56

Nutrition and Hollow Organs of the Upper Gastrointestinal Tract

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Nutrition is an integral part of the management of gastrointestinal illness. The following two sections will elucidate the basic mechanisms of how the hollow organs of the gastrointestinal (GI) tract handle and digest food, how illnesses of these organs affect nutritional status, and the role of nutrition in the management of these illnesses. The readers are referred to a GI textbook for further details on diseases mentioned in these sections. Neoplasms of the GI tract are not included (see Section 50).

Introduction

The general roles of the various parts of the digestive system are given in Table 56.1. Diseases of these various parts not only cause damage to individual organs but also disrupt the harmonious mechanisms that enable adequate handling and digestion of food.

Food enters through the mouth where it is lubricated and broken down into pieces by mastication. Lubrication serves several purposes including protection of the mouth from damage by food, ease of transfer of food over surfaces of the GI tract and, formation of a liquid medium in which chemical reactions of digestion can occur. Mastication is not only necessary for food breakdown, but also helps to increase the surface area of the food particles to allow reach by digestive enzymes.

Transport of food through the mouth and the pharynx into the esophagus is accomplished by the swallowing reflex. This reflex involves coordinated actions of the tongue, the soft and hard palates, the pharyngeal muscles, the glottis, the epiglottis, and the upper esophageal sphincter. It is extremely rapid with a duration less than a second, and is regulated by both peripheral nerves and a swallowing center in the brain stem.[1] The multiple levels of control of swallowing and the redundancy of the control mechanisms allow compensating for minor problems.

Once swallowing is initiated voluntarily or involuntarily and the content of the mouth is pushed back into the pharynx, the swallowing reflex results in closure of the larynx by the epiglottis and concomitant relaxation of the upper esophageal sphincter (UES) to enable reception of bolus into the esophagus. Subsequently, the esophageal body, which has a short segment of striated muscle proximally but mainly is made up of smooth muscle,

TABLE 56.1

Parts of the Digestive System and Their Functions

Parts	Functions
Mouth, salivary glands, and pharynx	Breakdown of food into parts for transport to downstream; lubrication of food pieces for transport; initiation of the digestion of carbohydrates in food
Esophagus	Transport and lubrication of food pieces; protection of the airway from food entry
Stomach	Storage and trituration of food into small pieces (<1 mm^3); initiation of the digestion of proteins with acid and proteases; initiation of the digestion of fats
Small intestines	Breakdown of foods into molecules; and absorption of macro- and micronutrients; maintenance of water and electrolyte balance
Colon	Absorption of water and electrolytes; synthesis of certain vitamins and breakdown of carbohydrates to short chain fatty acids by bacteria; excretion of waste

propels the bolus downward with peristaltic motion. As the bolus travels through the distal esophagus, the lower esophageal sphincter (LES) relaxes and food is transported into the stomach for short-term storage and digestion. The integrity of the entire esophageal food transfer mechanism is very important to prevent food entering the airway.

Food goes through two functionally distinct compartments in the stomach. The proximal compartment, consisting of the fundus and upper body, acts as a reservoir. An adequate capacity in this compartment is achieved through receptive relaxation of the stomach wall, mediated by inhibition of vagal pathways and hormones such as secretin, gastric inhibitory peptide, and cholecystokinin (CCK). This relaxation allows for a wide range of storage volumes up to 1 to 2 liters without significant increases in intragastric pressure. At the same time, release of acid and digestive enzymes into the reservoir initiates gastric digestion.

The distal and second compartment of the stomach consists of the lower body and antrum, whose main function is dissolution of food into gastric chyme with particle size <1 to 2 millimeters prior to exit through the pylorus. This process, termed trituration, is achieved by the strong propulsive motor activity of the stomach. After initiation of the electrical signal that is generated by specialized pacemaker cells located in the mid-portion of the greater curvature, the stomach begins to contract from the mid-body, the contraction gradually spreads towards the antrum in a peristaltic fashion, and partial closure of the pyloric channel occurs. The stomach contents are forced backward against the antral walls and a closed pylorus, with passage of only a small amount of well-ground food into the duodenum. The shearing physical forces generated in this repetitive propulsion and retropulsion of gastric contents attain the particle size required of solid foods before passage into the small intestine.

Antral contractions cause emptying of solid food from the stomach. Liquids exit proportional to the pressure gradient between the duodenum and the stomach. This pressure gradient increases after completion of a meal when receptive relaxation fades away and the gastric fundus returns to its normal tone, increasing intragastric pressure. The rate of emptying from the stomach is also determined by the chemical and physical composition of the meal, as well as the way the body reacts to the food via the vagus nerve and the GI hormones. Liquids empty faster than solids; foods with high carbohydrate contents empty faster than foods that contain fat or are high in fiber. Hypo- or hypertonic fluids, highly viscous fluids, acid (pH 3.5), chyme with a high caloric density, polypeptides, oligosaccharides, and fatty acids entering the duodenum, or overdistention of the small intestine inhibit gastric emptying. If nutrients rapidly enter or bypass the jejunum, rapidly reaching the ileum and colon, GI transit time is extended via an ileal "brake." This brake is mediated through neurohumoral mechanisms and GI hormones, the most important of which is peptide YY. These mechanisms assure that food is gradually released into the

small intestine, is optimally mixed with pancreatic and biliary secretions, and has adequate contact time with digestive enzymes and the small intestinal absorptive mucosa.

The small intestine is designed to have a large surface area, by arrangement of its cells into villi and crypts. The epithelial cells' lumenal surfaces have fingerlike projections termed microvilli that collectively make up the brush border. Most intestinal secretions come from the crypt cells, whereas the major function of the cells of the villi is digestion and absorption of water and nutrients. The villi, as well as their lining cells, are taller in the jejunum, and the height of both decreases caudally towards the ileum. Intestinal cells also become more specialized towards the ileum, where absorption of bile salts and certain vitamins occurs. Digestion of nutrients is accomplished both by brush border and intraluminal enzymes, especially pancreatic exocrine ones. The different types of nutrients and how they are digested by the various enzymes in the GI tract are shown in Figure 56.1.

After gastric chyme arrives at the small intestine, its acidity is rapidly neutralized by duodenal secretions and bicarbonate released from the pancreas. This neutralization is important for establishing a favorable milieu for optimal enzyme action. Furthermore, large amounts of electrolytes and water are secreted into the jejunal lumen to make chyme isoosmolar, dilute toxins, and enable mucosal defense mechanisms such as secretory IgA. Almost simultaneously, motor activity of the intestines changes: propulsive movement decreases and segmental motor contractility increases. The net effect is stirring of intestinal contents with slow forward motion, which in turn increases contact of nutrients with intestinal cells.

During this process, blood flow and lymphatic drainage of the intestine are tightly regulated. Both flows increase as food, electrolytes, and water are absorbed, rapidly carrying these away to facilitate further diffusion. This rapid circulation ensures meeting intestinal oxygen, salt, and water demands, especially during secretion.

The products of digestion get absorbed, utilizing various mechanisms such as passive diffusion and osmosis, facilitated diffusion, and active transport. The sites of absorption of different nutrients and the mechanism(s) involved in this process are given in Table 56.2. A small amount of macronutrients leaves the small intestine undigested. Undigested portions are larger for complex carbohydrates, vary with fat intake, and are minimal for proteins.

In the colon, bacteria act on the remaining nutrients and fiber, forming short chain fatty acids and a variety of vitamins. These and large amounts of electrolyte and water are avidly absorbed by the colon, resulting in a small amount of feces. Together with the enterohepatic circulation of bile, the absorption of 98% of all GI fluid and electrolytes makes the GI system one of the most efficient parts of the body. The various GI secretions are listed in Table 56.3, along with calculation of the net fluid balance.

