Chapter

Esophageal Motility Disorders and Dysphagia: Understanding Causes and Consequences

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Abstract

Esophageal motility disorders are common conditions that impede the normal movement of food and liquids from the esophagus to the stomach, frequently manifesting as dysphagia, chest pain, and regurgitation. These disorders arise from a variety of etiological factors and can greatly diminish patients' quality of life. If left untreated, esophageal motility disorders may lead to severe complications, including malnutrition, weight loss, and aspiration pneumonia. This chapter offers an in-depth examination of the etiology and pathogenesis of both primary and secondary EMDs. It thoroughly investigates the clinical manifestations and diagnostic methods, highlighting the critical role of differential diagnosis in the accurate identification of these conditions. Additionally, the chapter reviews current treatment options, including pharmacological interventions, endoscopic procedures, and surgical techniques, and discusses the potential of novel therapies and future research directions. Through a detailed analysis of these aspects, the chapter aims to provide a comprehensive understanding of esophageal motility disorders and to guide effective clinical management and innovative therapeutic approaches.

Keywords: esophageal motility disorders, esophagus, dysphagia, achalasia, distal esophageal spasm, jackhammer esophagus, gastroesophageal reflux disease, high-resolution manometry, endoscopy

1. Introduction

Esophageal motility disorders (EMDs) encompass a range of conditions that disrupt the normal passage of food and liquids from the esophagus to the stomach. Commonly marked by dysphagia (difficulty swallowing), chest pain, and regurgitation of food, these disorders are prevalent worldwide [1]. Dysphagia can result in malnutrition, weight loss, and dehydration due to swallowing difficulties. Additionally, the regurgitation of undigested food increases the risk of aspiration,

potentially causing pneumonia and other respiratory issues. Furthermore, the psychological burden of living with a chronic swallowing disorder can contribute to anxiety and depression, further diminishing the quality of life [2]. The association of EMDs with complications such as esophageal cancer is well-established [3]. Using the Chicago Classification version (CCV) 4.0, EMDs are categorized as follows: achalasia, esophagogastric junction (EGJ) outflow obstruction, distal esophageal spasm (previously diffuse esophageal spasm), hypercontractile (jackhammer) esophagus, absent contractility, and ineffective esophageal motility (IEM) [4]. Given their prevalence, impact on quality of life, and potential for serious complications, this chapter aims to investigate the pathogenesis, clinical presentation, diagnosis, and treatment of primary and secondary EMDs leading to dysphagia, with particular emphasis on achalasia, distal esophageal spasm (DES), and jackhammer esophagus.

2. Etiology

EMDs can be broadly classified into primary and secondary types. Primary disorders are idiopathic, whereas secondary disorders are mostly associated with systemic diseases [5]. During swallowing, involuntary esophageal motility is coordinated by extrinsic nerves. Normally inactive during fasting, the esophagus undergoes specific changes during voluntary swallowing: the upper esophageal sphincter (UES) and lower esophageal sphincter (LES) relax to allow food entry and exit, respectively. Once the food bolus passes through the UES, an involuntary peristaltic wave, known as the "primary peristaltic wave," swiftly propels it toward the stomach.

Initially, sensory signals travel *via* several cranial nerves to the solitary tract nucleus in the brainstem, where motor signals are coordinated. These motor signals then travel *via* vagal fibers to the cervical esophagus (through the recurrent laryngeal nerves) and the proximal esophagus (through thoracic vagal fibers) to initiate and sustain the primary peristaltic wave [6]. The specific etiology of primary EMDs remains unknown, but research indicates that a combination of genetic, lifestyle, and environmental factors can contribute to their onset [7–9]. Understanding these complex interactions is crucial for developing effective prevention and treatment strategies for these disorders. Ongoing research aims to unravel the mechanisms underlying these conditions, shedding light on new treatments and improved patient outcomes.

2.1 Genetic background

The genetic etiology of EMDs is a complex and evolving field. Understanding the genetic basis of these disorders could lead to improved diagnostic tools, targeted therapies, and personalized treatment approaches for affected individuals. As genetic research advances, it holds the promise of unlocking new insights into the underlying causes of these challenging and often debilitating disorders.

2.1.1 Achalasia

Achalasia is a primary EMDs characterized by the failure of the LES to relax and the absence of esophageal peristalsis [10]. Although the exact cause is unclear, familial cases and twin studies indicate a genetic component [11, 12]. Several gene mutations have been implicated. For example, certain alleles of the human leukocyte antigen (HLA) system, specifically HLA-DQ, are associated with an increased risk

of achalasia, suggesting an autoimmune component potentially triggered by genetic predisposition [13, 14]. Additionally, mutations in the ALADIN gene, which is associated with triple-A syndrome (alacrima, achalasia, adrenal insufficiency, neurologic disorder), further indicate a genetic link in some achalasia cases, providing insight into potential genetic pathways involved in the disorder [15].

2.1.2 DES

DES is defined by uncoordinated esophageal contractions, which result in symptoms such as chest pain and dysphagia [5]. While the genetic underpinnings of DES are not as well-documented as those of achalasia, existing evidence indicates a hereditary component. The presence of DES in multiple family members suggests that genetic factors may play a role in its pathogenesis [16, 17].

2.1.3 Jackhammer esophagus

This rare EMD results in dysphagia, chest pain, and gastroesophageal reflux symptoms [18, 19]. Research into its genetic etiology is still in its early stages. Future studies are needed to identify specific genetic mutations or polymorphisms associated with this condition. The terms "classic jackhammer esophagus" and "spastic jackhammer esophagus" have been introduced to distinguish between the types, indicating a heterogeneous disease with varying underlying pathophysiology [20].

Understanding these genetic factors is crucial for developing effective prevention and treatment strategies for EMDs. Ongoing research aims to unravel the mechanisms underlying these conditions, potentially leading to new treatments and improved patient outcomes.

2.2 Environmental and lifestyle factors in EMDs

Various environmental and lifestyle factors can influence the occurrence of EMDs. Factors such as diet, alcohol consumption, tobacco use, stress, and medication use can contribute to the development and exacerbation of these disorders by affecting the esophageal muscles, nerves, and overall function [7, 21].

2.2.1 Diet and eating habits

Consuming a diet high in fats can slow gastric emptying and affect esophageal motility. This can exacerbate symptoms such as reflux, acid regurgitation, postprandial fullness, heartburn, swallowing obstruction or pain, epigastric burning sensation, chest pain, chronic laryngopharyngitis, and cough in individuals with EMDs [22]. Similarly, spicy foods can irritate the esophagus and intensify symptoms due to capsaicin stimulating nerve endings in the esophagus, potentially triggering esophageal spasms [23, 24]. Additionally, eating large meals can increase pressure in the stomach and esophagus, leading to motility issues and gastroesophageal reflux, worsening symptoms such as chest pain and regurgitation [25]. Irregular eating patterns, such as skipping meals or eating at inconsistent times, can disrupt normal esophageal function and contribute to motility disorders [25]. Therefore, maintaining a consistent meal schedule is important for promoting healthy digestion and minimizing symptoms in individuals with EMDs. Obesity is also a significant risk factor for

esophageal dysfunction, as excess body weight increases intra-abdominal pressure, leading to LES dysfunction and reflux [26].

