The Sphinx and Sphincters of the Gastrointestinal Tract: A Clinical Review

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The term 'sphincter' likely has its origin in the legendary Sphinx (or sphynx), a prominent mythological figure in Egyptian and Greek mythology, a creature with the body of a lion and the head of a human that terrorized the people by demanding the trespassers to answer a riddle. Unlike the mythological Sphinx, which has a negative connotation, the sphincters in the human body are physiologically beneficial and needed to prevent several disorders. Of the sphincters in the gastrointestinal tract, several are made up of smooth muscle (lower esophageal, pyloric, sphincter of Oddi, ileocecal and internal), and striated muscle (upper esophageal and external anal sphincters). Sphincteric structure (striated or smooth muscle) and functions vary depending on the location. The individual dysfunctions are the pathophysiological basis of several common gastrointestinal disorders, such as transfer and transit/oropharyngeal dysphagia, gastroesophageal reflux disease (GERD), gastroparesis, pancreaticobiliary functional pain syndromes (sphincter of Oddi dysfunctions), small intestinal bacterial overgrowth (SIBO) and frequent constipation syndromes.

INTRODUCTION

Galen, the esteemed Greek physician of 129 CE, is credited with the first use of the term "sphincter," meaning "band" or "lace." A sphincter is a ring-like muscle that surrounds a lumen, regulating the flow of liquids, solids, or gases, which can contract or relax, shorten, or lengthen the lumen. Sphincters are classified as anatomical or functional, composed of smooth or striated muscle, voluntarily or involuntarily in regulation and they play a critical role in compartmentalization and directional movement in the gastrointestinal tract. The upper esophageal sphincter (UES), lower esophageal sphincter (LES), pyloric sphincter (PS), ileocecal sphincter (IS), the sphincter of Oddi (SO), and the external and internal anal (EAS & IAS) are the main sphincters of the gastrointestinal tract. The present review of the gastrointestinal tract sphincters (GIS) meant for clinicians summarizes the available data on the structure, function, and disorders. While discussing the individual sphincters, the role of the surrounding structures cannot be ignored.

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Upper Esophageal Sphincter (UES)

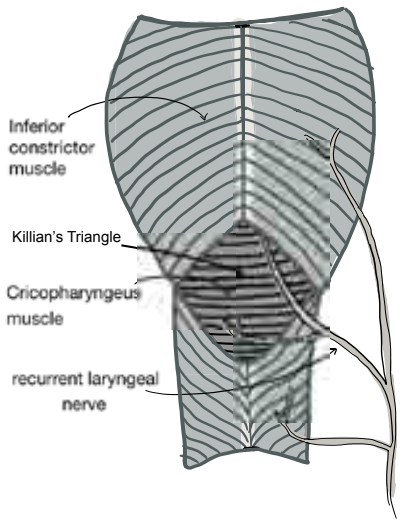
Structure

The UES is a tonically active sphincter made up of several striated muscles, including the cricopharyngeus (CP), inferior pharyngeal constrictor (IPC), and the longitudinal fibers of the cervical esophagus. The CP comprises the majority of the posterior and lateral portions of the lower third UES. The Killian's Triangle is located between the transverse fibers of the CP and the oblique fibers of the lower inferior constrictors. The glossopharyngeal (CN IX), vagus nerve (CN X), and its branches are the predominant nerves that supply the region. Acetylcholine is the neurotransmitter involved in the efferent pathway.[1,2]

Physiology

The UES is involved in various actions, such as swallowing, belching, retching, vomiting, and changes in respiration.[1,2] The physiology of swallowing is a complex process that involves the coordinated efforts of various muscles in the oropharynx and the esophagus, including the sphincter regions of the UES and LES, to move food from the mouth into the stomach. When food is being swallowed, the nuclei of the brainstem that control the UES are inhibited, leading to a decrease in UES pressure. As a result, the UES opens to allow the passage of food. During belching, rumination, vomiting, and regurgitation, the UES permits a retrograde transportation of food, fluid, or air. To open the UES during swallowing, the CP relaxes, and the suprahyoid muscle contract, allowing for efficient opening.[1] The stylopharyngeus muscle also shortens, widening the transverse diameter of the UES, while the infrahyoid muscle pulls the anterior wall forward for protection against aspiration. After the food passes through, the CP muscle returns to a contracted state and closes the UES. In the process of swallowing, in addition to the vagus and glossopharyngeal nerves, trigeminal (CN V), facial (VII), and hypoglossal nerves (XII) are involved. The factors influencing the resting UES pressure are tabulated in Table 1.

The UES pressure is impacted by its unique anatomy and physiology, which makes analyzing pressure difficult using traditional manometric systems. The recently available high-resolution manometry (HRM) that replaced the fluid-filled channels of traditional manometer has solid-state circumferential sensors which are closely spaced and can capture UES contractile and relaxation states more accurately.[9] The pressure varies from 35 to 200 mm Hg in HRM studies. HRM is being utilized for a variety of UES disorders which include cricopharyngeal (CP) dysphagia, Zenker diverticulum, and globus. Few studies have evaluated UES function after stroke/neurological disorders with HRM.[9]



Upper Esophageal Sphincter	
Structure	Striated Muscle
Nerve Supply	Cranial Nerve IX & X
Function	Physiology of Swallowing Prevention of Aspiration
Clinical Associations	Cricopharyngeal Dysphagia (CP Achalasia) Zenker's Diverticulum Globus Others

Figure 1. Dorsal View of Upper Esophageal Sphincter

Clinical Disorder(s): Pathogenesis, Diagnosis, and Management

Globus pharynegeus (GP) is a recurrent sensation of a lump or tightness in the throat unrelated to swallowing or pain. Per Rome IV criteria, the sensation must occur between meals, and there must be no evidence of dysphagia or odynophagia, gastric inlet patch, gastroesophageal reflux, or eosinophilic esophagitis. The symptoms must have been present for at least three months, with symptom onset at least six months prior to diagnosis with a frequency of at least once a week.[10] Additionally, major esophageal motor disorders such as achalasia/EGJ outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, and absent peristalsis must be absent.[11]

Temporary relief may be achieved by swallowing several times. The etiology is unclear. The risk factors considered in GP are stress factors, dysfunctional UES pressure, laryngopharyngeal reflux (LPR), conditions causing irritation or inflammation of the pharynx, and hypertrophy of the base of the tongue.

Globus is a possible esophageal disorder associated with GERD symptoms, but the role of GERD in causing globus is unclear. Previous studies have shown mixed results, with some finding GERD as a major cause of globus symptoms and others not finding a significant association.[11] This may contradict the new guidelines observed in Rome IV. Globus symptoms may be associated with dysfunctional UES findings. Diagnostic methods such as neck ultrasound, video fluorography, and endoscopy are not useful in diagnosis or management. The utility of HRM is limited. There is not a specific treatment for Globus, but when warranted, an ENT examination to rule out neoplasm may be appropriate. Cognitive behavioral therapy and speech-language therapy may also assist with managing symptoms.

