The Upper GI Physiology and Hormone Balance

HOMAYON IRANINEZHAD
JULY 2021

<table>
<thead>
<tr>
<th>ABDOMINAL PAIN</th>
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<tbody>
<tr>
<td>Gallstones</td>
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</tbody>
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GOALS

- Introduction
- GI Hormones/Physiology
- GERD
- Safety concerns of PPI’s
Gross Anatomy of the GI Tract

- **Mouth**: Breaks up food particles, assists in producing spoken language.
- **Pharynx**: Swallows.
- **Salivary glands**: Saliva moistens and lubricates food, amylase digests polysaccharides.
- **Esophagus**: Transports food.
- **Liver**: Breaks down and builds up many biological molecules, stores vitamins and iron, destroys old blood cells, destroys poisons, bile aids in digestion.
- **Gallbladder**: Stores and concentrates bile.
- **Stomach**: Stores and churns food, protein, HCl activates enzymes, breaks up food, kills germs, mucus protects stomach wall, limited absorption.
- **Small intestine**: Completes digestion, mucus protects gut wall, absorbs nutrients, most water, peptidase digests proteins, sucrase digests sugars, amylase digests polysaccharides.
- **Pancreas**: Hormones regulate blood glucose levels, bicarbonates neutralize stomach acid, trypsin and chymotrypsin digest proteins, amylase digests polysaccharides, lipase digests lipids.
- **Large intestine**: Reabsorbs some water and ions, forms and stores feces.
- **Anus**: Opening for elimination of feces.
- **Rectum**: Stores and expels feces.
Enteric Nervous System
Enteric Nervous System

The Brain in Your Gut
The gut’s brain, known as the enteric nervous system, is located in sheaths of tissue lining the esophagus, stomach, small intestine and colon.

SMALL INTESTINE CROSS SECTION

Submucosal plexus
Layer contains sensory cells that communicate with the myenteric plexus and motor fibers that stimulate the secretion of fluids into the lumen.

Myenteric plexus
Layer contains the neurons responsible for regulating the enzyme output of adjacent organs.

Lumen
No nerves actually enter this area, where digestion occurs. The brains in the head and gut have to monitor conditions in the lumen across the lining of the bowel.

Source: Dr. Michael D. Gershon, Columbia University
General

- **Enteric Nervous System**
  - Circular and Longitudinal layers $\rightarrow$ Auerbachs plexus (myenteric)
  - Muscularis Mucosa and Circular Muscle $\rightarrow$ Meisnners plexus
  - Excitatory $\rightarrow$ acetylcholine, Substance P
  - Inhibitory $\rightarrow$ NO, VIP, Somatostatin
Hypothalamus is the hunger center.

The cephalic phase of gastric secretion is initiated by the sight, smell, thought or taste of food. Neurological signals originate from the cerebral cortex and in the appetite centers of the amygdala and hypothalamus.

The gastric phase accounts for about two-thirds of gastric secretions. Ingested food stimulates gastric activity by stretching the stomach and raising the pH of its contents; this causes a cascade of events that leads to the release of hydrochloric acid by the parietal cells that lower the pH and break apart the food. Gastric secretion is stimulated chiefly by three chemicals: acetylcholine (ACh), histamine, and gastrin. Gastric distention here also stimulates pancreatic secretion.
The intestinal phase of digestion - the acid and semi-digested fats in the duodenum trigger the enterogastric reflex: the duodenum sends inhibitory signals to the stomach by way of the enteric nervous system. Pancreatic secretion is MAXIMAL here; the duodenum is stimulated to secrete Secretin to stimulate pancreatic secretion when it detects pH < 4.5.
Esophagus

- UES – composed of striated muscle \(\rightarrow\) combination of cricopharyngeus, cervical esophagus, and inferior pharyngeal sphincter
- Upper esophagus – striated; middle \(\rightarrow\) mixed; lower \(\rightarrow\) smooth muscle
- Outer longitudinal muscle, inner circular muscle (remember the term “inner circle”!)
- Swallow center in brain \(\rightarrow\) Medulla
- Nitric Oxide \(\rightarrow\) relaxes LES, which is typically contracted at rest.
- Primary Peristalsis \(\rightarrow\) Swallowing
- Secondary Peristalsis \(\rightarrow\) response to esophageal distention
- Both the circular smooth muscle of the distal esophagus (but NOT longitudinal) and the striated muscle of the right crus of the diaphragm contribute to the manometric high pressure zone at the end of the esophagus.
• Interstitial cells of Cajal are pacemaker cells located at interface between inner circular and outer longitudinal muscles
• Gastric accommodation refers to stomach fundus and body; these areas RELAX to allow food to build up and be broken down by acid
• The stomach initially receives and stores food by relaxation of the fundus, which is mediated by vagal efferent fibers and nitric oxide pathways.
  ○ This period termed the lag phase can vary from 15 to 40 minutes and is followed by the trituration process, which relies on the contractile and myoelectrical activities of the stomach.
• Fundus generates tonic (sustained) and phasic (short duration) contractions to propagate food through
• Antral contractions consist of slow waves
  ○ Gastric pacemaker cells, termed the interstitial cells of Cajal (ICC), initiate the gastric slow wave, which has a frequency of three cycles per minute.
Stomach

