REVIEW ARTICLE

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Gastric Emptying Abnormalities in Diabetes Mellitus

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Diabetes mellitus is associated with a spectrum of gastric emptying abnormalities, including transient slow gastric emptying, transient fast gastric emptying, persistent slow or delayed gastric emptying (gastroparesis), and persistent fast gastric emptying. Transient changes in gastric emptying are counterregulatory responses and do not require treatment. Delayed gastric emptying has been associated with abdominal symptoms and is considered to be a cause of severe illness. However, rapid gastric emptying is associated with similar symptoms. Whereas delayed gastric emptying may cause difficulty in glucose control in patients receiving insulin therapy, rapid gastric emptying plays an important role in the genesis and progression of type 2 diabetes mellitus. Treatment of rapid gastric emptying is emerging as an important target for the management of postprandial hyperglycemia.

The gastric emptying rate represents a highly regulated output of nutrients into the intestine. The stomach discharges 1 to 4 kcal of homogenized food per minute, regardless of the carbohydrate, protein, and fat composition, into the duodenum.[1] This remarkable feat is achieved through integrated motor activities of different parts of the stomach, regulated by intricate neurohumoral mechanisms[2] (for details, see the Supplementary Appendix, available with the full text of this article at NEJM.org).

Diabetes leads to patterns of abnormal gastric emptying by altering the motor activities of various segments of the stomach. These changes are mediated by dysfunction of vagovagal neural circuits, through interstitial cells of Cajal and smooth muscle (see the Supplementary Appendix). Sudden changes in blood sugar levels affect glucose-stimulated or glucose-inhibited neurons in the gastric inhibitory and gastric excitatory vagal circuits and lead to altered gastric emptying. Persistent hyperglycemia affects the molecular elements of neurons, smooth-muscle cells, and interstitial cells of Cajal through oxidative stress and products of the polarized M1 (proinflammatory) and M2 (prohealing, or repair) macrophages. These metabolites may have complex effects on cellular functions. They may induce transcriptional changes in proteins and in microRNA (miRNA), with consequent alteration of the cellular phenotype to hypercontractile or hypocontractile smooth-muscle cells.

Upper abdominal symptoms resembling functional dyspepsia were thought to be due to underlying delayed gastric emptying. However, similar symptoms are associated with rapid gastric emptying, suggesting that gastroparesis may not be the cause of the symptoms. The symptoms may instead be due to parallel activation of sensory receptors induced by inflammatory changes in the gastric wall. Therefore, maneuvers to accelerate gastric emptying may not provide symptomatic relief and may worsen hyperglycemia.

This review summarizes the pathophysiology of gastric emptying abnormalities

in diabetes mellitus and the rationale for their management. The current practice of treating symptomatic gastroparesis is extensively covered in recent reviews.[3-5]

METABOLIC CHANGES THAT AFFECT GASTRIC EMPTYING

Glucose enters cells mainly through the glucose transporter (GLUT) and the sodium–glucose cotransporter (SGLT).[6] Glucokinase converts intracellular glucose to glucose-6-phosphate, which undergoes glycolysis, a process that leads to the production of ATP and reactive oxygen species in mitochondria.[7,8] Mild oxidative stress causes transcriptional up-regulation of the enzyme NADPH oxidase 4 (NOX4), leading to moderate oxidative stress.[9] In addition, moderate oxidative stress, along with products of lipid oxidation, advanced glycation end-products, and reactive carbonyls, alters the proteins of the extracellular matrix and increases macrophage adhesion and activation. Depending on specific local signals, macrophages[10] undergo polarization to M1[11,12] or M2 macrophages, producing a number of cytokines. Oxidative stress and cytokines may act through transcriptional factors to modify signaling proteins directly or through regulation of miRNAs.[13,14] These noncoding RNAs are critical post-transcriptional regulators of gene expression. They can bind to their target messenger RNAs to suppress the translation into cellular proteins and lead to marked changes in the cellular phenotype.[9,15,16] Consequently, miRNAs are emerging as important therapeutic targets.[17]

Different metabolic changes each produce specific cellular alterations that result in distinct gastric emptying abnormalities. Immediate changes in the plasma glucose level activate vagal motor circuits, resulting in transient gastric emptying abnormalities. Chronic hyperglycemia in association with oxidative stress and macrophage polarization has distinctive effects on neuromuscular transmission, interstitial cells of Cajal, and smooth muscle, depending on the type of macrophage polarization and the degree of oxidative and inflammatory stress. Moderate oxidative stress disrupts neuromuscular transmission, causes a gain in the number of interstitial cells of Cajal, and converts smooth muscle to the hypercontractile phenotype. In addition, moderate oxidative stress promotes macrophage polarization to the M2 or M1 type. Polarization to M2 macrophages suppresses M1 macrophages and their inflammatory responses and results in severe loss of neurotransmission, loss of interstitial cells of Cajal, and conversion of smooth muscle to the hypocontractile phenotype (see the Supplementary Appendix).

