Chapter

47

Diabetic Gastropathy

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DIABETIC GASTROPATHY

An association between delayed gastric emptying and diabetes was known for more than half a century and in 1958, Kassender coined the term "Gastroparesis diabeticorum"[1]. Much is known since then but many aspects, mainly concerning its pathophysiology and treatment, still have no satisfactory answers. Diabetic gastropathy can be defined as symptom complex with functional, contractile, electrical and sensory dysfunction of the stomach associated with diabetes. In its classical form, it is associated with delayed gastric emptying and is called diabetic gastroparesis. On the other hand many patients with dyspeptic symptoms have normal or even enhanced gastric emptying. Thus, the exact relationship of gastric motility and clinically related abnormality remains unclear. The exact incidence of diabetic gastroparesis is also unrecognized. Several studies measuring its prevalence originate from tertiary care centers and over estimate the incidence. Some of these studies show delayed gastric emptying to the extent of 50-60% in diabetic patients[2]. However community based studies has demonstrated the prevalence of upper gastrointestinal symptoms in diabetic patients ranging between 10-15% only which is comparable to controls[2,3].

Normal Gastric Function

The essential physiology function of the stomach is to act as reservoir, pulverize solids and mix food, to empty into duodenum during digestive period and to empty food residues during inter digestive period. The rate at which the stomach empties is determined by physicochemical characteristics of the stomach content e.g. solid and liquid state, size of solids, osmolality and caloric content of the nutrients. In general, liquids empty faster than solids and out of all liquids, isotonic fluids travel faster than hypertonic fluids. The usual gastric transit time is between 1-4 hours depending upon the amount and nutrient content of the food.

During inter-digestive period, contraction wave arise proximally and distally to the gastroduodenal junction taking part of gastric content ahead of the wave. During this period, four phases of variable motor activity, which is, migrating motor complex (MMC) occurs in a cyclic fashion. Phase-I is a period quiescence characterized by lack of spontaneous contractions, phase II is notable for irregular motor activity where contractions are propagated distally over short distances. Phase –III contractions are rhythmic contractions occurring every 2 hours lasting for 10-15 minutes. This phase comprises of frequent (3 cycles / mt.), powerful contractions with strong propulsive action. During phase III, contractions of the stomach musculature are determined by the intrinsic electrical activity of the interstitial cells of Cajal (ICC) often referred to as pacemaker cell of stomach and gut. Undigested solids remaining in the stomach are emptied by migratory motor complexes (MMC) of phase III. These large amplitude contractions perform the function of clearing the stomach and preventing bezoars formation. Phase IV is brief period of irregular contractions, sometimes noted before the return of the period of quiescence (Phase I).

Gastric Dysfunction in Diabetes

Diabetic gastroparesis occurs in patients with long standing type 1 diabetes with or without evidence of peripheral and autonomic neuropathy. However, it is also seen in patients with type 2 diabetes of relatively short duration[4]. Delayed gastric emptying is more often observed with solids than liquids. Gastric symptoms i.e. nausea, vomiting, bloating, fullness, early satiety

abdominal pain or discomfort is more often observed in type 1 diabetes (up to 50%) than in type 2 diabetes (30%)[5]. However, symptomatic patients may not always demonstrate delayed gastric emptying as studied by scintigraphic emptying study[6]. On the other hand up to 50% of patients with delayed gastric emptying may have no symptoms referable to their stomach[7]. In all such asymptomatic cases, difficulty in controlling blood glucose levels may be the only indication of delayed gastric emptying. Interestingly, some patients especially of type 2 diabetes may complain of early satiety but have accelerated emptying despite the absence of any evidence of autonomic neuropathy[8]. In such cases, loss of nitergic innervations of the gastric fundus which impairs receptive relaxation and accommodation reflexes has been suspected.