2.2.2 Alcohol, tobacco, and medication use

Excessive alcohol intake can damage the esophageal mucosa and impair motility. Alcohol can also relax the LES, contributing to reflux and EMDs [27]. Smoking has been linked to various gastrointestinal disorders, including EMDs. Nicotine can relax the LES and impair esophageal motility, increasing the risk of reflux and dysphagia [28]. Additionally, certain medications can affect esophageal motility. For example, nifedipine, a calcium channel blocker commonly used for hypertension, can relax the LES and impair esophageal contractions [29]. Opioids and anticholinergic medications can also negatively affect esophageal motility [30, 31].

2.2.3 Stress and psychological factors

Psychological stress and anxiety have been shown to impact esophageal motility, with stressors potentially leading to increased esophageal sensitivity and altered motility patterns [32]. These effects can contribute to the development or worsening of disorders such as functional heartburn and globus sensation, characterized by the feeling of a lump in the throat. The relationship between stress and esophageal motility is complex and not fully understood. However, it is believed that stress-induced alterations in nerve signaling and hormonal responses may play a role in these effects [33].

2.3 Secondary EMDs

Secondary EMDs arise from various underlying conditions that affect the normal functioning of the esophagus. These disorders can manifest due to a wide range of etiologies, including collagen vascular diseases, diabetes, Chagas' disease, amyloidosis, multiple sclerosis (MS), idiopathic pseudo-obstruction, or the aging process [34]. They can affect esophageal motility through mechanisms such as nerve damage, muscle weakness, inflammation, and structural changes. Understanding the diverse causes of secondary EMDs is crucial for accurate diagnosis and effective management. Neurological diseases like Parkinson's disease, MS, and stroke can disrupt the neural pathways controlling esophageal peristalsis and sphincter function, impacting swallowing [35–37]. Systemic autoimmune conditions like systemic sclerosis (scleroderma) and systemic lupus erythematosus (SLE) can lead to fibrosis and thickening of esophageal tissues, resulting in impaired motility [38, 39]. Structural abnormalities such as hiatal hernia, esophageal strictures, and tumors (benign or malignant) can mechanically obstruct the esophagus, causing dysmotility and difficulty swallowing [40–42]. As outlined in the introduction, this section will explore the fundamental mechanisms by which secondary disorders contribute to esophageal motility dysfunction, with particular emphasis on gastroesophageal reflux disease (GERD) due to its high prevalence.

2.3.1 Neurological diseases

Neurological diseases represent a significant category of conditions leading to secondary EMDs. These disorders arise from disruptions in the neural control mechanisms responsible for coordinating esophageal peristalsis and sphincter function. Recognizing the impact of neurological diseases on esophageal motility is crucial for

implementing appropriate diagnostic and therapeutic strategies to improve swallowing function and quality of life for affected individuals. Parkinson's disease is characterized by the degeneration of dopaminergic neurons in the substantia nigra, resulting in dopamine deficiency affecting the basal ganglia, which are crucial for coordinating smooth muscle movements, including those in the esophagus [35, 43]. Patients with Parkinson's disease often experience dysphagia due to impaired peristalsis and reduced LES relaxation, leading to difficulty swallowing solids and liquids [35]. MS is an inflammatory disease affecting the central nervous system, causing demyelination of nerve fibers [44]. Lesions along the neural pathways controlling esophageal function disrupt the signal transmission necessary for coordinated peristalsis, resulting in dysphagia, regurgitation, and chest pain [36]. Stroke can damage brain areas that are responsible for swallowing reflexes and esophageal muscle coordination. Depending on the stroke's location and extent, patients may experience dysphagia ranging from mild difficulty swallowing to a complete inability to swallow, along with impaired esophageal motility [37]. Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by significant loss of motor neurons in the spinal cord, brainstem, and motor cortex [45]. As the disease progresses, patients may develop dysphagia due to the weakening of the muscles involved in swallowing, including those in the esophagus, leading to impaired peristalsis and reduced LES tone [46].

2.3.2 Systemic autoimmune conditions

Systemic autoimmune conditions significantly contribute to secondary EMDs by inducing structural changes and inflammation within the esophagus. These conditions result from the immune system's aberrant response, targeting various tissues and organs throughout the body, including the esophagus. This leads to impaired peristalsis, reduced LES function, and symptoms such as dysphagia and GERD. Scleroderma is a chronic autoimmune disease characterized by excessive collagen production and fibrosis in multiple organs, including the skin and internal organs. The systemic form of scleroderma, CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerosis, and telangiectasia), affects both the smooth muscle and connective tissue layers, resulting in a stiffened, less compliant esophagus [47, 48]. The LES may become hypertensive or fail to relax properly, contributing to GERD. Dysphagia in scleroderma often results from both mechanical obstruction due to fibrosis and impaired peristalsis. Genetic studies have identified several susceptibility loci for scleroderma, including HLA genes, particularly HLA-DR and HLA-DQ. Polymorphisms in the interferon regulatory factor 5 (IRF5) and signal transducer and activator of transcription 4 (STAT4) genes have also been linked to an increased risk of developing scleroderma [49–51]. SLE is an autoimmune disease characterized by the deposition of immune complexes in healthy tissues, leading to the accumulation of immune cells and tissue damage. Esophageal involvement in SLE is less common but can occur due to immune complex deposition and inflammation in the esophageal mucosa. This inflammation can disrupt normal esophageal motility, leading to symptoms such as dysphagia and odynophagia. Additionally, SLE patients may experience GERD symptoms due to esophageal dysmotility and impaired LES function [39, 52].