Nutrition in Selected Diseases of the Upper Gastrointestinal Tract

Gastroesophageal Reflux Disease (GERD)

Definition and Epidemiology

GERD exists in individuals who have symptoms or histopathological changes related to backflow of gastric contents into the esophagus (see Tables 56.4 and 56.5). There is no gold standard test to diagnose GERD; its incidence is estimated from either the disease symptoms (most frequently heartburn) or from findings of esophageal injury such as

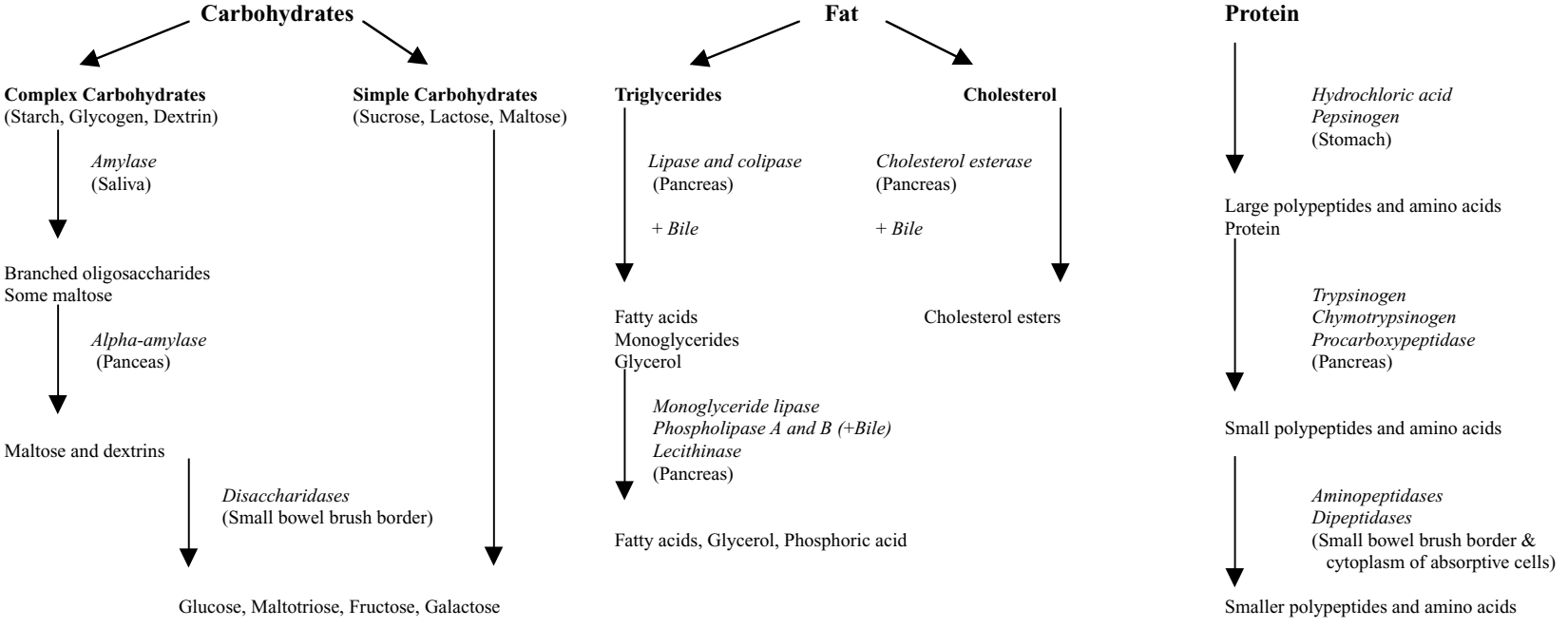

FIGURE 56.1
Digestion of macronutrients.

TABLE 56.2

Overview of Nutrient Absorption

Nutrient	Absorption Site	Mechanism of Absorption
Lipids	Proximal and distal jejunum, colon	Passive diffusion, facilitated diffusion*
Monosaccharides	Proximal and distal jejunum	Na-dependent active transport
Amino acids	Proximal and distal jejunum	Carrier-mediated active transport, simple diffusion
Small peptides	Proximal and distal jejunum	Na-independent tertiary active transport
Bile salts and acids	Distal ileum	Passive absorption, specific active absorption
Vitamin A	Duodenum, mid-jejunum	Passive diffusion**
Vitamin D	Duodenum, mid-jejunum, ileum	Passive diffusion**
Vitamin E	Duodenum, mid-jejunum	Passive diffusion**
Vitamin K_1	Duodenum, mid-jejunum, ileum, colon	Carrier-mediated uptake**
Vitamin K_2	Duodenum, mid-jejunum, ileum, colon	Passive diffusion**
Ascorbic acid	Mid-jejunum, ileum	Na-dependent active transport
Vitamin B_{12}	Ileum	Intrinsic factor binding, specific receptor med
Vitamin B_6	Jejunum	Passive diffusion
Thiamine	Duodenum, mid-jejunum	Na-dependent active transport***
Riboflavin	Duodenum, mid-jejunum	Na-dependent active transport***
Niacin	Duodenum, mid-jejunum	Awaits further study
Pantothenic acid	Mid-jejunum	Na-dependent active transport
Biotin	Duodenum, jejunum, colon	Na-dependent active transport
Folate	Duodenum, mid-jejunum, ileum	Specific carrier mediated Na-dependent active transport pH-sensitive process
Sodium	Colon	Ion-specific channel Carrier mediated coupling sodium and nutrients Antiport carrier
Chloride	Colon	Electrogenic diffusion created by Na absorption Transcellular transport linked to Na via dual antiport Anion exchangers
Potassium	Colon	Active transport by K-ATPase pumps
Calcium	Duodenum, mid-jejunum, ileum colon	Active transcellular process via specific channels, binding to calbindin and Ca-ATPase Passive paracellular diffusive process
Phosphorus	Duodenum, mid-jejunum	Active transport, passive diffusion
Magnesium	Duodenum, mid-jejunum, ileum	Passive paracellular diffusive process Transcellular carrier mediated saturable process
Iron	Duodenum, mid-jejunum	Passive paracellular diffusive process Nonessential fatty acid stimulated pathway Intracellular iron binding proteins
Zinc	Mid-jejunum	Saturable carrier mediated process Nonsaturable diffusion process
Iodine	Stomach	Active transport, passive diffusion†
Selenium	Duodenum	Active transport, passive diffusion†

TABLE 56.2 *(Continued)*

Overview of Nutrient Absorption

Nutrient	Absorption Site	Mechanism of Absorption
Copper	Stomach, duodenum	Unknown††
Molybdenum	Stomach, mid-jejunum	Unknown††
Chromium	Mid-jejunum	Unknown††
Manganese	Mid-jejunum	Unknown††
Fluoride	Stomach	Unknown††

* linoleic acid uptake occurs by facilitated diffusion
** bile salts are required for solubilization of the vitamins
*** includes hydrolytic acid phosphorilation steps
† some is also transported as amino acid complexes
†† possibly via facilitated diffusion or active diffusion or passive diffusion

TABLE 56.3

Gastrointestinal Secretions

Site	Approximate Volume (in ml)
1. Salivary glands	1500
2. Stomach	2500
3. Liver (as bile)	500
4. Pancreas	1500
5. Small intestine	1000
GI tract secretions(1+2+3+4+5)	+7000
Daily oral intake	+2500
Absorption	–9300
Net excretion in the form of stool	200