Cricopharyngeal dysphagia (CD), also referred to as transfer dysphagia or oropharyngeal dysphagia can lead to various symptoms such as globus sensation, coughing or choking while attempting to swallow solid or liquids, aspiration, odynophagia, regurgitation, fear of eating, avoiding social dining situations, and recurrent aspiration pneumonia. CD can occur due to either neuromuscular disorders or mechanical impairment of the UES. The underlying pathophysiology involves the failure of the cricopharyngeus muscle to relax and open during the initiation of swallowing, leading to difficulties in transferring the food bolus. Cerebrovascular accidents involving cranial nerves and associated brainstem nuclei V, VII, IX, X, and XII lead to impairment of muscle UES function, further leading to CD.[12,13]

During a videofluoroscopic examination, a cricopharyngeal bar or cricopharyngeal achalasia can be observed as a posterior impression on the esophagus, typically located at the C5 or C6 level. A CP bar refers to the enlargement or hypertrophy of the cricopharyngeal muscle. This bar-like structure may partially obstruct the UES passage.[14] CP bar is a radiographic discovery found in around 5% to 19% of elderly individuals who undergo a barium upper gastrointestinal series.[14] Among these patients, approximately 13% may experience dysphagia.[14]

In older adults, there may be a decline in the relaxation and flexibility of the UES, making swallowing more challenging and aspiration

Table 1. Factors Contributing to UES Pressure[3–8]

Factors that Increase UES Pressure	Factors that Decrease UES Pressure
Awaking	Sleeping
Phonation	Swallowing
Posture	Belching
Esophageal secondary peristalsis	Vomiting
Increase in intraabdominal pressure	Exhalation
Stress	Elderly
Gastroesophageal reflux (GERD)	

frequent. There might be a delay in initiating the swallowing process in the throat, a shorter duration of the swallowing action, and a reduced opening time of the CP.[15,16] Age-related changes can lead to prolonged clearance times and potential exposure of the larynx, particularly in elderly patients with dysfunctional UES or swallowing mechanisms.[16,17]

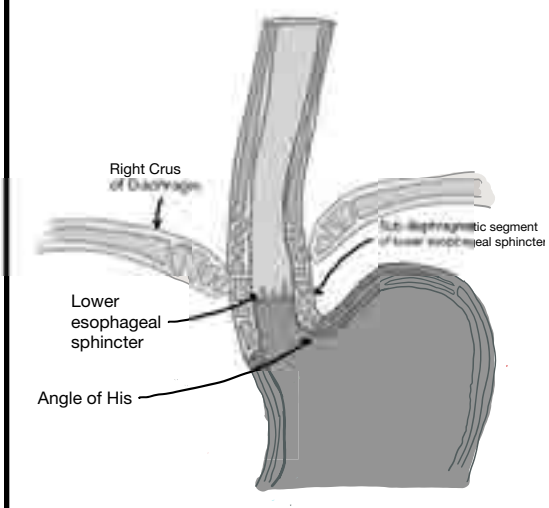
Multiple treatment options are available for CD. One of these options is botulinum toxin injection, which is a popular and preferred option for treatment due to its low-risk and cost-effective profile compared to surgery.[12] The success rates of botulinum toxin injection are slightly lower (69%) compared to myotomy (78%).[18] Treatment of CP dysphagia secondary to stroke does not focus on managing the UES dysfunction alone but using functional therapy to assist in triggering the components of the swallowing reflex.

Zenker's (pharyngoesophageal) diverticulum (ZD), named after the German Pathologist Friedrich Albert Von Zenker (1825-1898) in 1877, is the herniation of hypopharyngeal mucosa into the anatomical muscular weakness of the Killian's Triangle due to the dysregulated contraction of pharyngeal muscles. The prevalence of ZD is 1.8-2.3% of patients with dysphagia who have a radiographic examination, highest in elderly populations in the seventh and eighth decades. Patients may have a sensation of a lump in the throat with mucous build-up. The associated symptoms include dysphagia to liquids and eventually solids, halitosis, aspiration episodes, cough, food regurgitation, or rarely weight loss.[19] Modified barium swallow assists with the definitive diagnosis. HRM can reveal elevated residual UES pressures.[20] In symptomatic patients, surgical options include diverticulectomy, diverticulopexy, and myotomy. Endoscopic cricopharyngeal myotomy is becoming increasingly available in tertiary care centers.[19]

Lower Esophageal Sphincter

Structure

The primary function of the LES is to prevent the regurgitation of gastric contents back into the esophagus and allow the coordinated passage of food or fluid into the stomach. In addition, the LES allows for the venting of gas after meals, permitting belching.[21] The LES spans 3-4 cm in length and is composed of intrinsic and extrinsic muscles. The LES should be considered in the context of the gastroesophageal junction (GEJ), an anatomically complex anti-reflux barrier. As a result of recent studies, it has been noted that the LES is only a part of the mechanism of GEJ, with several participants.[22] The GEJ is the anatomical region, and the LES refers to the structures contributing to barrier function.[22] The GEJ is defined by the Z line, which demarcates the termination of the esophageal mucosa (squamous) and the beginning of the gastric mucosa (columnar). The distal margin



Lower Esophageal Sphincter and GE Junction	
Structure	Smooth Muscle
Nerve Supply	Cranial Nerve X & Splanchnic nerves
Hormonal Response	NO, VIP, Secretin
Function	Prevention of aspiration of gastric contents into the esophagus Coordinated passage of food and fluid into the stomach Venting of gas after meals leading to belching
Clinical Associations	GERD Achalasia Hiatal Hernia Scleroderma Others

The GEJ consists of the intrinsic LES muscle, extrinsic portion of the crural diaphragm, and gastric sling fiber/clasp complex.

Figure 2. The Lower Esophageal Sphincter and GE Junction

of the LES is situated about 2 cm below the Z line. Consideration of the components of the GEJ in the process of swallowing and the prevention of reflux is important rather than attributing all the functions solely to LES, as was done in the past.

The components of the GEJ involve 1) the sphincter itself, 2) the subdiaphragmatic segment of the esophagus, 3) the phrenoesophageal ligament, and 4) the acute angle of His (the angle of entry of the esophagus into the stomach).[22,23] The diaphragm is critical to maintaining the GEJ competence; the hiatus in the diaphragm is formed by a loop of muscle, the right crus. The hiatus allows for the passage of the esophagus, vagal trunks, and blood vessels. The phrenoesophageal ligament is a circumferential connecting ligament that creates a union with the right crus to the structures passing through the hiatus. The ligament connects with the GEJ, causing brief shortening of the esophagus and superior displacement of the GEJ during swallowing. The phrenoesophageal ligament aids in keeping the LES intraabdominal. During inspiration, the right crus of the diaphragm contracts causing pressure to be applied to the esophagus proximal to the GEJ, leading to contraction of the intrinsic muscles. During periods of high abdominal pressure, the barrier function of the GEJ is maintained through this mechanism. The right portion of the GEJ is created by the angle of his. The angle of His is a union between the gastric cardia and distal esophagus which functions as a pinchcock to inhibit gastric reflux into the esophagus.