TRANSIENT SLOW GASTRIC EMPTYING

Postprandial hyperglycemia is characteristic of glucose intolerance in diabetes mellitus. Acute hyperglycemia slows gastric emptying of digestible food during the digestive period and indigestible food residues in the fasting period. Deceleration of gastric emptying suppresses postprandial hyperglycemia and serves as a negative feedback loop. Slowing of gastric emptying is due to a reduction in the tone of the proximal stomach and suppression of antral contractions.[18] Hyperglycemia also suppresses powerful contractions of the interdigestive migrating motor complex,[19] resulting in slow gastric emptying during both digestive and interdigestive (fasting) periods.

As shown in Figure 1, hyperglycemia stimulates glucose-sensitive neurons in the vagal afferents by suppressing ATP-sensitive potassium (K_{ATP}) channels.[20] Stimulation of the gastric inhibitory vagal motor circuit may affect electrical slow waves, as well as smooth muscle. Acute hyperglycemia may disrupt the slow waves by affecting myenteric interstitial cells of Cajal, leading to isolated tachygastria (an increase in the cyclic electrical activity in the stomach, with a frequency of >3.6 cycles per minute [cpm]),[21] although high glucose levels do not directly affect interstitial cells of Cajal.[22] Tachygastria and other slow-wave abnormalities have been thought to cause reduced antral contractions; however, slow waves do not correlate with mechanical contractions.[18] High glucose levels stimulate the gastric inhibitory vagal motor circuit; such stimulation inhibits contractions and overcomes the hyperglycemia-mediated contraction of the isolated smooth muscle.[23] Transient slow gastric emptying due to acute hyperglycemia is a counterregulatory phenomenon and does not require treatment. The transient nature of the effects of hyperglycemia is attributed to the down-regulation of glucokinase.[24]