- Large, non-digestable foods are emptied by PHASE III MIGRATORY MOTOR MOTOR COMPLEX \( \rightarrow \) mostly cellulose based foods – this cycles every 60-90 minutes
  - Phase I of MMC \( \rightarrow \) quiescent
  - Phase II \( \rightarrow \) intermittent pressure
  - Phase III \( \rightarrow \) active
  - MMC is inhibited by meals but acts as a house keeper day and night to move food and secretions in a fasting state
    - Motilin is actually made in the small intestine, duodenum.
Gastrin - secreted by "G cells" in the antrum in response to cephalic response.

- Vagus nerve releases acetylcholine, activates GRP, which acts on G-cell to stimulate the release of Gastrin.
- Vagus nerve inhibits somatostatin-secreting D cells, also found in the antrum.
- Over time, pH of stomach falls, intraluminal H+ ions reactivate the D cells, somatostatin is released, and this down regulates gastrin release.
Stomach

- Gastric emptying $\rightarrow$ lag phase (digestion) and then linear phase (emptying)
  - Delay gastric emptying $\rightarrow$ CCK, Secretin, GIP, Peptide YY
  - Promote gastric emptying: Motilin, Ghrelin?
    - Vagotony $\rightarrow$ causes of loss of accommodation $\rightarrow$ and this accelerates gastric emptying
- Liquids empty faster than solids. The liquid pattern is initially linear and then it slows down. The solid pattern is initially slow (the lag phase) which then becomes linear.
- Females empty food slower than males, perhaps because of the inhibitory effects of estrogen and progesterone on gastric motility.
Stomach

![Graph showing the percentage of meal retained in the stomach over time for liquid and solid meals.]
Ghrelin

- Ghrelin is an orexigenic hormone produced by the stomach that stimulates appetite.
  - The primary role of ghrelin is the regulation of satiety.
  - It is a peptide hormone secreted by endocrine cells of the fundus.
  - ↑ with fasting and before meals stimulates hunger through vagal afferents.
  - ↑ with starvation, malnutrition, and weight loss.
  - ↓ with feeding and obesity.
  - ↓ after gastric bypass surgery as well as sleeve gastrectomy.

- Levels of leptin and CCK rise after meals, when ghrelin levels fall.
Regulator of bicarbonate secretion is duodenal pH → activates when duodenal pH is < 4.5
- CARBOHYDRATES DO NOT STIMULATE SECRETIN – ITS SOLELY THE pH!
- Secretin → Increases CAMP → stimulates bicarbonate secretion.
- BOTH Secretin and VIP → use CAMP.
- GRP, CCK, Ach, Substance P → use calcium and NOT CAMP to stimulate pancreatic secretion
- Cyclic AMP and calcium have synergistic effects on pancreatic stimulation
- Small bowel diarrhea is usually high volume – why? Small bowel is responsible for absorbing most of the water in the intestinal system.
Pancreas

- Pancreatic Secretion Phases
  - Cephalic Phase → Thought or smell of food
  - Gastric Phase → Gastric distention stimulates pancreatic secretion
  - Intestinal Phase → Pancreatic secretion is MAXIMAL here, and is stimulated when pH < 4.5 to stimulate secretin release

- B-cells → insulin; a-cells → glucagon; D-cells → somatostatin; F-cell → pancreatic polypeptide

- Trypsin is activated by enterokinase via removal of an N-terminal hexapeptide fragment and trypsin then catalyzes the activation of the other inactive proenzymes.
  - Amylase, lipase, DNase, RNase, sterol esterase and carboxylpeptidase are stored and secreted from the pancreas in their enzyme, not proenzyme, form.
Motilin

- Responsible for controlling MMC Complexes and made in the SI
- Stimulated in the fasting state
- Erythromycin is a motilin receptor agonist → stimulates intestinal peristalsis
Somatostatin

