. A complete physical examination will offer pointers to a rational and cost-effective ordering of investigations.

GASTRO-FRIENDLY MANAGEMENT

The management strategy of diabetic gastroparesis is multifactorial. A careful drug history must be taken to exclude prescription, over the counter, and alternative medicine drugs, as well as nutritional supplements which may worsen gastric motility [6]. In particular, the need for prescribing proton pump inhibitors or H2 receptor blockers must be reassessed in a person with gastroparesis. In a disorder of gastric motility, the drug of choice should be a prokinetic agent, and not an antacid or acid-

suppressing drug. Fixed dose combinations of these drug classes serve as a Trojan horse which prevents correction of gastroparesis, leads to poor glycemic control with high variability, and sets in motion a vicious cycle of complications and poor outcomes.

OVERCOMING CLINICAL INERTIA

A concerted effort must be made by diabetes care providers to overcome this clinical inertia. A high index of suspicion and a low threshold of tolerance for gastroparetic symptoms should help overcome the clinical inertia that we display towards this significant complication.

A careful clinical assessment may reduce dependence on resource-heavy investigations and prompt early institution of dietary and pharmacological therapy. Knowledge of gastrointestinal side effects of drugs that are used commonly in diabetes care will help craft prescriptions which are effective as well as safe and well tolerated. Finally, emphasis on early glycemic control, using modern, gastrointestinally friendly oral drugs and modern insulins with low risk of hypoglycemia should help prevent diabetic gastroparesis from having to prophesize negative consequences.

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