2.3.3 Structural abnormalities

Structural abnormalities of the esophagus can result from congenital malformations, acquired conditions, or mechanical obstructions [53]. These disorders, which

include hiatal hernias, esophageal strictures, and tumors, impair the normal passage of food and liquids through the esophagus, leading to symptoms such as dysphagia, odynophagia, chest pain, and food impaction. Hiatal hernia occurs when the gastroesophageal junction and a portion of the stomach protrude through the diaphragmatic hiatus into the chest cavity. There are two main types: sliding and paraesophageal [54]. Sliding hiatal hernias, where the gastroesophageal junction moves up into the chest alongside the stomach, are more common. This displacement can compromise the function of the LES, allowing gastric acid and contents to reflux into the esophagus. Chronic GERD associated with hiatal hernia can lead to esophagitis and subsequent fibrosis, contributing to impaired esophageal peristalsis and dysmotility [55]. Esophageal strictures are characterized by the narrowing of the esophageal lumen due to scar tissue formation. They can develop secondary to conditions that cause chronic inflammation or injury to the esophageal mucosa [56]. For instance, chronic GERD leads to inflammation and ulceration of the esophageal lining, which can progress to fibrotic scarring and stricture formation. Other causes include the ingestion of caustic substances, such as lye or acids, and radiation therapy for cancers in the chest region, which can lead to fibrosis and strictures [57, 58]. Esophageal strictures restrict the normal peristaltic movement of the esophagus, causing dysphagia, odynophagia, and the potential for food impaction. Esophageal tumors can be benign or malignant and can obstruct the esophageal lumen, affecting normal swallowing function. Benign tumors like leiomyomas arise from smooth muscle cells within the esophageal wall and typically present as well-circumscribed masses that can cause partial obstruction [59]. Malignant tumors, including adenocarcinoma and squamous cell carcinoma, often arise from the mucosal lining and can infiltrate the surrounding tissues, leading to significant luminal obstruction [60]. Esophageal cancer is associated with symptoms such as progressive dysphagia, unintentional weight loss, chest pain, and sometimes coughing or hoarseness due to tracheal compression. The presence of tumors in the esophagus disrupts normal peristalsis and can lead to severe dysmotility as the disease progresses [3].

2.3.4 Gastroesophageal reflux disease (GERD)

Chronic acid reflux, also known as GERD, can have serious consequences for the esophagus [61]. Repeated exposure of the esophagus to stomach acid can lead to inflammation, known as esophagitis [62]. This inflammation can cause irritation and damage to the esophageal lining, resulting in symptoms such as heartburn, chest pain, and difficulty swallowing. Over time, chronic inflammation can lead to the formation of scar tissue in the esophagus, known as esophageal fibrosis, which can cause esophageal stricture and subsequent difficulty swallowing and food impaction. In addition to inflammation and scarring, persistent exposure to stomach acid can weaken the muscles that control the movement of food down the esophagus, resulting in dysmotility. This condition prevents the esophagus from contracting properly to move food into the stomach [63]. Furthermore, acid reflux can irritate the nerves in the esophagus, leading to conditions such as esophageal spasms. These spasms can cause chest pain and difficulty swallowing, further complicating the motility of the esophagus.

2.3.5 Metabolic diseases

Metabolic diseases can significantly impact esophageal motility. For instance, diabetes mellitus is a major contributor to esophageal dysmotility. Diabetic

neuropathy can impair the nerves that control esophageal peristalsis and the LES, leading to conditions such as gastroparesis and diabetic esophagus, which manifest as dysphagia, heartburn, and regurgitation [64]. Obesity, a key feature of metabolic syndrome, is associated with a wide array of EMDs [65]. Additionally, hypothyroidism can influence esophageal motility by decreasing the duration and percentage of relaxation [66].

2.3.6 Infectious diseases

Infectious diseases can significantly contribute to the development of EMDs. A prominent example is Chagas disease, caused by the protozoan parasite *Trypanosoma cruzi*, which is endemic in parts of Latin America. In Chagas disease, esophageal dysfunction results from damage to the esophageal myenteric plexus. This leads to the loss of esophageal peristalsis, partial or absent relaxation of the LES, and the development of megaesophagus [67]. Additionally, esophageal candidiasis, often seen in immunocompromised patients such as those with HIV/AIDS, can cause inflammation, esophageal strictures, and secondary motility issues [68].

3. Pathophysiology

The most studied and well-known motility disorder of the esophagus is achalasia. Other motility disorders have not been as well studied, in part due to the lack of a clear consensus in nomenclature and diagnostic criteria, which have changed over the years. Available data suggest that these disorders have their own distinctive pathophysiological pathways and may overlap with other esophageal disorders.

3.1 Achalasia

The mechanism behind primary achalasia has been somewhat elucidated. It is now known that achalasia is definitively caused by the loss of inhibitory neurons and the interstitial cells of Cajal (ICC) in the Auerbach's (myenteric) plexus of the distal esophagus. These cells produce nitric oxide (NO) and vasoactive intestinal peptide (VIP), which are responsible for smooth muscle relaxation. Therefore, the loss of these neurotransmitters results in the hallmark of achalasia: impaired LES relaxation [69]. The process responsible for the destruction of neurons is selective, preserving excitatory neurons and their peptides [70].

3.1.1 Neuronal damage

Achalasia does not affect only the esophagus; certain regions of the central nervous system also undergo degeneration. Patients with achalasia have degenerated nerve cells in the dorsal motor nucleus (DMN) of the vagus nerve [71]. Animal studies have shown that bilateral DMN damage can result in achalasia-like dilatation of the esophagus [72]. Additionally, vagal nerve fibers have been found to be degenerated in patients with achalasia [73]. There is a possibility that the degeneration of the vagus nucleus and vagal nerve fibers is secondary to the loss of signal input from the esophagus [74]. The most significant damage occurs in the muscle layer of the esophagus, beginning in the Auerbach's plexus. Histopathological examinations have shown the infiltration of activated cytotoxic T lymphocytes and the activation of

the complement system within the myenteric ganglia, along with increased levels of IL-1β, IFNγ, TNF-α, and IL-2, especially in the early stages of the disease [75]. Thus, the primary pathological mechanism leading to myenteric ganglia loss is believed to be chronic ganglionitis [76]. This histopathological finding of ganglionitis with preserved intrinsic neurons and minimal fibrosis is linked to type III achalasia (also called "vigorous" or spastic achalasia) and is considered an early stage of achalasia. Prolonged inflammation leads to "classic" or type II achalasia through a decrease in the number of inhibitory neurons, as well as hypertrophy and neuronal fibrosis [77]. Further loss of neurons (eventually complete loss) and severe fibrosis correspond to type I achalasia. Therefore, some authors consider that the three types of achalasia represent a clinicopathological continuum [78].

3.1.2 Changes in the esophagus muscle layer

The smooth muscle of the esophagus, the muscularis propria, is irregularly and inconsistently hypertrophied in the early stages of the disease [79]. The classic dilation of the esophagus (sigmoid-like dilation and megaesophagus) proximal to the cardia occurs in the later stages of the disease. The esophagus dilates approximately 6 mm per year, while the esophagogastric junction reduces its lumen diameter by about 1 mm each year. Megaesophagus is rare and usually seen in elderly patients with longstanding disease [80]. Esophagus emptying has been studied in patients with achalasia, revealing that while the esophagus in type III achalasia patients is relatively easily emptied during most swallows, types I and II show impaired esophagus emptying. Type I achalasia shows no emptying, while food transit in type II achalasia is possible thanks to the contraction of the longitudinal muscle layer in the distal esophagus [81].

