DIABETIC GASTROPARESIS
(GASTROPARESIS DIABETICORUM)

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SUMMARY
Complications involving the gastrointestinal tract are common in patients with diabetes mellitus. Diabetic gastroparesis is a common condition. It can be diagnosed in 25% of diabetic patients. However it is generally clinically silent. Typical symptoms are early feeling of satiety, nausea, vomiting, regurgitation, abdominal fullness, epigastric pain and anorexia. It is a cause of "brittle diabetes". Gastroparesis should be considered in patients with irregular glucose control. Management requires rehydration and hospitalization for prolonged vomiting episodes due to diabetic ketoacidosis. An eating style with frequent and small amounts of meals with a low fat content, is suggested. Gastric prokinetic agents such as metochlopramide, cisapride, domperidon and erythromycin can be used. Gastric bezoars should be cleared by endoscopy. In severe gastroparesis where medications are not successful, jejunostomy may be performed for feeding. Surgery has not been proved to be successful.

Key Words: Diabetes, Gastroparesis.

ÖZET

Anahtar Kelimeler: Diyabet, Gastroparezi.

Diabetic Gastroparesis
(Gastroparesis diabeticorum).

Complications involving the gastrointestinal tract are common in patients with diabetes mellitus (1). These symptoms do not correlate with the duration of the disease, metabolic control and other chronic complications other than neuropathy (2). Gastrointestinal disturbances caused by autonomic neuropathy are generally common complications of diabetes leading frequently to morbidity (1). However, gastrointestinal symptoms are generally underdiagnosed and undertreated (3). One of the frequent and important consequences of diabetes is diabetic gastroparesis where stomach is involved. It can be diagnosed in 25% of the patients. It is more common in patients with type 1 diabetes mellitus, in particular if the patient has poor glycemic control, after 10 years of onset. There is no positive correlation between the

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Physiology of gastric emptying is mostly dependent to the function of vagal nerve (4). Basal rhythm of the stomach is initiated by a pacemaker and transmitted to pylor horizontally and circularly. Gastric pacemaker is at the joint part of the fundus and corpus in large curvature. In fasting state the interdigestive motor activity is divided into four phases. Peak activity is observed in phase 3 and in this phase migratory motor complex of the stomach occurs making three contractions in a minute (5). Gastric emptying is controlled by fundus and is dependent upon the volume of the gastric content. As a result of impaired vagal function proximal stomach relaxes less and the emptying of fluids in diabetic patients prolong. The emptying of non-fluid substances are affected by the strong contractions of the antrum. These contractions stains and mines hard substances and transform them into pieces smaller than 1 mm and thus non-fluid substances pass through pylor to duodenum. Phase 3 contractions of interdigestive migratory motor complex are generally not present in diabetic patients. As a result, this causes a loss in the function of digestion and emptying in the antral region and thus gastric retention. Moreover problems may appear about the receptors of gastric relaxation as a result of concomitant present of motility disorders in stomach and duodenum. Pylorospasm may develop as a deterioration and may lead to functional resistance of gastric flow. Disturbed gastric emptying puts patients under the risk for the development of gastric bezoars (6). The real pathophysiology of motility disorders of the stomach is not clear. It is obvious that it can be seen vagal parasympathic functional disturbance. The secretion of motilin, which is the peptide regulating gastrointestinal motility, is under vagal control (7). Motilin stimulates the initiation of third phase of motor activity in migratory motor complex of stomach in patients with gastroparesis. Hyperglycemia, itself, may cause a delay in gastric emptying both in diabetic and healthy individuals (1, 6). Gastic neuromuscular abnormalities that may occur in diabetic gastropathy are divided into two groups; functional and organic. Gastric dysrhythmias known as functional pathology are defined as bradygastry and tachygastry. Gastric dysrhythmias resembling normal gastric peristaltic contractions are present in 100% of diabetic patients with eating related symptoms. Loss in vagal tonus and increased sympathic nervous system activity are associated with gastric dysrhythmias. Acute hyperglycemia suppresses antral contractions by forming tachygastry (8). Typical symptoms of diabetic gastroparesis are early feeling of satiety, nausea, vomiting, regurgitation, abdominal fullness, epigastric pain and anorexia (9). The diagnosis of gastroparesis can be made after excluding mechanic or structural lesions in patients with symptoms (10). Patients with gastroparesis may vomit foods which they had eaten many hours even many days ago. Episodes of nausea and vomiting may continue for days, months or may appear time to time (11). Even in patients with mild symptoms gastroparesis affects the passage of food into small intestine and thus the relation between glucose absorption and exogenous insulin administration is disturbed. Such alterations result in wide fluctuation in glucose levels, unexpected postprandial hypoglycemia and marked “brittle diabetes”. Thus in patients with irregular glucose control gastroparesis should always be suspected. In cases where there is no obstruction, the presence of residual food in stomach after 8-12 hours of fasting is a gold standard for diagnosis (10). Upper gastrointestinal symptoms should not be evaluated as gastroparesis without excluding conditions such as gastric ulcer, duodenal ulcer, gastritis and gastric cancer. Basal diagnostic methods such as upper gastrointestinal endoscopy and direct graphies with barium are helpful for the diagnosis of structural or mucosal abnormalities of gastric system. Gastric emptying can easily be shown with sintigraphic techniques. Such methods requires the administration of fluids and non-fluids which are radionuclide stained.
Technesium-99 labelled solid phase and indium-111 labelled fluid phase sinitographies can be used. Normally solids should be divided into particles smaller than 2 mm to pass through pyloric syphincter. Solids leave stomach later than fluids. Horowitz et al. have reported a delay in solid food emptying in 58% and 30% of type 1 and type 2 diabetics, respectively (12).