TABLE 56.4

Symptoms of GERD

Esophageal	Extraesophageal
Heartburn (pyrosis)	Hypersalivation
Acid regurgitation	Nocturnal choking sensation
Dysphagia	Symptoms related to asthma:
Odynophagia	Wheezing
Chest pain	Shortness of breath
Globus sensation	Chronic cough
Nausea/Vomiting	Other symptoms of asthma
Symptoms of GI bleeding:	Symptoms related to posterior laryngitis:
Coffee ground emesis	Chronic hoarseness/Dysphonia
Melena	Frequent throat clearing
	Chronic cough
	Sore throat
	Other symptoms of laryngitis
	Symptoms related to dental caries

TABLE 56.5

Histopathological Changes Related to GERD

Reflux esophagitis:	Destruction of esophageal epithelium: erosions, ulcers, balloon cells in epithelium
	Neutrophilic or eosinophilic infiltration of the mucosa
	Large basal zone (>15% of the total epithelial thickness)
	Extension of mucosal papillae
	Regenerative changes in the epithelium
Barrett's esophagus:	Metaplastic columnar epithelium replacing normal esophageal mucosa
Adenocarcinoma of the esophagus	
Peptic strictures	
Inflammatory polyps of the esophagus	
Pseudodiverticula	
Esophageal fistulas	

TABLE 56.6

Major Mechanisms Thought to be Involved in the Pathogenesis of GERD

1. Incompetent lower esophageal sphincter (LES)
   a. Increased transient relaxations of LES
   b. Hypotensive LES, i.e., decreased LES tone
   c. High gastroesophageal pressure gradient
2. Irritant effects of the refluxed material (especially gastric acid and pepsin)
3. Abnormal esophageal clearance/ neutralization of the refluxed material
4. Delayed gastric emptying
5. Increased esophageal sensory perception

esophagitis. Heartburn is very common: 36% of the population experience heartburn at least once a month.[2] Esophagitis is estimated to occur in 3 to 5% of the general population.

Mechanisms

Factors and mechanisms important in GERD pathogenesis are listed in Table 56.6. Current dietary management of GERD is based on preventing or counteracting these mechanisms.

Effects on Nutritional Status

Uncomplicated GERD occasionally may lead to malnutrition in infants and children, although this is extremely rare in adults. Scurvy has been reported as a result of long-term avoidance of foods that contain vitamin C.[3] Additionally, megaloblastic anemia has occurred in association with long-term use of a proton pump inhibitor.[4]

In cases of significant malnutrition with GERD symptoms, diseases giving rise to similar symptomatology and complications of GERD need to be sought. Examples include eating disorders and scleroderma, which are easily overlooked. Complications of GERD are given in Table 56.7.

Lifestyle Factors That May Affect GERD

Lifestyle factors that may adversely affect the severity or frequency of GERD-related symptoms are given in Table 56.8.

TABLE 56.7

Major Complications of GERD

1. Acute GI bleeding
2. Chronic GI bleeding with anemia
3. Peptic strictures
4. Esophageal perforation
5. Barrett's esophagus
6. Adenocarcinoma of the esophagus

TABLE 56.8

Lifestyle Factors That May Adversely Affect Severity or Frequency of GERD

1. Obesity
2. Smoking
3. Exercise
4. Alcohol consumption
5. Recumbent body position
6. Tight clothing over abdomen

Obesity

GERD is associated with obesity, and the occurrence of GERD is positively correlated with increasing body mass index (BMI). The frequency and severity of GERD seems to be worse in obese individuals; a significantly higher number of GERD-related hospitalizations occurred among the obese in the NHANES study.[5] Obese individuals also tend to have a higher incidence of hiatal hernia that adversely affects LES function and competence.[6] In some obese individuals, LES pressures are lower than controls,[7] but this is not a consistent mechanism of GERD.[8] It is postulated that the gastroesophageal pressure gradient (difference between the pressures in the esophagus and stomach) may play a more important role. As a result of the mechanical effects of increased intraabdominal fat, this gradient may be high in many obese patients with GERD. This forces gastric contents towards the relatively lower pressure esophageal environment and may promote reflux during any sphincter relaxation. Additionally, obese individuals have a higher incidence of esophageal motility disturbances[8] and cannot clear acid/gastric contents from the esophagus as fast as non-obese controls.[9] Combination of the high gastroesophageal pressure gradient with decreased clearance may explain the frequency and severity of GERD with obesity.

One study among obese GERD patients who are not medication dependent for symptom control showed significant symptomatic improvement with weight loss.[10] The authors have anecdotal evidence that even loss of a few pounds may improve symptoms. However, definitive evidence that relates weight reduction to improvement in GERD is lacking. Some studies show no benefit, although most of these studies have been undertaken in individuals who are medication dependent with severely symptomatic disease. Large amounts of weight loss may be required in the morbidly obese before symptomatic improvement is evident. Nevertheless, most obese individuals should be encouraged to lose weight as first line treatment not only for GERD, but also for other health benefits.

Exercise

Exercise such as rowing, cycling, or jogging may cause GERD in healthy volunteers.[11] Reflux is further potentiated if the exercise is performed after meals.[11-13] There are no definitive studies of GERD patients in this area.

Tight Clothing

Tight clothing worn over the abdomen and stomach has been postulated to elevate the gastroesophageal pressure gradient, especially postprandially.[14] Therefore, loose-fitting clothing has been recommended, although no clinical data support this recommendation.

Food and Diet in GERD

Dietary Habits, Body Position after Meals, and GERD

Gastric distention is a potent stimulus for inappropriate transient LES relaxations. Especially after the first few hours of eating, meal size is the most important determinant of gastric distention. Therefore, GERD patients are advised to eat smaller meals and drink liquids between, as opposed to with, meals.

Recumbent body position and sleep both decrease the clearance of refluxed gastric contents from the esophagus, resulting in prolonged esophageal exposure to acid, pepsin, etc.[15] Such exposure is a major contributor to the severity of esophagitis and stricture formation. Intraesophageal pH recordings in sleeping GERD patients show that elevation of the head of the bed significantly improves nocturnal acid clearance times.[16-18] Combined with H_2 blocker therapy, use of blocks to raise the head of the bed decreases retrosternal chest pain better than medication alone.[19] This effect is especially prominent for smokers and alcohol consumers. Thus, GERD patients are advised not to sleep for at least two hours after eating, to assume an upright body posture while awake, and to elevate the head of their bed using blocks or a foam wedge.

Meal Types and Foods That May Adversely Affect the GERD Patient

A recent study comparing various different meals suggests that more than one component or feature of the meal determines induction of GERD.[20] Use of spices, caloric density, fat content, and alcohol consumption with the meal, alone or in combination, may affect initiation of symptoms.

Various foods that are known to induce GERD, worsen its severity, or adversely affect healing of esophagitis are given in Table 56.9 together with their mechanisms of action. Alcohol's effects on promoting reflux are well documented and may be potentiated in the presence of fatty meals. Different than other alcoholic beverages, wine is very hypertonic, acidic, and has high tyramine content. Tyramine competes with histamine for degradation and may therefore delay the breakdown of the latter, which increases gastric acid secretion. In a survey of 349 individuals with GERD, wine has been reported to cause reflux in 37%.[21]

While there is no evidence that meal consistency (solid vs. liquid) affects reflux, osmolality of food may be important. Hyperosmolar versus isoosmolar foods reproduce esophageal symptoms. Coffee is thought to provoke GERD symptoms because of its high osmolality and irritant effects on the esophageal mucosa[22,23] rather than its effects on LES pressure and transient LES relaxations, which are variable.