3.1.3 Changes in the esophagus mucosa

Although not primarily affected by the disease, the esophageal mucosa exhibits certain pathological alterations in achalasia, especially in patients with longstanding disease. Changes in the mucosa include diffuse squamous cellular hyperplasia, high-grade squamous dysplasia, and esophageal squamous cell carcinoma. Additionally, the esophageal mucosa of achalasia patients shows an increase in T lymphocytes. These changes are likely secondary to chronic inflammation caused by food stasis [82–84]. This state of chronic, continuous inflammation leads to an increased risk of esophageal squamous cell cancer, which may be elevated up to 140 times compared to the general population [85].

3.2 DES

The mechanism behind DES is poorly understood. Some authors believe it is a disorder similar to achalasia and that in some cases, it can progress to achalasia [86]. Full-thickness muscularis propria biopsies have shown atrophy and fibrosis of this layer, as well as a reduction in ICCs, a feature shared with achalasia [87]. Isolated case reports have found that DES symptoms can improve after corticosteroid or antiepileptic therapy, highlighting the general lack of understanding of this disease [88, 89]. The main characteristic of this disorder is the simultaneous contraction of multiple segments of the esophagus, primarily its distal portion. Some experimental studies have shown that the lack of NO neurotransmitter can cause DES-like simultaneous contractions of the esophagus, while reintroduction of NO reverses it. It is known that

patients taking opioids experience this syndrome more frequently and that opioid-induced DES is reversible upon their withdrawal [86]. Psychiatric disease (possibly through increased opioid use), along with GERD, has also been associated with DES [90]. Although the multiple possible etiologies present a challenge in understanding the exact pathophysiological mechanism that induces the spastic contractions, they also suggest the potential for personalized therapy in each case.

3.3 Jackhammer esophagus

Jackhammer esophagus is diagnosed by high-resolution manometry (HRM) with normal median integrated relaxation pressure and ≥ 20% hypercontractile swallows (>8000 mmHgscm). This condition appears to be distinct from achalasia. While the diagnosis has been clarified thanks to HRM, the pathological substrate of jackhammer esophagus remains enigmatic [4]. The disorder primarily affects the distal portion of the esophagus. Although the muscle layer of the distal esophagus is hypertrophied in jackhammer esophagus, the contractions are accompanied by a lack of synchrony between the longitudinal and circular layers of the smooth muscle [19]. Recent studies have shown eosinophilic infiltration in the mucosa, submucosa, and muscle layer of the esophagus in patients with EMDs [91]. Eosinophil infiltration of the mucosa with >15 eosinophils per high power field, after excluding other more common diseases, is diagnostic of eosinophilic esophagitis (EoE). EoE is likely a separate clinical and pathological entity, with dysmotility mainly due to reduced esophageal compliance, probably secondary to fibrosis of the esophagus [92]. In some cases, jackhammer esophagus is associated with GERD, and it appears that those patients could benefit from proton pump inhibitor (PPI) therapy [93]. In the idiopathic jackhammer esophagus, the primary driving factor is likely eosinophil infiltration of the esophageal muscle layer, sometimes referred to as eosinophilic esophageal myositis (**Table 1**) [94, 95].

EMDs	Genetics	Pathophysiology	Manometric Characteristics CCV 4.0 [4]
Achalasia	• Familial cases • Twin studies • HLA-DQ • ALADIN gene	• Impaired LES relaxation • Loss of inhibitory neurons and ICC; impaired NO and VIP production • Irregular and inconsistent hypertrophy of the smooth muscle in the muscularis propria	• Integrated relaxation pressure elevated • 100% absent peristalsis
DES	• Familial cases	• Simultaneous contraction of multiple segments of the esophagus • Reduction of ICC • Atrophy and fibrosis of muscularis propria	• Integrated relaxation pressure normal • ≥ 20% swallows with premature contractions
Jackhammer esophagus	• Unknown	• Lack of synchrony between the longitudinal and circular layers of the smooth muscle • Eosinophil infiltration of the esophageal muscle layer	• Integrated relaxation pressure normal • ≥ 20% swallows with hypercontractile contractions

Table 1.
Differences in genetics, pathogenesis, and manometric characteristics between achalasia, DES, and jackhammer esophagus.

4. Symptoms

The symptomatology indicating diseases of the esophagus is becoming an increasingly common problem that patients present to doctors. It is considered that every fifth person has experienced symptoms that would suggest a disorder in esophageal function at least once, regardless of gender and age [96]. The most common symptoms indicating a possible esophageal disorder include dysphagia, odynophagia, chest pain, heartburn, regurgitation, globus sensation, hiccups, and belching. It is also important to consider the presence of extraesophageal manifestations indicating esophageal dysfunction, such as wheezing, cough, throat pain, and hoarseness, after excluding primary diseases that lead to them [97].

4.1 Dysphagia

The leading symptom of EMDs is dysphagia. Around 15% of patients experience a sensation of difficulty swallowing, and its frequency increases with age. Dysphagia is of Greek origin and consists of two parts: "dis" (difficulty) and "phagia" (eating), representing a disorder in the passage of food from the mouth to the stomach. The sensation of difficulty swallowing may be associated with numerous neuromuscular and structural disorders, not only of the esophagus in the case of esophageal dysphagia but also of oropharyngeal diseases in the case of oropharyngeal dysphagia. The presence of this sensation has been confirmed in patients with psychiatric disorders, based on abnormal sensory perception at the level of the esophagus [98]. The swallowing process itself represents a complex neuromuscular action that affects oropharyngeal movements and esophageal peristaltic movements with the aim of transporting liquids and food to the stomach, lasting on average about 10 seconds. Any deviation from the correct act manifests in some of the symptoms of esophageal disorders, most commonly dysphagia [99].

Oropharyngeal dysphagia is defined as the inability to transport food from the oral cavity to the esophagus. The most common causes leading to the development of oropharyngeal dysphagia of neuromuscular origin are Parkinson's disease, ALS, MS, and polymyositis, while structural disorders are dominated by cancers, infections of the pharynx and throat, thyroid enlargement, and Zenker's diverticulum. In this type of dysphagia, symptoms occur immediately after swallowing food, indicating potential localization. Food impaction and difficulty swallowing saliva often occur, leading to manual evacuation of the bolus, vomiting, and increased saliva production. Potential causes that can lead to similar complaints are associated with atrophy of the masticatory muscles, inadequate chewing of food, lack of teeth, swallowing large food bites, and inadequate functioning of salivary glands [100].