As a result of such disparity in gastric emptying rate of diabetic patients, a broader term gastric gastropathy has been developed. Diabetic gastropathy refers to disorders in motility, sensation or other neuromuscular function that can occur in association with diabetes in absence of other identifiable causes and with or without scintigraphic evidence of delayed gastric emptying. Besides, a term diabetic enteropathy may also be used in all such patients where mobility disorders are encountered throughout the GI tract. Bacterial overgrowth can cause diarrhea while colonic dysmotility can lead to chronic constipation.

PATHOPHYSIOLOGY

In healthy individuals hyperglycemia slows gastric emptying and is associated with decreased antral motility[9]. Similarly patients of diabetes (both types) exhibit delayed gastric emptying during induced hyperglycemia[10]. This abnormality sometimes manifests as poor control of diabetes and administration of drugs that improve gastric emptying time have been shown to improve glycemia control as evidenced by reduced glycocylated hemoglobin values[11]. Nausea and vomiting are common symptoms during acute ketoacidosis and in most cases they subside with treatment of acute metabolic abnormality[12].

Many patients demonstrate signs of neuronal damage within a few years of the onset of clinical diabetes. Such damage ranges from subclinical alternations in nerve conduction velocities to life threatening autonomic dysfunction. Despite these pathologic changes, investigators could not associate gastroparesis with autonomic neuropathy consistently[6,13]. Surprisingly, in one study; the association was proved in reverse manner, i.e. presence of autonomic neuropathy was a poor predictor of delayed gastric emptying[4]. But, other studies were not consistent with the results of this study[14,15]. Where delayed gastric emptying was closely associated with cardiac autonomic neuropathy. Other pathophysiological changes seen commonly with autonomic neuropathy are alteration of gastric secretary function, antro-dnodenal motility and gastroesophageal reflux activity. All of them may contribute to symptoms experienced by patients with gastropathy.

Besides autonomic neuropathy, dysfunction of enteric nervous system may contribute to the pathophysiology of diabetic gastropathy. Though, no human analyses are available but animal studies had clearly shown that neuronal death could lead to loss of pyloric relaxation, which can lead to functional gastric outlet obstruction[16]. A recent case report of a type 1 diabetic patient with gastro paresis describes a significant reduction in neurons and several other neurotransmitters[17].

Clinical Features

There are a wide range of symptoms in diabetic gastroparesis and the degree of delayed gastric emptying correlates poorly with severity of symptoms. Still, most of the symptoms of gastroparesis originate from gastric stasis, i.e. postprandial fullness, bloating, nausea, vomiting, early satiety excessive belching after meals, epigastric discomfort and pain. Many patients are asymptomatic and their abnormal gastric emptying is recognized only when bezoar or a largely dilated stomach with retained contents is detected. Nonetheless, these patients have symptoms of anorexia, early satiety and postprandial abdominal fullness and discomfort that resembles simple dyspepsia Vomiting of old food is indicative of gastroparesis. It is worth noting that symptoms of gastroparesis usually relate to eating but some patients with diabetes may have nausea and vomiting during periods of prolonged fasting[18] (Fig. 1).

Prolonged gastric distension increases propensity for transient relaxation of the lower esophageal sphincter thus exacerbating gastroesophageal refux[19]. Apparently the mechanism of the reflux disease in diabetic patients with gastroparesis may be different than in general population. Presence of back pain or an increase in severity of typical symptoms may be indicative of bezoars formation and further jeopardizing gastric emptying. There is no evidence to link poor prognosis with gastroparetic patients. The fact proved by a study on the natural history of diabetic gastroparesis by Kong, et al[7] of the 86 patients, solid gastric emptying was