- Made by D-cells of pancreas and antrum
- Stimulated by acid and inhibited by vagal stimulation
- Decreases gastric acid, pepsinogen secretion, pancreatic, small intestine fluid secretion, gallbladder contraction, insulin and glucagon release
Peptide YY

- Released from ileum and colon in response to feeding
- Reduces appetite, anorexigenic (opposite of Ghrelin)
- Inhibits gastric motility and increases water and electrolyte absorption in the colon. Because it slows gastric emptying, it increases efficiency of digestion and nutrient absorption after a meal.
- Dietary fibers from fruits, vegetables, and whole grains increase the speed of transit of intestinal chyme into the ileum, to raise PYY, and induce satiety.
- Decreases by fasting
Pancreatic Polypeptide

- Polypeptide secreted by PP cells in the endocrine pancreas predominantly in the head of the pancreas.
- Its secretion in humans is increased after a protein meal, fasting, exercise, and acute hypoglycemia, and is decreased by somatostatin and intravenous glucose.
- It stimulates the gastric juice secretion, but inhibits the gastric secretion induced by pentagastrine. It is the antagonist of cholecystokinin and inhibits the pancreatic secretion which is stimulated by cholecystokinin.
- Glucose and fats also induce PP's level increase
- Reduced in conditions associated with increased food intake and elevated in anorexia nervosa.
VIP

- Stimulated by parasympathetic ganglia (vagal); Inhibited by adrenergic input
- Induces smooth muscle relaxation (lower esophageal sphincter, stomach, gallbladder), stimulates secretion of water into pancreatic juice and bile, and causes inhibition of gastric acid secretion and absorption from the intestinal lumen.
- Role is to greatly stimulate secretion of water and electrolytes, as well as relaxation of enteric smooth muscle, dilating peripheral blood vessels, stimulating pancreatic bicarbonate secretion, and inhibiting gastrin-stimulated gastric acid secretion. These effects work together to increase motility.
- Stimulates pepsinogen secretion by chief cells.
- Upregulated in IBD, such as in Crohn's disease.
GLP-1

- Made by L cells in the gastrointestinal mucosa (ileum)
- Incretin hormone, promoting insulin production and release in the pancreas (Trulicity, Byetta, Ozempic, Victoza)
- Reduces gastric emptying and intestinal motility
- Promotes satiety
- Involved in the ileal brake with PYY

GLP-2 → Promotes gut hypertrophy, Possible role in slowing gut motility to promote absorption
Leptin

- Reduces appetite in response to feeding, but obese people develop a resistance to leptin.
- Predominantly made by adipose cells and enterocytes in the small intestine that helps to regulate energy balance by inhibiting hunger, which in turn diminishes fat storage in adipocytes.
- Regulation of fat stores is deemed to be the primary function of leptin.
- In obesity, a decreased sensitivity to leptin occurs (similar to insulin resistance in type 2 diabetes), resulting in an inability to detect satiety despite high energy stores and high levels of leptin.
- Dieters who lose weight, particularly those with an overabundance of fat cells, experience a drop in levels of circulating leptin.
PPI’s

- Available since mid 1980’s
- Widely used: 113 million prescriptions/year
  - $14 Billion in sales in USA

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<td>2015</td>
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<tr>
<td>Total</td>
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Nexium sales (in billions of US dollars) Source: drugs.com
GERD Definitions

- GERD: Reflux of stomach contents into the esophagus causing troublesome symptoms and complications
- Severe GERD: having > 2 episodes per week
- Reflux (erosive) esophagitis: endoscopic evidence of inflammation
GERD: Clinical Spectrum

Physiologic Reflux → Symptomatic GERD → Esophagitis → Complicated Reflux

Typical
- Heartburn
- Regurgitation
- Worse: after meals
- lying down
- bending forwards
- Dysphagia

Atypical
- Chest pain
- Asthma
- Hoarseness
- Cough
- Laryngitis
- Bronchitis
- Tooth decay

Ulceration
Stricture
Bleeding
Barrett’s
Adenocarcinoma
GERD: Pathophysiology

- Decreased resistance to reflux
  - inappropriate LES relaxation
  - diaphragmatic or hiatus hernia
  - weak or hypotensive LES

- Decreased esophageal clearance
  - ineffective esophageal peristalsis

- Enhanced reflux/caustic potential
  - gastric & downstream factors
  - medications
Investigation

- **Empiric treatment as test (PPI test)**
  - Typical GERD - sensitivity 80%, specificity 57%
  - Atypical chest pain - sensitivity 78%, specificity 54%