The second type of dysphagia is esophageal dysphagia, which can also occur due to structural disorders such as cancers, diverticula, benign tumors, EoE, peptic changes, Schatzki's ring, and foreign bodies, as well as neuromuscular causes such as achalasia, DES, jackhammer esophagus, and hypertensive esophageal sphincter [101].

Valuable help in assessing the cause is obtained based on whether the patient has difficulty swallowing food or liquids, whether dysphagia is progressive or intermittent, whether heartburn occurs, and whether there is weight loss [101]. Patients experiencing a sensation of dysphagia during swallowing liquid and solid food, as well as after swallowing liquids, indicate a neuromuscular problem. In patients who

have dysphagia only when swallowing solid food, without problems swallowing mushy food or liquids, it is usually due to mechanical obstruction. When it comes to the impaction of a foreign body, it is most often accompanied by regurgitation and hypersalivation that passes after removing the foreign body. In patients who have liquid dysphagia, these complaints occur only during the consumption of liquids [102]. In patients with malignancy, there is a sudden onset of dysphagia symptoms, accompanied by weight loss and anorexia, as well as the appearance of heartburn with progressive worsening of symptoms. Dysphagia may also occur on the ground of previous esophagitis as well as on the ground of caustic damage to the esophagus in patients with esophagitis caused by drugs, when in addition to difficulty swallowing, there is also painful swallowing, a feeling of burning behind the sternum. In younger people who have previously had food bolus impaction, it is necessary to exclude the development of EoE. Any occurrence of dysphagia requires an adequate diagnostic approach to investigate it [103].

4.2 Chest pain

A major differential diagnostic challenge in medicine is chest pain. It can occur in patients with cardiovascular diseases, pulmonary system diseases, vascular diseases, and musculoskeletal disorders or may originate from the gastrointestinal tract [104]. It is considered that in 57% of patients who had chest pain and who underwent coronary angiography and did not have findings on coronary blood vessels, the pain was of esophageal origin [105]. Chest pain of esophageal origin can simulate pain of cardiac origin due to its retrosternal localization as well as due to the sharing of innervation pathways with the heart. Esophageal pain may have a lateral localization or spread to the neck, chin, or back, but less commonly, most often in the form of burning behind the sternum or smoldering. It occurs most often after a meal, can worsen with a meal, and can occur during the night. After taking PPIs or antacids, pain can be suppressed [104]. There are several theories that explain the appearance of esophageal pain of origin. So far, the most acceptable theory is associated with the action of hydrochloric acid on chemoreceptors in the esophagus, whose activation changes the electric charge of the membrane of smooth muscle cells and leads to spontaneous and repeated contractions of the muscles of the esophagus that cause pain. The above theory is followed by during the high-tone muscle tone, slow blood flow through the muscles of the esophagus, which leads to ischemia of the said organ and worsens the pain. In addition to the thermoreceptors, it is also important to consider the effect of the mechanoreceptors that are activated in the dilation of the esophagus, and there is no lesser importance. The cooling of the solutions comes to an end, activating the thermoreceptors, which manifests as dilation, and the esophagus comes to the activation of the mechanoreceptors, causing pain [106].

4.3 Regurgitation

Another important manifestation of the esophagus is the appearance of regurgitation. It is defined as the backward flow of food, stomach acid, and bile content into the mouth. It is necessary to make a distinction between regurgitation and vomiting, where the contents of the stomach are found in the mouth but there is no previous retching or activation of the abdominal muscles. Special importance is given to the difference between regurgitation and rumination, where the role of the short-term and

periodic re-orientation of food in the oral cavity is to eat. Regurgitation occurs most often at night and in patients who have been bending forward for a long time [107].

4.4 Impact on nutrition and quality of life

The diversity of symptoms in patients with esophageal dysmotility is significant. The onset of one or more symptoms leads to discomfort, frustration, and a reduction in daily activities. In addition to these manifestations, there are psychological changes such as anxiety, depression, and social isolation among these patients, further compromising their quality of life. A multidisciplinary approach to these patients is essential, starting with dietary habits. Firstly, it is necessary to chew food adequately during meals to prevent possible impaction and the sensation of difficulty swallowing, as well as consuming moderate amounts of fluids to facilitate easier passage of food boluses. Patients are advised to have more frequent meals throughout the day, with smaller quantities, which aids in easier emptying and reduces the activation of mechanoreceptors in the esophagus [108]. It is crucial to break daily habits such as alcohol consumption, which weakens the tight junctions between esophageal cells, allowing acid passage and activating chemoreceptors, as well as weakening the LES. In addition to alcohol, patients are advised to quit smoking and avoid sweets, chocolates, fatty foods, and excessively hot or cold beverages. Limited consumption of citrus juices and spicy foods is also recommended to avoid heartburn. Patients should avoid running and performing isometric exercises or lifting heavy weights [109]. Emotional instability in the form of frequent stress, worry, and discomfort also worsens existing symptoms by lowering visceral sensitivity. The use of certain medications has been noted to exacerbate symptoms, including calcium channel blockers, theophylline, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and bisphosphonates. In addition to the above, patients with esophageal dysmotility are advised against late meals and sleeping on the right side due to possible worsening of existing symptoms [110].

4.5 Association with other gastrointestinal symptoms

In addition to the previously mentioned symptoms of esophageal dysmotility, odynophagia, globus sensation, hiccups, and extraesophageal manifestations of esophageal dysfunction should be noted. Odynophagia, or painful swallowing, is a symptom associated with various conditions. The pain is typically retrosternal and is experienced while swallowing food or sometimes even saliva. It can result from inflammation of the esophageal mucosa or deeper structures and may occur due to caustic injuries, viral and fungal infections, or after radiation therapy to this area. Odynophagia can also be caused by improper use of tetracyclines. In severe cases of GERD, swallowing may become difficult and painful [111]. Globus sensation, or globus pharyngeus, is experienced by at least half of the population during their lifetime. It is believed to be primarily a psychological disorder leading to the sensation of a lump in the throat, difficulty swallowing, or throat tightening, without any abnormality in the tone of the upper esophageal sphincter or any other pathological changes within the esophageal lumen [112]. Hiccups represent a systemic manifestation of various conditions, not limited to gastrointestinal diseases such as achalasia, peptic ulcer, and GERD. They can also occur in patients with chest or abdominal trauma, or those with renal insufficiency. Despite being a multisystem manifestation, most patients with hiccups are initially evaluated by gastroenterologists, who may prescribe medications

such as metoclopramide, baclofen, or gabapentin. In extreme cases where hiccups are frequent and uncontrollable with medications, and other causes are ruled out, surgical ablation of the phrenic nerve may be necessary [113]. Patients with asthma, chronic cough, laryngitis, or pulmonary fibrosis are sometimes referred to gastroenterologists for further evaluation. Studies have shown that 35–80% of asthma patients also have GERD. The pathogenesis is bidirectional; therapy given to asthma patients often leads to GERD because bronchodilators relax the LES. Conversely, patients with the established reflux disease may develop asthma symptoms, particularly at night, including coughing, wheezing, hoarseness, and inflammation of the arytenoids. This is attributed to micro-aspiration of gastric contents and vagus-mediated neural reflexes [114].