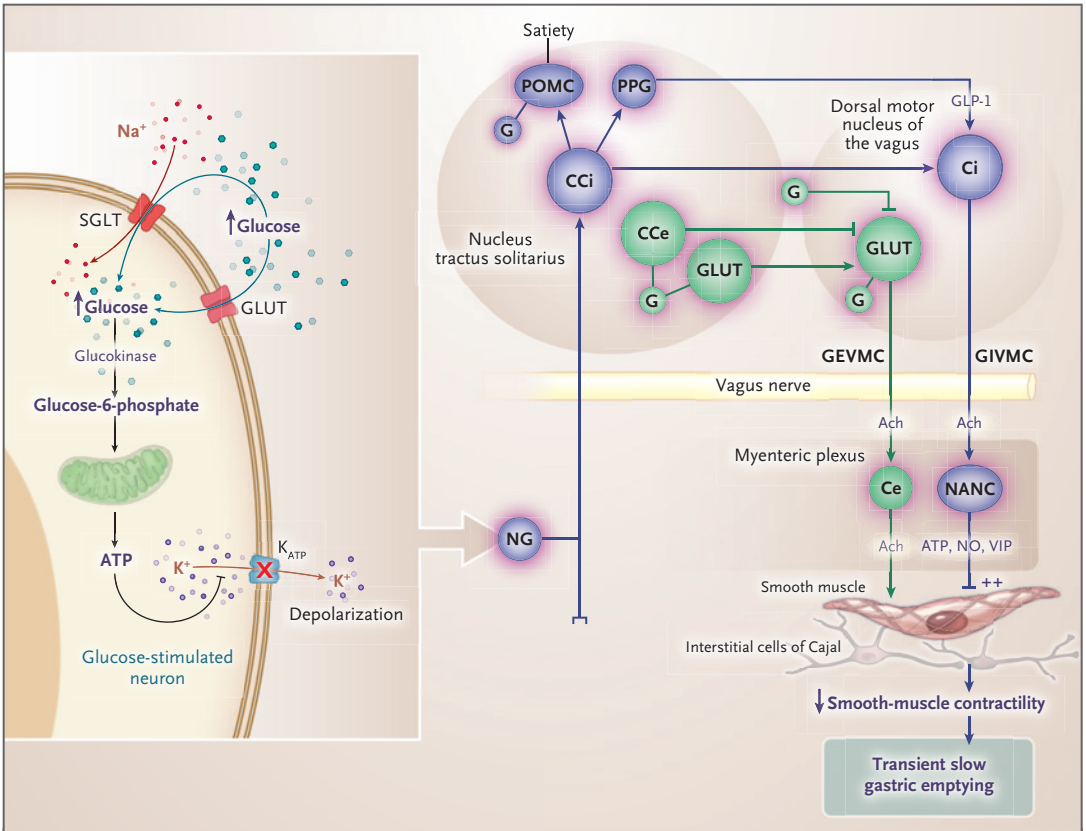

Figure 1. Acute Hyperglycemia Causing Slow Gastric Emptying.

Acute hyperglycemia triggers glucose-stimulated neurons of vagal afferents in the nodose ganglion (NG) and the nucleus tractus solitarius, which are part of the gastric inhibitory vagal motor circuit (GIVMC). They bear the glucose transporter (GLUT, type undefined) and sodium–glucose transporter (SGLT). Hyperglycemia results in a rapid increase in intracellular glucose levels. Glucokinase converts glucose to glucose-6-phosphate, which undergoes glycolysis to produce pyruvic acid, leading to the production of ATP in mitochondria. ATP inhibits ATP-sensitive potassium (K_{ATP}) channels, causes depolarization, and triggers afferent neurons to stimulate the GIVMC. However, the stimulatory effect of hyperglycemia is terminated because hyperglycemia also causes down-regulation of glucokinase. Activation of the GIVMC releases inhibitory transmitters (nitric oxide [NO], ATP, and vasoactive intestinal peptide [VIP]), which decrease smooth-muscle contractility and cause dysfunction of interstitial cells of Cajal, with resulting slow-wave abnormalities. Ach denotes acetylcholine, CCe catecholaminergic neuron of the excitatory pathway, CCi catecholaminergic neuron of the inhibitory pathway, Ce cholinergic neuron of the excitatory pathway, Ci cholinergic neuron of the inhibitory pathway, dorsal motor nucleus of the vagus, G γ-aminobutyric acid–producing (GABAergic) neuron, GEVMC gastric excitatory vagal motor circuit, NANC nonadrenergic noncholinergic neuron, POMC proopiomelanocortin neuron, and PPG preproglucagon neuron.

TRANSIENT RAPID GASTRIC EMPTYING

Acute hypoglycemia causes fast gastric emptying. Iatrogenic hypoglycemia is a common and serious complication of insulin treatment. Acute hypoglycemia causes activation of the gastric excitatory vagal motor circuit (GEVMC), which provides cholinergic excitatory innervation to the gastric smooth muscle, enhancing contractile activity and thus leading to rapid gastric emptying. The GEVMC is also connected to glucagon-secreting alpha cells, to orexigenic (appetite-stimulating) neurons, to the sympathoadrenal pathway, and to hypothalamic neurons involved in the counterregulatory responses to hypoglycemia. A blood glucose level below the normal range induces parasympathetic activity and glucagon secretion. Further reduction of glucose levels triggers sympathetic activity.[25]

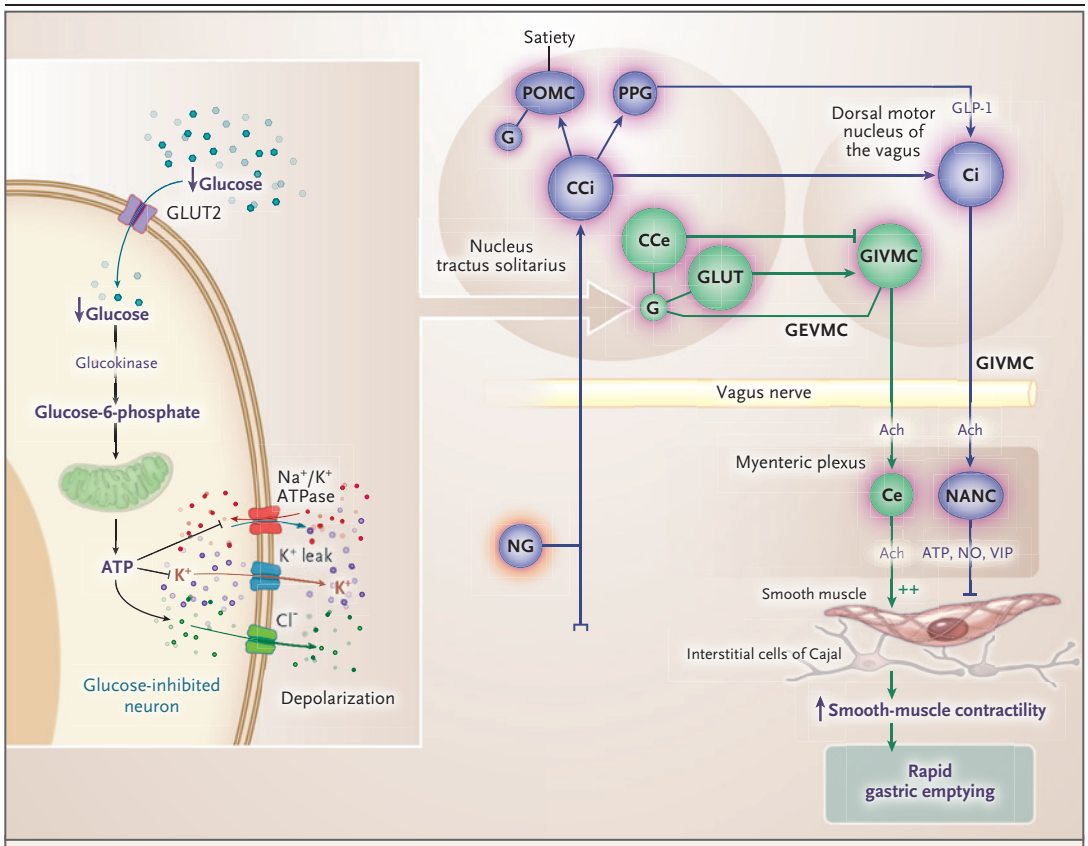

Figure 2. Acute Hypoglycemia Causing Rapid Gastric Emptying.

GABAergic interneurons (G) in the GEVMC are very sensitive to glucose deprivation. Hypoglycemia causes loss of mitochondrial glycolysis and a decrease in ATP production. This leads to inhibition of Na^+/K^+ ATPase, blockade of the K^+ leak channel, and, probably, opening of chloride channels, with resulting depolarization. Stimulation of GABAergic neurons leads to stimulation of the GEVMC, with release of acetylcholine at the neuromuscular junction, excitation of smooth muscle, and rapid gastric emptying. A recurring episode of hypoglycemia may lead to up-regulation of glucokinase and up-regulation of alternative sources of energy, bypassing the signals of hypoglycemia.

The activation of GEVMC is due to stimulation of GLUT2-expressing, γ-aminobutyric acid–producing (GABAergic) neurons in the nucleus tractus solitarius. Hypoglycemia leads to a decrease in intracellular glucose and lowers intracellular ATP levels, causing reduced Na^+/K^+ ATPase activity and membrane depolarization[26] (Fig. 2). Responses to acute hypoglycemia are transient because of the rapid up-regulation of glucokinase and the use of energy sources other than glucose. Transient rapid gastric emptying is part of the counterregulatory response and should not be treated. In recurrent hypoglycemia, these changes may serve as protective mechanisms against hypoglycemia-associated autonomic failure and impaired awareness of hypoglycemia, which are potentially life-threatening conditions.[26,27]

PERSISTENT RAPID GASTRIC EMPTYING

Formerly, persistent rapid gastric emptying was not seriously considered as a complication of diabetes mellitus. Almost 20% of patients with poorly controlled, long-standing, type 1 or type 2 diabetes mellitus, regardless of the presence or absence of upper abdominal symptoms, have rapid gastric emptying even in late stages of the disease.[28-30] Dumping syndrome, with symptoms of postprandial nausea, bloating, light-headedness, flushing, palpitation, abdominal pain, cramps, borborygmi, and diarrhea, occurs after gastric-bypass surgery.[31] However, such symptoms do not occur in patients with an intact stomach. Upper abdominal symptoms are indistinguishable from

Table 1. Prevalence of Normal, Rapid, and Delayed Gastric Emptying among Patients with Diabetes.*

Gastric Emptying	Prevalence among Patients with or without Upper Abdominal Symptoms	Prevalence among Patients with Upper Abdominal Symptoms	Effect on Postprandial Hyperglycemia
	percent		
Normal	33–46	43–52	No effect
Rapid	20–22	20–37	Accentuates early postprandial hyperglycemic peak
Delayed (diabetic gastroparesis)	40–47	19–28	Delays early postprandial hyperglycemic peak

* Patients with diabetes and upper abdominal symptoms have normal, rapid, or delayed gastric emptying; there is no specific relationship between the presence of symptoms and delayed gastric emptying. Patients who have diabetes with or without upper abdominal symptoms have similar distributions of gastric emptying abnormalities. Rapid gastric emptying may worsen postprandial hyperglycemia, whereas delayed gastric emptying postpones the hyperglycemic peak. Data for patients with or without upper abdominal symptoms are from Bharucha et al.[28,29] Data for patients with upper abdominal symptoms are from Park et al.[32] and Chedid et al.[33]

those of functional dyspepsia or gastroparesis. Approximately 20 to 37% of patients with diabetes and upper abdominal symptoms have rapid gastric emptying.[32,33] This rate is similar to that among patients with long-standing diabetes, whether or not they have upper abdominal symptoms[28-30] (Table 1), which suggests that upper abdominal symptoms are not specifically related to rapid gastric emptying. The disorder may respond to intensive insulin therapy in patients with type 1 diabetes.[29,34]

Rapid gastric emptying has a profound effect on glucose intolerance,[35] and it has been implicated in the genesis and propagation of type 2 diabetes mellitus.[36] Correction of rapid gastric emptying by means of dietary manipulations and pharmacologic therapy is central to the management of postprandial hyperglycemia.[37] Amylin or leptin deficiency is associated with chronic hyperglycemia and rapid gastric emptying.[38,39] Agents such as metformin, amylin analogues, and short-acting glucagon-like peptide 1 agonists decelerate gastric emptying.[34,40-42]

Rapid gastric emptying is associated with reduced relaxation and increased contractility of the fundus as a result of impaired inhibitory transmission and enhanced smooth-muscle contractility. Antral peristaltic contractions are augmented because of increased smooth-muscle contractility and possibly because of an increase in the number of myenteric interstitial cells of Cajal.[43]

As shown in Figure 3, moderate oxidative stress leads to loss of inhibitory neuromuscular transmission, a transcriptional increase in c-Kit, and an increased number of interstitial cells of Cajal.[39] Oxidative stress also causes transcriptional down-regulation of miRNA-133a, leading to up-regulation of the small guanosine triphosphatase protein RhoA and Rho-associated protein kinase (RhoA–ROCK) signaling.[44,45] These changes result in impaired gastric accommodation and increased contractility, promoting rapid gastric emptying.[46] Products of M2 macrophages such as interleukin-10 and the enzyme heme oxygenase suppress M1 macrophages and prevent gastroparesis. Increased smooth-muscle contractility in other parts of the gut may involve other signaling pathways[47] (see the Supplementary Appendix for details).

GASTROPARESIS

Diabetic gastroparesis is the most talked-about gastric complication of diabetes mellitus. Simply stated, diabetic gastroparesis is a gastric motility complication of diabetes characterized by persistent delayed gastric emptying. Mechanical outlet obstruction and other coexisting conditions that affect gastric emptying must be ruled out to establish the diagnosis.

MOTOR ABNORMALITY

The prevalence of delayed gastric emptying in untreated cases is 40 to 47% among patients with type 1 diabetes mellitus and 32 to 47% among

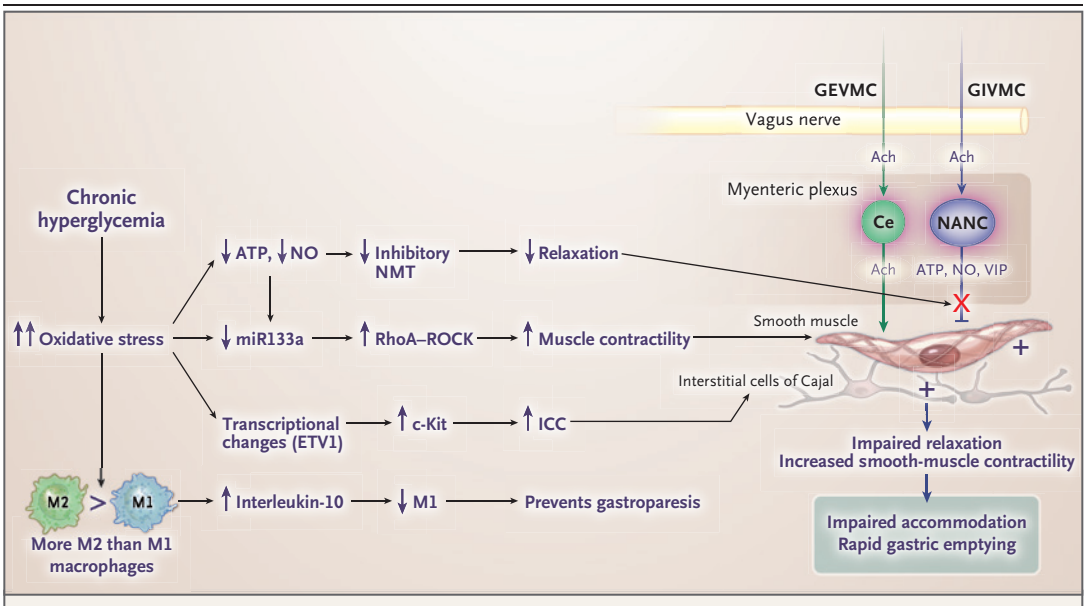

Figure 3. Pathogenesis of Rapid Gastric Emptying in Diabetes Mellitus.

Chronic hyperglycemia may be complicated by moderate oxidative stress and the production of cytokines (e.g., interleukin-10) by M2 macrophages. Oxidative stress causes loss of purinergic and nitrergic neuromuscular transmitters (NMT), leading to loss of inhibitory neurotransmission. In addition, oxidative stress can down-regulate microRNA-133a (miR133a), which leads to reciprocal up-regulation of RhoA and Rho-associated protein kinase (RhoA–ROCK) signaling and sustained smooth-muscle contractility. Oxidative stress also causes a gain of interstitial cells of Cajal (ICC) as a result of up-regulation of c-Kit.

those with type 2 diabetes.[28-30] Diabetic gastroparesis does not change over time,[29,48] and it occurs with both liquids and digestible solids, as well as with indigestible food residues. However, impaired gastric emptying of indigestible solids may be an earlier abnormality.[49]

Delayed gastric emptying may have a beneficial effect in type 2 diabetes, since it postpones the postprandial hyperglycemic peak. In patients receiving insulin therapy for diabetes, however, such a delay may result in episodes of early postprandial hypoglycemia unless careful adjustments are made in the dose of insulin and the timing of administration. Treatment to hasten gastric emptying may even worsen glycemic control.[50]

Diabetic gastroparesis is associated with motor abnormalities in various components of the stomach, including defects in smooth muscles, interstitial cells of Cajal, and neurotransmission. The gastric fundus is characterized by loss of relaxation due to suppression of inhibitory neurotransmission, as well as reduced tonic contraction because of impaired muscle contractility. There are no phasic contractions or slow waves in the fundus. Reduced relaxation results in reduced accommodation, and poor tonic contraction impairs gastric emptying.

A decrease in the propulsive contractions in the gastric antrum leads to poor grinding and mixing of food and ejection into the duodenum. These changes involve loss of cholinergic excitatory neuromuscular transmission and weakness of the smooth muscle. In addition, abnormalities of slow waves may contribute to contractile weakness. The gastric antrum may have periods of rapid slow-wave activity. Normally, the rate of slow-wave activity varies between 2.4 cpm and 3.6 cpm. Tachygastria indicates a slow-wave rate greater than 3.6 cpm, and bradygastria indicates a rate less than 2.4 cpm. Abnormalities in the rate of slow waves may contribute to contractile weakness. However, the slow-wave abnormalities correlate with symptoms of nausea rather than weakness of the contraction and may serve as the electrical marker of nausea.[51] Diabetic gastroparesis is characterized by abnormal initiation and conduction of slow waves on high-resolution electrical mapping. These abnormalities may contribute to disordered propagation of contractions and slow gastric emptying.[52]

Although smooth muscle appears morphologically normal in most cases of diabetic gastroparesis, in very advanced cases, smooth-muscle degeneration, fibrosis, collagen deposits, and eosinophilic inclusion bodies are observed.[53] However, functional studies show that the contractility of smooth muscle is impaired in diabetic gastroparesis. Augmentation of antral contractions is one of the main mechanisms of action of the gastric prokinetic agents used to enhance gastric emptying.[3,4,54]

In diabetic gastroparesis, pyloric and duodenal relaxation may be impaired, resulting in outflow obstruction. Loss of pyloric relaxation and antroduodenal coordination is caused by the loss of inhibitory neuromuscular transmission.[55,56] In mice that lack neuronal nitric oxide synthase isoform α (nNOSα –/–), the failure of inhibitory neuromuscular transmission has been associated with functional outlet obstruction. However, in diabetic gastroparesis, impaired smooth-muscle contractility may weaken the outlet obstruction. In some cases, clinically significant pyloric obstruction may be documented with the use of techniques such as Endoflip impedance planimetry. Sham-controlled trials are needed to establish the usefulness of pyloric interventions to promote gastric emptying in specifically defined cases of gastroparesis.[3] It is known that placement of a wide cannula in the pylorus does not accelerate gastric emptying in the absence of efficient antral contractions.

As shown in Figure 4, diabetic gastroparesis is associated with M1 macrophage polarization and release of inflammatory products. These products cause severe oxidative stress, leading to loss of inhibitory neurotransmission through the uncoupling of nNOSα and scavenging of the released neurotransmitter, nitric oxide. Severe oxidative stress also causes loss of purinergic inhibitory transmission.[46]

The loss of interstitial cells of Cajal is due to tumor necrosis factor (TNF) or TNF-α and transcriptional up-regulation of caspase.[57] Interstitial

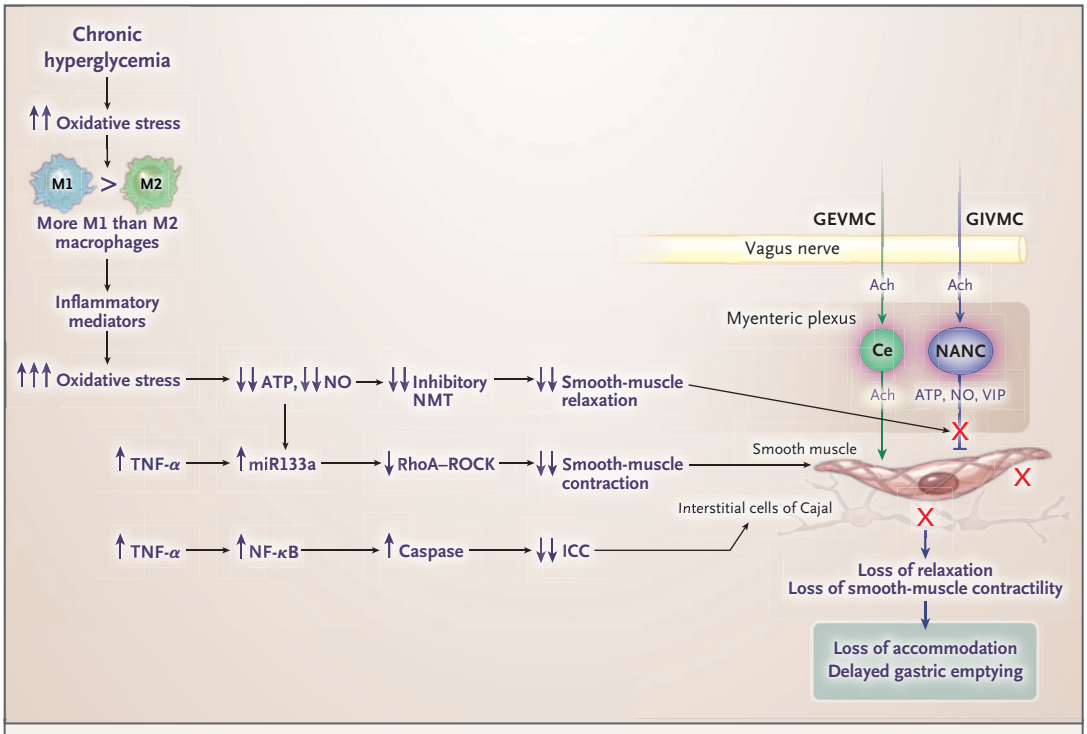

Figure 4. Pathophysiological Features of Gastroparesis.

Inflammatory stress and products of M1 macrophages such as tumor necrosis factor α (TNF-α) may cause a transcriptional increase of miR133a and reciprocal suppression of RhoA–ROCK signaling. Impaired RhoA–ROCK signaling leads to impaired sustained contraction. Defective smooth-muscle contractility due to impaired RhoA–ROCK signaling has been reported in ob/ob mice. NF-κB denotes nuclear factor κB.

cells of Cajal are very fragile and can be reduced through other pathways, including reduced insulin and insulin-like growth factor signaling,[22] myopathy of smooth muscle and subsequent loss of the stem-cell factor,[58] and loss of nitric oxide.[59]

Reduced muscle contractility may be due to M1 macrophage polarization, with release of TNF, interleukin-6, and other inflammatory cytokines.[60] TNF is known to cause up-regulation of miRNA-133a through the transcription factor nuclear factor κB, with an associated decrease in RhoA–ROCK signaling in gastrointestinal smooth muscles.[44] Severe oxidative stress may lead to reduced muscle contractility.[45] Reduced RhoA–ROCK signaling associated with hypocontractile smooth muscle has been reported in diabetic gastroparesis.[61] These observations from studies carried out in experimental models resemble transcriptomic signatures of immune dysregulation in human gastroparesis.[54,62]

UPPER ABDOMINAL SYMPTOMS

Diabetic gastroparesis was originally described in 1958 by Kassander[63] in a group of patients with diabetes who had irreversible delayed gastric emptying and gastric stasis without mechanical obstruction (gastroparesis diabeticorum), which was thought to be due to an abnormality of gastric motility. Later, patients with diabetic gastroparesis were found to have upper gastrointestinal symptoms. *Merriam-Webster's Medical Dictionary* defines gastroparesis as "partial paralysis of the stomach" and, citing G.F. Cahill et al., notes that "diabetic gastroparesis is characterized by a triad of postprandial symptoms: nausea, vomiting, and abdominal distension." Diabetic gastroparesis with upper abdominal symptoms has been called "clinical or symptomatic gastroparesis." Other symptoms, including severe upper abdominal pain, have been added to the definition of gastroparesis, resulting in ever-changing definitions.[3-5,64]

To identify symptoms of diabetic gastroparesis that are distinct from those of functional dyspepsia, the Gastroparesis Cardinal Symptom Index (GCSI) and the Patient Assessment of Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM) were developed. Cardinal symptoms of gastroparesis included postprandial fullness, early satiety, nausea, vomiting, and bloating, which did not distinguish between functional dyspepsia and clinical gastroparesis.[65] Therefore, clinical gastroparesis is considered to be part of functional dyspepsia. Upper abdominal symptoms suggestive of functional dyspepsia occur in up to 10% of the general population.[66] Delayed gastric emptying is reported in 19 to 28% of patients with diabetes who have upper abdominal symptoms[32,33] (Table 1). Cherian et al., in their study of symptoms of diabetic gastroparesis, included patients with coexisting medical conditions who were receiving treatment with opiates or psychotherapeutic agents that may produce symptoms unrelated to diabetic gastroparesis.[67] A revised GCSI with a daily diary score for symptoms was developed to quantitate the severity of the symptoms. No significant correlation was found between the symptom score and gastric emptying.[67]

The available studies do not support a causal relationship between motor abnormalities and symptoms in diabetic gastroparesis. The most telling argument against gastric motor abnormalities in diabetic gastroparesis is the fact that patients with diabetes and upper abdominal symptoms have normal, delayed, or rapid gastric emptying[32,33] (Table 1). The frequency of reduced gastric accommodation is not higher among patients with gastroparesis than among those with normal or accelerated gastric emptying.[33] Moreover, the normalization of gastric emptying does not ameliorate symptoms with any consistency,[68-71] nor does the amelioration of symptoms result in improved gastric emptying.[72]

In recognizing that there is no causal relationship between motor abnormalities and symptoms, some clinicians wondered whether gastroparesis is a separate entity or simply part of dyspepsia.[73] Moreover, the use of invasive maneuvers to target gastric emptying for the relief of symptoms has been discouraged.[74] The observation that acceleration of gastric emptying may worsen hyperglycemia[50] further arouses concern about the indiscriminate use of such interventions. It appears that functional dyspepsia–like symptoms in gastroparesis may arise not through motility changes but rather through the parallel effects of oxidative stress and inflammation on nociceptors and on other afferents that produce the symptoms.[75] Recent concepts of the mechanism of functional dyspepsia suggest the involvement of low-grade inflammation and noxious mediators in symptoms related to functional dyspepsia.[76] The effective treatment of symptoms in diabetic gastroparesis may be similar to the treatment of functional dyspepsia.

CONCLUSIONS

The recent development of easy-to-use, reproducible tests (gastric scintigraphy or a stable-isotope ^{13}C breath test) has helped to identify different gastric emptying abnormalities, particularly rapid gastric emptying. Recent studies have shown that symptoms attributed to gastroparesis are not specific but can also be seen in rapid or normal gastric emptying. Rapid gastric emptying is now emerging as an important mechanism in postprandial hyperglycemia. Studies in animals have shown that vagus nerves may control gastric emptying through vagovagal circuits and that metabolic products associated with hyperglycemia may have distinct effects on gastric motility. An understanding of the mechanisms of these complications may help to identify new targets for rational treatment.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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