The LES receives innervation from the autonomic nervous system, specifically through parasympathetic (vagus) and sympathetic (splanchnic) inputs. Sensory signals from the LES are transmitted to the NTS through vagal sensory afferents, while vagal motor efferents originating from the preganglionic fibers of the dorsal motor nucleus project back down to the LES.[24]

Physiology

The components of GEJ participate in maintaining the tone of the LES. Resting tone in normal individuals ranges from 10 to 30 mm Hg compared to intragastric pressure, with the greatest pressure readings at night.[23] This tone is achieved through a combination of transmitted intra-abdominal/thoracic pressures, passive muscle recoil, and active tone.[21,23] During a swallow, the LES contracts to prevent reflux, and this contraction persists for a short period of time after swallowing due to the inhibitory pathway of the vagus nerve and postganglionic myenteric neurons that release nitric oxide.

Frequent transient LES relaxations (TLESR) are often mentioned as the predominant factor in promoting reflux contents and symptoms of GERD. TLSESRs are spontaneous and independent relaxation of the LES and diaphragm that lasts anywhere from 10-60 seconds and are vagally mediated.[21,23] TLESRs occur without an associated pharyngeal contraction or esophageal peristalsis and are triggered by gastric distention, particularly of the cardia. TLESRs are responsible for most reflux events in healthy individuals. TLSERs occur without pharyngeal contraction or esophageal peristalsis and can last longer than LES relaxations induced by swallowing. However, not all TLESRs cause reflux. They play a significant role in belching and can be increased by gastric distention.

There is evidence for a myogenic basis of LES tone. Asoh and Goyal observed that the sphincter muscle shows a continuous electrical spike activity distinct from the esophageal body.[24] The vagus nerve provides major inhibitory and excitatory innervation to the LES, with the sympathetic nerve minimally influencing LES tonic contraction and relaxation.[25] The preganglionic fibers of the vagus nerve communicate with excitatory and inhibitory postganglionic myenteric neurons to innervate the LES smooth muscle. The preganglionic fibers release acetylcholine to the postganglionic fibers of the myenteric neurons. The postganglionic excitatory neurons release acetylcholine and substance P to cause constriction of the sphincter. The postganglionic inhibitory neurons release NO and lead to the relaxation of the LES, with neuronal nitric oxide synthase as a source of NO in the nerves. These inhibitory and excitatory nerves influence the myogenic tone of the LES. The lack of inhibitory innervation may lead to achalasia.

Overactivity of the excitatory input can lead to hypertensive contraction of the LES at resting states.[24]

Several neurotransmitters and hormones influence the tone of the LES. LES tone is decreased by including nitric oxide (NO), vasoactive intestinal peptide (VIP), beta-adrenergic agonists, dopamine, possibly cholecystokinin (CCK), and secretin.[23] On the other hand, substances like gastrin, alpha-adrenergic agonists, and muscarinic receptor agonists can increase LES tone. Other factors, such as peptides and hormones, may influence LES pressure, but the role in humans is not clear. Intraabdominal pressure and gastric distention also influence LES pressure.

Clinical Disorder(s): Pathogenesis, Diagnosis, and Management

Gastrointestinal Esophageal Reflux Disease (GERD) GERD has been extensively discussed in numerous publications by several experts (Katz, Goyal, Spechler, Yadlapati, and others). This topic is summarized substantially to limit the size of this article. The underlying cause of GERD involves the malfunction of one or more components of the GEJ. Other factors which complement the pathogenesis of GERD include excessive TLESR, hiatal hernia, hyposalivation, and dysmotility, including defects in secondary peristalsis involved in acid clearing. Studies have investigated the mechanism of TLESRs and the increased prevalence of reflux events in GERD patients, highlighting differences in the compliance or gradients of the GEJ and the localization of the acid pocket on top of the meal.[25–27] Acid pocket, defined by Kahrilas et al., is a relatively new term in the concept of the pathogenesis of GERD.[28] Acid pocket is an area of accumulated unbuffered gastric acid in the proximal stomach after meals and serves as a reservoir of acid in GERD patients. From the acid pocket, there is upward migration of acid film that contributes to mucosal injury in the squamocolumnar junction.

The role of several individual food items on LES is controversial in relation to GERD. In several studies, citrus and spicy food had little to no effect on LES pressure, although they are noted to exacerbate symptoms when esophagitis is present.[29,30] The effect of caffeine on LES is variable. Alcohol, tobacco smoking, peppermint, high-fat foods, and chocolate influence the pathogenesis of GERD; in laboratory studies, these food items reduce LES tone. However, larger clinical trials are needed to investigate the association.

GERD symptoms include heartburn which is substernal burning from the epigastrium toward the neck. Heartburn and regurgitation are the main symptoms of GERD, but symptoms of GERD are non-specific and can overlap with those of other disorders of the LES sphincter, such as achalasia.[31]

The management of GERD is well discussed in a recent practice guideline article by the ACG, which primarily involves controlling gastric acid secretion but is not directed toward the pathophysiology of the GEJ.[31] There are no medications available to increase LES pressure or prevent frequent TLESR contractions. Prokinetic therapy with propusid, a 5-HT4 receptor agonist, increases LES sphincter pressure and promotes esophageal peristalsis while decreasing the pyloric sphincter.[32] The medication is unpopular in the US due to its cardiac side effects but is used in several countries as a supplementary option to PPI in the management of GERD. Other prokinetics, such as metoclopramide, are shown to increase LES pressure in addition to enhanced peristalsis of the esophagus and improved gastric emptying. Baclofen is a GABAb agonist that can reduce TLESR, enabling reflux episodes, decreasing postprandial acid and non-acid reflux events, and belching episodes.

Achalasia

The term *achalasia* was first used by Sir Arthur Hurst in 1927, derived from a Greek term meaning "lack of relaxation." Primary achalasia is characterized by impaired relaxation of LES in response to swallowing and aperistalsis of the esophagus smooth muscle.[33,34] The pathogenesis of primary achalasia involves the dysfunctional interplay of inhibitory neurotransmitters such as NO and VIP and excitatory neurotransmitters such as acetylcholine in the myenteric plexus, leading to increased LES pressure. Symptoms include progressive dysphagia from solids and liquid, and weight loss may be modest or non-existent.[35,36]

Secondary achalasia is characterized by the same symptoms but often of shorter duration, usually secondary to cardio-esophageal junctional

cancer. Significant weight loss is a feature. Chagas disease, frequently seen in several parts of Central America, is due to infection by the parasite Trypanosoma cruzi. In Chagas disease, there is damage to the myenteric esophageal plexus leading to partial or absent LES relaxation accompanied by aperistalsis. As a result, there is the development of megaesophagus and megacolon in the gastrointestinal tract.[37]

To establish the diagnosis of achalasia, the standard procedures are barium esophagram, esophageal manometry, and endoscopy.[33] The results are complementary and barium studies show a dilated esophagus with a classic bird beak sign. The main function of endoscopy is to exclude cardio esophageal junctional cancer by retroversion of the scope. Diagnosis of achalasia by HRM is the current standard gold test. Characterizing achalasia using Chicago classification subtypes is useful for the management of the patient.[38] In all three subtypes, there is impaired GEJ relaxation with distinct esophageal pressurization and contraction. In types I and II, there is 100% failed peristalsis. Type I is characterized by the absence of pan esophageal pressurization to > 30 mm Hg. Achalasia type II is characterized by 100% failed peristalsis (aperistalsis) with pan-esophageal pressurization to > 30 mm Hg. Achalasia type III is characterized by spastic contractions because of abnormal lumen obliterating contractions with or without periods of pan-esophageal pressurization. Type I and II are associated with a good response to myotomy. Type III may require extensive myotomy.

