

Advances in Diabetic Gastroparesis

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This review addresses the advances in our understanding of the epidemiology and mechanisms in diabetic gastroparesis and dyspepsia. The mechanisms discussed include: blood glucose levels at the time of presentation, “autovagotomy,” and the intrinsic innervation (particularly the interstitial cells of Cajal and nitrergic nerves). In animal models of diabetic gastroparesis, there is evidence that homeostatic mechanisms are activated in the enteric nervous system to compensate for the loss of extrinsic innervation. Understanding these advances is key to the development of novel therapeutic strategies and for making rational choices in the management of diabetic gastroparesis and dyspepsia.

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Gastrointestinal symptoms are frequently encountered in patients with diabetes mellitus. *Diabetic enteropathy* refers to all the gastrointestinal complications of diabetes and may include dysphagia, heartburn, nausea and vomiting, abdominal pain, constipation, diarrhea, and fecal incontinence.¹ Although not generally considered important causes of mortality in diabetic patients, these symptoms can be encountered in up to 75% of diabetic outpatients evaluated at a tertiary referral center.¹ However, the prevalence of gastrointestinal symptoms among community diabetic patients is lower and will be discussed under the heading of epidemiology.

Table 1
 Prevalence (%) of Gastrointestinal and Neurological Symptoms
 Among Diabetic Residents of Olmsted County, MN,
 Compared to Their Respective Community Controls

Symptoms/Syndrome	IDDM Patients (n = 138)	IDDM Controls (n = 170)	NIDDM Patients (n = 217)	NIDDM Controls (n = 218)
Irritable bowel syndrome				
Rome criteria	10.9	7.6	5.1	8.3
Manning criteria	8.0	8.8	5.5	7.8
Constipation				
Symptoms only	16.7	13.5	10.1	11.5
Symptoms and/or laxatives	27.0	19.0	17.0	15.0
Dyschezia	2.9	3.5	2.3	2.3
Diarrhea	0	0	0	0
Fecal incontinence	0.7	1.2	4.6	1.8
Nausea/vomiting	11.6	10.6	6.0	5.5
Dyspepsia	18.8	20.6	13.4	17.4
Heartburn				
Symptoms only	11.6*	22.9	19.8	24.3
Symptoms and/or antacids	18.8*	36.5	24.0	36.2
P neuro symptoms (overall)	50.0	47.1	65.9*	50.5
Numbness	34.8	28.2	41.5*	21.6
Muscular weakness	33.3	31.2	54.4*	43.6
A neuro symptoms (overall)	9.4	5.9	7.8	7.3
Insufficient sweating	6.5*	1.8	5.5	5.5
Gustatory sweating	3.6	4.1	2.3	2.8

* $P < .05$ (univariate association, diabetes subgroup vs corresponding controls).

P neuro, peripheral neuropathy; A neuro, autonomic neuropathy; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus.

Note that people with IDDM have increased prevalence of constipation and/or use of laxatives and decreased prevalence of heartburn.

Prevalence of dyspepsia is not greater in diabetics than in controls. Data from Maleki et al.⁶

Kassender recognized asymptomatic gastric retention in diabetics in 1958² and coined the term *gastroparesis diabetorum*. Since the original report, the term has been used to

reflect symptomatic as well as asymptomatic gastric retention, and more recently, the term *diabetic dyspepsia* has been used to reflect the spectrum of postprandial symptoms

in diabetics attributable to upper gastrointestinal dysfunctions, including those associated with delayed gastric emptying.² Thus, whereas nausea, vomiting, and early satiation after

meals were the classical symptoms of gastroparesis, the term dyspepsia in addition reflects bloating, fullness, and pain in the upper abdomen.³

Epidemiology of Gastrointestinal Symptoms in Diabetes

The first community-based epidemiological studies of symptoms in diabetics were performed in Germany and Finland by the groups of Enck and colleagues⁴ and Janatuinen and colleagues.⁵ These studies provided the surprising information that the only gastrointestinal problems with higher prevalence in diabetics than

study demonstrated a lower prevalence of heartburn among the participants with type I diabetes. Factors that may contribute to this finding are the possibility of vagal neuropathy reducing the sensation of heartburn and the strong recommendation by diabetologists to patients to avoid nonsteroidal anti-inflammatory medications to protect their renal function.