The relationship between fat intake and GERD is unclear. Fat may increase GERD by decreasing LES pressure[24] caused by cholecystokinin (CCK) release, and by slowing gastric emptying, which in turn is thought to increase the frequency of transient LES relaxations resulting from a vagovagal reflex originating in stomach mechanoreceptors.[25]

Survey findings show that fatty foods precipitate symptoms of GERD in 38% of normal subjects. Earlier studies show that in healthy volunteers, LES pressures decrease after ingestion of a fatty meal, as opposed to increase with a protein meal. When adjusted for body position, this effect of fat on LES pressure was present only in recumbency in one study,[26] and only in the upright position in another.[27] In a third study, high fat content (50%) compared to low (10%) made no difference.[28] However, nonphysiological fat expo-

TABLE 56.9

Foods That May Worsen GERD

Food	Effect(s)
Methylxanthines (e.g., theophylline in tea)	↓ LES pressure 2° inhibition of phosphodiesterase → increased cAMP and smooth muscle relaxation
Carminatives (e.g., peppermint)	↓ LES pressure ↑ transient LES relaxations
Chocolate	Methylxanthines in it cause ↓ LES pressure High fat content ↓ gastric emptying ↑ transient LES relaxations
Alcohol	↓ or ↑ LES pressure ↓ esophageal peristalsis → ↓ acid clearance Caustic effect on mucosa Adverse effects on protective mucus ↑ gastric acid secretion ↑ number of reflux episodes ↑ nocturnal acid reflux
Citrus juice	Directly irritant to the esophageal mucosa
Tomatoes	Directly irritant to the esophageal mucosa ↑ transient LES relaxations possibly secondary to salicylate content
Capsaicin (found in peppers)	Directly irritant to the esophageal mucosa ↑ gastric acid and pepsin secretion
Spearmint	Directly irritant to the esophageal mucosa
Coffee	Directly irritant to the esophageal mucosa ↑ gastric acid secretion ↓ or ↑ LES pressure (effects worse with concomitant food intake) (effects vary with brand and treatment prior to consumption)
Onions	↑ transient LES relaxations ↑ acid-pepsin injury possibly through inhibition of arachidonic acid metabolism (raw ones create worse symptoms compared to cooked)
Milk	↑ gastric acid secretion

sures (100% fat infused into the duodenum) increased the rate of reflux episodes and the incidence of reflux during transient LES relaxations.[29] The discrepancy in results may be related to variations in composition of the diets used, the small number of patients involved, and the differences in baseline characteristics of the study subjects.

Results are more consistent for GERD patients. In terms of esophageal acid exposure when identical protein content, volume, and kcalories are provided to patients, fat does not seem to matter.[27] Recent work confirms that a high fat meal (52%), compared to 24% fat meal in an isovolumic and isoosmolar balanced one, affects neither the acidity of the esophagus nor resting LES pressures and the rate of transient LES relaxations three hours postprandially in healthy subjects and GERD patients.[30] However, these studies involve small numbers of subjects; findings may not apply to various subgroups of patients, and there may not be enough power to detect significant differences. Nevertheless, based on these results, a low fat diet cannot be recommended for all patients with GERD. For the individual symptomatic patient who cannot tolerate fat, avoidance of fatty meals is reasonable.

The type of fat in a meal may also affect GERD. In preterm infants, medium-chain triglycerides have been shown to significantly increase gastric emptying compared to long-chain triglycerides. One study investigating reflux rates two hours postprandially has found no difference with or without medium-chain triglycerides in pediatric formulas.[31] In healthy adults, new non-digestible fats (e.g., olestra) do not alter esophageal acid exposure or delay gastric emptying.[32]

TABLE 56.10

Summary of Tips for the GERD Patient

1. If overweight, lose weight
2. Try avoiding foods that may worsen GERD (given in Table 56.9)
3. Eat small quantities of food at a time
4. Eat in an upright position
5. Avoid drinking large quantities of liquids with meals
6. Do not recline for at least 2 hours after meals
7. Do not exercise for several hours after meals
8. If night time symptoms are present, try elevating the head of the bed with a wedge
9. If taking proton pump inhibitors, take medication 30 minutes before a meal

Data on other macronutrients and components of diet and GERD are sparse. High protein meals increased LES pressure in volunteers in one study,[24] but a commercially available amino acid solution infused intravenously or given intragastrically did not change reflux episodes or transient LES relaxations.[33] Oral L-Arginine did not promote reflux, despite increasing nitric oxide and lowering LES pressures.[34] High fiber did not cause reflux in 20 patients with suspected GERD.[35]

Gas-containing foods such as carbonated beverages are commonly believed to initiate reflux episodes through belching. Although no definitive data exists, in one study among GERD patients, postprandial gas reflux made up 47% of the reflux episodes versus liquid reflux, which happened 78% of the time. Only 24% of liquid retroflow into the esophagus was preceded by gas reflux, which suggests that most episodes occur without belching.[36] Another reflux-promoting mechanism may be stimulation of gastric acid secretion, as seen with cola beverages.

Do We Really Need a Certain Diet for GERD? Is There Enough Scientific Evidence for a Particular Diet?

There is no scientific evidence for a specific diet for all or most GERD patients. While a combination of lifestyle modifications such as weight loss, bland diet, elevation of the head of the bed, and antacids has been used in the past, the majority of patients with chronic symptoms and complications (about 81% in one study) do not respond, and ultimately require use of medications like H_2 blockers and proton pump inhibitors (PPIs), or surgical therapy. However, this may not apply to numerous individuals with less severe GERD, who may not even present to physicians. Given the high disease prevalence, the potential side effects of medications, and the expense of chronic PPI therapy, studies pertaining to the utility of diet therapies alone or in combination with other lifestyle modifications in patients with less severe disease are needed urgently. In the meantime, the authors assert that all patients should be educated about various aspects of diet and its effects on GERD. Patients should be given a chance to experience and experiment with the nutritional tips for GERD patients given in Table 56.10. Treatment with a diet consisting of avoidance of reflux-promoting foods (as in Table 56.9) should be reserved for the individual patient responding with the most symptomatic relief. The physician should ascertain that such treatment does not impair the patient's quality of life, as effective alternative management exists.

GERD Therapy and Diet

In general, patients with GERD tolerate all foods while on treatment with medications. Patients who do not symptomatically or histologically improve with standard therapy may have allergic eosinophilic esophagitis. Most such patients are children,[37] for whom therapy is withdrawal of the offending protein and feeding an elemental diet.

Surgical treatment of GERD may be complicated with dumping syndrome, dysphagia, and gas-bloat syndrome. Dietary treatment of dumping syndrome is given below. Dietary treatment of dysphagia and gas-bloat syndrome after fundoplication is based on common sense and anecdotal evidence. For dysphagia, authors suggest that patients eat soft foods, eat slowly, and chew food well. For gas-bloat syndrome, the suggestions are the following: 1. to decrease aerophagia: avoid talking and laughing during meals, avoid chewing gum, hard candy, mints, etc., chew foods well, do not rush through meals or eat on the run; 2. to decrease intestinal gas production: avoid gas-forming foods such as legumes, beans, etc., or foods that contain significant amounts of nondigestible materials like sorbitol, olestra, etc.

Nutritional tips for patients with GERD are summarized in Table 56.10.