The goal of the treatment of achalasia is to reduce the hypertonicity of the LES, which can improve esophageal emptying. Treatment options include pharmacologic, endoscopic, and surgical.

Botulinum toxin blocks the excessive unopposed cholinergic stimulation of the LES and only affects the neurogenic component of the sphincter with no influence on the myogenic tone. The treatment results only in a 50% reduction of basal LES pressure with short-acting benefits.[33] Botulinum toxin injection, however, is a therapy of choice for patients unfit for definitive surgical therapy such as pneumatic dilation or laparoscopic Heller myotomy (LHM).[33] Pneumatic dilation (PD) uses a balloon dilator which opens the muscularis propria of LES, leading to symptomatic relief. Surgical myotomy involves the division of the muscle fibers of the LES, circular layer, without disruption of the mucosal layer.[33] The recently available laparoscopic myotomy has decreased morbidity and faster recovery.

Hiatal Hernia (HH)

In the sliding type of HH, the LES is above the diaphragm reducing the function of the GEJ. In HH, there is a separation between the LES and crural diaphragm that can diminish the basal pressure of the GEJ and lead to a greater pressure gradient during relaxation, influencing the pathogenesis of GERD.[23]

Pyloric Sphincter

Structure

An excellent review by Ramkumar and Schulze provides clinically useful information on pyloric sphincter (PS).[39] The gateway connecting the antrum of the stomach to the duodenum is known as the pyloric sphincter. The term "pylorus" comes from the Greek word "pylon," which translates to "gatekeeper." Essentially, the PS promotes forward flow from mechanical and chemical digestion (stomach) areas to the site of absorption of nutrients (duodenum and small intestine). The PS is a narrow zone 1cm wide, defined by thickened circular smooth muscle loops.

The PS connects the antrum to the duodenum through the proximal pyloric loop (PPL) and distal pyloric loop (DPL), respectively.[39] DPL is rich in connective tissue that influences resting PS diameter and resistance. PPL is located 2-3 cm above the pyloric opening near the greater curvature of the stomach. The DPL and PPL join at the lesser curvature of the stomach, forming a connective tissue and layer of fat known as the pyloric torus.[39] The contraction of the DPL and the PPL controls the pyloric diameter. The distal corpus and pyloric antrum serve as peristaltic pumps. The entire segment contracts as a unit with the distal antrum.[40] See Figure 3.

Functionally the PS can be viewed in the context of other gastric segments. The fundus generates the tone, while the corpus and antrum process the food before emptying. The PS regulates

(continued on page 28)

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the gastric emptying rate.[41,42]

The PS is under the influence of the autonomic nervous system. The vagus nerve supplies afferent and efferent signals from and to the pylorus. The afferents contain sensory nerve fibers, primarily stretch receptors, that respond to lower levels of a stretch compared to the antrum and proximal stomach. The parasympathetic nervous system, through CN X, causes the relaxation of the PS Motor fibers of vagal efferents and releases inhibitory responses through VIP and NO, leading to the relaxation of the sphincter. Several of these nerve fibers contain nitric oxide synthase (nNOS).[43-45]

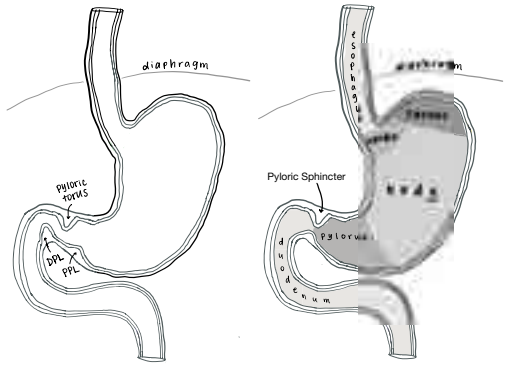
The pylorus has an abundance of sympathetic nerve fibers. Through the greater and lesser splanchnic nerves from the celiac ganglion, the sympathetic nervous system causes constriction of the pylorus and the sphincter. Constriction of the pylorus is mediated by vagal efferent excitatory fibers that release acetylcholine. In addition, the pylorus has intrinsic innervation from the stomach's myenteric plexus that extends through the pylorus into the duodenum, deeply integrating into the sphincter muscles and influencing contraction and relaxation.[40]

One must review the gastric motor functions to understand the pyloric sphincter function since they share integrated processes. Smooth muscle cells (SMC) of the stomach, with connective tissue interspersed between, play a significant role in the trituration of food and gastric emptying.[42] SMC are coupled by gap junctions and transmit electrical impulses to neighboring cells leading to the synchronicity of contractions.[42] SMCs are coupled with the Interstitial Cells of Cajal (ICC) by gap junctions, which help regulate the stomach's motor patterns.

Physiology

The PS plays a vital role within the stomach's migrating motor complex (MMC), a cyclical motor process that aims to eliminate undigested particles.[40] The MMC encompasses four distinct phases. Phase 1, lasting 45-60 minutes, is characterized by slow waves independent of contraction. In Phase 2, slow waves occur with frequent phasic contractions. Phase 3, mediated by neural signals, involves contractions that persist for 5-15 minutes and move towards the pyloric sphincter, independent of slow waves. Throughout this process, the pylorus and duodenum remain relaxed and open, facilitating the movement of food remnants out of the stomach during phase III. In Phase 4, contractile activity is inhibited, merging with the subsequent phase of the digestive cycle. The absence of pyloric relaxation can result in gastric outlet obstruction. During the inter-digestive period, certain hormones such as motilin and ghrelin play a role in regulating the activity of gastric pumps and inhibition of PS contraction.[40]

Gastric emptying is a complex process that involves coordination from several intricate neuro-hormonal processes, from the smooth muscle cells, ICC, and parasympathetic and sympathetic nervous systems. The PS and duodenum function in



	Pyloric Sphincter
Structure	Smooth Muscle
Nerve Supply	Cranial Nerve X
Hormonal Response	NO & VIP
Function	Passage of gastric contents to duodenum
Clinical Associations	Gastroparesis Congenital hypertrophic stenosis Others