- **Endoscopy**
  - Evaluates for mucosal inflammation, complications
  - Yield for reflux evidence in treatment naïve patients is only 50-60%

- **Ambulatory pH testing/impedance pH testing**
  - Quantifies acid exposure, correlates symptoms to reflux events
  - Impedance - detects nonacid reflux

- **Manometry**
  - Excludes achalasia, scleroderma; assesses peristalsis preoperatively
  - Excludes concurrent motility disorders

- **Barium swallow - anatomic considerations, hiatal hernia size**
Documentation of GERD on Endoscopy

- Erosive esophagitis
- Peptic stricture
- Barrett’s
- Barrett’s
Alarm symptoms are indications for endoscopy

- Dysphagia, odynophagia
- Weight loss
- Age > 45 or symptoms > 5 years
- GI bleeding
- Immunocompromised host
- Family history of GI cancer
- Atypical manifestations
Principles of GERD Therapy

Reduce reflux events

- **surgery**
  - Improve LES tone
  - Enhance gastric emptying

- **baclofen & analogues**
  - Decrease postprandial tendency

Improve esophageal clearance

- Enhance esophageal motility
- Promote gravitational benefits
- Improve salivation
- Eliminate hernia

Decrease caustic quality of refluxate

- **surgery**
  - Neutralize pH
  - Inhibit pepsin activity

Life-style changes

- Promote gravitational benefits
- Improve salivation
- Eliminate hernia

Acid suppression

- Improve LES tone
- Enhance gastric emptying
- Decrease postprandial tendency
- Improve salivation
- Eliminate hernia
- Neutralize pH
- Inhibit pepsin activity
Lifestyle changes in treatment of GERD

- Consumption of small meals
- No food or drink within 3 to 6 hours of bedtime
- Head-of-bed elevation of 4 to 6 inches
- Reduced consumption of coffee, alcohol, chocolate, fat
- Reduction or elimination of cigarettes
- Weight loss by obese patients
- Avoidance of tight-fitting garments
**Lifestyle changes in treatment of GERD**

**Diet and Gastroesophageal Reflux Disease (GERD)**

**What is GERD?**
Gastroesophageal reflux is a chronic disease that occurs when stomach contents flow back (reflux) into the food pipe (esophagus). It is usually caused by failure of the muscle valve (called the lower esophageal sphincter) between the stomach and the esophagus to close properly. The backwash of stomach acid irritates the lining of the lower esophagus and causes the symptom of heartburn.

**TRIGGER FOODS**
Some foods are known to trigger symptoms of GERD. By keeping a food diary, you can identify your trigger foods and change your diet to reduce discomfort. Below is a list of some foods recognized to trigger symptoms of GERD and how they affect the digestive tract:

- **Coffee** (with or without caffeine) and caffeinated beverages relax the lower esophageal sphincter.
- **Citrus fruits and juices** such as orange, grapefruit and pineapple have high acid content.
- **Tomatoes** and processed tomato-based products such as tomato juice, and pasta and pizza sauces are highly acidic.
- **Carbonated beverages** ( fizzy drinks) cause gaseous distension of the stomach (bloating) which increases pressure on the lower esophageal sphincter causing acid reflux.
- **Chocolate** contains a chemical called methylxanthine from the cocoa tree, which is similar to caffeine. It relaxes the lower esophageal sphincter, which causes acid reflux.
- **Peppermint, garlic and onions** relax the lower esophageal sphincter causing acid reflux.
- **Fatty, spicy or fried foods** relax the lower esophageal sphincter as well as delay stomach emptying and therefore cause acid reflux.

Contact your health care provider if symptoms do not improve with diet and lifestyle changes. Initial treatment may start with over-the-counter (OTC) medications that control stomach acid.

For more information, visit [www.asge.org](http://www.asge.org).

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GERD: Principles of Pharmacological Treatment

- Acid and pepsin damage esophageal mucosa
- **Acid suppression:**
  - controls symptoms
  - heals esophagitis
  - does not correct pathophysiology

- **Proton pump inhibitors**
  - Most potent agents for acid suppression
  - Heal complicated esophagitis

- **H2 receptor antagonists**
  - Minimum of BID dosing, higher doses may be needed
  - Works best between meals, bedtime dose for nocturnal symptoms
  - Tachyphylaxis is a problem

- **Recurrence is common when treatment withdrawn**
GERD: Surgery

- Indications:
  - Inadequate response of documented reflux to medical therapy
  - Need for lifelong medical therapy
  - Reflux induced aspiration pneumonia
  - Inadequate response of extra-esophageal manifestations to medical therapy
  - Success rate ~85%
  - Complications ~10%