The Patient on Enteral Nutrition and GERD

Theoretically, GERD may get worse with nasogastric or nasoenteric feedings as well as with gastrostomy placement. However, these interventions usually involve sick patients who may already have GI motility problems as a result of underlying illnesses. Therefore, worsening of GERD in such settings may not be reflective of these interventions.

Aspiration is the number one complication of enteral feeding via tube placement. Nasoenteric tubes can promote transient LES relaxations[38] and therefore may put patients at a higher risk of aspiration compared to gastrostomy tubes. Differences between gastrostomy and jejunostomy tubes have been evaluated in small or poorly designed studies without clear documentation of tube position. The American Gastroenterological Association recommends reservation of jejunostomy to patients with a history of GERD or recurrent aspiration secondary to gastrostomy tubes.[39]

Peptic Ulcer Disease (PUD)

Definition and Epidemiology

Peptic ulcer disease is characterized by defects in the mucosa that extend through the muscularis mucosa (i.e., ulcers) in the presence of acid-peptic injury. PUD is common, with a lifetime prevalence of 5 to 10%. The etiologies for the disease are given in Table 56.11.

Mechanisms

Proposed mechanisms of peptic ulcer pathogenesis are given in Table 56.12. Of these, the most important is the presence of gastric acid. Many studies have shown that when acid is eliminated, ulcers do not form. Therefore, the current treatment of PUD is directed at

TABLE 56.11

Causes of PUD

Common	Uncommon
Helicobacter pylori	Diseases that cause hyperacidity:
Nonsteroidal anti-inflammatory drugs	Zollinger Ellison syndrome (gastrinoma)
Stress-related mucosal damage	Mastocytosis/Basophilic leukemia
	Antral G cell hyperplasia or hyperfunction
	Infections of the gastric mucosa:
	Cytomegalovirus
	Herpes simplex
	Vascular diseases:
	Chronic radiation injury
	Crack cocaine-related injury
	Chemotherapy related injury

TABLE 56.12

Major Mechanisms of Tissue Damage and Repair Involved in the Pathogenesis of PUD

1. Epithelial cell injury resulting from:
   a. Exogenous irritants like NSAIDs and alcohol
   b. Endogenous irritants like acid, pepsin, bile acids, and lysolecithin
   c. Breakdown of epithelial defense mechanisms:
      i. Weak mucus and bicarbonate layer
      ii. Low resistance of the apical cell membrane to acid back diffusion
      iii. Inadequate acid clearance intracellularly because of derangements of the Na^+/H^+ antiporter
      iv. Inadequate acid clearance extracellularly because of altered mucosal blood flow
2. Inadequate repair of epithelial injury:
   a. Inadequate epithelial cell restitution and growth
   b. Inadequate wound healing

decreasing gastric acidity with medications. If *H. pylori* is present, treatment with antibiotics is undertaken to preven recurrence.

Effects on Nutritional Status

PUD may affect nutritional status, especially if complications related to PUD or to the cause of PUD are present. These are given in Table 56.13. *Helicobacter pylori* or medication-induced atrophic gastritis may lead to vitamin B_{12} deficiency. Repeated blood loss from bleeding ulcers may cause iron deficiency anemia. Chronic long-standing gastric outlet obstruction as a result of scarring of the pyloric channel or development of severe dumping syndrome following surgical treatment of ulcers can cause protein and kcalorie malnutrition. These complications are rare in the U.S.

Diet in PUD

The role of diet in PUD occurrence and treatment has changed tremendously as our knowledge about the pathogenesis of PUD increased. In the early 1900s, with the rationale that food buffers stomach acid, Lenhartz[39a] proposed that frequent small meals might be of benefit in PUD treatment. Physicians of the day followed with restrictive dietary treatment programs that advocated small quantities of bland food at frequent intervals, in the hopes that such a feeding regimen would also stimulate less acid secretion and thereby hasten healing. One PUD treatment consisting of milk, cream, and eggs with subsequent addition of soft and "nonirritating" foods, the Sippy diet, was formulated by Sippy and Hurst in 1910.[40] This diet and its modifications prevailed in PUD treatment over eight decades. A 1977 survey by Welsh et al. of 326 hospitals in the U.S. demonstrated that 77% used a bland diet and 55% routinely or usually gave milk to PUD patients.[41] Marked variations were seen in the composition of these supposedly similar diets.

The benefits of restrictive diets, including the Sippy and its modifications, are refuted in numerous studies.[42-45] First, acidity of the stomach following bland diets and freely

TABLE 56.13

Major Complications Related to PUD

1. Atrophic gastritis
2. Gastric carcinoma related to *H. pylori*
3. Obstruction, esp. at gastric outlet
4. Hemorrhage (acute or chronic)
5. Perforation
6. Penetration of ulcers

chosen diets do not differ.[46] More importantly, controlled studies of radiological ulcer healing or resolution of clinical symptoms show no improvement on these diets.[47,48] The same is true for ulcer recurrence, which is not different with or without such diets when patients are followed up to a year or more.[47,49] Instead, these diets in the long-term may be harmful; they can result in nutritional deficiencies such as scurvy.[50] Given this evidence, there is no reason to support the use of a restricted or bland diet for PUD. Further evidence for and against various dietary interventions are given below.

Small Frequent Feedings

Food-related gastric acid stimulation is prolonged in PUD patients, and therefore it is not logical to expect adequate acid buffering with any type of meal.[51,52] Even though peak acid secretion may be higher as a result of gastric distention with larger meals, studies show that mean acid concentration does not differ when patients are fed two-hourly portions as opposed to four-hourly ones.[53]

Increased Use of Milk

Milk had been advocated as part of the early diets for PUD (including the Sippy and its modifications) because of its acid-buffering capacity. However, in a study of a large group of PUD patients, intragastric milk drip did not improve radiological healing of PUD, although pain relief was quicker.[54] In another study of 65 patients taking equal doses of cimetidine, endoscopic ulcer healing or pain relief at four weeks was worse in the group given milk with seasonal fruits as opposed to the group given a regular diet.[55]

Milk increases gastric acid secretion (about 30% in duodenal ulcer patients)[56] and its capability to neutralize acid is short-lived.[57] Whether milk is whole, low-fat, or non-fat does not make a difference.[57] Amino acids released as a result of hydrolysis of milk proteins stimulate gastrin secretion.[56] The relatively high calcium in milk acts as a second messenger for gastrin and acetylcholine stimulated acid release, and ulcer patients are more sensitive to such effects of calcium.[58]

Milk can also be harmful to ulcer patients who consume large amounts of absorbable antacids concomitantly. These PUD patients may develop acute or chronic milk-alkali syndrome leading to alkalosis, renal insufficiency/calculi and hypercalcemia.[59]

Changing the Macronutrient Composition of Diet

Protein stimulates gastric acid more than carbohydrates and fat;[60] however, there is also evidence that high protein may result in lower gastric and duodenal acidity following meals.[61] Whether this effect is due to satiety induced by the high protein is unknown. Thus, no recommendations concerning the protein content of the meal for PUD can be made. Although fat in the small intestine inhibits gastric acid secretion,[62] there is no satisfactory evidence that high-fat diets are beneficial to ulcer patients, either. In fact, many of the bland diets, including the Sippy diet, are high in fat and have been shown to be harmful by increasing the risk of cardiovascular disease among PUD patients.