A more recent questionnaire-based community study in South Eastern Australia (Table 2) reported more diarrhea, fecal incontinence, dysphagia, and postprandial fullness among diabetics than among controls.⁷ In

associated with diabetic complications but not with current glycemic control (blood glucose and HbA1c).⁸ The latter study also confirmed the findings of Kim and colleagues⁹ in a tertiary referral group at the Mayo Clinic.

Symptoms and Signs of Gastroparesis and Dyspepsia in Diabetics

Nausea and vomiting, often accompanied by weight loss and early satiety, are common gastrointestinal symptoms among patients with diabetes. Episodes of nausea and vomiting may last days to months or occur in cycles, and blood glucose concentrations may be poorly controlled. Frequent episodes of hypoglycemia are encountered when food delivery to the small bowel for absorption is not sufficient to match the hypoglycemic effect of exogenously administered insulin. *Diabetic gastroparesis* is frequently associated with retinopathy, nephropathy, peripheral neuropathy, and other forms of autonomic dysfunction, including abnormal pupillary responses, anhidrosis, gustatory sweating, orthostatic hypotension, impotence, retrograde ejaculation, and dysfunction

Episodes of nausea and vomiting may last days to months or occur in cycles.

in controls were constipation, use of laxatives, and history of gall bladder surgery. The main findings were confirmed (Table 1) by a questionnaire-based study in Olmsted County, Minnesota.⁶ This showed that only constipation and use of laxatives were more prevalent in type I (not type II) diabetics than in controls matched for age and gender.⁶

The high prevalence of functional gastrointestinal disorders such as irritable bowel syndrome, constipation, and functional dyspepsia in Western civilizations confounds any estimates of the prevalence of diabetic enteropathy based on symptoms alone. Prevalence figures do not assess the impact or severity of the upper gastrointestinal symptoms suggestive of dyspepsia or gastroparesis. Thus, although Maleki and colleagues identified nausea, vomiting, or dyspepsia in around 11% of type I diabetics and around 6% of type II diabetics, these prevalence figures were not significantly different from age- and gender-matched nondiabetic community controls.⁶

Paradoxically, the Olmsted County

contrast to the three prior studies,⁴⁻⁶ which included at least 10% type I diabetics, in the study from Australia, 95% of the cohort were type II diabetics. Constipation (other than the symptom of "anal blockage") was not significantly more prevalent in diabetics, in contrast to the three other epidemiological studies. The odds ratio for nausea was close to signifi-

Diabetic gastroparesis is associated with abnormal motor and sensory functions.

cant (OR .98–2.35). The nature of these symptoms suggests that they may result from motor and sensory abnormalities of the gastrointestinal tract. Epidemiological studies attempted to identify risk factors for developing gastrointestinal symptoms among diabetics. In two Australian studies,^{7,8} a community evaluation found an association between self-reported poor glycemic control and gastrointestinal symptom complexes.⁷ A clinic questionnaire-based study showed that gastrointestinal symptoms were

tion of the urinary bladder. A succussion splash or large gastric residual after overnight fast may be documented clinically. Rarely, patients with gastroparesis present with retrosternal or epigastric pain, and cardiac, biliary, or pancreatic disease may be considered.

Dyspepsia refers to postprandial upper-abdominal discomfort, early satiety, bloating, distention, as well as nausea and vomiting. There are some patients who have increased gastric sensitivity, whereas others lack an accommodation response to

Table 2
Epidemiology of Gastrointestinal Symptoms and Complexes
in Diabetics (94.8% Non-Insulin-Dependent Diabetes Mellitus)
and Controls in Southeastern Australia