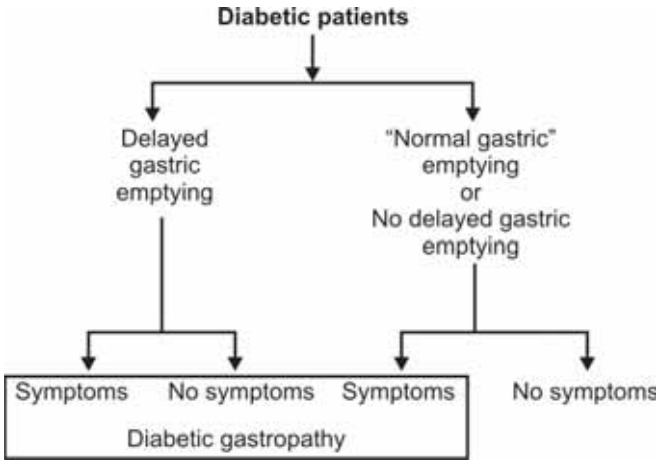

Fig. 1: Classifying diabetic patients according to their symptoms

delayed in 56% and liquid emptying was delayed in 28%. During follow up between 9-14 years, twenty one patients had died who had greater duration of diabetes and higher score for autonomic neuropathy than the patients who were alive. But there was no difference in gastric emptying or esophageal transit between the two groups.

In summary, patients with diabetes can be classified into four groups according to their presentations (Fig. 1). First group will have evidence of delayed gastric emptying on nuclear scintigraphy as well as recognizable symptoms compatible with diagnosis of gastroparesis. Another group will have delayed gastric emptying but no symptoms attributable to gastric stasis except difficulty in controlling blood glucose levels. It can be speculated that absence of symptoms is because of altered visceral sensation and vagal nerve damage seen in diabetic patients and may be considered similar to patients with myocardial infarction without any chest pain. Changed personality or variations in cerebral appreciation of visceral sensory information as in irritable bowel syndrome may be other causes of lack of symptoms. A third group may have normal gastric emptying by nuclear scintigraphy but symptoms are seen compatible with gastric stasis, while the fourth group of patients have no evidence of delayed gastric emptying and no symptoms.

Diagnosis

Delayed gastric emptying is the hallmark test of diabetic gastroparesis and a number of methods are employed for measuring gastric emptying in humans. Simple tests as plain X-ray abdomen Ba meal study can detect major problem of stasis and presence of gastric bezoars. Gastrointestinal endoscopy can help exclude presence of any mechanical obstruction.

Gastric scintigraphy is considered near to "gold standard" for diagnosing delayed gastric emptying. This test can be performed to detect emptying of either solids or liquids (with the use of dual markers) but solid phase emptying is more sensitive for documenting gastroparesis[20]. After ingesting the test meal, camera images abdomen every 15-30 minutes for four hours and emptying of greater than 50% of the meal by 2 hours is considered normal while gastric retention of greater than 10% at 4 hours interval is considered delayed. Scintigraphy involves minimal radiation exposure and the radiation burden is less than half of the exposure resulting from a plain x-ray of the abdomen[21].

A suitable alternative to scintigraphy is tracer method that indirectly measures gastric emptying. It assesses gastric emptying by measuring the time it takes for marker substance to appear in either the blood or the breath. It is relatively inexpensive method where a participant ingests a meal containing octanoic acid labeled with ^{13}C. This test is based on the assumption that octanoic acid when digested is quickly absorbed in duodenum and metabolized in liver. After it is broken down, carbon dioxide is exhaled and recovery of radio labeled (^{13}C) carbon dioxide can be quantified in expired air. This test demands normal absorption, liver metabolism and lung function and can be useful for screening large populations. The disadvantages of this test are that the test requires complicated calculations and is possibly too inaccurate to be put for clinical use.[22] But one trial ranks its results comparable to scintigraphy in an office based setting[23].

Electrogastrography (EGG) is a non-invasive method, which measures myoelectrical activity of the stomach. By placing electrodes in epigastrium EGG can detect normal electrical rhythm (3 cpm) and abnormal gastric dysrrhythmia i.e. tachygastria (3.6-9.9 cpm) and bradygastria (1.0-2.4 cpm)[4,24]. Some workers claim that dyspeptic symptoms correlate better with EGG than scintigraphic studies[25]. But contradictory studies are also available[26,27]. Another method, antroduodenal manometry, where intraluminal pressure is measured by a catheter in the fasting and post prandial states can be useful in diagnosing a variety of motor disturbances. However, it is time consuming, difficult to validate and subjects patients to radiation[28]. Other tests like MRI, computed tomography CT, impedance epigastrography, impedance tomography, real time ultrasonography and positron emission tomography (PET) are additional modalities used to document delayed gastric

emptying[29]. A metal detector test has also identified transit disorders in different GI segments of patients with diabetes mellitus[30].