PPL: proximal pyloric loop and DDL: distal pyloric loop

Figure 3. Pyloric Sphincter in Relation to Stomach

a synchronized manner. Prior to gastric emptying, the terminal antrum and PS serve as grinders and filters, respectively.[40]

During the digestive phase, the fundus of the stomach can hold large volumes of food without an increase in pressure, known as accommodation.[40] In this filling phase, gastric smooth muscles are not contracted. Liquids leave the stomach much faster than solids. Solids that remain in the stomach then move to the antrum and become triturated into chyme of particles less than 2mm in size and leave 2-3 hours after a meal.[46] Following the filling phase, a pumping phase is present with contraction of the fundus and increased peristaltic contractions in the antrum. Through this process, undigested food is mixed with gastric acid and pepsin, and the antrum is filled to a threshold prior to food entering the duodenum.[40]

The pylorus plays a major role in preventing the regurgitation of duodenal contents while regulating the emptying of chyme.[39,40] Following stimulation from the pacemaker and activation of ICC, gastric motility begins. The peristaltic contraction from the fundus propels digested food and chyme from the proximal to the distal antrum, where the PS is relaxed. A small portion of chyme moves into a relaxed pylorus into the duodenum, with some chyme moving back into the proximal antrum. The peristaltic contraction becomes more vigorous and faster and reaches the terminal antrum, constricting the pylorus and restricting emptying. These contents are retropulsed back into the stomach leading to shearing forces that break down food particles into smaller pieces. The PS continues to be contracted and provides a sieve/filter function to reduce food particles to less than 2mm before emptying occurs. The contractions in the pylorus lead to an anterograde flow of chyme into the duodenum and a retrograde flow of food that escapes grinding.[39,40,42] During the digestive period, PS can influence gastric emptying. Failure of the antral contractions or pyloric relaxation can decrease gastric emptying.[42]

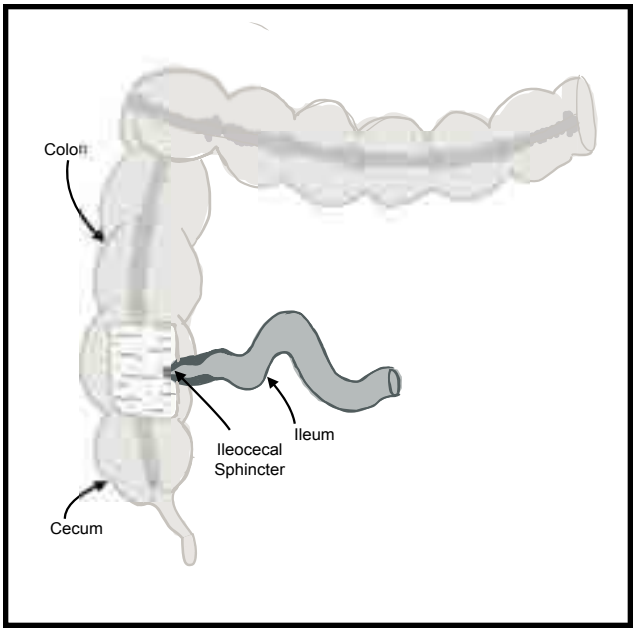


Figure 4. Ileo-Cecal Sphincter

The soluble fiber in the diet influences gastric motility, creating a gel formation with liquid in the stomach, resulting in a substantial delay in gastric emptying.[47] Slower gastric emptying is associated with lower postprandial blood glucose levels.[47]

Clinical Disorder(s): Pathogenesis, Diagnosis, and Management

Gastroparesis & the Pyloric Sphincter

Gastroparesis is a functional disorder defined by delayed gastric emptying without mechanical obstruction associated with nausea, vomiting, early satiety, bloating, and abdominal pain.[48] While idiopathic gastroparesis is seen in 30% of cases, several etiologies contribute to symptoms ranging from neuromuscular diseases affecting the non-sphincter gastric muscles to post-surgical complications and pyloric dysfunction. Patients with gastroparesis may also have pyloric dysfunction. Pyloric dysfunction can consist of pylorospasm or intermittent contractions that cause increased baseline tone at the pylorus and sphincter. Diabetes contributes to the significant pathogenesis of gastroparesis. Patients with gastroparesis are found to have abnormal interstitial cells of Cajal and neuropathy of the myenteric plexus, leading to loss of gastric pacemaker activity.

Diabetic gastroparesis patients are shown to have lower PS distensibility and higher pyloric sphincter pressures.[48] Distensibility refers to an elastic tissue's ability to stretch and expand in response to applied pressure.[49] The term applies to ring-shaped sphincters compared to similar terms such as compliance, which refers to a hollow organ. PS distensibility is inversely correlated to gastric

Table 2. Treatment Modalities for Gastroparesis

Modality	Effect	Comments
Prokinetic Agents: • Erythromycin • Metoclopramide * Other medications in development include: felcistetag (5-HT4 agonist) tradipitant (NK1 antagonist) relamorelin (ghrelin agonist) trazpiroben (dopamine D2/D3 receptor agonist)[42]	Erythromycin is a commonly used antibiotic that accelerates gastric emptying through activation of the MMC[42] Metoclopramide, a peripheral cholinergic and antidopaminergic agent, peripherally improves gastric emptying and central action resulting in an anti-emetic effect[54]	Erythromycin prokinetic effects are limited by tachyphylaxis[42] Metoclopramide has serious central nervous system adverse effects, partially irreversible tardive dyskinesia[54]
Diet modification	Appropriate glycemic control, especially for patients with diabetes[36] Avoidance of alcohol and tobacco Low fat, low soluble fiber diet of small portions	Increased blood glucose can slow gastric emptying, especially in diabetics Alcohol and tobacco can modify gastric emptying Fat, soluble fiber, and large volume can slow gastric emptying
Intrapyloric botulinum toxin	Neurotoxic protein that leads to relief of pylorospasm & improvement of gastric emptying[53]	No current systematic evidence evaluating its effectiveness[55]
Surgical pyloroplasty	Surgery that widens the pylorus to promote short-term gastric emptying[53]	No current randomized trials evaluating its effectiveness for gastroparesis[53]
Endoscopy pyloromyotomy (G-Poem)	Division of the pylorus from the mucosal surface with incision of the circular muscular layer to improve gastric emptying[56]	More studies are needed to evaluate its effectiveness
Gastric electrical stimulation	Direct stimulation of the pacemaker to improve gastric emptying[36]	No current systematic evidence evaluating its effectiveness[36]

emptying, and studies have shown that pyloric distensibility was altered in 30-50% of patients with gastroparesis.[48]

Gastric emptying study using scintigraphy is an available test in many institutions and is considered to be the gold standard for diagnosing gastroparesis.[50,51] Radioactive tracers, such as technetium-99 m, are added to liquid and solid foods. Other tests to diagnose gastric emptying include a breath test with carbon 13-octanoic acid or acetic acid.[52] However, these are more time-consuming compared to scintigraphy. Intraduodenal/pyloric manometry and Functional Luminal Imaging Probe (FLIP) can help to assess the PS but are available only in tertiary care centers and at this time of limited clinical interest.