Symptom/Symptom Complex	Controls	Patients with Diabetes	Unadjusted Odds Ratio (95% CI)
Abdominal pain or discomfort	10.8	13.5	1.20 (0.97-1.73)
Early satiety	4.3	5.2	1.22 (0.79-1.91)
Postprandial fullness	5.2	8.6	1.72 (1.21-2.45)
Bloating	11.4	12.3	1.09 (0.81-1.46)
Heartburn	10.8	13.5	1.30 (0.97-1.73)
Nausea	3.5	5.2	1.51 (0.97-2.35)
Vomiting	1.1	1.7	1.58 (0.73-3.44)
Dysphagia	1.7	5.4	3.33 (2.12-5.23)
Diarrhea or constipation	10.0	15.6	1.69 (1.29-2.21)
Anal blockage	5.0	7.7	1.60 (1.10-2.32)
>3 bowel movements per day	5.3	8.4	1.64 (1.14-2.34)
<3 bowel movements per week	3.6	4.3	1.19 (0.73-1.93)
Lumpy or hard stools	5.5	7.4	1.36 (0.93-1.98)
Loose or watery stools	5.4	10.0	1.95 (1.40-2.72)
Urgency	5.2	9.3	1.88 (1.33-2.65)
Fecal incontinence	0.8	2.6	3.39 (1.77-6.47)
Esophageal symptoms	11.5	15.4	1.40 (1.06-1.83)
Upper dysmotility symptoms	15.3	18.2	1.24 (0.96-1.59)
Any bowel symptom	18.9	26.0	1.51 (1.21-1.89)
Diarrhea symptoms	10.0	15.6	1.67 (1.27-2.19)
Constipation symptoms	9.2	11.4	1.26 (0.92-1.72)

Note higher prevalence of diarrhea, incontinence, dysphagia, and postprandial fullness, and of gastrointestinal symptom complexes in diabetics than controls. Note upper dysmotility symptoms just fail to reach significance. Reproduced, with permission, from Bytzer et al.⁷

feeding. Food ingestion may stimulate tension receptors in the nonaccommodating gastric wall, resulting in perception of bloating, early satiety, nausea, indigestion, or pain.

Pathophysiology and Mechanisms in Diabetic Gastroparesis

Diabetic gastroparesis is associated with abnormal motor and sensory

functions. The factors involved in the development of abnormal sensory or motor functions of the upper gut in diabetes are shown in Table 3.

Autonomic Neuropathy

Abnormal gastrointestinal motility in diabetes mellitus is incompletely understood and is likely multifactorial. It results in impaired gastric contractility or abnormal myoelectrical con-

trol.¹⁰ The syndrome is typically seen in patients with type I or insulin-dependent diabetes mellitus (IDDM). Peripheral neuropathy is present in the majority of patients with enteropathy, and other forms of autonomic neuropathy (eg, orthostatic hypotension) are common. Previous work has attributed these motility disorders mainly to vagal nerve dysfunction or autovagotomy.¹¹ Motor

Table 3
Pathophysiology of Diabetic Gastroparesis

Autonomic (vagal) neuropathy
Intrinsic neuropathy:
Excitatory and inhibitory nerves
Interstitial cells of Cajal
Acute elevations of blood glucose
Psychosomatic factors

abnormalities of the small intestine observed in symptomatic diabetic patients^{12,13} are often indistinguishable from those seen in patients with other syndromes affecting postganglionic sympathetic function.¹⁴ Vagal dysfunction is probably critical in gastric stasis of solid food. Electrolyte imbalances due to diabetic ketoacidosis (eg, hypokalemia) and uremia may further aggravate impaired motor function in diabetic patients.

Vagal neuropathy was considered a likely cofactor preventing the gastric accommodation response.¹⁵⁻¹⁷ However, a recent study of patients with diabetes and vagal neuropathy showed normal postprandial change in gastric volume measured using single photon emission computed tomography imaging.¹⁸ This is consistent with the normalization of gastric accommodation in rats within 30 days after vagotomy.¹⁹ This normalization is suggestive of an adaptive response, which was inhibited in rats treated with tetrodotoxin, suggesting that enteric neurons are involved in the adaptation to chronic vagal denervation.¹⁹ In patients with prior gastric surgery that included vagotomy, the tonic response to a meal was maintained, whereas the phasic contractile response was reduced.²⁰ The effect of glycemia on proximal gastric motor and sensory function is also controversial; Hebbard

and colleagues²¹ showed significant disturbances in these functions. In contrast, other studies^{18,22} showed no reduction of gastric relaxation or inhibition of the volume increase postprandially, despite the diabetes being associated with hyperglycemia in the former study and chronic vagal neuropathy in the latter study.