Alcohol Consumption

Alcohol ingestion can cause acute erosive gastritis with ulcerations and bleeding. Alcohol concentrations of at least 8% were required to break the gastric mucosal barrier in one study,[63] while higher levels of 40% or more were needed in another study.[64] Alcohol as low as 5% stimulates gastric acid secretion both through direct stimulation of parietal cells and through release of antral gastrin, although the effects may vary depending on the type of beverage consumed.[65] Beer, for example, can increase acid independent of its ethanol content. Intake of alcohol with salicylates may contribute to its irritant effects by

causing back-diffusion of acid and stimulating pepsin secretion. Furthermore, acute alcohol ingestion can weaken duodenal defenses against ulcer formation by inhibiting basal and secretin-stimulated pancreatic fluid and bicarbonate secretion,[66-68] which is not entirely due to alcohol-induced contraction of the sphincter of Oddi.[69]

Epidemiological studies, however, show no difference in alcohol consumption between high and low PUD areas throughout different parts of the world, and alcohol intake is not independently predictive of PUD prevalence in surveys (although most studies were conducted before testing for *H. pylori* was implemented.) Indeed, in one prospective study, alcohol consumption was lower among PUD patients compared to controls. Alcohol does not adversely affect ulcer healing either. In one study, moderate alcohol consumption (20g/day or less) promoted healing of duodenal ulcers. An author of this study, Sonnenberg, also reported that alcohol in small amounts is protective against NSAID injury, and hypothesized that alcohol may be similar to mild irritants in that low doses may heighten mucosal defenses through stimulation of prostaglandin production.[70]

Caffeine/Coffee/Tea/Carbonated Drinks

Caffeine stimulates both acid and pepsin release, and patients with duodenal ulcer have a greater and longer response. The effects of coffee and tea, however, exceed what their caffeine content induces.[71] Serum gastrin and gastric acidity (especially in ulcer patients) is higher than caffeine, and decaffeination diminishes this acid-secretory potency only minimally.[71] In one study, the addition of milk and sugar to tea lessened this effect.[72] Whether these translate into clinical significance is unknown. Habitual coffee consumption in college students was linked to development of PUD in later life. Conversely, a very large survey of 37,000 subjects failed to show an association between coffee and PUD. Carbonated beverages similarly stimulate acid production, but this may also be unrelated to caffeine.[71]

Salt Intake

A large oral load of salt can be an irritant to the gastric mucosa, leading to gastritis.[73] In epidemiological studies, PUD mortality correlates linearly with increasing salt consumption.[74] Case control studies also show that gastric ulcer patients have a higher level of salt intake compared to healthy controls.[75]

Avoidance of Certain Spices

Application of spices on upper GI mucosa revealed that cinnamon, nutmeg, allspice, thyme, black pepper, cloves, and paprika cause no endoscopic damage, whereas hot pepper, chili powder, and mustard lead to edema, erythema, and mucosal breakdown.[76] The latter spices also lead to epigastric discomfort in patients.[76] Furthermore, peppers induce supramaximal acid output in duodenal ulcer patients, and have been associated with gastritis.[77] In one study using gastric lavage, both red and black pepper caused higher levels of gastric cell exfoliation, acid and pepsin secretion, and microbleeding, although this was not confirmed endoscopically.[78] In several others, gastric aspirates after use of capsaicin (found in red peppers and paprika) and black peppers showed increased DNA fragment levels, indicating mucosal damage.[72] In other studies, peppers increased production of mucus with only minimal acid secretory effects. Duodenal ulcer patients on acid-suppressive therapy eating 3 g of red chili powder had clinical and endoscopic healing rates similar to patients not eating the spice.[42] Authors of this study suggested that direct installation of spices via tubes in a fasting state in previous studies, as opposed to more physiological consumption of the spice, might explain the discrepancy between prior reports of gastric damage and their findings. Concomitant antacid intake may have altered the effects of the spice in this study. It is also unknown whether chronic consumption of

potentially irritant spices leads to an adaptation response by stimulating gastric defenses, explaining some of the earlier work showing high levels of mucous production.

Dietary Fiber

Fiber has been postulated to be beneficial for PUD because of its buffering effects, shortening of GI transit leading to decreased acid secretion, and binding of irritant bile acids.[79] The role of dietary fiber in treatment or prevention of PUD is controversial. Reduction in clinical and endoscopic ulcer recurrence with high-fiber diets has been shown,[80,81] although epidemiological studies have found elevated incidence of PUD in areas of the world with high fiber consumption. Low fiber consumption may predispose to PUD, rather than high fiber having protective effects.[82]

Supplementation of fiber in the form of pectin has not affected ulcer recurrence.[83] Guar gum may reduce gastric acid; it has not been shown to normalize it.[84] Therefore, components of the high fiber diet other than fiber itself may be protective.

Fiber given as wheat bran can bind bile acids and may reduce their elevated concentration in gastric ulcer patients;[85] it may be beneficial in biliary reflux-associated ulcerations.

Essential Fatty Acids

Linoleic acid, an essential fatty acid (EFA) and a major substrate for synthesis of prostaglandins that are protective for upper GI tract mucosa, has been shown to be deficient in the diets of duodenal ulcer patients.[86] Additionally, Hollander and Tarnawksi have shown that the declining incidence of PUD parallels a 200% increase in dietary availability of EFAs.[87] They have hypothesized that this association reflects a cause-and-effect relationship and that higher intakes of EFA induce mucosal prostaglandin E synthesis, thereby conferring protection against mucosal irritants and NSAIDs. Although the epidemiological evidence for this hypothesis is strong, direct evidence is lacking.

Many dietary factors may be significant in the pathogenesis and treatment of ulcer disease, but most studies have been conducted before *H. pylori* was implicated in ulcer formation. Therefore, some of the evidence, especially the epidemiological, for or against various interventions may not be applicable to current PUD patients. The available information is summarized in Table 56.14. A summary of nutritional tips for patients with PUD is given in Table 56.15. With the potent antisecretory medications available today, diet

TABLE 56.14

Summary of Evidence on Diet and PUD

Definitely Not Beneficial and Potentially Harmful to PUD Patients
Bland and restrictive diets including the Sippy diet and its modifications
Frequent milk intake
Probably Harmful to PUD Patients
Alcohol
Caffeine
Coffee/Tea
Carbonated beverages
Certain spices
High salt load
Probably Beneficial to PUD Patients
Essential fatty acids
Fiber intake

TABLE 56.15

Summary of Nutritional Tips for PUD Patients

1. Avoid restrictive diets
2. Avoid frequent milk intake
3. Avoid high salt intake
4. Avoid concentrated alcoholic beverages
5. Avoid directly irritant foods and spices such as peppers, chili powder, etc.
6. Take proton pump inhibitors, 30 minutes before a meal

therapy has a limited role in treatment of PUD. Patients with PUD should be allowed to eat as they desire, with few exceptions.

Food and PUD Medications

Proton pump inhibitors frequently used in the treatment of acid-peptic diseases including PUD are expensive medications that irreversibly bind and block the hydrogen pump of the parietal cell. These drugs are rapidly cleared from the bloodstream within a few hours following intake. Therefore, for utmost efficacy, they should be timed so that effective concentrations are in the circulation when acid secretion is maximally stimulated. This usually requires these drugs to be taken about 30 minutes prior to a meal.

Gastroparesis

Abnormally slow emptying of the stomach from causes other than mechanical obstruction is called gastroparesis. The many causes are given in Table 56.16, with diabetes the most common.

The various factors and medications that affect the rate of gastric emptying are given in Table 56.17. The mainstay of the dietary treatment of gastroparesis involves avoidance of the factors that delay emptying (as shown in Table 56.17) while adopting a diet that exits the stomach easily. No one diet has been shown effective.

In general, dietary fiber usually needs to be decreased, as it may result in bezoar formation. Koch promotes six smaller meals in order to decrease symptom severity, and he advocates a three-step nausea and vomiting diet.[88] These recommendations need to be tested to prove their usefulness.