The role of the PS in gastroparesis and management has been discussed and reviewed in the following articles.[42,53] A summary is shown in Table 2.

Hypertrophic Pyloric Stenosis

Hypertrophic pyloric stenosis (HPS) involves a thickening of the pyloric lumen to greater than 1-3mm, associated with rigid and overlapping mucosal folds that create a point of obstruction. HPS is seen in young infants 1 to 2 months after birth. Ultrasound is the preferred diagnostic test choice due to its ease of use with no contrast or no radiation exposure.[40] Laparoscopic pyloromyotomy, involving the hypertrophied pyloric muscle incision, is the treatment of choice.[39,57]

Ileo-Cecal Sphincter

Structure

The junctional region between the ileum and colon, the Illeo-colonic junction (ICJ), has been dubbed the 'apothecary barrier' due to its role in reinforcing water absorption in the colon.[58] This segment, also known as the ileocecocolonic segment, consists

of the ileocecal sphincter (ICS) and cecum and behaves similarly to the LES region discussed earlier. The ICS has an episodic and intermittent propagating motor activity and functions to transfer digestive contents and residue from the ileum to the cecum, leading to the early concept of the ICS as an intestinal stomach.[58]

The ICS exhibits several features of other sphincters. Anatomically the site is marked by considerable thickening of the circular muscle coat.[59] The terminal ileum and cecum join at an acute angle. The ileum's muscular components merge with the layers of the cecum and colon, creating an ileal papilla, further supported by ligamentous connections between all three structures. The smooth muscle in the distal portion of the ileum wall thickens to create a sphincter. This intricate relationship between the structures of this region may play a role in the ICS's competency.[59,60] The vagus and splanchnic nerves innervate the ICS. The vagal efferent stimulation reduces the sphincteric pressure and increases motor activity of the ileum.

Physiology

ICS maintains a sustained isometric tone of myogenic origin.[59,59,61] Manometry studies have been unable to assess the position of the manometric pressures of the ICS.[62]

The ICS controls forward and backward flow through integration with the distal ileum and proximal colon motility. The gastro-ileal and ileocolonic reflexes involving the ICS affect the sphincter's overall motility. The ICS tone increases immediately after a meal and lessens during the inter-digestive phase.[58]

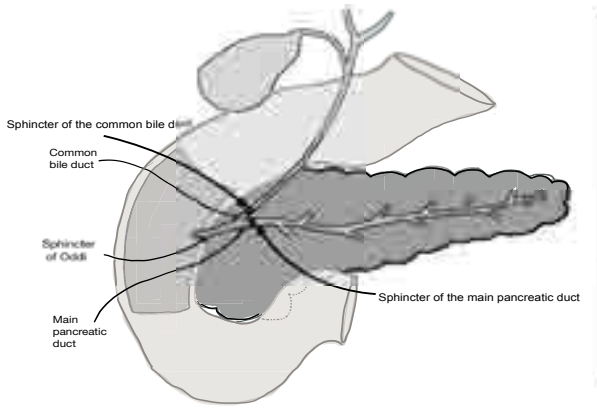
The ileocolonic reflex involves colonic distension, which is followed by ICS contraction.[63] Higher distending pressures cause higher excitatory responses. Ileal distension can have variable responses of the ICS; distention closer to the ICS causes excitatory and inhibitory responses likely due to descending excitatory and inhibitory pathways.[58]

The distal ileum synthesizes several hormones that influence digestive motility, including peptide YY (PYY), glucagon-like peptides, and neurotensin. Neurotensin is a hormone and neurotransmitter that functions as a hormone in the distal ileum.[64] We are not discussing in depth the absorptive features of the terminal ileum; however, the terminal ileum plays a significant role in B12 absorption and entero-hepatic circulation of bile acids.

Clinical Disorder(s): Pathogenesis, Diagnosis, and Management

Small Intestinal Bacterial Overgrowth Syndrome (SIBO)

Clinically the role of the ICS in preventing small intestinal bacterial overgrowth syndrome (SIBO) has been discussed previously.[65] The ICS separates the small and large bowel, which have distinct physiological properties, especially in bacterial content. The ICS limits colo-ileal reflux, which can prevent the colonization of the ileum by colonic microflora. Surgical removal of the ICS



Sphincter of Oddi	
Structure	Smooth Muscle
Nerve Supply	Myenteric plexus located between the muscles and submucosal plexus
Hormonal Response	CCK (mainly) Motilin and somatostatin Nitric Oxide Synthetase Vasoactive Intestinal Peptide (VIP) and Neuropeptide Y (NPY)
Function	Prevention of reflux of duodenal contents Regulation flow of bile and pancreatic secretions Promotion of retrograde filling of gallbladder
Clinical Associations	Sphincter of Oddi Dysfunction (SOD) SOD Stricture

Figure 5. The Sphincter of Oddi

may enhance the development of SIBO due to retrograde bacterial migration from the large to the small bowel.

The Sphincter of Oddi

Structure

The sphincter of Oddi (SO) consists of three layers of smooth muscle surrounding the common bile duct, main pancreatic duct, and ampulla of Vater.

Function

The SO plays a role in preventing duodenal reflux, regulating bile and pancreatic flow, and facilitating retrograde gallbladder filling. The SO has a basal pressure of 10mm Hg in humans, and pressure gradients dictate the flow.

Anterograde phasic contractions at the SO propel bile and pancreatic secretions into the duodenum. This is followed by a relaxation phase allowing the passive filling of bile into the SO. Increasing basal pressure leads to resistance to flow into the duodenum, allowing the gallbladder to fill. Bile and pancreatic juices flow into the duodenum when basal pressure decreases below CBD and PD pressure.