Enteric (Intrinsic) Neuropathy

The enteric nerves have been studied most thoroughly in experimental animal models of diabetes. Immunohistochemical findings contrasted with the observations of Yoshida, Schuffler and colleagues,²³ who used silver staining techniques to evaluate the myenteric plexus. These nerves appeared morphologically normal in patients with diabetes.²³ In contrast, Belai, Burnstock, and colleagues²⁴⁻²⁸ documented disturbances in intrinsic nerves and the protective role of gangliosides in a series of elegant studies in the streptozotocin model of diabetes. For example, they showed reduced substance P (an excitatory neurotransmitter), increased VIPergic (an inhibitory neurotransmitter), and increased calcitonin gene-related peptide (sensory transmitter) intrinsic neurons in non-sphincteric muscle. Nitrergic neurons

in the pyloric sphincter were also deficient.²⁸ Neuropeptide Y and serotonin were altered in the same model, and these may contribute to abnormal fluid and electrolyte handling in the intestine.

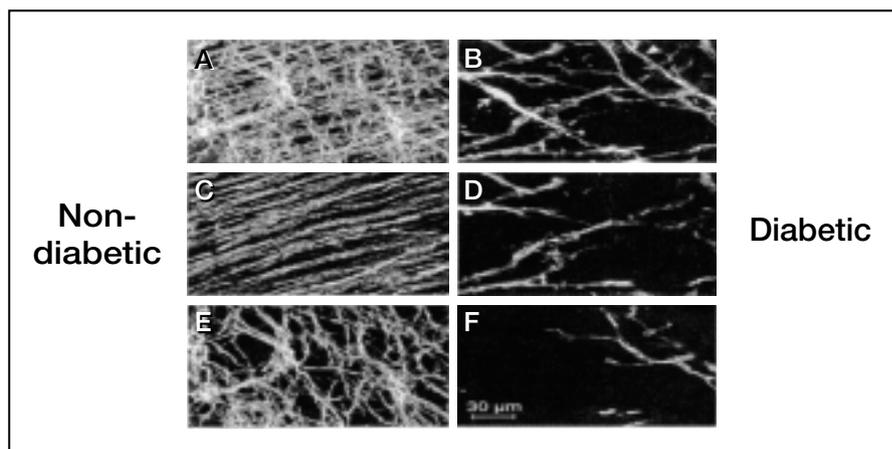
Abnormal Interstitial Cells of Cajal

Two recent reports suggest that the pacemaker cells in the wall of the upper digestive tract are abnormal in experimental diabetes and in a single patient with diabetes mellitus. Thus Ordog and colleagues²⁹ showed electrophysiological disturbances associated with long-standing diabetes, which was associated with reduced volume of interstitial cells of Cajal (ICC) in the antrum and fundus; at both sites, the nerve trunks in the wall of the stomach were rarely associated with ICCs, compared to control animals (Figure 1). A single case study reported by workers at Cleveland and Mayo Clinics showed a reduced ICC network in the jejunum, and this was also associated with reduced numbers of neurons staining for nNOS, VIP, and pituitary adenylate cyclase associated peptide (PACAP).³⁰

Effect of Changes in Blood Glucose

In recent years, it has been suggested that glycemic control alters several

Figure 1. Networks of antral interstitial cells of Cajal are markedly damaged in diabetic compared to nondiabetic rats. Reproduced from Ordog et al.²⁹ with permission from the American Diabetes Association.