5. Diagnosis

5.1 Clinical assessment

EMDs encompass a range of conditions that disrupt the normal function of the esophagus, hindering the passage of food from the mouth to the stomach. Clinical assessment of patients with these disorders requires a thorough medical history, detailed physical examination, and specific diagnostic tests. Gathering information about symptoms such as dysphagia, retrosternal pain, regurgitation, and possible weight loss is crucial. These symptoms may progress gradually over several months or years. Patients often report difficulty swallowing solid foods, while liquids pass more easily. Symptoms such as heartburn, the sensation of food sticking in the esophagus, and related issues should also be noted. Typically, physical examination does not reveal significant abnormalities but is essential for ruling out other potential causes of symptoms. Collecting a detailed medical history and family history can provide insights into genetic predispositions or inherited risk factors. Risk factors such as smoking, alcohol consumption, and previous gastrointestinal diseases should also be considered. Diagnostic procedures include upper gastrointestinal endoscopy, which allows visualization of the esophageal mucosa and exclusion of mechanical obstructions such as strictures or tumors. Esophageal manometry is used to assess functional aspects of motility, identifying abnormalities in peristalsis and LES tone, which may indicate disorders like achalasia. Radiological tests, such as barium swallow, can depict esophageal dilation, delayed emptying, and other characteristic changes indicating motility disorders. In certain cases, pH monitoring may be necessary to assess acid reflux, which can contribute to symptoms and complications [115].

5.2 High-resolution manometry

Manometry of the esophagus is a crucial diagnostic method for identifying esophageal motility disorders. This procedure allows for detailed analysis of the functional aspects of the esophagus, which is essential for the precise diagnosis of various forms of dysmotility. Disorders such as achalasia, DES, and hypomotility can significantly impair patients' quality of life, causing symptoms like dysphagia, chest pain behind the sternum, and regurgitation. Esophageal manometry is performed using a catheter equipped with pressure sensors, which is inserted through the nose or mouth into the stomach. During the procedure, the patient swallows small amounts of water, allowing for the measurement of pressures and peristaltic waves along the esophagus. Modern manometry utilizes HRM, providing a more detailed and precise

pressure map within the esophagus compared to traditional methods. Manometry is essential for the differential diagnosis of various esophageal motility disorders. In the case of achalasia, manometry reveals the absence of esophageal peristalsis and elevated pressure of the LES that fails to relax properly during swallowing. In DES, manometry shows simultaneous, high-pressure contractions that disrupt normal food transport. Hypomotility of the esophagus is characterized by reduced amplitude of peristaltic waves or their complete absence. The results of manometry enable a personalized approach to treatment [116].

5.3 Barium swallow studies

Swallowing barium is a non-invasive radiological method that plays a crucial role in assessing patients with esophageal motility disorders. This procedure allows for detailed visualization of the anatomical structure and functional state of the esophagus, which is essential for making an accurate diagnosis and planning appropriate treatment. During this procedure, the patient consumes a barium suspension that coats the esophageal mucosa, enabling detailed imaging of the esophagus using fluoroscopy. As the barium passes through the esophagus, radiographs are taken to capture a series of images showing peristaltic waves, the shape of the esophagus, and any abnormalities present. Swallowing barium is particularly useful for detecting structural and functional abnormalities that may contribute to esophageal motility disorders. This method can identify strictures, diverticula, tumors, or hernias that

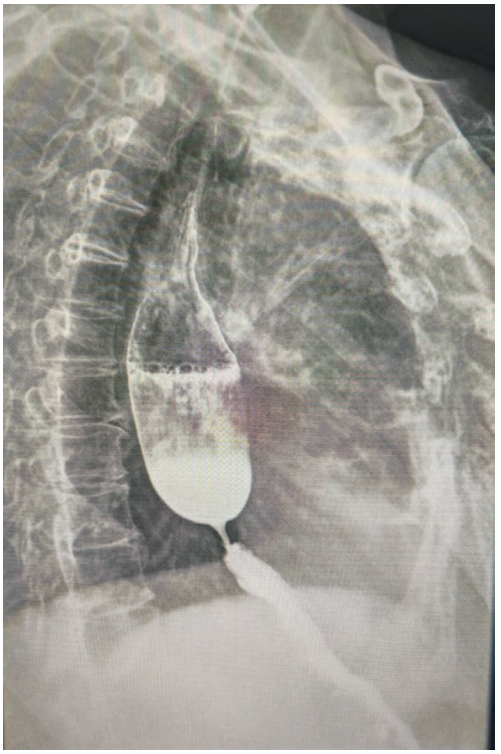

Figure 1.
A dilated esophagus with a retained column of barium and a "bird's beak" appearance indicates achalasia.

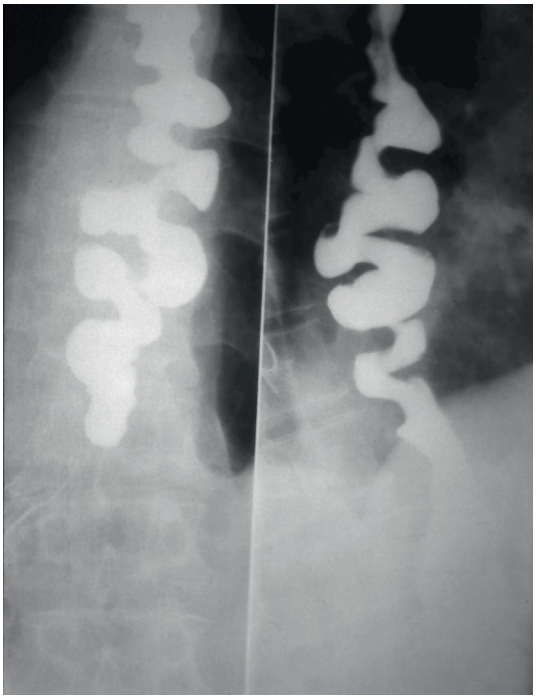

Figure 2.
The esophagus exhibits a corkscrew appearance caused by DES. Attribution to: © Nevit Dilmen, https://commons.wikimedia.org/wiki/File:Radiology_0012_Nevit.jpg, "Radiology 0012 Nevit," https://creativecommons.org/licenses/by-sa/3.0/legalcode.

may obstruct normal food passage. Additionally, swallowing barium can reveal delayed emptying of the esophagus, dyskinesia, and non-rhythmic contractions, which are characteristic of various types of esophageal motility disorders [117]. The results of barium swallow provide valuable information for differential diagnosis and further evaluation of patients with symptoms such as dysphagia, chest pain, and regurgitation. Combining this method with other diagnostic procedures such as manometry and endoscopy allows for a comprehensive understanding of the pathophysiology of esophageal motility disorders. For example, in patients suspected of achalasia, barium swallow may reveal characteristic findings such as esophageal dilation and a "bird's beak" narrowing at the junction of the esophagus and stomach (see **Figure 1**). In DES, images may show segmental contractions that disrupt the normal passage of barium (see **Figure 2**). This data is crucial for planning therapy, whether it involves endoscopic interventions, pharmacological treatment, or surgical procedures [118].