Magnetic resonance imaging and percutaneous electrogastrography are good alternatives for future clinical applications (13). Electrogastrography recording the electrical activity of the stomach by putting electrodes on the surface measures the fasting and postprandial myoelectric activity of the stomach (14, 15). It is not widely used but technically provides detailed information on the pathogenesis of gastrointestinal disturbances. There is a good correlation between gastric emptying and electrogastrography, so abnormalities in the postprandial electrogastrography seem to be able to predict delayed emptying of the stomach (16). The electrical activity of various parts of stomach are different because each part has its own mechanical activity. The electrical activity of distal stomach is marked and characterized by cyclic depolarization and has a rate of three cycles in a minute. Every cycle begins in the gastric pacemaker at large curvature in gastric body and moves to the distal to pylor with an acceleration of 0.5-4 cm/sec. Gastric neuromuscular function is shown in figure 1.

If the depolarization is larger with the effect of neurotransmitters and hormones action potentials cause gastric contractions. The decrease in the amplitude of depolarization may be related with abnormal rhythm, in other words dysrhythmia such as tachygastry and bradygastry or gastric arrhythmias. Gastric arrhythmias may occur in some of the patients with diabetic gastroparesis. In figure 2, normal gastric myoelectric activity and the effect of hyperglycemia on gastric electrical rhythm are shown in the electrogastrography.

Normally the slow wave depolarization amplitude after meals is very high and is mostly associated with larger contractions. In a study, it was observed that there is normal slow wave cycle in diabetic gastroparesis but the increase in postprandial slow wave length disappears. Gastroduodenal manometry, may be useful to show pylorospasm or the coordination disorder between stomach and duodenum, eventhough patients posses normal gastric emptying but symptomatic. Gastric antral cross-sectional ultrasonography is available for the determination of gastric emptying ratio (15). Neither hemodynamic autonomic function tests nor the glycolysated hemoglobin levels are good indicators of diabetic gastroparesis. On the contrary, in the study of Lacigova et al., among 25 type 1 diabetic patients, cardiovascular and gastrointestinal autonomic neuropathies were

![Figure 1: Gastric neuromuscular function](image-url)
found to be correlated (r=0.634, p<0.0007), but no significant correlation was found between gastrointestinal neuropathy and subjective gastrointestinal symptoms (2).

Treatment of diabetic gastroparesis.

1-Management of underlying pathophysiological cause: In cases of dehydration and prolonged vomiting episodes due to diabetic ketoacidosis, hospitalization is required. In such a case nasogastric tube administration should be performed to the fasting patient. Intravenous fluid should be administered and insulin should be given according to serum glucose and keton levels. In the treatment of diabetic gastroparesis regulation of diabetes should especially be considered. Physiological control of blood glucose levels may improve functional disruption of gastric motility.

2-Regulation of diet: Diet must be arranged for the symptomatic patients. For gastroparesis frequent meals with few food and a low fat content (40 gr/day) is appropriate. Because fatty meals cause prolongation of gastric emptying. To prevent the formation of bezoar a diet with fiber content is suggested in gastroparesis (18).