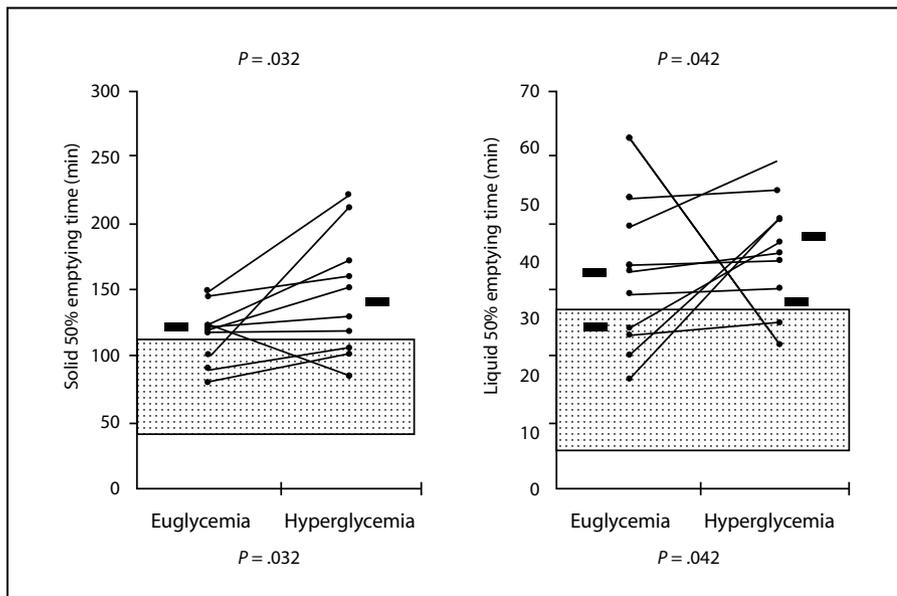


Figure 2. Prolongation of gastric emptying time for solids and liquids in insulin-dependent diabetics during hyperglycemia. The average difference in t50% is modest (15 minutes for solids, 5 minutes for liquids). Reproduced from Fraser et al,³³ with permission from the publisher, Springer-Verlag.

gastrointestinal functions,³¹⁻³³ such as gastric emptying, gastric myoelectric activity, antroduodenal motor activity, gastric visceral sensation, and the colonic response to feeding. Alterations in glucose control may also alter glucose counterregulatory hormones, some of which directly affect gastrointestinal motility. These include glucagon, glucagon-like peptide 1, amylin, epinephrine, somatostatin, growth hormone, and cortisol. The effects of autonomic nerve damage on release of these hormones from the pancreas, intestine, and liver could also contribute to the motor dysfunction.

The magnitude of the changes in motor function related to glycemia deserves further evaluation. First, we need to consider the epidemiology of diabetic dyspepsia and gastroparesis and clinical studies of the association with current glycemia. In a clinic sample of diabetics, Bytzer and colleagues reported that gastrointestinal symptoms were associated with diabetic complications but not with cur-

rent glycemic control measured by blood glucose and glycosylated hemoglobin levels.⁸ In contrast, another Australian study based on a community rather than a clinic sample suggested that, after adjusting for age and gender, there was an association between self-reported poor glycemic control and gastrointestinal symptom complexes.⁷ The contribu-

Gastrointestinal symptoms were associated with diabetic complications but not with current glycemic control.

tion of poor glycemic control on self report could not be documented for four specific symptoms: early satiety, vomiting, less than three bowel movements per week, and loose or watery stools.

Second, in physiological studies of clamped hyperglycemia in healthy controls, the magnitude of change in gastric emptying parameters was quite small (eg, a difference in t_{1/2} of around 15 and 5 minutes [median],

respectively, for solids and liquids).³³ In diabetic patients, statistically significant though biologically unimpressive changes in gastric emptying of solids and liquids have been reported (Figure 2).³⁴ More detailed study of postprandial antral contractile responses were described in healthy subjects exposed to moderate hyperglycemia.³⁵ Work from our laboratory has suggested that non-insulin-dependent diabetes mellitus patients without evidence of autonomic neuropathy have normal gastric emptying of solids on scintigraphy and also normal gastric accommodation measured by barostatically controlled balloon, despite elevated blood glucose and HbA1c levels.²² Moreover, we reported accelerated gastric emptying of nutrient liquids,²² confirming other observations in early diabetes.³⁶ There is a positive correlation of glycemic response during the first 30 minutes postprandially and the percentage of glucose drink emptied in the first 30 minutes.³⁷ One interpretation is that glycemia influences the rate of emptying; alternatively, the glucose levels may reflect the rate of emptying of liquids.