Differential Diagnosis

Any disease causing neuromuscular dysfunction of the stomach can lead to gastroparesis. Besides diabetes, drug induced delayed gastric emptying, post surgical gastroparesis and idiopathic gastroparesis are important. All these causes can lead to chronic often-severe gastroparesis. Up to 9% of patients who undergo gastric surgery may develop gastroparesis especially if surgery involves vagatomy and partial gastrectomy[31]. A sizeable number of idiopathic gastroparesis have a history of viral syndrome preceding symptoms of delayed gastric emptying.[32] Rotavirus, Norwalk virus, Epstein Bars virus, CMV and herpes simplex viruses have been implicated. However, post viral gastroparesis demonstrate substantial improvement gradually systemic sclerosis, lupus, malignancy or thyroid disease may also be considered as a cause of gastroparesis which can be excluded on physical exam. Lastly, other causes of similar gastroparesis complaints i.e. ch. cholecystitis, ch. pancreatitis or metabolic disorders (hypercalcemia, hypokalemia adrenal deficiency and uremia) should be carefully excluded.

Treatment

Treatment of diabetic gastropathy (Fig. 2) entails correcting gastric emptying when abnormal and improving symptoms. These goals are often difficult to accomplish resulting in disappointment for both doctors and patients alike. Therapy includes, dietary adjustments, tackling treatable causes, glycemic control and judicious use of available pharmacologic agents (Fig. 2). The heterogeneous nature of both the pathogenesis and motor dysfunctions involved in gastroparesis implies that it may be extremely difficult to control symptoms or improve gastric emptying with any one drug[27].

Dietary and Lifestyle Modifications

Patients of gastroparesis should have a diet low in fiber and dietary roughage. Additionally, the diet should have small frequent meals and liquids are better tolerated so diet can be supplemented with high caloric liquid items. Since hyperglycemia itself disrupts normal gastric emptying, careful attention to blood glucose control is essential. Brisk walking has been shown to accelerate gastric emptying.

Pharmacotherapy

The drugs used to treat gastroparesis can be classified according to the mechanism of action as either prokinetic agents, antiemetic agents or a combination of both. Most of the drugs used these days are prokinetics and aimed at increasing the frequency and amplitude of contractions within the stomach. The commonly used drugs are metoclopramide, erythromycin cisapride or domperidone. Unfortunately, there are only a few trials, comparing the efficacy of these drugs so decision to use a particular drug depends upon clinical scenario, drug toxicity and preference of clinician and patient[33].

Metoclopramide

Metoclopramide is a dopamine receptor antagonist, $5HT_3$ receptor antagonist, an acetylcholine releaser and a cholisterase inhibitor. This is the only drug approved by FDA for treating diabetic gastroparesis. When administered orally or parenterally, metoclopramide can increase the amplitude and frequency of fundic and antral contractions and induce associated pyloric and duodenal coordination. Though, in clinical studies, metoclopramide enhances the rate of gastric emptying of both solids and liquids and reduces symptoms in patients with diabetes, some patients may not demonstrate improvement in gastric emptying which leads us to believe that amelioration of symptoms may have more to do with its central antiemetic property[34]. Unfortunately, the efficacy of metoclopramide may lessen over time.

Metoclopramide use is associated with numerous adverse effects. As it is capable of crossing into CNS, it can cause a number of CNS adverse effects. i.e. drowsiness, restlessness, dystonic symptoms, Parkinson's like symptoms etc. Increase risk of convulsions in patients with underlying seizure disorders and breast enlargement, nipple tenderness, galactorrhoea and amenorrhoea are some of the other serious side effects.