5.4 Endoscopy

Upper gastrointestinal endoscopy is a crucial diagnostic tool for evaluating patients with esophageal motility disorders. This procedure allows for direct visualization of the interior of the esophagus using a flexible endoscopic device, providing a detailed examination of the mucosa and identification of potential structural or functional abnormalities. Equipped with a high-quality camera, the endoscope enables precise visualization of the mucosal condition, assessing its color, integrity,

and any pathological changes that may affect esophageal motility [119]. Endoscopy is essential for identifying various pathological conditions that can impact esophageal function. This procedure can detect benign or malignant tumors, strictures, Barrett's esophagus, and other anatomical variations that may be causes or contributors to symptoms of esophageal motility disorders. In clinical practice, endoscopy is used to comprehensively evaluate the esophageal mucosa to accurately diagnose and plan further therapeutic approaches. Based on endoscopic findings, additional diagnostic steps such as biopsy or therapeutic interventions like dilation of strictures or ablation of pathological changes may be undertaken [120]. Integrating endoscopy with other diagnostic methods such as esophageal manometry and barium swallow allows for a comprehensive analysis of esophageal motility. This multidisciplinary approach is crucial for understanding the pathophysiology of disorders and tailoring individualized therapy, significantly contributing to treatment efficacy and patients' quality of life.

5.5 Differential diagnosis

Differential diagnosis of esophageal motility disorders encompasses a wide range of conditions. Dysphagia is a significant finding. It is essential to differentiate between oropharyngeal dysphagia (difficulty swallowing in the mouth and throat) and esophageal dysphagia (difficulty swallowing in the esophagus). Diagnostic approaches include upper endoscopy, HRM, barium swallow, and others (see **Figure 3**). Malignancy should be primarily ruled out, followed by investigation into other causes of dysphagia such as EMDs, scleroderma, peptic stricture, esophageal ring, dysphagia lusoria, and thyroid enlargement [121]. In addition to dysphagia,

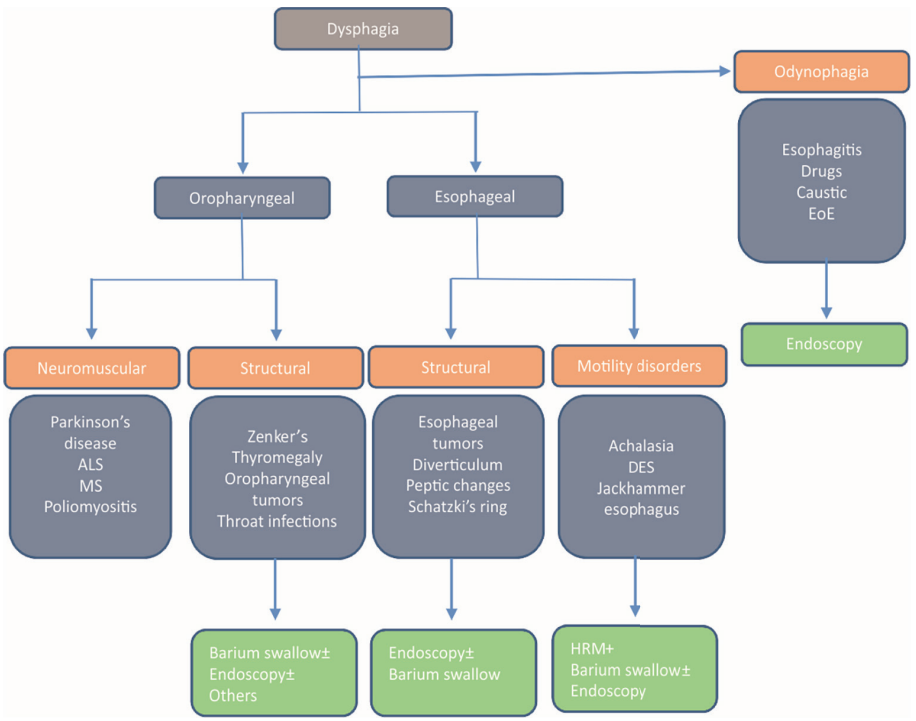

Figure 3.
Differential diagnosis of dysphagia with diagnostic workup.

chest pain, often associated with difficulty swallowing, commonly prompts patients to seek cardiology evaluation. Chest pain can also indicate pneumonia, pleuritis, pneumothorax, aortic dissection, musculoskeletal chest pain with radiation to the arms, and neck in cervical spine disorders. It is crucial to exclude pericarditis, pericardial tamponade, and thromboembolism [122]. Accurate diagnosis and management of these disorders require a multidisciplinary approach involving gastroenterology, cardiology, pulmonology, and other relevant specialties to ensure appropriate treatment tailored to each patient's condition.

6. Treatment

6.1 Pharmacologic treatment

Pharmacologic treatment for achalasia is generally considered the least effective option and is typically used only as a temporary measure before more effective interventions or for patients who do not respond to botulinum toxin injections and are not suitable for myotomy [123]. The primary medications used are calcium channel blockers and nitrates. Calcium channel blockers work by inhibiting calcium uptake in cells, which is necessary for the contraction of the LES, thereby promoting relaxation. However, these drugs often lead to tolerance, reducing their long-term effectiveness [124]. Nifedipine has shown some long-term benefits and even physiological normalization in a small subset of patients [125]. Nitrate therapy aims to counteract the decrease in NO, reducing LES tone and pressure. Sublingual isosorbide dinitrate effectively decreases basal LES pressure and improves esophageal emptying, but significant side effects such as hypotension, headaches, and peripheral edema limit its use [123, 125]. Other less commonly used treatments include anticholinergics, beta-adrenergic agonists, theophylline, and phosphodiesterase inhibitors. These inhibitors work by preventing the breakdown of cyclic GMP, which mediates nitric oxide-induced relaxation, thereby reducing LES tone [1, 125]. While experimental data are promising, further clinical studies are needed to confirm their efficacy in treating achalasia [125]. All the aforementioned smooth muscle relaxants might be used in patients with spastic esophageal disorders (DES and jackhammer esophagus) and non-cardiac chest pain as the primary symptom. Moreover, neuromodulators can be considered for this indication, such as tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and selective serotonin reuptake inhibitors. Additionally, PPIs are indicated in these disorders whenever there is increased gastric acid secretion and symptoms of GERD, such as regurgitation and heartburn [123].