Third, more convincing data on the role of glycemia is provided by

studies of gastric emptying in diabetic mice. In a series of elegant studies, Watkins and colleagues³⁸ evaluated the gastric emptying of 20% glucose in a variety of mice: wild-type mice, non-obese diabetic (NOD) mice in prediabetic phase, NOD mice in the diabetic stage, and streptozotocin diabetic mice (Figures 3 and 4). Only the latter two groups (which were hyperglycemic) had delayed gastric emptying; in streptozotocin mice, gastric

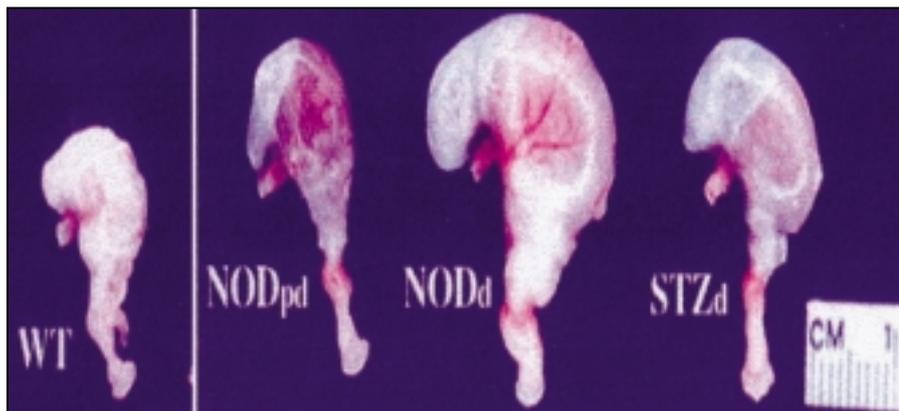


Figure 3. Comparison of stomach size of wild type (WT), prediabetic and diabetic non-obese diabetic (NOD), and streptozotocin-diabetic (STZd) mice. Note that the stomachs in diabetic mice are enlarged. Reproduced from Watkins et al,³⁸ with permission from the publisher, The Rockefeller University Press.

emptying was normalized 12 hours after insulin treatment. Moreover, pylori from the diabetic mice showed lack of nitric oxide-mediated relaxation and nNOS protein expression, which were reversed with insulin treatment. These are among the most convincing mechanistic data, but they pertain to the effect of glycemia on the emptying of liquids in mice. Further data on the emptying of solids would be helpful. Human studies at Mayo Clinic had previously shown that diabetic gastroparesis is associated with pylorospasm.³⁹ These data suggest that inhibition of pyloric tone might be a novel approach to therapy of gastroparesis. This might be achieved by restoring nitrergic innervation, replacing the cellular effects of nitric oxide by enhancing intracellular cyclic guanosine monophosphate (cGMP) in pyloric muscle with a phosphodiesterase-5 inhibitor (eg, sildenafil), or blocking the excitation of pyloric tone, as has been preliminarily reported with botulinum toxin injection of the sphincter.^{40,41}

Psychological Factors

Lustman, Clouse, and colleagues^{42,43} have provided evidence that symptoms in diabetics are significantly influenced by psychological factors.

Treatment of Diabetic Gastroparesis and Diabetic Dyspepsia

General points in the management of diabetic enteropathy include optimal control of blood glucose and restoration of hydration, nutrition, and normal intestinal propulsion.

Medications

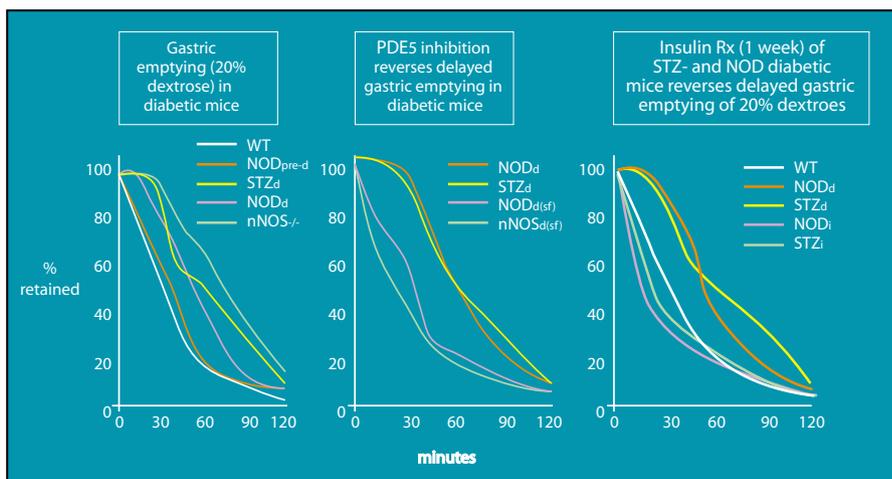
Patients with severe exacerbation of symptoms should be hospitalized and may require nasogastric suction. Intravenous fluids should be provided