Thus, a lack of strong evidence of its efficacy and poor tolerability profile, the use of metoclopramide as a long term treatment for diabetic gastroparesis is debatable[35].

Erythromycin

Erythromycin, a macrolide antibiotic, is a motilin receptor agonist. Motilin receptors are located throughout the enteric nervous system with greatest density in the stomach and proximal GI tract[35]. Erythromycin induces MMC in humans and serves to increase the frequency and amplitude of antral contractions. Lower doses tend to generate premature antral contractions via cholinergic pathways, whereas higher dosage produces a more sustained contraction via noncholinergic pathways including direct

stimulation of smooth muscle motilin receptors[35]. Oral erythromycin is less potent in comparison to intravenous erythromycin and the long term efficacy of oral erythromycin is questionable[27,36]. More so, erythromycin accelerated gastric emptying may result in impairment of the normal sieving function of the distal stomach which can result in delivery of large particles into small bowel thus causing malabsorption or a dumping syndrome[37].

To date there is no controlled study documenting a beneficial effect of intravenous or oral erythromycin therapy on symptoms of gastroparesis. One study reported greatly accelerated solid phase gastric emptying in patients with type 1 diabetes receiving intravenous erythromycin[38]. Another study suggested improvement in glycemic control in patients with oral erythromycin[39]. Long term efficacy of erythromycin is again debatable because of the fear of down regulation of motilin receptors or development of tachyphylaxis. From a practical point of view, intravenous erythromycin can be used for short term in case of acute flare of diabetic gastroparesis.

Domperidone

Domperidone is a benzimidazole derivative that acts as a peripheral antagonist at D_2 receptors. Through this drug is used in Canada and Europe, US FDA has never approved its use in gastroparesis. It does not cross blood brain barrier as readily as metoclopramide so it is associated with a lower incidence of neurologic side effects[40,41]. Domperidone enhances the frequency and amplitude of antral and duodenal contractions, improves antroduodenal coordination and enhances the rate of gastric emptying of both solids and liquids. The effect of domperidone on gastric emptying as seen in patients is controversial as some studies demonstrating accelerated emptying while other studies show no benefits or a failure to sustain benefits in gastric emptying over time[25,42,43]. Koch at al[25] studied the effect of domperidone treatment on symptoms of gastroparesis, the rate of gastric emptying of a radionuclide labeled solid meal and gastric electrical activity as recorded by EGG. After six months of treatment with domperidone, all six patients started showing improvement but the mean rate of gastric emptying did not significantly improved. Interestingly, all six patients demonstrated normalization of the gastric electrical activity on EGG. In a large multicentric randomized controlled trial, domperidone was shown to reduce upper gastrointestinal symptoms significantly and improve quality of life in patients with diabetes[44].

Cisapride

Cisapride has no antidopaminergic property but enhances the release of acetylcholine in the intestinal myenteric plexus. Cisapride increases the number of antral, pyloric and duodenal pressure waves localized to the pylorus[45], Cisapride was indicated for the treatment of GERD primarily due to its effect on LES but accelerated gastric emptying may be contributing to this effect significantly. In patients with diabetes, it improves the rate of gastric emptying of both digestible and indigestible solids and liquids[46,47]. However, there is no correlation between the degree of cisapride mediated improvement in clinical symptoms and the magnitude of enhancement of gastric emptying. Cisapride is not associated with time dependent deterioration of beneficial effects. Horowitz and Roberts demonstrated that with acute therapy, cisapride not only reduced clinical symptoms but also improved the rate of emptying of both solids and liquids. In chronic therapy of more than four weeks, the pattern of symptomatic improvement continued[48].

Cisapride is associated with a low incidence of side effects as it does not have neurologic side effects and does not possess antidopaminergic properties. However, the occurrence of more than 250 reported cases of cardiac arrhythmias associated with the use of cisapride between 1993-99 led the USFDA to withdraw cisapride from the open market. High cisapride concentrations has been shown to prolong the cardiac QT interval with increases the risk of torsade de points, a potentially life threatening ventricular arrhythmias. Patients with recurrent severe hypoglycemia or renal impairment may be at increased risk of cisapride related cardiotoxicity. The unavailability, toxicity and unclear long term efficacy of cisapride warrants a limited role for the management of patients with chronic gastroparesis.