6.2 Endoscopic treatment

6.2.1 Botulinum toxin

Botulinum toxin, a strong inhibitor of acetylcholine release from nerve endings, was introduced as a treatment for achalasia in 1995. It counteracts the unopposed contraction of the LES mediated by cholinergic nerves, thus reducing LES pressure [126]. Botulinum toxin is endoscopically injected at the squamocolumnar junction, extending up to 1 cm proximally. This minimally invasive treatment has a low rate of side effects and complications but is less effective than other non-pharmacological treatments. The success rate drops from 82% after 1 month to 48% after 1 year and is

particularly less effective in patients younger than 50 years [127]. Consequently, ACG guideline recommends botulinum toxin injection as first-line therapy for achalasia patients who are unfit for definitive therapies. While botulinum toxin can initially provide effective results, with only slightly lower effectiveness compared to myotomy, its benefits quickly diminish over time. This makes it a suboptimal intervention for patients with a reasonable life expectancy who are suitable candidates for endoscopic or surgical interventions [1]. For spastic disorders, botulinum toxin injections have demonstrated significant improvement and a reduction in chest pain. However, the sample sizes in these studies are small, and the effects appear to be short term. More research is needed in this area to confirm these findings [128].

6.2.2 Pneumatic dilation

Pneumatic dilation (PD) is a highly effective treatment for achalasia, especially when standard dilators fail to achieve symptom relief by disrupting the muscularis propria. Patients undergoing PD must also be candidates for surgery due to the potential risk of esophageal perforation, which occurs in about 1.9% of cases. The most frequently used dilators are non-radiopaque graded polyethylene balloons (Rigiflex), available in sizes of 3.0, 3.5, and 4.0 cm, typically used in a sequential manner. The procedure is carried out under sedation, with or without fluoroscopy, and requires significant operator expertise. During the procedure, the balloon is precisely positioned across the LES and inflated to a pressure of 10–15 psi for 15–60 seconds to achieve maximum dilation. After the procedure, patients are closely monitored for signs of perforation, with imaging tests conducted if perforation is suspected. If no complications are detected, patients can be discharged with antiemetics and instructed to seek immediate medical attention if they experience severe chest pain or fever, as delayed perforation can occur [1]. PD offers an excellent success rate of 91% after a 5-year follow-up, with 25% of PD patients requiring redilation during this period [129].

6.2.3 Peroral endoscopic myotomy

The hybrid technique of peroral endoscopic myotomy (POEM) was developed in Japan, combining endoscopic approaches with natural orifice transluminal endoscopic surgery principles to perform a myotomy. The procedure involves creating a submucosal plane with an endoscope to access and cut the circular muscle fibers over at least 6 cm into the esophagus and 2 cm below the squamocolumnar junction [1]. The International POEM survey, conducted across 16 expert centers and reporting 841 completed procedures, signifies a groundbreaking advancement in the treatment of achalasia, demonstrating a high overall clinical response rate of 98% [130]. POEM also demonstrates high long-term effectiveness, achieving over 90% clinical success at the 5-year follow-up, but with a higher incidence of GERD compared to PD [131, 132]. POEM has been employed for other EMDs, such as diffuse esophageal spasm, though with less success than with achalasia [133].

6.3 Surgery

6.3.1 Heller myotomy

Heller myotomy, first performed approximately a century ago, was considered the gold standard for achalasia before the emergence of POEM. Initially performed

through a thoracotomy, this procedure involves dividing the muscle fibers of the LES without disrupting the mucosa. While thoracoscopic myotomy has been used successfully, laparoscopic myotomy is now the preferred method due to its lower morbidity and faster recovery [1, 133]. Laparoscopic Heller myotomy (LHM) offers significant symptom relief, with approximately 90% of patients experiencing improvement. The most frequent complication associated with this procedure is GERD. However, when fundoplication is added to the laparoscopic myotomy, the incidence of postoperative GERD significantly decreases from 31.5 to 8.8% [134]. A meta-analysis of nine studies on LHM (583 patients) indicated that LHM is effective, but its success rate varies by achalasia subtype. Patients with types I and II achalasia experienced higher success rates post-LHM at 81 and 92%, respectively, compared to 71% for type III patients [135]. Overall, graded PD, LHM, and POEM are all first-line treatment options for type I or type II achalasia, offering similar efficacy. POEM and LHM are more invasive than PD, with POEM having higher rates of post-myotomy GERD compared to PD and LHM with fundoplication. For type III achalasia, POEM and LHM are recommended over PD. For patients not suitable for any of these definitive treatments, endoscopic botulinum toxin injection and smooth muscle relaxants are recommended [1]. LHM has shown effectiveness in treating "diffuse esophageal spasm." Studies using the criteria of the new classification for DES and jackhammer esophagus, along with surgical treatment of these conditions, are still not available [136].

6.3.2 Esophagectomy

Patients with achalasia often manage symptoms like dysphagia and regurgitation through dietary and lifestyle changes, making it challenging to accurately assess treatment outcomes. Both patients and physicians may initially underestimate the severity of the condition or the effects of interventions. As achalasia progresses, it can lead to severe complications such as significant esophageal dilation (megaesophagus) or tortuosity (sigmoid esophagus), increasing the risk of aspiration, aspiration pneumonia, and malnutrition. For these patients, treatments such as PD, surgical myotomy, or POEM may be less effective. Ultimately, up to 5% of achalasia patients may require esophagectomy, which can be safely performed by experienced surgeons in appropriately selected cases [1, 137, 138]. Esophagectomy can be performed *via* open transthoracic, thoracoscopic, or transhiatal routes. The surgical approach depends on the anastomosis location and the choice of esophageal replacement conduit (stomach, colon, or small bowel), with resection options ranging from limited to the EGJ to near-total esophagectomy [137].

7. Conclusion

While significant progress has been made in the diagnosis and treatment of EMDs, ongoing research, and a multidisciplinary approach will be crucial for enhancing patient outcomes and developing new, more effective therapies. Conducting long-term follow-up studies on the efficacy and safety of different treatment options will provide more robust data to guide clinical practice.

Conflict of interest

The authors declare no conflict of interest.

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