3-Gastric prokinetic agents: Metoclopramide, cisapride, domperidon and erythromycin may be used.

Metoclopramide is also used as an antiemetic agent. Oral and intravenous forms are available, so it may be used for the severe gastric obstruction due to gastric bezoars. Recommended dose of metoclopramide is 10 mg, 30-60 minutes before meals, four times a day.

Domperidon can not pass blood-brain barrier, so side effects due to central nervous system are minimal (19). It improves gastrointestinal motility by increasing antral contractions. Recommended dose is 20-40 mg, 30 minutes before meals, four times a day. Koch et al. showed that administration of domperidon for 6 months improved gastric electrical activity according to electrogastrography results (20). However, in the study of Horowitz et al., acute administration of domperidon caused acceleration in emptying both fluids and solids from stomach, but at the fourth week of treatment, emptying of solids decreased though no such decrement was observed for fluids (21).

Cisapride stimulates gastric emptying. In severe cases, cisapride may be used with the combination of metoclopramide. It is effective even in the long term administration. It may cause ventricular arrhythmias and prolongation of QT in ECG. Patients with frequent hypoglycemia and renal impairment are also prone to have cardiotoxicity due to cisapride. So cisapride can be dangerous for the highly risky diabetic patients even in monotherapy (22). The drug is now withdrawn from the market due to serious potential side effects.

Erythromycin increases the activity of motilin which is responsible from migratory motor complex activity by binding to motilin receptors and activating them. Erythromycin improves gastric emptying of solids and fluids and
increases antral contractions (23, 24). Recommended oral dose is 250 mg, 30 minutes before meals, three times a day (25, 26). Intravenous erythromycin (3 mg/kg every 8 hours by infusion) is a useful drug for clearance of gastric bezoars.

4-Treatment of associated conditions: Gastric bezoars should be cleaned by endoscopy. Alternatively 1-2 liter fluid is given or 0.5 gr/dl cellulose solution in water for 24 hours on two days is administered, 40 mg metoclopramide is given in 24 hours by infusion for three days. Depressive patients are treated for their condition. Behavioral therapy is also helpful.

5- Jejunostomy for feeding: If drug treatment is not successful or severe gastroparesis remains, feeding jejunostomy may be required. Jejunostomy should be performed to the normal functioning intestine. Both gastrostomy and jejunostomy can be inserted endoscopically. These are palliative procedures for the regulation of hydration and nutrition (27).

6- Surgery: Surgery has not yet been proved to be effective. Gastroenterostomy, vagotomy, pyloroplasty are not successful. In surgical approach for prevention of gastric retention, subtotal or near total gastrectomy and Roux-en-Y gastrojejunostomy are suggested. Patients with diabetic gastroparesis and persistent vomiting can have sufficient efficacy with radical surgical procedure. The 70% of stomach, including antrum and pylor are taken out and Roux-en-Y jejunal loop anastomosis is performed (28). Histopathological findings show that gastromyopathy cause this syndrome.

No effective treatment is available for patients with gastroparesis refractory to standard medical therapy. However, gastric pacing, which is an alternative therapy, seems to be able to improve symptoms of gastroparesis and to accelerate gastric emptying in patients with gastroparesis (29). After placement of the gastric pacemaker, patients rated significantly fewer symptoms and had a modest acceleration of gastric emptying (30).

In symptomatic treatment food can be given at night, freeing patients during the day, and insulin can be adjusted to accommodate the feeding schedule (31). In addition resting the stomach with intravenous alimentation and nasogastric sucking may provide the return of the gastric functions in a few days. Prokinetic agents are frequently used for the treatment of gastroparesis, as well. Unfortunately, in the case of severe gastroparesis, usefulness of oral agents is limited, so they have no advantageous in such cases. Those cases are needed to use intravenous or rectal forms of prokinetic drugs. Tachyphylaxis to the prokinetic agents results in progressive decrease of the biological effects of the agents. The periodical withdrawal of the drugs provides their effects back and must be performed in unresponsive patients.

Shortly, diabetic gastroparesis consists of one of the most intractible and difficult problem in diabetes mellitus practice. It may cause brittle diabetes and patients must be treated carefully. Because it is silent in general, physicians have to consider any gastrointestinal symptom in diabetic patients and find out if gastroparesis is an underlying cause or not.
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