Dietary treatment frequently needs to be combined with prokinetic medications, usually administered before meals. Oral medications should preferably be in liquid formulations that are absorbed faster than capsules and tablets, which may lie in the stomach for hours.

As the disease progresses, dietary and medical treatment may not suffice, and refractory patients may require drainage gastrostomy with jejunal enteral feeding. Although no controlled studies exist, in one retrospective study, enteral feeding via a jejunostomy improved overall health status in diabetic patients.[89] Nutritional tips for the gastroparetic patient are summarized in Table 56.18.

Dumping Syndrome

Dumping syndrome is the collection of symptoms triggered by rapid entry of large boluses of food into the small bowel. The syndrome most often occurs in patients who have had a vagotomy and/or gastrectomy, frequently done in the past for PUD. The two main types of the syndrome, the symptoms, and possible mechanisms are given in Table 56.19.

Dietary treatment of early dumping aims to slow emptying of the stomach and decrease the volume and osmolality of food boluses delivered to the small bowel. For this purpose,

TABLE 56.16

Causes of Gastroparesis

Metabolic and Endocrine:
Diabetes, thyroid disease, uremia, porphyrias, pregnancy, electrolyte imbalance, Addison's disease

Iatrogenic:
Surgical damage to vagal trunk, drugs, radiation damage to stomach

Neurological:
Intracranial/spinal cord lesions, Guillain-Barré syndrome, acute dysautonomic syndrome, Shy-Drager syndrome, Parkinson's disease, seizure disorder, multiple sclerosis, labyrinthitis

Psychogenic:
Anorexia, bulimia, psychological stress

Inflammatory:
Viral gastritis, Chagas disease, Botulinum toxin, celiac sprue

Rheumatologic:
Scleroderma, SLE, PM/DM, amyloidosis
muscular disorders

Paraneoplastic:
Small cell lung cancer, breast cancer

Idiopathic

TABLE 56.17

Factors that Affect the Rate of Gastric Emptying

Factor	Fast Emptying	⟷	Slow Emptying
Luminal:			
Consistency of food	Liquid		Solid
Macronutrient composition	Fat	Protein	Carbohydrate
Fiber content of food	Low		High
Osmolality in stomach or duodenum	Low		High (>800 mOsm/L)
Change in temperature of stomach	Hot/Cold		Body temperature
Gastric distention	High		Low
Volume in duodenum	Low		High
pH in duodenum	High		Low
Drugs:	Cholinergic Erythromycin Metoclopropamide Cisapride Domperidone		Anticholinergic
Gastrointestinal hormones:	Gastrin Motilin		Cholecystokinin Glucagon Secretin

patients are advised to avoid consuming liquid and solids simultaneously, stay away from highly osmolar foods, and eat small meals. Dietary treatment of late dumping syndrome aims to decrease rapid entry of large amounts of carbohydrates, especially concentrated simple sugars, into the small intestine. Patients are advised to keep away from concentrated sweets such as candy, honey, syrup, etc. These latter recommendations have not been rigorously tested but are consistent with the pathophysiology of dumping.

TABLE 56.18

Summary of Tips for the Gastroparesis Patient

1. Eat small quantities at a time
2. Eat in upright position
3. Do not recline until several hours after meals
4. Chew every bite of food well
5. Consume a low fat diet
6. Avoid fiber/roughage
7. Eat well-cooked foods
8. Turn foods into liquid/pureed form if unable to tolerate solids
9. Take medications in liquid formulation, 30 minutes before meals

TABLE 56.19

Types of Dumping Syndrome

	Timing Following a Meal	Cause	Mediators	Symptoms*
Early	15-30 min	Rapid fluid shift from intravascular space to small intestinal lumen	Release of vasoactive intestinal hormones (e.g., VIP, neurotensin, motilin, etc.)	Flushing Dizziness Nausea Palpitations Diaphoresis Syncope
Late	2-4 h	Rapid rise of blood glucose	Rapid rise in insulin in response to glucose	

* Symptoms are similar for both early and late dumping.

TABLE 56.20

Summary of Nutritional Tips in Dumping Syndrome

1. Eat small and drink quantities at a time
2. Spread meals throughout the day
3. Avoid drinking liquids with meals, instead drink liquids in between meals
4. Avoid hypertonic foods and concentrated sweets (such as soft drinks, juices, pies, cakes, cookies, candy, etc.)
5. Avoids foods rich in simple carbohydrates, replace with complex carbohydrates
6. Consume high-protein, moderate fat foods
7. Increase fiber intake if tolerated
8. Lie down after meals if possible

Additionally, in order to delay gastric emptying, and especially bind the liquid component of the meal, fiber such as guar gum and pectin has been added to meals. Results with pectin are variable: in small studies it delays gastric emptying in the majority of patients but may also increase it; therefore, doses may need to be individualized to achieve a particular viscosity.[90,91] In one study, muffins that contain 5 g of pectin failed to alter symptoms or gastric emptying.[92] In open-label studies, addition of 5 g of guar gum to meals for four weeks symptomatically benefited 8/16 patients with proximal selective vagotomy-induced dumping, although the effect was minimal in 3 patients.[93] Recent work also suggests that increasing viscosity of the liquid phase of a meal by pectin or guar gum may stimulate more propulsive forces in the stomach, causing a detrimental effect.[94] Most patients with severe dumping do not respond to the commonly used dietary instructions. In these refractory patients, octreotide is useful.[95]

Nutritional tips for patients with dumping syndrome are summarized in Table 56.20.