and metabolic derangements (ketoacidosis, uremia, hypo/hyperglycemia) corrected. Parenteral nutrition may become necessary in cases of malnutrition. Bezoars may be mechanically disrupted during endoscopy, followed by gastric decompression to drain residual nondigestible particles. Erythromycin at a dose of 3 mg/kg body weight intravenously every 8 hours appears to be effective in acute studies.

A week's treatment with oral erythromycin, 250 mg, t.i.d., is worthwhile once patients start to tolerate oral intake of food.⁴⁵ Erythromycin stimulates gastric motility, enhancing gastric emptying.⁴⁶ It also affects postprandial symptoms in experimental hyperglycemia in healthy subjects.⁴⁷ To date there have been no reports of its effects on sensory function, though two studies using invasive or noninvasive methods showed that erythromycin reduces gastric accommodation postprandially,^{48,49} an effect that may result in greater postprandial discomfort, which is often reported by patients receiving this medication.

Because both liquids and homoge-

Figure 4. Gastric emptying of 20% dextrose in prediabetic and diabetic mice. Left panel, delayed gastric emptying in diabetic and nitric oxide knock-out mice. Center panel, insulin treatment restores gastric emptying to normal in wild type (WT) mice. Right panel, sildenafil, a phosphodiesterase-5 inhibitor, restores gastric emptying to normal in prediabetic and diabetic non-obese diabetic (NOD) and streptozotocin-diabetic (STZd) mice. Reproduced from Watkins et al,³⁸ with permission from the publisher, The Rockefeller University Press.



nized solids are more readily emptied from the stomach than solids, liquid or blenderized food will be better tolerated. Frequent monitoring of blood glucose levels is essential during this phase. Rarely, it is necessary to bypass the stomach with a jejunal feeding tube if the motor dysfunction is limited to the stomach and there is no response to prokinetic therapy. This procedure should be preceded by a trial for a few days of nasoenteric feeding with infusion rates of at least 60 mL iso-osmolar nutrient per hour. Jejunal tubes may be placed by laparoscopy or mini-laparotomy or via percutaneous endoscopic insertion. Such tubes allow restoration of normal nutritional status, but they are not without adverse effects.

If the patient remains symptomatic, other prokinetic agents may be considered as adjuncts. Metoclopramide is a peripheral cholinergic (via activation of 5-HT₄ receptors), antidopaminergic agent with central antiemetic activity. During acute administration, it initially enhances

gastric emptying of liquids in patients with diabetic gastroparesis, but its symptomatic efficacy is probably related to its central antiemetic effects. However, its long-term use is also restricted by a decline in efficacy and by a troubling incidence of central nervous system side effects. Newer 5-HT₄ agonists are being developed,⁵⁰ and it is anticipated that these may have a greater benefit-risk ratio than previous agents that caused cardiac arrhythmias by their effects on the delayed rectifier potassium current in the heart. It is, however, important to recall that there are 5-HT₄ receptors in cardiac muscle (eg, atria),⁵¹ and that 5-HT₄ agonists that have no effect on the delayed rectifier potassium current may nevertheless induce tachycardia if given at high dose.

Erythromycin loses much of its stimulatory effect beyond the first few weeks of treatment, possibly due to downregulation of motilin receptor expression. The macrolide prokinetic, ABT-229, which has no antibacterial properties, proved ineffective in

patients with diabetes and dyspepsia.⁵² It is regrettable that the patients evaluated included few with delayed gastric emptying at baseline, and gastric emptying responses were not checked at the end of the study.