Nissen fundoplication
GERD: Development of Barrett’s Esophagus and Cancer

Healthy esophagus

Squamous epithelial injury

Barrett’s Esophagus

Dysplasia

Adenocarcinoma

Reversible

Gastroesophageal reflux

Role established

Gastroesophageal reflux

Role not established
Incidence of esophageal adenocarcinoma

Risk factors (Barrett’s):
- Age >50
- Male
- White
- Longstanding reflux
- Obese
- Smoker, Alcohol use

Risk of adenoca:
- White: 3.6/100,000
- Barrett’s: 0.4-0.5%/yr
- Dysplasia (high grade): 30%/5yr

- Devasa, Cancer 1998
- Sharma, Gastro 2004
- Wang, AJG 2008
Barrett’s esophagus

Screening
In patients with multiple risk factors for esophageal adenocarcinoma:
   Age 50 years or older, male gender, white race
   Chronic GERD, hiatal hernia
   Elevated BMI, intra-abdominal distribution of body fat
General population with GERD do not need to be screened for BE

Surveillance
No dysplasia: 3-5 years
Low grade dysplasia: 6-12 months
High grade dysplasia: 3 months (if not eradicated)

Wang & Sampliner AJG 2008
Spechler, Sharma, et al, Gastroenterology 2011
PPIs Associated with Reduced Incidence of Dysplasia in Barrett’s Esophagus

Use of PPI’s in Barrett’s

- PPIs may decrease progression to neoplastic Barrett’s esophagus
- ACG guidelines recommends that patients with Barrett’s esophagus receive once-daily PPI but this “deserve consideration” when without reflux symptoms
- AGA guidelines recommend that risks and potential benefits of long-term PPI be discussed carefully with Barrett’s patients given the 0.25% annual risk of non-dysplastic Barrett’s esophagus to adenocarcinoma, and absolute benefit will be small.
WHO NEEDS TO STAY ON A PPI

- Barrett’s esophagus
- Chronic NSAIDS ulcers with bleeding risk
- Severe esophagitis
- Documented history of bleeding GI ulcers
DE-ESCALATION OF PPI

- ALTERNATIVES
  - DGL licorice
  - Acupuncture
  - MATY’S ACID REFLUX RELIEF
  - Plant slippery elm - powder mix with water and slurry fiber source
  - Carafate
  - Anxiety component
  - Breathing exercises
DGL LICORICE

Supplement Facts

Serving Size 3 Chewable Tablets
Servings per Container 33

Amount per Serving % DV

Calories 10
Total Carbohydrate 2 g <1%
Total Sugars 1 g **
Includes 1 g Added Sugars 2%*

Glucosamine 150 mg **
Calcium 75 mg **

Percent Daily Values (DV) are based on a 2,000 calorie diet. **Daily Value not established.

Other ingredients: fructose, mannitol, sorbitol, stearic acid, cellulose, natural flavor, silica, magnesium stearate.
MATY'S ACID REFLUX RELIEF

Great For

HEARTBURN
INDIGESTION
REFLUX
UPSET STOMACH
NAUSEA
PREGNANCY HEARTBURN
SOUR STOMACH
GERD
DIGESTIVE SUPPLEMENT
**MATY’S ACID REFLUX RELIEF**

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<th>Honey</th>
<th>Flavor</th>
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<tr>
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<td>Mineral Oil</td>
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<td>FD&amp;C red #40</td>
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<td>FD&amp;C yellow #6 Aluminum Lake</td>
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# Proton Pump Inhibitors

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<th>Adverse effects</th>
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<tr>
<td>Gastroesophageal reflux disease</td>
<td>Headache, diarrhea, abdominal pain</td>
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<tr>
<td>Peptic ulcer disease</td>
<td>Impaired absorption of medications (e.g. ketoconazole)</td>
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<tr>
<td>Empiric PPI test</td>
<td>May decrease activation of clopidrogrel</td>
</tr>
<tr>
<td>Acute nonvariceal GI bleeding</td>
<td>May impact calcium homeostasis, and lead to bone demineralization</td>
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<tr>
<td>Gastroprotective (e.g. with NSAIDs)</td>
<td>May impair absorption of vitamins, iron</td>
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<tr>
<td>Empiric management of dyspepsia, heartburn, atypical chest pain</td>
<td>May increase GI infections, including C difficile colitis, infectious colitis, SIBO</td>
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<tr>
<td>Hypersecretory states (ZES)</td>
<td>May increase community acquired pneumonia</td>
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