References

1. Jean A. *Brain Behav Evol* 25:109; 1984.
2. Nebel OT, Fornes MF, Castell, DO. *Am J Dig Dis* 21:953; 1976.
3. Hiebert CA. *Ann Thorac Surg* 24:108; 1977.
4. Bellou A, Aimone-Gastin I, De Korwin JD, et al. *J Intern Med* 240(3):161; 1996.
5. Ruhl CE, Everhart JE. *Ann Epidemiol* 9:424; 1999.
6. Wilson LJ, Ma W, Hirschowitz BI. *Am J Gastroenterol* 94:2840; 1999.
7. O'Brien TF, Jr. *J Clin Gastroenterol* 2:145; 1980.
8. Jaffin BW, Knoepflmacher P, Greenstein R. *Obes Surg* 9:390; 1999.
9. Mercer CD, Rue C, Hanelin L, Hill LD. *Am J Surg* 149:177; 1985.
10. Murray FE, Ennis J, Lennon JR, Crowe JP. *Ir J Med Sci* 160:2; 1991.
11. Yazaki E, Shawdon A, Beasley I, Evans DF. *Aust J Sci Med Sport* 28:93; 1996.
12. Peters HP, Wiersma JW, Koerselman J, et al. *Int J Sports Med* 21:65; 2000.
13. Clark CS, Kraus BB, Sinclair J, Castell DO. *JAMA* 261:3599; 1989.
14. Dent J. *Baillieres Clin Gastroenterol* 1:727; 1987.
15. Demeester TR, Johnson LF, Joseph GJ, et al. *Ann Surg* 184:459; 1976.
16. Johnson LF, DeMeester TR. *Dig Dis Sci* 26:673; 1981.
17. Hamilton JW, Boisen RJ, Yamamoto DT, et al. *Dig Dis Sci* 33:518; 1988.
18. Stanciu C, Bennett JR. *Digestion* 15:104; 1977.
19. Harvey RF, Gordon PC, Hadley N, et al. *Lancet* 2:1200; 1987.
20. Rodriguez S, Miner P, Robinson M, et al. *Dig Dis Sci* 43:485; 1998.
21. Feldman M, Barnett C. *Gastroenterology* 108:125; 1995.
22. Lloyd DA, Borda IT. *Gastroenterology* 80:740; 1981.
23. Price SF, Smithson KW, Castell DO. *Gastroenterology* 75:240; 1978.
24. Nebel OT, Castell DO. *Gastroenterology* 63:778; 1972.
25. Franzi SJ, Martin CJ, Cox MR, Dent J. *Am J Physiol* 259:G380; 1990.
26. Iwakiri K, Kobayashi M, Kotoyori M, et al. *Dig Dis Sci* 41:926; 1996.
27. Becker DJ, Sinclair J, Castell DO, Wu WC. *Am J Gastroenterol* 84:782; 1989.
28. Pehl C, Waizenhoefer A, Wendl B, et al. *Am J Gastroenterol* 94:1192; 1999.
29. Holloway RH, Lyrenas E, Ireland A, Dent J. *Gut* 40:449; 1997.
30. Penagini R, Mangano M, Bianchi PA. *Gut* 42:330; 1998.
31. Sutphen JL, Dillard VL. *J Pediatr Gastroenterol Nutr* 14:38; 1992.
32. Just R, Katz L, Verhille M, et al. *Am J Gastroenterol* 88:1734.
33. Gielkens HA, Lamers CB, Masclee AA. *Dig Dis Sci* 43:840; 1998.
34. Luiking YC, Weusten BL, Portincasa P, et al. *Am J Physiol* 274:G984; 1998.
35. Floren CH, Johnsson F. *J Intern Med* 225:287; 1989.
36. Sifrim D, Silny J, Holloway RH, Janssens JJ. *Gut* 44:47; 1999.
37. Kelly KJ, Lazenby AJ, Rowe PC, et al. *Gastroenterology* 109:1503; 1995.
38. Mittal RK, Stewart WR, Schirmer B. *Gastroenterology* 103:1236; 1992.
39. Kirby DF, Delegge MH, Fleming CR. *Gastroenterology* 108:1282; 1995.

39a. Lawrence JS. *Lancet* 1:482-485, 1952.

40. Sippy BW. Landmark article May 15, 1915. *JAMA* 250:2192; 1983.
41. Welsh JD. *Gastroenterology* 72:740; 1977.
42. Marotta RB, Floch MH. *Med Clin North Am* 75:967.
43. Berstad A. *Scand J Gastroenterol Suppl* 129:228; 1987.
44. Kirsner JB, Palmer WL. *Am J Dig Dis* 1940:85; 1940.
45. Bingle JP, Lennard-Jones JE. *Gut* 1:337; 1960.
46. Lennard-Jones JE, Babouris N. *Gut* 6:113; 1965.
47. Doll R, Friedlander P, Pygott F. *Lancet* 1:5; 1956.
48. Truelove SC. *Br Med J* 2:559; 1960.
49. Buchman E, Kaung DT, Dolan K, Knapp RN. *Gastroenterology* 56:1016; 1969.
50. Zucker GM, Clayman CB. *JAMA* 250:2198; 1983.

51. Fordtran JS, Walsh JH. *J Clin Invest* 52:645; 1973.
52. Malagelada JR, Longstreth GF, Deering TB, et al. *Gastroenterology* 73:989; 1977.
53. Barbouris N, Fletcher J, Lennard-Jones JE. *Gut* 6:118; 1965.
54. Doll R, Price AV, Pygott F. *Lancet* 1:70; 1970.
55. Kumar N, Kumar A, Broor SL, et al. *Br Med J (Clin Res Ed)* 293:666; 1986.
56. Mathewson M, Farnham C. *Crit Care Nurse* 4:75; 1984.
57. Ippoliti AF, Maxwell V, Isenberg JI. *Ann Intern Med* 84:286; 1976.
58. Feldman M. In: *Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management.* Sleisenger MH, Fordtran JS, Eds, 6th ed. Philadelphia, W.B. Saunders, 1998, p 587.
59. Pursan S, Somer T. *Acta Med Scand* 173:435; 1963.
60. Rune SJ. *Scand J Gastroenterol* 8:605; 1973.
61. Lennard-Jones JE, Fletcher J, Shaw DG. *Gut* 9:177; 1968.
62. Christiansen J, Rehfeld JF, Stadil F. *Scand J Gastroenterol* 11:673; 1976.
63. Davenport HW. *Proc Soc Exp Biol Med* 126:657; 1967.
64. Hollander D. *Nutr MD* 14:1; 1988.
65. Lenz HJ, Ferrari-Taylor J, Isenberg JI. *Gastroenterology* 85:1082; 1983.
66. Davis AE, Pirola RC. *Med J Aust* 2:757; 1966.
67. Marin GA, Ward NL, Fischer R. *Am J Dig Dis* 18:825; 1973.
68. Mott C, Sarles H, Tiscornia O, Gullo L. *Am J Dig Dis* 17:902; 1972.
69. Pirola RC, Davis AE. *Gut* 9:557; 1968.
70. Sonnenberg A. *Scand J Gastroenterol Suppl* 155:119; 1988.
71. Cohen S, Booth GH, Jr. *N Engl J Med* 293:897; 1975.
72. Tovey FI, Jayaraj AP, Lewin MR, Clark CG. *Dig Dis* 7:309; 1989.
73. MacDonald WC, Anderson FH, Hashimoto S. *Can Med Assoc J* 96:1521; 1967.
74. Sonnenberg A. *Gut* 27:1138 and 1523; 1986.
75. Stemmermann G, Haenszel W, Locke F. *J Natl Cancer Inst* 58:13; 1977.
76. Schneider MA, De Luca V, Gray SJ. *Am J Gastroenterol* 2:722; 1956.
77. Solanke TF. *J Surg Res* 15:385; 1973.
78. Myers BM, Smith JL, Graham DY. *Am J Gastroenterol* 82:211; 1987.
79. Rydning A, Weberg R, Lange O, Berstad A. *Gastroenterology* 91:56; 1986.
80. Malhotra SL. *Postgrad Med J* 54:6; 1978.
81. Rydning A, Berstad A. *Scand J Gastroenterol Suppl* 110:29; 1985.
82. Baron JH. *Lancet* 2:980; 1982.
83. Kang JY, Tay HH, Guan R, et al. *Scand J Gastroenterol* 23:95; 1988.
84. Harju E. *Am Surg* 50:668; 1984.
85. Rydning A, Berstad A. *Scand J Gastroenterol* 20:801; 1985.
86. Grant HW, Palmer KR, Riermesma RR, Oliver MF. *Gut* 31:997; 1990.
87. Hollander D, Tarnawski A. *Gut* 27:239; 1986.
88. Koch KL. *Dig Dis Sci* 44:1061; 1999.
89. Fontana RJ, Barnett JL. *Am J Gastroenterol* 91:2174; 1996.
90. Leeds AR, Ralphs DN, Ebied F, et al. *Lancet* 1:1075; 1981.
91. Lawaetz O, Blackburn AM, Bloom SR, et al. *Scand J Gastroenterol* 18:327; 1983.
92. Andersen JR, Holtug K, Uhrenholt A. *Acta Chir Scand* 155:39; 1989.
93. Harju E, Makela J. *Am J Gastroenterol* 79:861; 1984.
94. Prather CM, Thomforde GM, Camilleri M. *Gastroenterology* 103:1377; 1992.
95. Scarpignato C. *Digestion* 57:114-8; 1996.