The filling of the SO triggers varying phasic contractions during different digestive phases. A meal stimulates the release of CCK, causing gallbladder contraction and relaxation of the SO. CCK also directly stimulates SO smooth muscle. Somatostatin, released from endocrine cells throughout the digestive tract, causes gallbladder contraction and SO relaxation.[66]

Clinical Disorder(s): Pathogenesis, Diagnosis, and Management

Sphincter of Oddi dysfunction (SOD)

Sphincter of Oddi dysfunction (SOD) is commonly present in females ages 20-50, with a general population prevalence of 1.5%. The biliary or pancreatic sphincter may become stenotic, causing blockage of bile and pancreatic juice flow. Furthermore, the sphincter's smooth muscle may have an inappropriate response to neuronal or hormonal stimuli that normally cause contraction.[66,67]

The disease presentation and clinical findings

Table 3. SOD Classification, Biliary and Pancreatic(Adapted from Rome IV Criteria)[10,68,69]

Functional Biliary Sphincter of Oddi Dysfunction	Functional Pancreatic Sphincter of Oddi Dysfunction
1. Criteria for biliary pain include: ▯ Pain located in the epigastrium and/or right upper quadrant and all of the following: o Builds up to a steady level and lasts 30 minutes or longer o Occurring at different intervals (not daily) o Severe enough to interrupt daily activities or lead to an emergency department visit o Not significantly related to bowel movements o Not significantly relieved by postural change or acid suppression 2. Elevated liver enzymes or dilated bile duct, but not both 3. Absence of bile duct stones or other structural abnormalities Additional Supportive Criteria: 1. Normal amylase/lipase 2. Abnormal sphincter of Oddi manometry 3. Hepatobiliary scintigraphy	1. Documented recurrent episodes of pancreatitis (typical pain with amylase or lipase >3 times normal and/or imaging evidence of acute pancreatitis) 2. Other etiologies of pancreatitis excluded 3. Negative endoscopic ultrasound 4. Abnormal sphincter manometry Diagnostic criteria must include all of the above

are on a spectrum, and the ROME IV criteria can assist in describing the clinical features.[10,68,69] The diagnostic criteria for SOD dysfunction are tabulated.

Patients with idiopathic recurrent pancreatitis (IARP) may have a prevalence of SOD as high as 72%.[70] Toouli et al. observed 57% of patients with IARP had elevated SO pressures in a study with 28 patients with IARP.[71] In the pathogenesis of acute pancreatitis, however, it is well-recognized that a stone at the ampulla can initiate pancreatic injury.

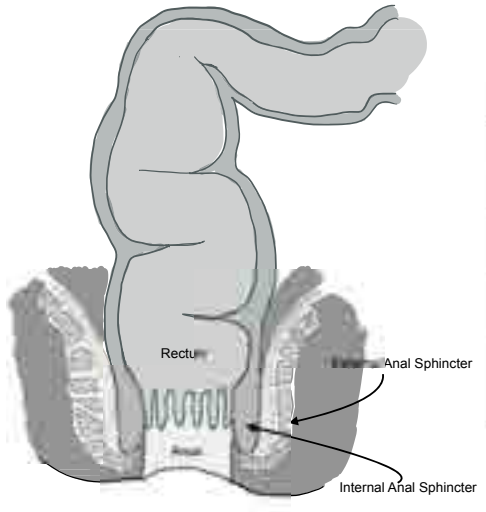
Once, the most widely used Milwaukee classification for SOD was carefully re-evaluated in Rome IV criteria, and as a result, type III SOD was eliminated to avoid unnecessary or unwanted sphincterotomy as the diagnosis was based solely on patient history. Thus, SOD is divided into two types using a structural perspective based on symptoms, radiographic findings, and laboratory abnormalities. Type I SOD has abnormal chemistries and dilated biliary or pancreatic duct imaging. Type II SOD has abnormal biochemical markers *or* abnormal imaging.[72]

Risk factors for SOD include patients who underwent cholecystectomy, irritable bowel syndrome (IBS), and use of exogenous agents such as opiates. As mentioned previously, CCK relaxes the SO in patients with intact gallbladders. In patients six months after cholecystectomy, CCK can fail to relax the SO. Patients with postcholecystectomy may have elevated basal SO pressures with increased retrograde SO phasic contractions. The gallbladder may act to prevent sudden increases in retrograde intraductal pressures from ductal obstruction. The incidence of SOD after cholecystectomy is variable, with approximately 1.5% of patients developing the disorder.[73]

Patients with IBS may have an association with SOD. Patients with IBS who undergo cholecystectomy may exhibit a diminished response to CCK compared with postcholecystectomy patients without IBS, leading to the pathogenesis of SOD. Opiates are known to alter flow through the SO, with morphine increasing the amplitude and frequency of the phasic wave through the mu receptor.[66]

Manometry is the gold standard for diagnosing SOD, especially diagnosing SOD type I. The therapy is only offered at select tertiary care centers due to its time-consuming nature, technical expertise requirements, and potential complications such as post-ERCP pancreatitis.[66,74]

Certain exogenous agents reduce the pressure and resistance of the SO, leading to the relaxation of the sphincter. These agents include calcium-channel blockers, botulinum toxin, and glyceryl trinitrate, showing some evidence of symptomatic relief.[75–77] There currently is a lack of large, randomized, and controlled trials to demonstrate the efficacy of these pharmacological agents for



Internal Anal Sphincter	
Structure	Smooth Muscle
Nerve Supply	Parasympathetic fibers arising from spinal cord levels S2-S4 Sympathetic innervation from superior hypogastric plexus
Hormonal Influence	NO
Function	Maintenance of continence Controlling defecation Passing flatus
Clinical Associations	Constipation, Obstetric anal sphincter injury, rectal prolapse, scleroderma, anal fissure, internal sphincter achalasia, and others

External Anal Sphincter	
Structure	Striated Muscle
Nerve Supply	The perianal branch of S4 and the inferior rectal branch of the internal pudendal nerve(motor) and inferior rectal nerve (sensation)
Function	Maintenance of continence Controlling defecation Passing flatus
Clinical Associations	Dyssynergic Defecation and others

Figure 6. Anal Sphincters: External and Internal Anal Sphincter

the treatment of SOD.

For both types of SOD, endoscopic sphincterotomy is the best treatment option with significant pain reduction. Roughly 90% of patients with type I biliary SOD and 60–94% of SOD type II patients have had improvement in pain following a biliary sphincterotomy.[66,67]

Anal Sphincter

Structure

Internal Anal Sphincter (IAS)

The IAS and EAS are the two sphincters of the anal canal. The IAS, an extension of the circular ring of the involuntary smooth muscle of the rectum, terminates 10mm above the anal verge and is 2.5cm long, 2-5mm thick in size, and is comprised of both circular and longitudinal muscle separated by connective tissue. The IAS is surrounded superiorly by the levator ani muscle and is encased by the EAS, comprised of skeletal muscle, and is under voluntary control.[78,79]

The IAS is under dual innervation from the autonomic and enteric nervous systems. The sympathetic nerve fibers arise from the lower thoracolumbar ganglion to form the superior hypogastric plexus.[80] Parasympathetic fibers arising from spinal cord levels S2-S4 form the inferior hypogastric plexus giving rise to the superior, middle, and inferior rectal nerves that supply the anal canal.[80] The parasympathetic input is primarily inhibitory in nature, prompting relaxation mainly through muscarinic receptor stimulation. The sympathetic nervous system is shown to have both an inhibitory and excitatory influence, dependent on receptor activation. Alpha and beta adrenoreceptors are present in the IAS, with stimulation of alpha adrenoreceptors leading to excitation and stimulation of the beta receptors leading to an inhibitory effect.[81–83] Anal pressure and tone are primarily influenced through the parasympathetic nervous system.