Newer Drugs

Levosulpride (a drug related to metoclopramide) has been shown to accelerate emptying of solids from the stomach of patients with chronic diabetic gastroparesis[49]. Alzapride, another D_2 receptor antagonist has been shown to be helpful in relieving nausea and vomiting but its prokinetic effects on the upper GI tract are uncertain[50]. Tegaserod, a $5HT_4$ receptor partial agonist and prucalopride, a $5HT_4$ receptor complete agonist are also being tried for their potential use in delayed gastric emptying.

Gastric pacing: Surgical placing of cardiac pacing wires into the serosa has shown some renewed interest

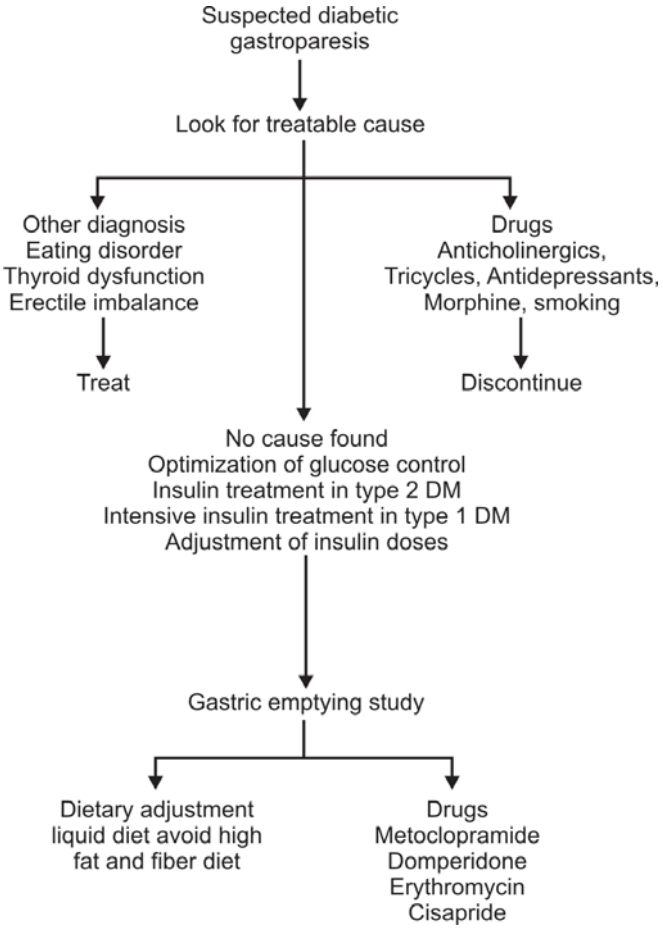

Fig. 2: Strategies in the treatment of symptomatic diabetic gastroparesis

in medically refractory gastro paresis. Many trials in recent days have shown equivocal results and unfortunately all of them are uncontrolled[51,52]. Gastric pacing should only be considered in patients with the most medically refractory symptoms i.e. symptoms for over 1 year refractory to medical therapy, greater then 7 episodes of vomiting per week and evidence of abnormal gastric retention as measured by scintigraphy (> 60% retention at 2 hours or > 10% at 4 hours).

Thus, in conclusion, it can be stated that gastric emptying in diabetes may affect up to 50% of patients. Though, the pathophysiology remains unknown and treatment options are limited, many patients can derive relief from symptoms through medical therapy. Research is still on to find out effective treatment of this chronic disorder. Some novel agents are under investigation and emphasis is now paid for not only designing new prokinetic drugs that help enhance gastric emptying but also on developing drugs that coordinate gastric motility or alter visceral hypersensitivity. More work is needed to understand the pathophysiology of the disorder and only then a suitable and effective drug can be discovered.

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