Gastric pacing is also extremely controversial despite approval by the U.S Food and Drug Administration. Diabetic gastroparesis has been attributed to impaired myoelectrical activity in the antrum. Antral contractile activity and propulsion are regulated by underlying electrical slow-wave activity that originates in the pacemaker region of the stomach (at the transition between fundus and corpus on the greater curvature) and migrates aborally towards the pylorus. Hence it has been postulated that gastric pacing could be able to correct and entrain gastric slow-wave activity and therefore improve gastric emptying. However, studies have produced conflicting results. Two approaches have been proposed: McCallum and colleagues⁵³ have used stimulation with an attempt to capture the pacesetter potentials; in contrast,

Main Points

- Diabetic enteropathy includes dysphagia, heartburn, nausea and vomiting, abdominal pain, constipation, diarrhea, and fecal incontinence.
- Gastroparesis includes nausea, vomiting, and early satiation after meals; dyspepsia in addition reflects bloating, fullness, and pain in the upper abdomen.
- Diabetic gastroparesis is frequently associated with retinopathy, nephropathy, peripheral neuropathy, and other forms of autonomic dysfunction, including abnormal pupillary responses, anhidrosis, gustatory sweating, orthostatic hypotension, impotence, retrograde ejaculation, and dysfunction of the urinary bladder.
- Abnormal gastrointestinal motility in diabetes mellitus results in impaired gastric contractility or abnormal myoelectrical control and is typically seen in patients with type I or insulin-dependent diabetes mellitus.
- Studies of experimental animal models of diabetes have shown disturbances in intrinsic nerves and the protective role of gangliosides.
- A recent report suggests that the pacemaker cells in the wall of the upper digestive tract are abnormal in experimental diabetes.
- Patients with severe exacerbation of symptoms should be hospitalized and may require nasogastric suction; if there is no response to therapy and the motor dysfunction is limited to the stomach, the stomach may be bypassed with a jejunal feeding tube.
- Gastric pacing is also extremely controversial despite approval by the U. S. Food and Drug Administration, and studies have produced conflicting results.

a multicenter study⁵⁴ used electrical stimulation rather than pacing and showed improved symptoms but no evidence of improved emptying. In the absence of positive control treatment, it is still unclear whether the stimulation is effective in treatment of gastroparesis.

Conclusion

Diabetic gastroparesis and dyspepsia remain important and frequent clinical problems. The intrinsic nerves (nitrergic and interstitial cells) are recognized as increasingly important mechanisms and potential targets for novel therapies. These novel approaches might include motilides (with less tendency to desensitize) to stimulate antral contractility consistently, phosphodiesterase-5 inhibitors which have the potential to increase intracellular cGMP and replace the deficient nitrergic innervation, or intrapyloric botulinum toxin injection to reduce pyloric tone. Formal placebo-controlled studies are needed to test these novel approaches as well as the efficacy of other prokinetics with improved benefit-risk ratio. ■

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Pathophysiology of Diabetic Gastroparesis. Paul Enck and. Thomas Frieling. Our understanding of the nature of diabetic gastroparesis has advanced in the last decade due to new investigational procedures (electrogastrography, visceral evoked potential recording), and transferring these insights into clinical routine will be our task in the future. Meanwhile, the clinical relevance of gastroparesis—whether overt or silent—remains unquestioned: proper gastric emptying is a prerequisite for adequate metabolic control, and its disturbance may result not only in further progression of the chronic complications of the disease, but also in the false assumption that these patients are well controlled. Diabetic gastroparesis is the result of damage to the vagus nerve, which controls the movement of food through the digestive system. In a person with this condition, the stomach takes too long to empty its contents. Symptoms include heartburn, nausea, vomiting undigested food, and weight loss. In most cases, treatment does not cure the problem -- it is usually a chronic condition. What Is Diabetic Gastroparesis? Gastroparesis, also called delayed gastric emptying, is a disorder in which the stomach takes too long to empty its contents. It often occurs in people with type 1 diabetes or type 2 d...