The enteric nervous system affects the IAS through neurotransmitters, mainly NO. The circular muscle layer is embedded with inhibitory neurons that release NO, leading to relaxation. VIP is also shown to influence inhibitory responses in the IAS.[84]

Due to the specialized cell properties of the smooth muscle, the basal tone is myogenic, with tone and phasic contractile activity being independent of nervous system input.[85]

External Anal Sphincter (EAS)

The EAS is composed of striated muscles, voluntary, and encompasses the IAS, extending to the anal verge. The subcutaneous and superficial muscle bundles make up the EAS. The nervous system innervation comes from the perianal branch

Table 4. IAS Pathology and IAS Pressure
Adapted from Kumar & Emmanuel et al.[78]

Pathology Associated with Low Resting IAS Pressure	Comment
Obstetric anal sphincter injury during childbirth	A significant correlation between IAS injury is observed during childbirth and fecal incontinence
Anorectal surgical procedures: • anal dilatation • fistula surgery • low anterior resection • hemorrhoidectomy	Advances in surgical techniques have decreased iatrogenic injuries
Rectal prolapse	Pathogenesis is not clearly understood but may involve IAS dilation and altered RAIR mechanisms
Radiation toxicity	Following radiotherapy significant reduction in RAP and physiological sphincter length in patients, indicating IAS dysfunction
Scleroderma	Affects the anorectal region Low IAP
Pathology Associated with Low Resting IAS Pressure	**Comment**
Anal fissure	Elevated resting pressure in the anal canal greater than 90mm Hg leads to ischemia of the anal lining
Internal sphincter achalasia	A rare and multifactorial disorder

of S4 and the inferior rectal branch of the internal pudendal nerve, while sensation comes from the inferior rectal nerve, a branch of the pudendal nerve.[80] The EAS is under conscious input from higher cortical centers.

Physiology

The anal sphincter play an important role in maintaining continence, controlling defecation, and passing flatus. The complex process is accomplished through the integrated motor functions of the anal sphincter muscles, rectum, pelvic floor muscles, the sensory visceral somatic components of the pelvic nerves, and higher cortical centers.[85]

Table 5. Treatment Options for Low and High Resting Anal Pressure States of the IAS
Adapted from Kumar & Emmanuel et al.[78]

Low Pressure	
Modality	**Effect**
Lifestyle Modification	Promotion of improved stool consistency and stable bowel movements through dietary modification and reflex mechanisms
Medication	Anti-diarrheal medications
Surgical Repair	Direct repair
Augmentation Techniques	Unclear mechanism
Artificial anal sphincters	
Biofeedback	Rectal sensitivity training involving the patient to squeeze EAS on activation of RAIR reflex
Neuromodulation	Sacral nerve stimulation (SNS) Percutaneous Tibial Nerve Stimulation (PTNS)
High Pressure	
Modality	**Effect**
Topical Therapy (nitroglycerin, diltiazem)	Relaxation of IAS smooth muscle through activation of NO or blockade of calcium channels
Botulinum Toxin	Neurotoxin causes a reduction in resting anal pressure and an increase in blood flow.
Lateral Sphincterotomy	Division of IAS to reduce RAP

The IAS is a complex muscle responsible for maintaining continence and is divided into upper and lower portions. The lower portion contributes significantly to the basal anal resting tone, responsible for 50-85% of the resting anal pressure (RAP).[85] The control of the IAS involves intrinsic and extrinsic neurons and myogenic neurons. The lower IAS has a high resting pressure to prevent leakage of fecal contents or flatus and is coordinated with the contraction of the EAS to maintain continence. The upper IAS relaxes reflexively during rectal filling/distention, a process known as recto anal inhibitory reflex (RAIR) plays a critical role in maintaining continence. The RAIR permits the passage of feces from the rectum to the upper anal canal, allowing the anal sensory epithelium to "sample" and distinguish luminal contents of solid, liquid, and gaseous origin. The volume of distension/filling can affect RAIR, with larger volumes contributing to prolonged relaxation periods of the IAS. Relaxation of the IAS occurs during the RAIR, which is a direct evaluation of IAS function. The contraction of IAS is mediated by sympathetic nerves through alpha adrenoreceptors and relaxation through Beta receptors.

Unlike the IAS, the EAS only contributes to a small portion of the anal resting tone. EAS is unique compared to other striated muscles as it has continuous tonic activity even at rest. However, changes in posture and increased intra-abdominal pressure can trigger an anal reflex, increasing the resting tone of the EAS. The second sacral spinal segment enables the EAS to have integrated activity, resulting in voluntary contraction that can last between 40-60 seconds. This contraction is vital for deferring defecation and facilitating rectal accommodation. Additionally, higher cortical signals can also transmit inhibiting signals that can cause relaxation of the EAS, allowing for the fecal bolus to pass.[86,87]

Clinical Disorder(s): Pathogenesis, Diagnosis, and Management

An excellent and exhaustive review by Kumar

and Emmanuel highlights the IAS pathology in the context of anal pressure.[78] Insufficient IAS pressure at rest can result in different degrees of fecal incontinence, often accompanied by diarrhea. High-pressure states generated in the IAS can cause the inability to defecate. Understanding these causes is crucial for the appropriate diagnosis and treatment of individuals with low and high internal anal sphincter pressure. Due to space limitations, the following important topics are summarized in Table 4.

Anal rectal manometry (ARM) is the gold standard for assessing sphincter and anorectal function. ARM involves evaluating resting and squeeze pressures of the anal sphincter, RAIR, rectal sensation, changes in anal and rectal pressures during attempted defecation, rectal compliance, and a balloon expulsion test. However, there is currently no standardized protocol for interpreting or performing the test, and variations exist in manometry probes and study populations. High-resolution manometry (HRM) can be utilized to measure circumferential pressures, providing additional information in the evaluation of anal rectal function.[78]

Dyssynergic defecation (DD) is a condition characterized by a lack of coordination of muscle contractions of the anorectal region, specifically puborectalis, and EAS, leading to difficulties in evacuating stool. Diagnosing DD involves ruling out underlying abnormalities and considering factors such as inadequate fiber and liquid intake, immobility, medications, and metabolic, neurological, or structural disorders. The balloon expulsion test (BET) and anorectal manometry ARM help to evaluate the pressure activity in the rectoanal region and aid in the diagnosis of DD.[88]

CONCLUSION

The gastrointestinal sphincters are gatekeepers that regulate the flow of solids, liquids, and gases in the digestive system. They are made up of both striated and smooth muscles and are influenced by nerves and hormones. These essential sphincters permit unidirectional or bidirectional flow. However, apart from the LES and anal sphincters, technical difficulties have prevented a thorough examination of the UES, PS, SO, and Ileocecal sphincters, resulting in gaps in our knowledge regarding their neuro-motility and disease prevention roles. Recent advances in technology and increased interest in their study offer hope for a better understanding of their structure, function, and impact on clinical disorders. With current advances in neuro-motility physiology and the technical feasibility of studying previously inaccessible sphincters, we can gain a better understanding of their roles in physiology and disease. ■

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Answers to this month's crossword puzzle: